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The Aims of Diabetes Care

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Key points

- People with diabetes are individuals who have a condition that has medical, psychological, personal, and social risk factors and consequences. They are not passive recipients of healthcare and are not defined by their disease state.
- Optimal diabetes management occurs when the multidisciplinary diabetes care team and the person with diabetes actively work together as equal partners to achieve diabetes-related goals.
- Life-threatening diabetes emergencies, such as diabetic ketoacidosis, must be effectively managed, and attention paid to their prevention.
- Acute symptoms of hyperglycaemia need to be addressed by careful pharmacological management and lifestyle modification support.
- Diabetes management is a balance between supporting short-term optimal glycaemic management and quality of life while at the same time

reducing the risk of long-term complications. This is achieved through effective medical treatment of glycaemia, cardiovascular risk factor management, and appropriate psychosocial support and education.

- The time of diagnosis can be traumatic and is a key milestone in the management of diabetes when effective education, support, and treatment are needed. It is important to ensure parity of esteem, by valuing mental health equally with physical health.
- Regular lifelong contact between the person with diabetes and their healthcare team is essential in order to provide person-centred care to support healthy adjustment to, and coping with, the demands of this complex condition that changes throughout a person's life.
- Diabetes-related complications should be managed effectively if and when they present to reduce their morbidity.

Diabetes is a lifelong condition that for the majority is currently incurable. It is associated with premature mortality and morbidity, from an increased prevalence of macrovascular disease and microvascular complications affecting the kidney, nerve, and eye [1,2]. High-quality randomized trials have shown that improving glycaemic levels is associated with a reduction in microvascular complications [3–5], while a multifaceted approach to cardiovascular risk factors will reduce cardiovascular morbidity and mortality [6]. Addressing the psychosocial challenges faced by people with diabetes reduces psychological distress and improves self-management behaviours [7,8]. A holistic approach to supporting the person with diabetes in making choices based on the best evidence available and providing them with autonomy in consultations leads to greater self-care and improved metabolic management [9].

The person living with diabetes will spend the vast majority of their time managing their own diabetes and only an estimated 1% of their time in contact with healthcare professionals. Therefore, it is crucial to provide individuals with appropriate medical and psychosocial support to help them optimally self-manage their diabetes. It is important that the purposes of the consultation or other contacts with the diabetes healthcare team are well defined, with clear aims to make them relevant and useful. To ensure that the individual derives the maximum benefit from the time spent with their diabetes healthcare team, whether this is in a hospital,

primary care, or community setting, the consultation should be collaborative, patient centred, and goal focused. In addition, telemedicine provision of diabetes care, via phone, video-conference, or email contact or through educational sessions outside a traditional clinic setting has proven effective [10].

This chapter provides an overview of the aims and philosophy of diabetes care. Separate aspects of care will be covered in greater detail in subsequent chapters. The aims of diabetes care and management to improve the quality of life of the person with diabetes are fourfold. Life-threatening diabetes emergencies, such as diabetic ketoacidosis or severe hypoglycaemia, should be managed effectively, including preventive measures. The acute manifestations of hyperglycaemia, such as polyuria and polydipsia, need to be addressed. In practice, these occupy only a minority of the work undertaken by diabetes healthcare professionals. Much of the focus of care is therefore directed towards minimizing the long-term complications through screening and working together with the person with diabetes to support improved glycaemic and cardiovascular risk factor management. This provides a challenge for the diabetes team, because people with type 2 diabetes often have no symptoms at the time of care, yet are asked to make lifestyle changes and take medications that may place a considerable burden on them. The fourth aim of care is to avoid iatrogenic side effects, such as hypoglycaemia, and relies on collaborative care planning with the person with diabetes.

St Vincent declaration

During the 1980s, there was a transformation in the widely held perceptions of the roles of people with diabetes and philosophy of care. Instead of their being viewed as passive recipients of healthcare, there was an increasing recognition that people with diabetes are individuals with a condition that has medical, personal, and social consequences. During this time there was an increasing awareness and acceptance of the concept that each person with diabetes should take on part of the responsibility for their diabetes management and act as equal partners with healthcare professionals. In response to this paradigm shift, representatives of government health departments and organizations for people with diabetes from all European countries met with diabetes experts under the auspices of the Regional Offices of the World Health Organization (WHO) and the International Diabetes Federation (IDF) in the hillside town of St Vincent, Italy, on 10–12 October 1989. They unanimously agreed a series of recommendations for diabetes care and urged that action should be taken in all countries throughout Europe to implement them (Box 25.1) [9]. Since that time this philosophy of partnership working between people with diabetes and healthcare professionals has been adopted within individual nations' strategies to improve the quality of diabetes care.

Diabetes care team

The diabetes care team involves a multidisciplinary group of healthcare professionals who are available to support the person with diabetes (Figure 25.1). A key component of diabetes care is to ensure that the individual with diabetes is at the centre of the provision of care. This means that they should be an equal member of the diabetes care team, working together with the healthcare professionals. This relationship should be based on the exchange of information, advice, and education to enable the healthcare team to provide best practice-tailored support for the individual with diabetes so that they feel sufficiently empowered to manage their condition themselves. This approach ensures that the care offered is personalized appropriately for the individual and their circumstances.

The large number of diverse health professionals involved in the diabetes care team means that the roles and responsibilities of all must be clearly presented and agreed. It is often helpful for the person with diabetes if the key members of their diabetes care team are identified, as they will have more contact with some healthcare staff than others.

Most routine type 2 diabetes care takes place in a primary care setting, but some people who have complications or complex medical or psychological needs will require management and support in a specialist setting for some or all of their care [12]. The diabetes physician usually takes overall responsibility for the diabetes medical care, but other specialists may be involved, for example an ophthalmologist may be needed to examine the eyes carefully and treat diabetic retinopathy, if present. Diabetes care is multidisciplinary, involving doctors, nurses, and many allied healthcare professionals whose responsibility is to support the person living with diabetes in the management of their condition. A close collaboration between primary and secondary healthcare professionals and among specialists is needed to ensure that all involved are aware of the issues that are relevant to the individual with diabetes, and that care is integrated and coordinated across the wide range of disciplines

Box 25.1 St Vincent declaration [11]

- Elaborate, initiate, and evaluate comprehensive programmes for detection and control of diabetes and of its complications, with self-care and community support as major components.
- Raise awareness in the population and among healthcare professionals of the present opportunities and the future needs for prevention of the complications of diabetes and of diabetes itself.
- Organize training and teaching in diabetes management and care for people of all ages with diabetes, for their families, friends, and working associates, and for the healthcare team.
- Ensure that care for children with diabetes is provided by individuals and teams specialized both in the management of diabetes and of children, and that families with a child with diabetes get the necessary social, economic, and emotional support.
- Reinforce existing centres of excellence in diabetes care, education, and research.
- Create new centres where the need and potential exist.
- Promote independence, equity, and self-sufficiency for all people with diabetes, children, adolescents, those in the working years of life, and the elderly.
- Remove hindrances to the fullest possible integration of people with diabetes into society.
- Implement effective measures for the prevention of costly complications:
 - Reduce new blindness due to diabetes by one-third or more.
 - Reduce numbers of people entering end-stage renal failure by at least one-third.
 - Reduce by one-half the rate of limb amputations.
 - Cut morbidity and mortality from coronary heart disease by vigorous programmes of risk factor reduction.
 - Achieve pregnancy outcomes in women with diabetes that approximate those of women without diabetes.
- Establish monitoring and control systems using state-of-the-art information technology for quality assurance of diabetes healthcare provision and for laboratory and technical procedures in diabetes diagnosis, treatment, and self-management.
- Promote European and international collaboration in programmes of diabetes research and development through national, regional, and WHO agencies and in active partnership with persons with diabetes and with diabetes organizations.
- Take urgent action in the spirit of the WHO programme 'Health for All', to establish joint machinery between WHO and IDF European Region, to initiate, accelerate, and facilitate the implementation of these recommendations.

involved. Ensuring the person with diabetes remains at the centre of care is likely to facilitate the collaboration.

Given the chronic nature of diabetes, continuity of care is essential. Ideally this should be provided by the same doctors and nurses from visit to visit, but where this is not possible, the healthcare team should have access to previous records so that they are fully aware

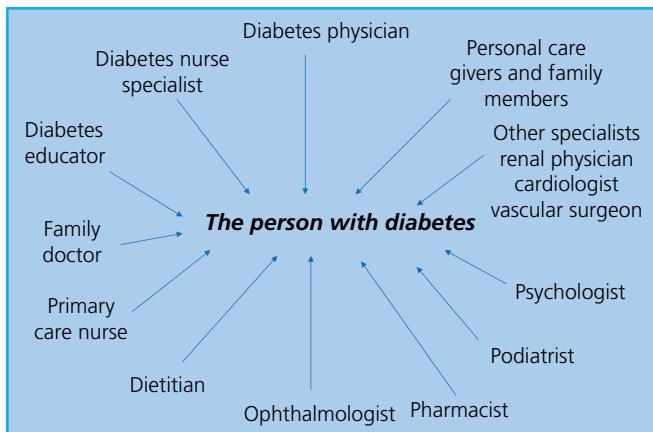


Figure 25.1 The multidisciplinary group of healthcare professionals who are available to support the person with diabetes.

of the medical history, background, and lived experience of the person with diabetes. In some developing countries this is particularly challenging, where medical records are often focused around single episodes of acute care of infectious diseases [13].

With the involvement of the person with diabetes in the diabetes team, the individual assumes several responsibilities. The task of implementing the day-to-day management plan of the diabetes lies with the individual; it may sometimes be difficult for healthcare professionals to accept this, particularly if their frame of reference is within an acute medical model of healthcare delivery. It is important to understand that diabetes self-management is challenging and so the diabetes care team should be available to support the person through their experiences with their condition. Diabetes distress, burnout, and impaired psychosocial functioning are all commonly reported by people with diabetes [14]. There have been increasing efforts to standardize psychosocial outcomes alongside biomedical outcomes. The recent US Food and Drug Administration Medical Device Development Tools (MDDT) qualification of the INSPIRE measures demonstrates the rigour now expected of psychosocial assessment in diabetes [15]. In addition, the International Consensus of Health Outcome Measures (ICHOM) produced a standard set of measure outcomes, biomedical and psychosocial, to promote robust assessment thereof across nations globally [16].

Adolescence can be a particularly challenging time, as this period of the person's life coincides with a time of rapid change, transition to adulthood, and increasing independence. Risk taking, experimentation, and increasing responsibility along the path to diabetes self-management by the adolescent are to be expected (Chapter 70).

Improving the outcome of the consultation

The time that a person with diabetes spends with a healthcare professional is limited and should be used as effectively as possible. Clinicians often give conflicting advice, both within the team and from one consultation to the next [9]. Goals are often not followed up, leaving the person with diabetes feeling frustrated. Studies have shown that typically physicians interrupt their patients 18 seconds after the patient starts to describe their problems, approximately half of patients' concerns are not discussed, and in half of consultations the patient and physician disagree on the central problem presented [9]. Such disagreement and inconsistency are associated

with poorer outcomes. Better self-care and metabolic management are achieved through supporting the person with diabetes to make choices based on the best evidence available and providing autonomy in consultations. In the UK, the Department of Health has produced literature entitled 'Questions to ask' (Table 25.1), which provides guidance about the questions a person with diabetes might want to ask during a consultation to maximize the benefits from the visit to their healthcare team [17].

The consultation or educational programme should help the person with diabetes gain a clearer understanding of their condition and the behaviours required for optimal outcomes. This can only be achieved effectively when professionals and people with diabetes are enabled to work together. Taking a holistic approach, such as embodied in the Kaleidoscope model of care [9] (Figure 25.2), can facilitate this collaborative, patient-centred, joint goal-setting process.

The Kaleidoscope model of care presents a novel, holistic, tailored, and individualized approach to healthcare delivery for people with diabetes through an assessment of an individual's current

Table 25.1 Checklist of questions to ask your doctor at your appointment.

Tests, such as blood tests or scans

- What are the tests for?
- How and when will I get the results?
- Who do I contact if I do not get the results?

Before your appointment

- Write down your two or three most important questions.
- List or bring all your medicines and pills – including vitamins and supplements.
- Write down details of your symptoms, including when they started and what makes them better or worse.
- Ask your hospital or surgery for an interpreter or communication support if needed.
- Ask a friend or family member to come with you, if you like.

During your appointment

- Do not be afraid to ask if you do not understand. For example 'Can you say that again? I still do not understand'.
- If you do not understand any words, ask for them to be written down and explained.
- Write things down or ask a family member or friend to take notes.

Before you leave your appointment

Check that:

- You've covered everything on your list.
- You understand, for example 'Can I just check I understood what you said?'
- You know what should happen next – and when. Write it down.

Ask:

- Who to contact if you have any more problems or questions.
- About support groups and where to go for reliable information.
- For copies of letters written about you – you are entitled to see these.

After your appointment, do not forget to

- Write down what you discussed and what happens next. Keep your notes.
- Book any tests that you can and put the dates in your diary.

Ask:

- 'What's happening if I'm not sent my appointment details?'
- 'Can I have the results of any tests?' (If you do not get the results when you expect – ask for them.) Ask what the results mean.

Source: Diabetes UK and Association of British Clinical Diabetologists 2005 [12].

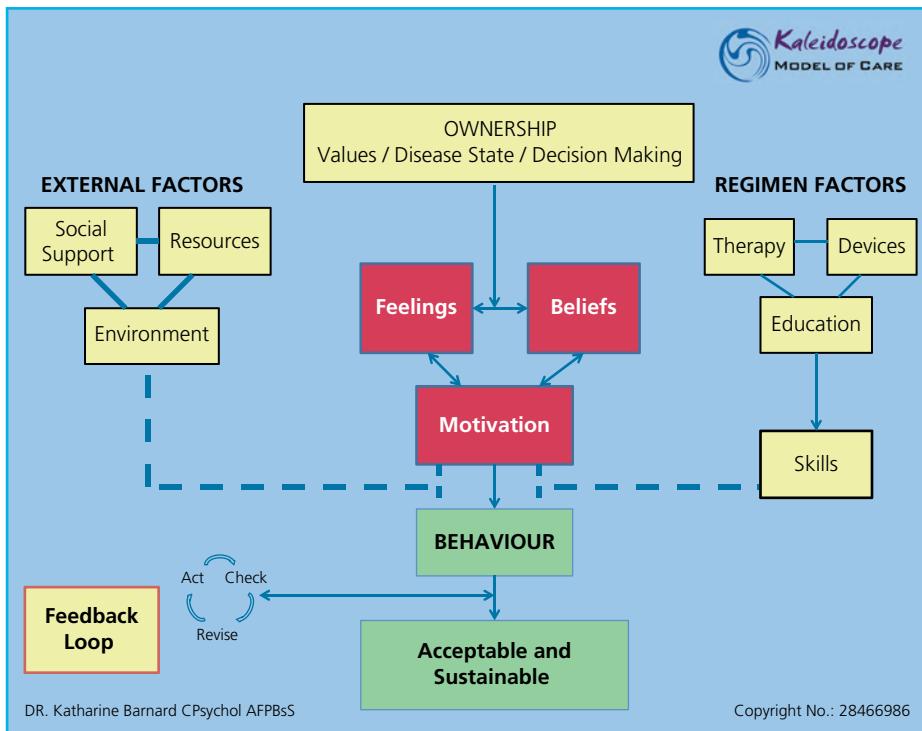


Figure 25.2 The Kaleidoscope model of care.
Source: Barnard et al. 2014 [9].

regimen, barriers and motivation, and available support resources. It is flexible and applicable in different health settings, fundamentally promoting the specific needs of the individual with diabetes. These needs are dynamic, taking a different shape at different points in time, while recognizing and adapting to the range of care needed [9].

It is good practice to provide the person with diabetes with copies of any letters written about them [18, 19]. Questions about treatment recommendations should be encouraged and people should be aware of what will happen next, including any requirement for further investigation. Regular review of management plans through joint dialogue, listening, discussion, and decision making between the individual and the healthcare professional, sometimes known as care planning, is the key to enhancing relationships and partnership working [20]. Contact details should be made available to enable the individual with diabetes to seek help if further questions arise.

In 2018 the UK National Health Service (NHS) published its 'Language matters: Language and diabetes' [21] document. This recognizes that the language used by healthcare professionals can have a 'profound impact on how people living with diabetes, and those who care for them, experience their condition and feel about living with it day-to-day'. The document sets out some basic principles for good practice for interactions between healthcare professionals and people living with diabetes. Furthermore, it lays out some common examples of language use and presents suggestions for alternative responses or ways to deal with them. Finally, the document encourages healthcare professionals to engage positively and avoid the use of negative language.

time when they may be least able to do so, perhaps because of shock, denial of, or anger at the diagnosis [22]. Empathy and considerable skill are therefore needed to support the person with diabetes at this time. The diabetes team should perform a medical examination (usually the physician) and work with the individual to develop a programme of care that is individualized and includes treatment-oriented goals. Psychological support should be offered, and ongoing psychosocial assessment of coping, adjustment, and diabetes-related distress should be conducted.

Issues relating to diagnosis

The diagnosis of diabetes is based on the finding of one or more glucose values above internationally agreed values [23, 24] (Chapter 2). Usually a diagnosis has been made prior to referral to the diabetes clinic, but this is not always the case. In the absence of symptoms, individuals require two glucose or glycated haemoglobin ($\text{HbA}_{1\text{c}}$) values above the diagnostic criteria to fulfil the diagnosis of diabetes.

Advice may be required to determine the type of diabetes, as the distinction is not always as clear as may be expected. When a young preschool child develops weight loss, polyuria, polydipsia, and ketoacidosis over a short period of time, the diagnosis is type 1 diabetes, while by contrast if an asymptomatic older overweight individual is found to be hyperglycaemic, the diagnosis is most likely to be type 2 diabetes (Chapter 24). These presentations lie at two ends of a spectrum, and the diagnosis of the type of diabetes may be less clear when the onset occurs in an overweight adult in their 30s who is found to have islet cell antibodies. Diabetes healthcare professionals should also be alert to the possibility of monogenic causes of diabetes (Chapter 20).

Although a precise diagnosis may not be needed from the outset, an early decision should be made about the necessity for insulin therapy (Chapter 24). While there may be clinical features that suggest the type of diabetes, time is often a useful diagnostic tool to determine whether the person with diabetes requires insulin.

Following diagnosis

The period following the diagnosis of diabetes is crucial for the long-term management of diabetes. A huge amount of information and skills need to be assimilated by the person with diabetes at a

Diabetes education

A key component to empower the person with diabetes is the provision of diabetes education [25] (Chapter 26). This information should be offered in a patient-centred manner, as it is retained more effectively when delivered in this way. Education may be provided individually or in a group setting.

It is essential that the person with diabetes understands their diabetes and develops the skills and competencies required to self-manage the condition as well as possible. People with newly diagnosed diabetes should have the chance to speak with a diabetes healthcare professional who can fully explain what diabetes is [26]. This will offer an opportunity to discuss the treatment and goals, as well as providing a practical demonstration of any equipment required to support self-management, for example blood glucose meters or insulin devices. The importance of ketones testing for those with type 1 diabetes should be explained. Where self-monitoring has been advocated, it is essential that the individual knows how to interpret the results and how to act appropriately in response to that information.

A qualified dietitian should provide advice about how to manage the relationships between food, activity, and treatment (Chapter 27). Where necessary, they should explain the links between diabetes and diet and the benefits of a healthy diet, exercise, and optimal diabetes management. As an essential member of an effective clinical care team, a diabetes specialist nurse or practice nurse also has a role in providing dietary advice together with relevant literature [26].

The social effects of diabetes should be discussed, as they may relate to employment, insurance, or driving (Chapter 66). Some countries require individuals with diabetes to inform the appropriate licensing authorities. Advice about diabetes and foot care should also be given (Chapter 53).

Although education is essential following diagnosis, it is important to appreciate that this is a lifelong process that should consider recent advances in medical science and changes in circumstances of the person with diabetes [25]. Education should be available via different modalities that best meet the needs of each individual.

The best measure of effective education is not simply that someone knows more, but rather that they are able to apply the new knowledge to enhance their diabetes self-management. The simple provision of knowledge by itself is often insufficient to influence behavioural change. High demands are placed on the person with diabetes regardless of the type of diabetes, especially when the benefits are not immediate, may only accrue with time, and even then may not be appreciated. The individual with diabetes needs to gain an understanding that improved glycaemic levels can help prevent the long-term complications of diabetes, such as a myocardial infarction or proliferative retinopathy, even though they may have never experienced these conditions.

The diagnosis of diabetes may provoke a grief reaction and the diabetes team needs to support the person with diabetes as they work through this (Box 25.2). Efforts should be made to help the individual adapt to their new reality of living with diabetes and engage in optimal self-management. If this does not happen, they can be left feeling overwhelmed by diabetes or expect that their healthcare team can take control for them. For some it may take a very long time to accept their diabetes and the demands placed on their life. Therefore, emotional and psychological support and techniques need to be available in the long term and should be discussed at every clinic appointment.

People with newly diagnosed diabetes often want to speak with others who have diabetes or who have had similar experiences

Box 25.2 Case study

Dave is 25 years old and recently diagnosed with type 1 diabetes. The diagnosis was made following an acute admission to hospital with diabetic ketoacidosis and insulin therapy was initiated.

Initially appearing to accept the diagnosis, Dave quickly became very angry about his perceived loss of control over his life and the reduction in his quality of life because of the new demands placed by diabetes and its treatment. Feeling guilty about whether he could have prevented it, and despairing about the lifelong condition, Dave found it increasingly difficult to keep up with the daily tasks of self-management, which in turn contributed to his feelings of despair and loss of control.

The healthcare team helped Dave identify some short-term goals for diabetes self-management and signposted social media support online, including on Twitter, as well as a local support group. Dave and his healthcare team worked together on problem-solving techniques to help make some of the diabetes tasks more achievable in his daily routine.

while developing diabetes. Many countries have diabetes-related charities that can provide this support, and it is important that information about what help is available, including local centres or peer support groups, is provided in a timely fashion.

Ongoing clinic visits

The diabetes team needs to work together with the person with diabetes to review the programme of care, including the management goals and targets at each visit [27]. It is important that the individual shares equally in all treatment decisions, as this improves the chances of jointly agreed goals being adopted following the consultation. ‘No decision about me without me’ is central to the NHS philosophy [28]. A family member, friend, or carer should be encouraged to attend the clinic appointment to support the person with diabetes, and to stay abreast of developments in diabetes care [29].

An important goal of management is to prevent the microvascular and macrovascular complications of diabetes without inducing iatrogenic side effects. This involves active management of hyperglycaemia together with a multifaceted approach targeting other cardiovascular risk factors. Ensuring parity of esteem by valuing mental health equally with physical health is crucial at all times. Funding, commissioning, and training should be on a par for both physical and mental health services [30].

Glycaemic management

It is important to enquire about and discuss hyperglycaemic symptoms and problems with medications, including issues relating to injections, hypoglycaemia, and self-monitoring of blood glucose.

Hyperglycaemic symptoms

Symptoms relating to hyperglycaemia usually occur when the blood glucose rises above the renal threshold, leading to an osmotic diuresis. Polyuria, particularly at night, polydipsia, and tiredness may ensue. General malaise may also occur and is not always ascribed to the hyperglycaemia.

Medications

The diabetes care team is responsible for ensuring that the person with diabetes has access to the medication and equipment necessary for diabetes management. In many, but not all, countries this is available for free or at a reduced rate; many people with diabetes may be unaware of this and timely advice may alleviate some of the anxieties about the cost of diabetes.

Oral glucose-lowering drugs

Each of the oral glucose-lowering drugs has its strengths and profile of side effects (Chapter 35) and these should be discussed. Strategies may be devised to maximize the tolerability of diabetes medications. For example, the timing of metformin in relationship to meals, or the use of long-acting preparations, may reduce the risk of gastrointestinal upset. Where treatments are not being tolerated, these should be changed in order to facilitate improved medication taking. Another example is the need to discuss the risks of hypoglycaemia with sulfonylureas.

Insulin

Insulin therapy is complex: it must be given by self-injection or pump and there is considerable variation in the doses, regimens, and devices available to people with diabetes. In addition, the use of continuous glucose monitoring and closed-loop systems by people with type 1 diabetes require discussion on suitability, use, and effectiveness. It is important that during the clinic visit, the individual has an opportunity to discuss injection technique and any difficulties with injection sites, which should be examined at least annually. Information about the appropriate storage of insulin and safe disposal of sharps (needles) is needed.

The commonest side effects of insulin are hypoglycaemia and weight gain (Chapter 31). In addition to these, there are a number of other issues that should be addressed including injection site problems, such as lipohypertrophy, and device and needle problems.

Assessment of glucose levels

Supporting the person with diabetes to achieve optimal glycaemic levels is a vital component of diabetes care. The methods of assessing glucose levels essentially involve short-term measures, such as self-monitoring of blood glucose, and long-term measures, such as HbA_{1c} (Chapter 29). Not all people with diabetes will need to undertake self-monitoring of blood glucose, but where they do it is incumbent on the healthcare professional to discuss with them the findings and how these will affect future management. The HbA_{1c} provides a measure of the longer-term adequacy of glycaemic management and sometimes there may be a discrepancy between this measure and self-monitored blood glucose. It is important to explore the reasons that underlie the differences, which may range from biological issues, such as genetically determined rates of glycation, through inappropriately timed glucose readings to fabricated results. A pristine sheet (with no blood stains from finger-sticks) and the use of a single pen colour may be a clue to the latter. It is important to explore in a non-judgmental way why the individual might engage in such a practice. This could reflect a poor relationship with the healthcare team or potential psychosocial challenges with disease and self-management. The use of computers and the ability to download results may help to observe patterns of hypo- and hyperglycaemia, although it is important to make sure that the meter has not been shared. Increasingly it is possible to use the internet to review glucose remotely.

People with diabetes must be supported in an open and non-judgmental way. Sometimes clinicians can appear to show the opposite, which is unhelpful and counter-productive to joint goal setting and collaborative consultation. Feeling reprimanded or misunderstood can be frustrating and upsetting, and it is understandable why someone would not choose to put themselves through the experience if they did not have to. It is better to build a relationship whereby the person with diabetes feels that the healthcare professional is there to support them and work together to find solutions and overcome barriers to optimal self-management. It must be remembered that the chronic nature of diabetes means there is never, nor will there ever be, a day off self-management. This can be exhausting and feel relentless to those living with the condition. Empathy and understanding go a long way in building positive, enduring therapeutic relationships.

The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS) have clearly established that lower levels of glycaemia are associated with reduced risk of long-term microvascular complications in type 1 diabetes and type 2 diabetes, respectively [3–5]. For this reason, learned societies such as the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) and government bodies such as the National Institute for Health and Care Excellence (NICE) have set tight glycaemic targets to minimize the risk of complications for individuals with diabetes [31–33]. Furthermore, in the UK general practitioners are incentivized financially to achieve tight glycaemic levels for their patients. However, there has been an increasing awareness of the need to individualize targets for the person with diabetes, depending on factors such as life expectancy, duration of diabetes, comorbidity including cardiovascular disease, resources, and availability of support (Figure 25.3).

The natural history of the development of complications is long and, in some situations, may be longer than the life expectancy of the person with diabetes. It would be a poor trade to insist on switching a frail, complication-free 90-year-old person to insulin if they subsequently fell and broke their hip or died as a result of insulin-induced hypoglycaemia. Less melodramatic but still important is the consideration about dietary and lifestyle change in people with low risk of disabling complications: is it really necessary to deny an older person with diabetes a piece of birthday cake if this is one of the few food pleasures in their life? A more sensible approach would be to advise a limit to portion size, rather than insist on severe dietary restriction.

Although there is an appropriate clinical emphasis on glycaemic targets, the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [35], the Action in Diabetes and Vascular disease: preterAz and diamicron MR Controlled Evaluation (ADVANCE) trial [36], and the Veterans Affairs Diabetes Trial (VA-DT) have led to a note of caution [37]. These trials have shown that tight glycaemic management in people with a longer duration of diabetes did not prolong life. In the case of the ACCORD trial, increased cardiovascular mortality was seen in those receiving intensive glycaemic management [35]. Again, these findings highlight the need for individualized targets.

Despite clinical guidance and the availability of effective treatments, many people with diabetes are unable to achieve the desired glycaemic levels. It is important for the healthcare professional to explore the reasons why this might be the case together with the individual. Advice about adjustment of treatment or further education or psychological support may be needed.

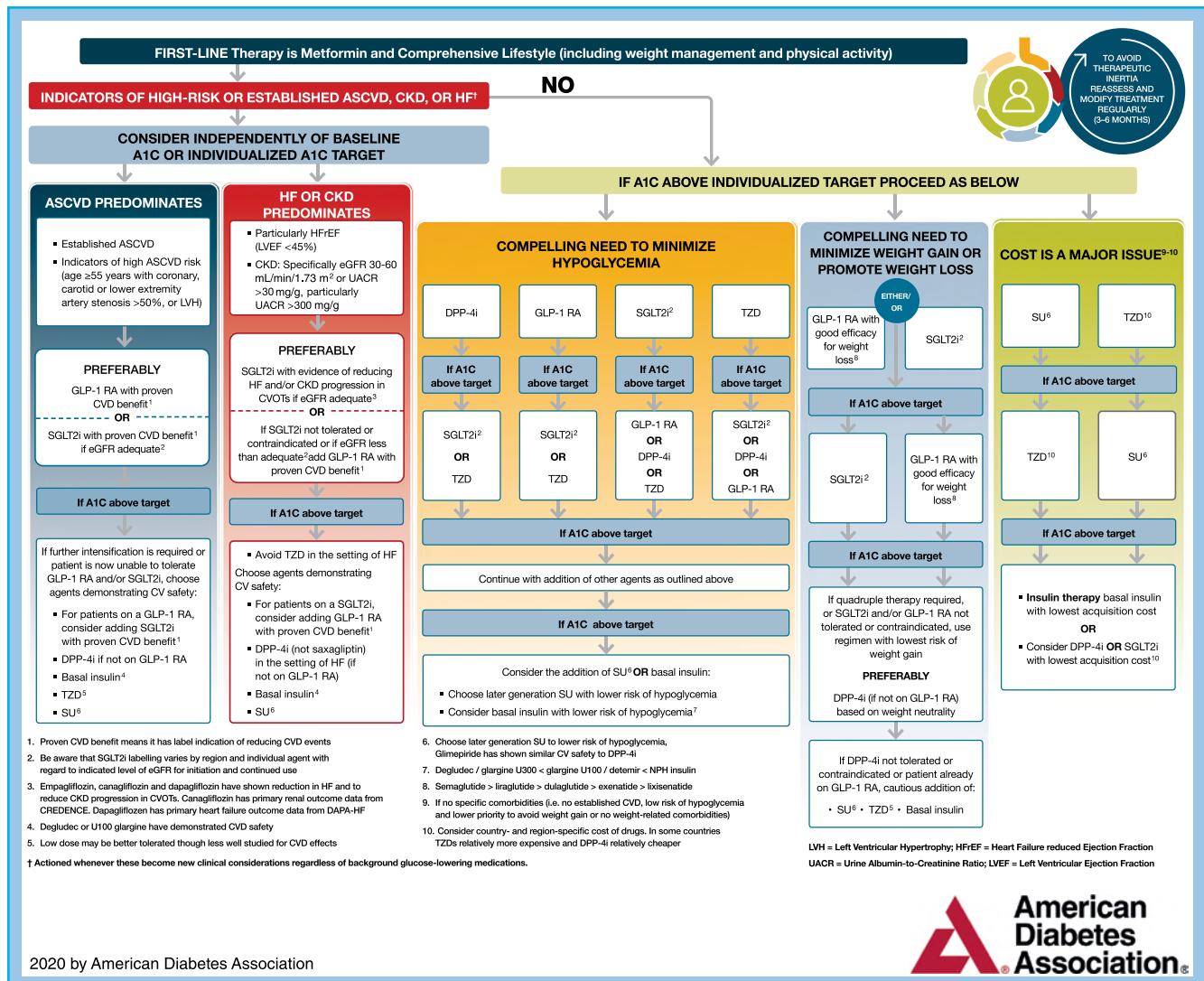


Figure 25.3 European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) approach to management of hyperglycaemia. Source: Buse et al. (2020) [34].

A common limiting factor in the ability to achieve optimal glycaemic levels is hypoglycaemia, which is one of the most unpleasant, socially aversive, inconvenient, and feared side effects of diabetes medication (Chapter 40). The frequency and severity of hypoglycaemic episodes should be discussed. An exploration of the underlying causes and advice about prevention are required for the future.

When a person with diabetes is treated with insulin, it is important to ensure that they carry a readily accessible source of fast-acting glucose, such as glucose tablets. Concentrated glucose solution and glucagon should also be made available for use in more severe hypoglycaemia. As these treatments may only be used infrequently, it is worth regularly checking whether they are in date. Furthermore, as they need to be administered by a third party, it is important to ensure that the friends and relatives of the person with diabetes know how to administer them and are confident in doing so before they are needed.

In some instances, the only way of avoiding disabling hypoglycaemia is to accept a higher HbA_{1c}. This recalibration of glycaemic goals should be decided with the individual and a target appropriate for the circumstances should be agreed. As well as the risk of

hypoglycaemia, other factors should be considered when discussing the target, including the overall clinical situation and risk of complications affecting the individual.

Assessment of cardiovascular risk

For many years, the commonest cause of death in people with diabetes was cardiovascular disease and much effort has been expended to develop strategies that will reduce its morbidity and mortality [38].

Cardiovascular risk should be assessed at least once a year for people with diabetes. This should include a history of cardiovascular risk factors, such as family history and smoking, an examination to include weight, waist circumference, and blood pressure, as well as investigations such as a lipid profile. The results of this assessment can be used to calculate cardiovascular risk using the various risk engines available. Some, such as the UKPDS risk engines for coronary heart disease and stroke, were designed specifically for use in people with diabetes and are readily available on the internet [39,40].

Diabetes is a major risk factor for cardiovascular disease [41]. This has influenced prescribing guidelines, which now recommend that specific pharmacological interventions are required to reduce

the incidence of cardiovascular disease in people with diabetes regardless of risk assessment. Large randomized controlled trials have shown the effectiveness of these interventions and are discussed in greater detail in Part 8 [42].

Although physicians may appreciate the close connection between diabetes and cardiovascular disease, many people with diabetes have never been told about this increased risk and the importance of blood pressure and lipid control. Thus, many individuals are not taking appropriate drugs for cardiovascular prevention, or if they are the doses may be inadequate to achieve recommended targets. When working with someone with diabetes, it is important that strategies to reduce cardiovascular disease and the need for preventive drugs are discussed. In addition, the increased vascular damage promoted by smoking in the setting of diabetes may not be appreciated.

The main classes of drugs used are lipid-lowering drugs, predominantly statins, and antihypertensives, particularly drugs acting on the renin–angiotensin system. Antihypertensives are also important in the prevention of microvascular complications, as discussed in the following section. Specific guidance about blood glucose–lowering agents recommends the use of human glucagon-like peptide-1 (GLP-1) receptor agonists and sodium glucose cotransporter 2 (SGLT-2) inhibitors because of the cardiovascular benefits observed in clinical trials of these agents.

While each individual intervention for the various risk factors is important in the prevention of macrovascular disease, the Steno 2 trial has demonstrated that a coordinated approach to the management of cardiovascular risk can be successful [6]. In this study, the clinic setting and protocol-driven approach to overall cardiovascular risk led to significantly improved mortality compared with routine care.

Microvascular complications

With time, most people with diabetes will develop microvascular complications [43]. Many complications will remain asymptomatic until they have catastrophic consequences. The management of microvascular complications involves measures to prevent, detect, and treat. General measures, such as optimal glycaemic and blood pressure management, lead to a reduction in the incidence and progression of microvascular complications, but specific preventive measures are also needed and are discussed next [3–5, 44].

Eyes

Globally diabetic retinopathy remains the commonest cause of blindness in people of working age (Chapter 43). It is almost invariably asymptomatic until there is a catastrophic sight-threatening haemorrhage. For this reason, it is important to screen regularly for retinopathy to allow treatment before haemorrhage and visual loss occur. Traditionally this has been performed by examination of the visual acuity and fundoscopy within the diabetes clinic at least on an annual basis, although longer screening frequencies are being considered. Alternatively, in many countries dilated ophthalmological examinations are regularly performed by a specialist.

The gold standard for screening now, however, is digital retinal photography, which may be undertaken in several different settings. When this is performed outside the traditional diabetes clinic, communication between the screener and diabetes team is essential if other aspects of diabetes care are to take account of the development of retinopathy.

Where retinopathy is detected within the clinic, it is the responsibility of the clinic to ensure that the individual is referred for specialist ophthalmological attention in a timely fashion.

Neuropathy

Distal symmetrical polyneuropathy is the commonest form of neuropathy in diabetes and is addressed in the following section on the diabetic foot. Autonomic neuropathy may affect the person with diabetes in several ways, for example gustatory sweating, postural hypotension, or bloating (Chapter 45). Healthcare professionals should be alert to this possibility if symptoms suggestive of these conditions are raised.

Foot problems

Diabetes is the commonest cause of non-traumatic lower-limb amputation in high-income countries (Chapter 53). Around 10–15% of people with diabetes develop a foot ulcer as a result of the combination of peripheral neuropathy and vascular insufficiency to the foot.

Prevention of ulceration is an important goal and requires educating the person with diabetes so that they are aware of this possibility. It is important to inform people that they should not delay obtaining professional help if problems ensue.

An assessment of the risk of foot ulceration is needed at least annually and more frequently when neuropathy or vascular disease is present. The assessment should include a history of previous ulceration and trauma, as well as an examination of the skin, vascular supply, and sensation. Opportunistic foot screening should also be performed if an individual with diabetes is admitted to hospital.

In people with numbness, close attention to discovering unsuspected foot lesions, including examination of the sole of the foot using a small mirror, must be performed by the individual on a regular basis. This can lead to rapid intervention and prevent an early infection from progressing, potentially averting such devastating consequences as osteomyelitis and gangrene.

Prompt referral to the podiatrist and foot clinic should be arranged by the diabetes clinic if needed.

Kidneys

Diabetic nephropathy is characterized by a progressive increase in urinary albumin excretion that is accompanied by increasing blood pressure and decline in glomerular filtration rate, ultimately culminating in end-stage renal disease (Chapter 44). It is also associated with a marked increase in the rate of cardiovascular disease.

Microalbuminuria, the earliest stage of nephropathy, affects around 50% of people with diabetes after 30 years, while frank proteinuria affects a quarter of people with type 1 diabetes after 25 years. Diabetic nephropathy is a common reason for the initiation of renal replacement therapy. Although it appears that with modern treatments of diabetes the risk of an individual with diabetes developing end-stage renal disease is falling, the absolute numbers requiring renal replacement therapy are increasing in line with the increased prevalence of diabetes worldwide.

Diabetic nephropathy is asymptomatic and so screening is required annually. This is usually achieved by measurement of urinary albumin excretion (UAE). The commonest method is a single urinary albumin-to-creatinine ratio (ACR) measurement, which should be repeated two to three times if abnormal. An estimation of glomerular filtration rate should be obtained annually.

The primary prevention of nephropathy relies on excellent glycaemic management as well as tight blood pressure control. Once nephropathy is present, blood pressure management is the mainstay, as there is little evidence that glycaemic management at this stage slows the rate of progression. The antihypertensive drugs of choice are angiotensin-converting enzyme (ACE) inhibitors

or angiotensin-2 (AT-2) receptor antagonists, as they have specific effects on renal blood flow [45,46]. SGLT-2 inhibitors also reduce the progression of nephropathy, independently to their effect on glucose.

It is important that the person with diabetes understands the need for screening followed by treatment if nephropathy develops. Timely referral to the nephrology team is needed to ensure that the management of renal disease is undertaken promptly in those with abnormal renal function.

Diabetes emergencies

Diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome

Diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome are potentially life-threatening emergencies (Chapter 41). The person with diabetes needs to be educated about the risk of these and strategies to prevent them from happening should be discussed. If a person with diabetes has been admitted with diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome, the opportunity should be taken to explore the reasons why this episode occurred and to identify what might be changed to prevent it from happening in future. The commonest causes of hyperglycaemic emergencies in those with pre-existing diabetes are infections and insulin omission and errors. Bolus calculators are increasingly commonly used; however, it is crucial to regularly check that set parameters remain accurate, including insulin-to-carbohydrate ratio and insulin action time (sometimes called insulin on board, IOB), to ensure that the correct amount of insulin is being advised and delivered. It is particularly important that people with diabetes also understand the ‘sick-day’ rules, where insulin should never be discontinued and indeed doses may need to be increased even when appetite is diminished.

Hypoglycaemia

Hypoglycaemia is a common diabetic emergency affecting most people with type 2 diabetes and ~60% of insulin-treated people with type 2 diabetes (Chapter 40). Hypoglycaemia may have a major adverse effect on quality of life and fear of hypoglycaemia is the most important limiting factor in the achievement of optimal glycaemic levels.

It is important that the person with diabetes is educated about the symptoms of hypoglycaemia and the actions to be taken to prevent and treat it. As noted earlier, friends and family members should be invited to learn about hypoglycaemia and its management in order to intervene when necessary, for example by providing glucagon treatment if the person with diabetes is unconscious. If hypoglycaemia becomes disabling or recurrent, it is important to explore underlying causes (Table 25.2).

Lifestyle issues

Diabetes has social, psychological, and medical consequences and an important aspect of diabetes care is to discuss how diabetes may be affecting social issues such as driving, education, and employment (Chapter 66). The healthcare professional may need to act as an advocate for the person experiencing discrimination. Some aspects of lifestyle also affect diabetes care, such as diet, exercise, smoking, and alcohol. These issues should be discussed sensitively in order help the person with diabetes understand how their lifestyle affects their diabetes and general health. Support should be given to help and encourage the individual to make changes to their

Table 25.2 Causes of hypoglycaemia.

- Excessive insulin administration
 - Person with diabetes, doctor, or pharmacist error
 - Deliberate overdose during a suicide or parasuicide attempt
- Excessive sulfonylurea administration
- Unpredictable insulin absorption
 - Insulin is absorbed more rapidly from the abdomen
 - Lipohypertrophy
- Altered clearance of insulin
 - Decreased insulin clearance in renal failure
- Decreased insulin requirement
 - Missed, small, or delayed meals
 - Alcohol
 - Inhibits hepatic glucose output
 - Vomiting
 - May occur with gastroparesis, a long-term complication of diabetes
 - Exercise
 - Promotes glucose uptake into muscle
 - Increases rate of insulin absorption
- Recurrent hypoglycaemia and unawareness

lifestyle where these are appropriate. Psychological support should be offered where necessary.

Psychological issues

Both the diagnosis of diabetes and the chronicity of the condition can provoke a number of psychological reactions, such as anger and sadness in the individual that may be akin to a bereavement reaction or a chronic sorrow response (Chapter 63). More serious mental health problems, such as depression, are common in people with diabetes and these can impede the person’s ability to achieve optimal glycaemic management [47] (Chapter 65).

It is important for those working in diabetes care to explore with the individual whether they are experiencing psychological problems, as they may be reluctant to raise this in the consultation. While all members of the diabetes team should be able to recognize and address basic psychological problems, an essential team member is a psychologist who can address more complex needs. Despite the importance of psychological issues, this need is frequently unmet because of a lack of trained healthcare professionals.

The Diabetes Attitudes Wishes and Needs (DAWN™) study, a global survey of people with diabetes and healthcare professionals involved in their care, substantiated the association of diabetes with multiple psychological challenges and the close interrelationship between emotional well-being and diabetes outcome [48]. It also pointed to important deficiencies in the emotional care of and support for people with diabetes, which became the basis for the DAWN Call to Action with the goal of implementing person-centred diabetes care.

In 2012, the second global DAWN study (DAWN2™) was conducted to re-evaluate the state of diabetes care, both globally and within each of the 17 participating countries. In the global DAWN2 study, nearly half of the surveyed people with diabetes reported diabetes-related distress, 12% rated their overall quality of life ‘poor’ or ‘very poor’, and approximately 14% had likely depression [49]. Notably, family members were also considerably affected by having an adult with diabetes in their household, with 35% experiencing the care for the person with diabetes as a burden [29]. In 45% of family members, diabetes care had its most negative impact on emotional well-being [29].

Sexual health

Sexual dysfunction

Sexual dysfunction is more common in both men and women with diabetes than in the general population (Chapter 54). This can affect the person's quality of life considerably [50, 51]. Many people are reluctant to discuss this aspect of their lives because of embarrassment, and so it is the responsibility of the healthcare professional to enquire about this. There are now effective treatments for erectile dysfunction and failure to ask about this can deny the person with diabetes the opportunity to receive this treatment.

Pregnancy planning

Starting a family is an important milestone for many and the presence of diabetes can make this decision more difficult for women with diabetes (Chapter 71). Women are often worried about the effects that diabetes will have on their pregnancy and vice versa. The implications for the long-term risk of diabetes in the offspring are also of concern.

Planning for a pregnancy by a woman with diabetes can dramatically improve the outcome, reducing the risk of miscarriage, congenital malformations and macrosomia, with its attendant risks of shoulder dystocia, and neonatal hypoglycaemia [52]. Most oral medications should not be used in pregnancy and the treatment regimen may need to be altered as part of the planning process.

Despite this, many women enter pregnancy without adequate preparation or pre-conception care. It is therefore incumbent on the healthcare professional to discuss pregnancy with all women of child-bearing age, including adolescents, to ascertain their plans regarding pregnancy. The answers are often not black and white; women may not actively be planning to become pregnant, but are sexually active and not using effective contraception. Contraceptive advice is needed and where a pregnancy is being planned, women should be referred to a dedicated pre-conception clinic, as these have been shown to improve the outcomes of diabetic pregnancies.

With an increasing number of women with type 2 diabetes of child-bearing age, it is important that pre-conception advice is not solely focused on those with type 1 diabetes. This is particularly relevant because many women with type 2 diabetes are not seen in specialist centres.

Prompt referral to a joint diabetes antenatal clinic is necessary once a woman becomes pregnant.

Men may also have concerns about embarking on a family because of the increased risks of diabetes in their offspring and these anxieties need to be discussed sensitively.

Inpatient diabetes care

It is estimated that around 10–15% of people in hospital have diabetes (Chapter 39). In many instances the diabetes is coincidental to the admission and the individual remains capable of managing

their own diabetes, often with greater skill than the healthcare professionals around them. Optimal diabetes management remains an important goal, as this improves the rate of recovery and may lead to an earlier discharge.

Admission to hospital is a worrying time, but much of the fear can be alleviated if a full explanation of the treatment in hospital is given along with an opportunity to discuss any particular concerns. Being given the opportunity to discuss the management of diabetes can be reassuring. Where possible, the person with diabetes should be allowed to continue to self-manage their diabetes. The individual should be encouraged to bring in their own insulin supplies where admissions are planned. There should be access to their regular diabetes healthcare team where possible, as the admission may provide an occasion to check techniques and results. Ready access to carbohydrate and appropriate coordination of mealtimes, snacks, and medication should obviate the need for more dramatic treatment of hypoglycaemia.

There will be times when the person with diabetes is unable to manage their diabetes themselves. In these instances, the responsibility will fall entirely on the healthcare team, for example during surgery when the person with diabetes is unconscious and requires intravenous insulin and dextrose.

Following discharge, clear communication with the primary care and hospital diabetes teams is essential so that any changes in management or medication are made known to those involved in the individual's care.

Involving people with diabetes in the planning of healthcare and service development

Involving people with diabetes and their carers in the planning and decision making of local health services enables these to be built around the needs of those who use the service, rather than the needs of the system [53]. An open dialogue is needed, and service users should feel that their views are listened to. This will improve the accountability for and legitimacy of any decisions made and is likely to ameliorate clinical and care outcomes. People with diabetes should be encouraged to express their views and concerns about their services, as better feedback about service provision should help to improve and shape future provision of care.

Conclusion

The aim of diabetes care is to improve the lives of those with diabetes. This can only be achieved through a partnership between the person with diabetes and a multifunctional healthcare team that should be in place to support the person with diabetes.

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26

Education to Empower the Person with Diabetes

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Key points

- Diabetes education and psychosocial support are critical elements of care for all people with diabetes and their family members.
- Being able to self-manage diabetes requires substantial knowledge, motivation, and behavioural competencies on the part of people with diabetes and their family members.
- Diabetes education needs to be implemented in a sufficiently flexible manner to be incorporated into multiple settings, not just formal and structured diabetes education.
- People with diabetes must be placed at the centre at all times in diabetes education. Active involvement in their own healthcare must be prioritized over educator-dominated involvement.
- Diabetes education programmes are more effective if they are based on participant- and empowerment-oriented principles and principles of adult learning.
- Group-based diabetes education has a positive effect on clinical outcomes, health behaviours, and psychosocial outcomes, including glycated

- haemoglobin (HbA_{1c}), fasting blood glucose concentration, diabetes knowledge, self-management, empowerment, and self-efficacy.
- The provision of appropriate training of diabetes educators, including the management of psychosocial issues, cannot be overestimated.
- Group processes and active participation during diabetes education appear to be more important for improving coping skills than the didactic content of the programme.
- People with diabetes should be supported to work specifically and realistically with setting goals and to think about potential obstacles and facilitators to achieving them.
- Family-based diabetes education interventions seem to be a potentially important supplement to enhance diabetes management in everyday life.
- Evaluation of diabetes education should focus on understanding how, for whom, and under what conditions specific programmes will work.
- The main limiting factor of diabetes education is that it almost always does not include ongoing care and education.

The foundation of diabetes self-management education and support

There is broad consensus in the global diabetes community that diabetes education and psychosocial support are critical elements of care for all people with diabetes and their family members [1]. Yet questions remain about the extent to which diabetes education effectively enhances self-management or addresses the psychosocial aspects of living with diabetes. The purpose of this chapter is to support enhanced competency in the delivery of self-management education and psychosocial support by clearly specifying the values, attitudes, and competencies that promote self-management.

Many issues that impair the efforts of diabetes educators in promoting self-management are grounded in communication challenges [2]. Educators unwittingly restrict participation from people with diabetes through time constraints, pre-planned topics, and persuasive recommendations [3] that operate counter to the evidence that goals generated by people with diabetes produce better

outcomes than goals generated by healthcare professionals [4]. It makes sense that a person will be more committed to pursuing their own goals than goals that are *given* to them by another person. A health technology assessment of education programmes concluded that those for people with diabetes are more effective if they are based on participant- and empowerment-oriented principles and principles of adult learning [5]. The best outcomes of patient education seem to be produced with an empowerment approach, which is problem based, and individually and culturally tailored to address psychosocial, behavioural, and clinical issues relevant to people's needs and readiness to learn [6]. In reality, educators are responsible for translating abstract concepts and theories into concrete programmes tailored to the needs of different individuals with diabetes [7].

Diabetes education and support has the potential to empower people with diabetes to live well with diabetes. For the individuals with diabetes and their family, this means the freedom to live as they want while feeling healthy and being safe. For people with diabetes and their healthcare team, this also means achieving

desirable clinical outcomes such as glycaemic, blood pressure, and cholesterol targets [8–10].

Diabetes self-management education and support (DSMES) is an ongoing process to provide the individual with the knowledge, skills, and confidence to self-manage [11, 12]. DSMES is intended to support informed decision making, problem solving, health behaviour change, and active collaboration with a healthcare team. The process of DSMES must be based on the needs, goals, and life experiences of the person with diabetes. As such, it is less about teaching and more about collaborating.

Modalities of education

There are many evidence-based curricula available for diabetes education. The UK National Institute for Health and Care Excellence (NICE) defines structured diabetes patient education as ‘A planned and graded programme that is comprehensive in scope, flexible in content, responsive to an individual’s clinical and psychological needs, and adaptable to his or her educational and cultural background’ [13]. In its review of the evidence, NICE identifies principles of good practice, including the following [14]:

- It is evidence based and suits the needs of the person.
- It has specific aims and learning objectives and supports the person and their family members and carers in developing attitudes, beliefs, knowledge, and skills to self-manage diabetes.
- It has a structured curriculum that is theory driven, evidence based, and resource effective, has supporting materials, and is written down.
- It is delivered by trained educators, who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme.
- It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.
- The outcomes are audited regularly.

There are many programmes and methods available for diabetes education and support, with more or less evidence of effect (e.g. [15–17]). There is evidence for the effect of one-on-one education as well as group education [18]. Group-based education can be cost-effective and equally or more satisfying to recipients [6, 19, 20]. Group-based education including peer support has the advantage of observational learning and modelling [21, 22], which may be at least as important for improving coping skills as the didactic content of the programme [23, 24].

Individual differences and contextual factors are critical to success in diabetes education. Support is likely to be especially beneficial in relation to specific events in life such as being diagnosed in adulthood [9, 25], starting to use diabetes technology, a wish to participate in extreme physical activity such as a marathon [26], the Covid-19 pandemic [27, 28], or other new situations in the lifespan generating specific needs [29, 30]. Given that at least half of people with diabetes do not participate in formal diabetes education services [31], DSMES needs to be adapted to settings beyond formal diabetes education services such as primary or specialty care, community settings, and public health [32]. DSMES is based on three main building blocks: values, tools, and competencies. This chapter is structured around these three areas, which will be described in more detail in what follows.

Values, competencies, and tools

Diabetes is managed on a daily basis by the person with diabetes in the context of their sociocultural environment [33, 34]. It is critical to accept that diabetes is not a goal sought by the individual: no one chooses to have diabetes. It is an unwanted intrusion into a person’s life that is a major source of threat and burden. The implication of this is that it can be expected that the person with diabetes would want to minimize the intrusiveness of the disease in their life. The irony is that self-management requires significant vigilance and effortful health behaviours, which increase psychological intrusion. Successful self-management support can help the individual to psychologically reframe diabetes self-management from an intrusive burden, which impairs quality of life, to a chosen strategy that enhances quality of life; that is, as empowerment. In this way, DSMES is inseparable from managing the emotional and psychosocial aspects of living with diabetes. DSMES must facilitate this fundamental psychological reframing, which is an internal process of the person with diabetes and not controlled but supported by the healthcare team.

Accepting that diabetes is a self-managed disease that no one chooses to have and that requires considerable, continuous, and arduous self-care behaviours places the educator in the proper context. The power in the relationship does not belong to the educator, but to the individual. Thus, tools and procedures should not be prioritized over the person with diabetes and the healthcare professional relationship. Rather, tools should be used to empower the person with diabetes and enhance the collaboration between the person with diabetes and the healthcare team. Diabetes self-management occurs outside of the clinical encounter where the individual is in charge of their choices. To make the most of DSMES, the educator needs to implement an evidence-based care plan. However, this plan should not prioritize tools and procedures over the use of the patient–healthcare professional relationship to empower the person with diabetes to *choose* to follow recommended procedures and tools. As such, the foundation of DSMES is more value based than tool based. This is illustrated in Figure 26.1, where values are the bedrock that define the competencies needed to facilitate self-management.

The value of DSMES includes respecting the *autonomy* of the individual (their questions are most important to address, and their decisions carry the greatest weight) by *collaborating* (being person

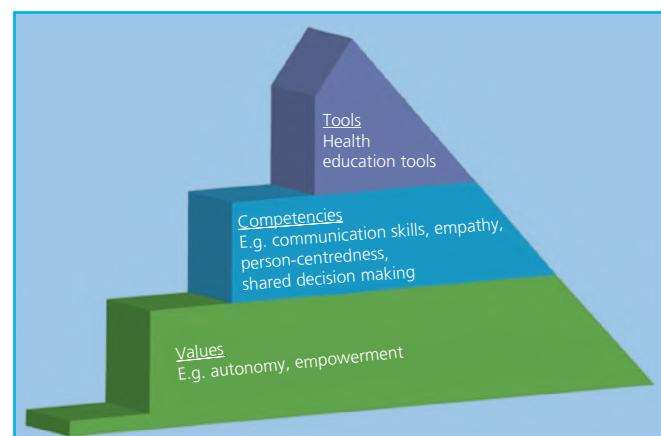


Figure 26.1 Values, competencies, and tools in diabetes education and support.
Source: Hansen et al. 2018 [35].

centred and using shared decision making) to achieve *empowerment*. Healthcare professional competencies and the use of relevant tools should be perceived as a stepwise execution of these values. In fact, value-based education and support by competent educators may obviate the need for tools. A meta-analysis of motivational interviewing discovered that manual-based implementations were less effective than implementations that were not manual based, but instead based on the 'spirit of motivational interviewing' [36].

Organizing the activities of the educator around the concepts of person-centredness, collaboration (shared decision making), and empowerment represents a major shift towards placing the relationship in front of education [34, 37]. It is unacceptable for a diabetes healthcare professional to say 'I did not have time to address the psychosocial aspects of diabetes'. Many diabetes educators are more comfortable with providing recommendations and teaching management skills than with addressing the psychosocial context of a person's life [38, 39]. This raises a stressful situation for the educator; that is, issues unrelated to diabetes may be overriding priorities for the person with diabetes, limiting the goals and expectations of the educator at any moment in time. Educators experience numerous barriers regarding the facilitation of person-centred and participant-involving education [39, 40], despite the evidence in favour of these experiences [41]. Thus, DSMES should be standardized by function, not by content [39, 40, 42]. Traditional education focuses on input (what healthcare professionals present to the patient). We are claiming that output is more important (what is important for the person with diabetes to do or to hear about).

The role of the healthcare professional: how do we guide people with diabetes to self-management behaviours?

Person-centred DSMES is intended to empower people with diabetes to engage in the challenging behaviours associated with managing glycaemic, lipid, and blood pressure levels and prevention of complications. For many individuals, this means becoming motivated and skilled to engage and sustain behaviours that are challenging to maintain. For healthcare professionals, this requires shifting from being an educator to being a collaborator first and an educator second [2, 39, 40, 43]. Preechasuk et al. reported a broad survey of diabetes educators, doctors, and administrators in Thailand regarding diabetes self-management education [44]. Only 30% of educators reported that self-management education was effective, with obstacles to care including time, behaviour change skills for the healthcare professional, and perceived lack of interest and motivation for the person with diabetes. Clearly, universal uptake of DSMES is lacking. Based on the values of autonomy, collaboration, and empowerment, the competencies of the diabetes educator are in the ability to establish a change-based relationship with the person with diabetes. As such, it is the roles that the educator takes in the relationship that define DSMES competencies. Effective change-based relationships will promote behaviour change interventions that can be supported by tools.

The fundamental relationship dynamic that will promote DSMES involves the educator basing their relationship on dialogue and participation.

Dialogue, as a way of conducting diabetes education [45, 46], differs from the traditional one-way didactic model: the monologue. Didactic education can successfully convey information, but it is

less successful in supporting individuals with diabetes to take responsibility for self-management [5]. Much diabetes education does not engage the person with diabetes [47]. Behaviour change theory indicates that educators should elicit commitment, identify challenges, set goals, increase self-efficacy, and address barriers to change, and the main way to do this is through dialogue [48, 49]. It is useful to take the position that behaviour change is hard, and sustained behaviour change is even harder. Once behavioural habits become entrenched, much behaviour is cued by the environment, as well as natural preferences. For example, a 55-year-old man with type 2 diabetes who has never liked exercise and dislikes the idea of medication and being labelled as ill (preferences), and who has developed unhealthy eating and drinking habits as part of a stable and supportive friendship circle (cued environment), is unlikely to change behaviour as a result of listening to lectures on the benefits of healthy eating, taking medication as prescribed, and physical activity.

Participation likewise implies a shift in perspective from a disease- and expert-centred approach towards the needs of the person with diabetes. Effective and meaningful diabetes education requires that people with diabetes are actively involved and that teaching is tailored to their needs and preferences [45, 50, 51]. One way of conceptualizing this is as in a journey. The educator might make the first step, in the form of a recommendation or educational intervention, but then needs to see if the individual is able to follow that step. Traditional education involves the educator conveying huge amounts of information, effectively leaving the person with diabetes far behind as more and more knowledge and recommendations are conveyed. Evidence on the value of the teach-back method (having the individual summarize their learning throughout the encounter and not moving on till the person with diabetes has understood the message) in chronic disease management supports this notion of participation [52]. A useful concept here is *talk time*: monitoring who is talking more in an encounter ensures that the person with diabetes has enough time to express themselves fully [53, 54].

Educator knowledge, attitudes, wishes, and needs must take second place to the decisional processes of the person with diabetes. Consider the same 55-year-old man with diabetes who dislikes exercise, has never been physically active, and has many individual, social, and financial barriers to increasing activity. What are the conditions under which this person will choose to do all the work necessary to add a disliked behaviour to his routine? Overcoming the personal barriers to change is less likely to arise from teaching and telling than it would from effective understanding and supportive negotiation of health behaviour choices (participation through dialogue). In this example, the educator could communicate understanding and respect of the challenges to the recommended behaviour, and explicitly acknowledge that the person is in charge of the decision, while seeking permission to discuss ways to overcome barriers, be they informational, motivational, emotional, relational, or practical. The AADE7 Self-Care Behaviors framework [55] recommends orienting services around the behaviours of healthy eating, being active, glucose monitoring, medication taking, problem solving, reducing risk, and healthy coping. However, many educators will need to change their approach in order for self-management support to be implemented effectively. Involvement through dialogue requires the person–healthcare professional relationship to be one in which the patient feels comfortable sharing their truth without judgement by the healthcare professional. The majority of people with chronic illness avoid telling their clinician

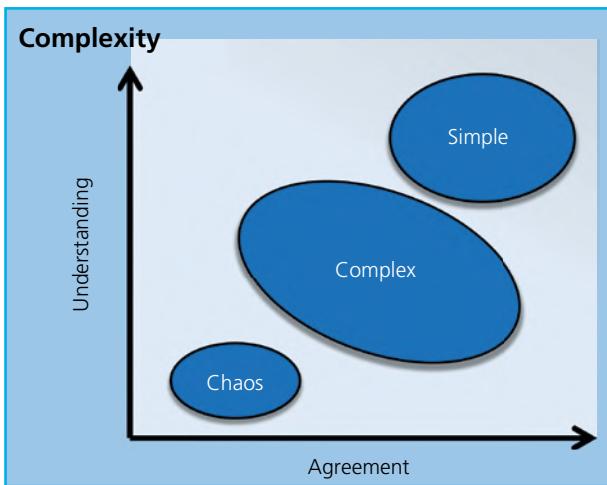


Figure 26.2 Complexity, understanding, and agreement.

important information and non-disclosure is based primarily on fear of judgement by healthcare professionals [56].

Many educators have developed the belief that their professional role is to provide the person with diabetes with the knowledge and skills they believe are needed to perform the recommended behaviours. They are the expert and it is their responsibility to educate. This relationship dynamic has been described as the 'expert clinician with the uninformed help-seeker' and can be understood through an appreciation of complexity (Figure 26.2) [57]. Some constructs, functions, or domains are simple, some are complex, and some are chaotic. This distinction can be understood by considering the degree of understanding and the degree of agreement regarding a phenomenon [57].

When the degree of understanding about a phenomenon is high and the degree of agreement on how to address the phenomenon is high, this is an indication of a simple system and a situation where reductionist protocols are effective. Since most medical professions base their training on the scientific method that emphasizes reductionism (determining the diagnosis) and determinism (understanding the mechanism of action), it naturally follows that this is a default relationship position an educator takes. However, not all systems are simple. When the degree of understanding and the degree of agreement are low, this is called a chaotic system; there is no precise guidance available. In this situation, gathering and organizing information to gain understanding is most effective (pattern recognition or phenotyping). When degrees of understanding and agreement are partial, this is called a complex system. Behaviour, including diabetes self-management behaviour, can be considered to be at least complex. As such, appropriate interventions are not so much guided by procedure but by principle. Different procedures may be equally appropriate if they have similar impacts on the principle. For example, if self-efficacy is the principle that predicts sustained behaviour, then any procedure recommended by an educator that increases self-efficacy is acceptable.

Effective self-management support shifts the professional role from method (what one does) to principle (the guiding rationale for what one does). Given that self-management necessarily places the responsibility on the person with diabetes, it becomes necessary to respect the choices made by the person. If the educator focuses on the principle, then they can negotiate the method without threatening personal choice.

Reflecting on the dominance of the scientific method in healthcare, it is no surprise that educators often do most of the talking in

clinical encounters, that they make frequent recommendations in the form of statements, and that they commonly interrupt individuals with diabetes if they stray from the agenda of the educator [58]. These relational dynamics reflect the educator as expert, where professional competency is based on conducting an assessment to make a diagnosis, determining a treatment intervention based on evidence, and evaluating how well the person responds to the intervention. This professional competency model of diagnose, determine treatment, and measure outcomes works well if the outcomes being achieved are under the direct control of the clinician. When outcomes are not determined by the competency of the clinician but by the behavioural choices made by the person with diabetes outside of the clinician encounter, these competency standards no longer apply. Dialogue and participation explicitly reframe this dynamic from *teach and tell* (educate and recommend) to a shared interaction. Figure 26.3 shows how competency can be reframed using the concepts of dialogue and participation. The left-hand panel in Figure 26.3 shows the traditional model where outcomes, which are based on the clinician's expertise, follow from the diagnosis, treatment, and focus on outcomes [38]. In simple biomedical contexts, this is fine. In behavioural and sociocultural contexts, the task of diagnosing can be replaced with the task of describing. It is not the clinician's job to tell the person what their problem is, but it is the clinician's job to understand the patient's behaviour. For instance, medication taking or vaccinations can be understood by examining the person's beliefs regarding perceived need for treatment and perceived concerns about treatment. Once behaviour is understood, it is the job of the clinician to help the person with diabetes appreciate the predicted outcome of their current behavioural choices. Rather than judging the outcomes of the person's efforts, the clinician must link important (to the person) outcomes to the choices made and encourage different choices consistent with recommendations. So, using dialogue to engage the person in a participatory approach can improve self-management via the skills of description, prediction, and choice – not diagnosis, treatment determination, and outcome judgement (Figure 26.3).

Working with dialogue and participation

Dialogue and participation enable the educator to shift from the expert (*teach and tell*) to collaboration (collaboration and empowerment). In doing so educators manage different roles and the shifting between roles; the juggling is, however, challenging [59]. Juggling is the ability to master switching between different roles to meet the needs of the individual or group and to evoke readiness to change [46]. Some well-recognized juggler attributes are:

- *Humility* – the ability to be approachable without projecting one's self and beliefs onto the group.
- *Flexibility* – openness to try new process approaches, willingness to change, or stretch outside one's boundaries in the facilitator role.
- *Professionalism* – being ready to deal professionally with feelings in the group [60].

The roles that are juggled include the embracer, the facilitator, the translator, and the initiator [46, 61].

The *embracer* role is based on empathy [62, 63], which encompasses the desire and ability to understand people with diabetes on their own terms [62]. Morse et al. [64] propose a descriptive model of clinical empathy with affective, moral, cognitive, and behavioural dimensions. Norfolk et al. [62] propose a model about the empathic

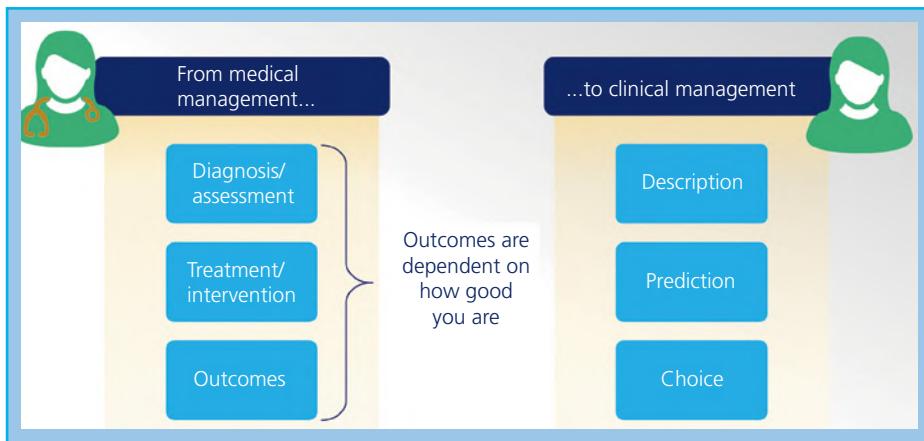


Figure 26.3 Are behavioural interventions doomed to fail? Source: Vallis 2018 [38].

journey towards therapeutic rapport in consultations focusing on the doctor's behaviour, motivation, and required skills. The factors mentioned in these studies are important competencies for educators' ability to act in the embracer role.

The *facilitator* role is rarely described in the literature. Notable exceptions are guidelines for facilitating patient empowerment programmes [65] and a study about speech practices facilitating patient participation in health counselling, in which concrete facilitation skills are suggested [3]. However, other professional fields, such as business and organization, provide more extensive literature on facilitation [60, 66].

The *translator* role, in which the educator translates medical concepts into relevant and understandable information, implies a change of the typical health educator roles. In traditional medical and disease-specific patient education, educators give information and advice, handle acute situations, and perform problem solving [63]. Following patient demands for a more active role in healthcare, the Ottawa Charter emphasized the need to view the individual as a *whole person* [67]. As translators, healthcare professionals recognize that they are experts in medical knowledge and that individuals with diabetes are experts on their lives [68].

The *initiator* role closely links to principles of motivational interviewing [69] and empowerment interventions [70]. The initiator faces the challenge of avoiding confrontation or authority traps such as *knowing best*. In general, facilitation and participatory methods are rarely part of the healthcare professional curriculum [63], which may explain the challenges experienced when delivering participatory, group-based diabetes education.

The tool in Figure 26.4 to self-assess professional skills in facilitating group-based diabetes education seems useful and stimulating, and is suggested as an excellent starting point to promote more person-centred communication between individuals with diabetes and healthcare professionals [71]. It is easier for healthcare professionals to embrace the roles of translator and embracer than those of facilitator and initiator [72].

develop competency in eliciting behaviour change. One of the learnings from behavioural sciences is the importance of theory-driven interventions. Behavioural theories explain why people engage in certain behaviours and provide a guide to promote behaviour change. By contrast, the use of tools, without theory, might be misguided. Theory can guide the selection of which tool is useful in a given situation. For instance, the literature supports regular weighing as a way of maintaining a healthy weight. However, regular weighing may be negative for one person and positive for another. If a person feels disappointed and shameful when the weight on the scale is not what was hoped for, regular weighing may be demotivating rather than motivating.

At the centre, the person with diabetes is an individual who will make specific behavioural choices (person as decision maker). A dominant theoretical model describing how people make behavioural choices is the Self-Regulation Model, also referred to as the Health Belief Model [73]. There are five dimensions of illness beliefs:

- Consequences (e.g. perceived seriousness)
- Personal control
- Treatment control
- Timeline
- Emotional representation.

Understanding these beliefs can be a valuable guide to the diabetes educator for supporting the person with diabetes. Consider the person who perceives the consequences of their diagnosis as minor (low seriousness) or someone who does not believe that treatment will reduce complications, perhaps based on a family history of early, devastating complications (low treatment control), or consider the person who reports overwhelmingly distressing emotions following diagnosis. Understanding these common-sense beliefs will guide the educator to potential solutions. A variant of the Health Belief Model, which is a useful screen for potential lack of medication taking, is needs and concerns analysis [74]. Consider a recommendation by a professional to start medication or insulin. Asking the person with diabetes the extent to which they need the medication and the extent to which they have concerns about medication can be accomplished quickly and frames potential adherence challenges. High perceived need and low perceived concern would favour acceptance; high perceived need and high perceived concern suggest ambivalence; low perceived need and low perceived concern suggest indifference; while low perceived need and high perceived concern suggest scepticism. The Health Belief Model can be useful in supporting the acceptance of the diagnosis of diabetes. Supportive counselling can be helpful in empowering the person to come to view diabetes as serious but manageable, in which needs and concerns are addressed and balanced.

A framework to guide selection of education methods

Juggling the roles of embracer, facilitator, translator, and initiator using dialogue and participation defines many of the competencies needed for effective DSMES. In addition, the educator is required to

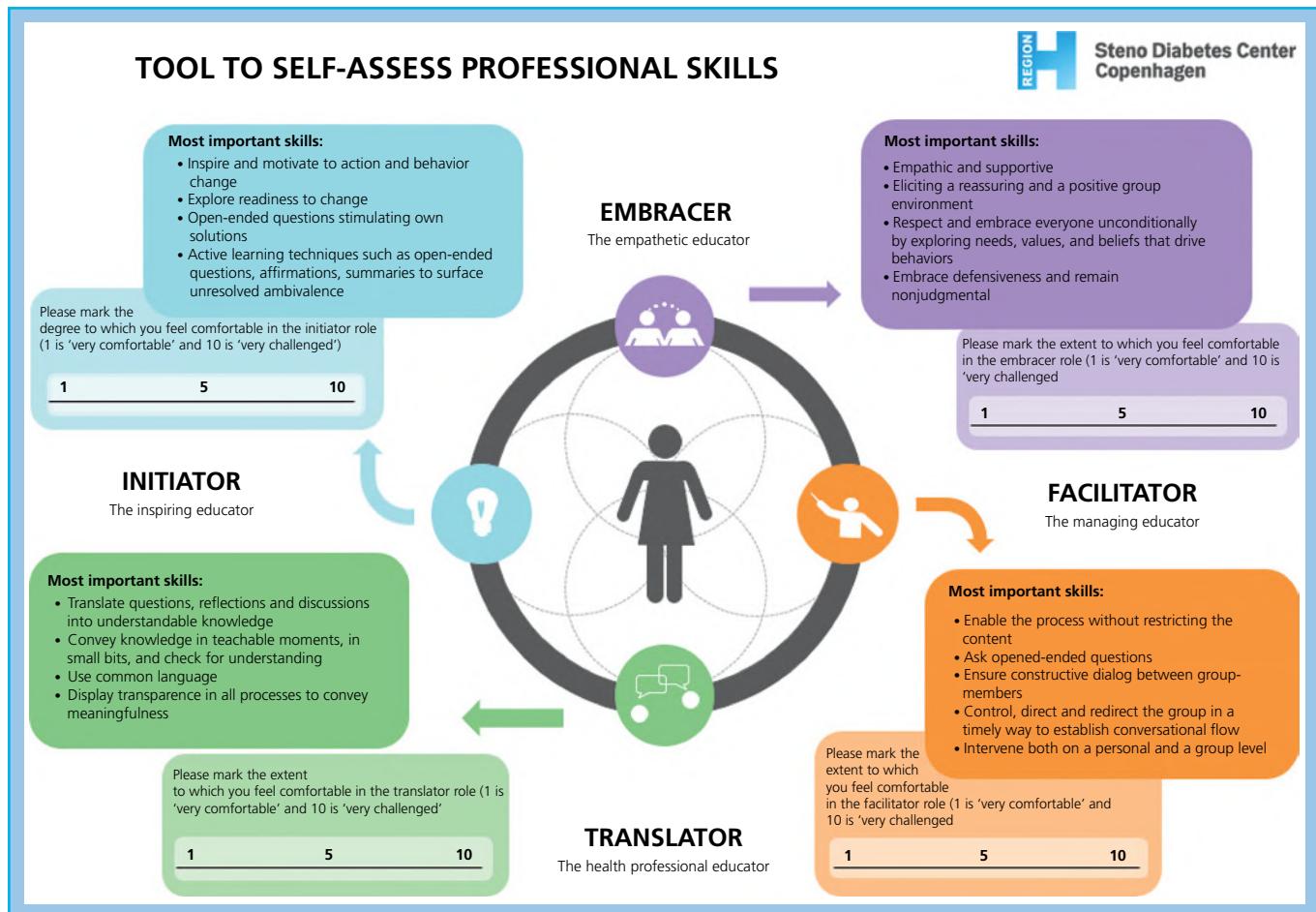


Figure 26.4 Self-assessment tool to develop skills of a person-centred approach in diabetes education and support. Source: Stenov et al. 2017 [71].

Additional theoretical models explaining the drivers of health behaviour have shown great promise in supporting acceptance of disease, acceptance of treatment, and health behaviour change. Prominent among them are social cognitive theory [75], the theory of planned behaviour [76], self-determination theory [77], and the trans-theoretical model [78]. These perspectives help to explain what determines a person's behaviour and can help the educator identify important motivational constructs that are associated with change (Table 26.1).

Perhaps most important are the principles that guide the educator on how to counsel a person with diabetes to help them develop the motivation to change. Here the principles of patient-centredness [79], empowerment [80], and motivational interviewing [81] provide specific knowledge and pathways to guide people towards change. Table 26.2 illustrates the tasks required of people with diabetes and healthcare professionals, and links these guiding principles with theory and constructs that can be brought into the clinical exchange.

Supporting the behaviour change process

Guiding the person towards sustained behaviour change can be understood as using the relationship between the person with diabetes and the healthcare professional to establish four tasks through dialogue and participation [84,85]:

- *Establishing a change-based relationship.* This is an explicit shift away from the expert teach-and-tell role to one of collaboration and empowerment. It is achieved by recognizing the dangers of a teach-and-tell approach and, using motivational communication, establishes empathy, non-judgmental curiosity, as well as an appreciation of the role of ambivalence. The relationship between the person with diabetes and the healthcare professional achieves common ground regarding the bond alliance, the task alliance, and the goal alliance.
- *Identification of a specific behaviour to change and determining the readiness of the person with diabetes to change that behaviour.* Not being ready to do the work of change is common and readiness is state based, not trait based. This allows one to avoid becoming preoccupied with changing a behaviour that the person is not ready to work on by finding a behaviour that the person is ready to change. Working with those who are ambivalent about change or not ready to change is a fertile area for behaviour change counselling, and virtually the entire content of this chapter speaks to how professionals can support change.
- *Using behaviour modification interventions to promote successful behaviour change.* Numerous behaviour change tools can be implemented when a person is ready to do the work of change.
- *Addressing the psychosocial determinants of behaviour.* Those relational, environmental, and structural issues that make change hard can be addressed. Importantly, with regard to scope of practice, addressing these issues can be successful if the healthcare

Part 5 Managing the Person with Diabetes

Table 26.1 Behaviour change theories in diabetes education.

Theory	Description	Key elements	Application to diabetes education
Social cognitive theory	Specifies determinants of health behaviour, mechanisms through which they work, and ways to translate this knowledge into health practices	Knowledge, perceived self-efficacy, outcome expectations, perceived facilitators, social and structural impediments	Diabetes education should address the determinants of people's health behaviour. The educator can acquire different roles in the education to facilitate this
Self-determination theory	Motivation is either intrinsic or extrinsic and is driven by the needs for competence, autonomy, and relatedness	Assess intrinsic versus extrinsic motivations (doing it for self or for the healthcare team), as well as the impact of self-management on autonomy and connection to others	Diabetes education should promote intrinsic motivation by supporting a person's competence in a way that does not impair connectedness to important others
Theory of planned behaviour	Proposes that the intention to engage in a specific behaviour depends on attitude towards the behaviour, subjective norms regarding the behaviour, and perceived behavioural control	Attitude, subjective norms, perceived behavioural control, intention	Diabetes education should explore attitudes, norms, and perceived behavioural control among individuals to assess their intention to change behaviour
Trans-theoretical model of change/stages of change model	Outlines behaviour change through five stages from a situation where individuals are not aware of a risk to a situation where they are changing their behaviour and fighting relapse	Pre-contemplation, contemplation, preparation, action, maintenance	Diabetes education should guide and support people with diabetes in the process of behaviour change. This includes exploring patient perceptions about importance, confidence, and readiness with regard to behaviour change

Table 26.2 Counselling principles to facilitate self-management motivation.

	Guiding principle	Theoretical model	Example constructs
Person with diabetes	Health beliefs	Self-regulation model [82]	Perceived consequences, personal control, treatment control, timeline, and emotional impact
	Motivation	Social cognitive theory [75] Theory of planned behaviour [76] Trans-theoretical model [78]	Self-efficacy, perceived social norms, readiness to change/intentions
	Emotion	Diabetes distress scale [83]	Emotional burden, regimen-related distress, physician-related distress, interpersonal distress
Person with diabetes—educator relationship	Patient-centredness	Patient-centred clinical method [79]	Understand the whole person, explore the person's illness experience, find common ground, and cultivate the relationship to overcome barriers
	Motivational communication	Motivational interviewing [69]	Non-judgmental curiosity, effective use of questioning and listening, working with ambivalence, and supporting self-efficacy
	Empowerment	Person empowerment [43]	Appreciating the process of respecting the autonomy of the person with diabetes

professional adopts the principles of identify, educate, recommend, and support. When a psychosocial issue of relevance is encountered (identify), there is great value in having a healthcare professional assist the person in understanding how the issue affects self-management (educate), increase awareness of how to manage the

issue (recommend), and then support the person with diabetes in their efforts to actualize these recommendations.

Recently, a great deal of work has been devoted to integrating the vast array of theories of behaviour change into an overarching model. West et al. examined behaviour change theories, which

included 128 theoretical constructs related to behaviour change, and integrated them into a single framework, called the Theoretical Domains Framework (TDF) [86]. This framework can guide both the development of behaviour change interventions and their implementation. The TDF is made more elegant by its integration into a simplified behaviour change model called COM-B. In this model *Behaviour* is seen to be the result of *Capability*, *Opportunity*, and *Motivation*. The 128 theoretical constructs related to behaviour change interventions were reduced to 14 domains, which were then integrated in the COM-B perspective [86].

This model has great potential in diabetes education and support. For instance, the healthcare professional and the person with diabetes collaboratively identify a *behaviour* they would like to change. The professional can then assess the factors that might be associated with success in changing this behaviour using this framework. The result of this assessment can identify resources (strengths that the person with diabetes presents that support change) as well as areas for intervention.

Capability involves both psychological and physical components. Physical capability is the skill in the behaviour, where psychological capability involves knowledge, psychological skill, memory, attention, and decision processes as well as behavioural regulation skills. *Opportunity* includes social influence factors as well as environmental context and resources. This comprehensive model has been helpful both from the perspective of designing an intervention as well as guiding the behaviour change counselling within any given interventions. Finally, *motivation* can involve reflective as well as automatic aspects. Reflective motivation results from intentions, goals, beliefs about capabilities, beliefs about consequences, social role and identity, and optimism (six domains). Automatic motivation results from reinforcement, emotion, optimism, and social role and identity (two new domains, two domains overlapping with reflective motivation). Professional counselling to enhance motivation can utilize these constructs as interventions.

Empowerment through language and the flourishing mindset

Several medical journals, national health services, diabetes organizations, as well as academics and professional groups have, during the last decade, advocated for an improvement in the language used in diabetes. As an example, Diabetes Australia and researchers in diabetes psychology provide the following recommendations [87]: ‘On average, people with diabetes experience greater emotional distress than those without diabetes. One source of distress can be the language used to refer to diabetes, its management and the person with diabetes. The way verbal and written language is used reflects and shapes people’s thoughts, beliefs and behaviours. Language has the power to persuade, change or reinforce beliefs and stereotypes – for better or worse. Words do more than reflect people’s reality: they create reality and affect how people view the world and their diabetes.’

An example from the *New England Journal of Medicine* shows how language can be used to anchor the importance of the patient first. Michael Berry and Susan Edgeman-Levitin suggest a substitution of ‘What is the matter with you?’ with ‘What matters to you?’ [88]. This shows a movement away from psychopathology (*what is the matter with you?*) to quality of life (*what matters to you?*).

A useful way of framing the juggling of self-management support roles in DSMES has origins within positive psychology and is

Table 26.3 Comparison of coping and flourishing treatment strategies.

Treatment characteristics	Coping mindset	Flourishing mindset
Approach	Cope and repair	Design and build on what is already working
Goal	Come up to ‘normal’	Go beyond ‘normal’ and flourish physically and psychologically
Direction	Avoid what you don’t want	Move towards what you do want
Focus	The disease, what is going wrong, and corrective actions	The patient in a personal life context, what is going well, and building on successes
Healthcare provider–patient relationship	The healthcare provider is the expert and decides, tells, and explains what the patient should do	The healthcare provider and the patient are both experts who leverage each other’s strengths to co-design a way forward
View of diabetes and impact on one’s life	A burden that one must fight/battle/overcome and that makes life smaller/limiting	Bestows benefits, integrates into one’s life, and makes life bigger/offers possibilities

Source: Modified from Greenberg and Bertsch 2013 [90].

described by the American psychologist Martin Seligman as the concepts of learned helplessness and flourishing [89]. Riva Greenberg, an American diabetes activist, has been the leading front person of developing a mindset called the *flourishing mindset*. This mindset builds on positive experiences by focusing on health rather than illness [90]. The operationalization happens by supporting people in finding their innate resilience, particularly through open dialogues aiming to identify what people do well in everyday life and then how to build on that, as opposed to focusing on illness and corrections of behaviour. This can create a relationship of trust, connection, and support between healthcare professionals and people with diabetes, which is the bedrock from which, engaged and encouraged, people can move forward (Table 26.3 and Box 26.1).

Outcomes must mirror biomedical as well as behavioural and emotional challenges

One of the most challenging aspects of diabetes education is that diabetes is both a biomedical disease and a behavioural, social and emotional challenge [48, 90, 91]. For positive diabetes outcomes to be realized, the person with diabetes must engage in intentional, effortful, and sustained behaviours. However, the importance of outcomes to the educator (e.g. $\text{HbA}_{1c} < 7.0\%$, 53 mmol/mol) cannot supersede the importance of outcomes for the person with diabetes (e.g. living life as normally as possible) and things go well only when the two are in synchrony. Thus, the essential outcomes should include biomedical as well as psychosocial outcomes [92].

There is an association between psychosocial problems and poor diabetes outcomes such as risk of hypoglycaemia and frequent omission of prescribed medicine [93, 94]. At the same time, poor diabetes outcomes can cause psychosocial problems, such as

Box 26.1 Tips for working from a flourishing mindset

- Begin each session by asking ‘What’s improved since we last met?’ This encourages the patient to reflect on successes, thereby guiding the visit in a positive direction.
- Ask the patient to share a challenge or difficult life event and describe the steps they took to overcome it. Listen for strengths that were used, provide congratulations, and ask, ‘How can you use these strengths to help improve your diabetes management?’
- When looking at a patient’s logbook or discussing proposed nutrition interventions, focus on what they are doing well, such as blood glucose numbers that are in range or the two vegetables a week they do eat. Ask ‘How did you do this?’ and ‘What can you do to make this happen more often?’
- Provide patients with suggested areas where improvement is needed and ask them to identify areas of focus and goal setting. Patients are more likely to be successful when they feel ownership for the goal. Discuss ideas for improvement and encourage the patient to implement one or two of them. Even if the selected approach(es) is(are) not successful initially, the patient is more likely to engage in alternative approaches and future recommendations by the healthcare provider if given the opportunity to choose.
- Be present, attentive, and mindful in your visit with a patient. Show genuine curiosity and interest. As is often quoted in medicine, ‘Patients don’t care how much you know until they know how much you care.’

Source: Modified from Greenberg and Bertsch 2013 [90].

It is also useful for the diabetes educator to be mindful of how diabetes fits into the social world of an individual. The idea of diabetes-specific as well as general social support is important here [100, 101]. People with diabetes can benefit from having sensitive discussions with their diabetes educator about the presence or absence of support from others regarding diabetes self-management. The potential of engaging peers in supporting diabetes outcomes should also be noted [102].

Diabetes self-management education and support in the social context

The second Diabetes, Attitudes, Wishes and Needs (DAWN2) study included a survey of 2057 adult family members of adults with diabetes. According to this study, supporting a relative with diabetes was perceived as a considerable burden by 35% of family members. The study also revealed that 40% of family members experienced high levels of distress related to concerns about their relative with diabetes, and 61% stated they were very worried about hypoglycaemia in their family member with diabetes [103, 104].

People with diabetes generally engage in self-management of their diabetes within a family setting and family members play a role in many everyday tasks such as meal preparation, often providing moral, emotional, and practical support. Thus, struggles with self-management and blood glucose levels, poor well-being, and psychological distress are relevant not only to the individual adult with diabetes. To the contrary, these problems affect – and are affected by – the entire family. Unfortunately, most education programmes exclusively target individuals with diabetes [105–108]. Furthermore, research targeting the interface between adults with chronic disease and their families is relatively scarce and family factors have until recently been virtually ignored in relation to adults with diabetes. A recent study shows how professional support may contribute to the creation of a shared illness identity and a reduction of diabetes-related conflicts within the family as well as enhanced support of self-management [109]. Another study shows that maintaining resilient, good-quality intimate relationships optimizes physical and psychological outcomes for people with diabetes [110]. The vast majority of psychoeducational interventions in type 1 diabetes focus exclusively on people with diabetes, with only a few offering support for family members [95]. However, the importance of partner support is increasingly recognized and its enhancement has become one of the main goals of current psychoeducational interventions in diabetes [111, 112]. The family provides the frame for the potential effects of culture, race, and ethnicity on disease outcomes, and we need to improve our understanding of family influences on diabetes management and ways to engage family members through family-tailored education and support [113].

Appreciation of culture is also essential when considering the context of the person with diabetes. Cultural factors such as self-efficacy, levels of health literacy, and effects of stigma impair accessibility and acceptability to diabetes education [114]. Ethnic minority groups are specifically vulnerable [115, 116]. To reduce the *literacy burden* of ethnic minorities and enhance support for self-management, the cultural context needs to be included to make diabetes education more accessible for all people with diabetes [117, 118].

fear of hypoglycaemia, diabetes distress, and functional or occupational interference. Depressive phenomena are common in those with diabetes, particularly diabetes distress. Diabetes distress is distinct from and more prevalent than depression among adults with diabetes [95, 96]. Further, compared to depression, diabetes distress is independently and more strongly associated with suboptimal diabetes self-management and hyperglycaemia [96]. People with diabetes distress may be incorrectly diagnosed as having depression and thus experience an ineffective approach to treatment [97]. A recently published paper by Fisher et al. emphasizes that emotional distress is best considered as a *continuous psychological characteristic*, rather than a distinct *comorbid clinical condition* [98]. In this way, diabetes distress is distinct from mental health disorders and thus is a characteristic to be considered in diabetes education.

While it can be stressful for diabetes educators without a background in psychology to address psychosocial issues within their scope of practice, it can be helpful to know that the ability to communicate one’s distress (i.e. to be heard) is often experienced as beneficial in and of itself. If the educator takes the position that they are not the expert and that it is not their responsibility to fix the potential problems, then supportive communication can be easier. For instance, it would not be inappropriate for a professional to declare, ‘I’d be interested in hearing about what you are going through and possibly make any recommendations that I think might be helpful.’ Research indicates a positive association between the presence of physician empathy and better diabetes outcomes [99].

The final step: using health education tools to promote and support change and self-management

Using cultural probes and design thinking [119] is a promising method in diabetes education. Design thinking is a research method deriving from the design world [120] as well as ethnographic studies [121, 122]. Methods include, for example, the use of postcards with questions concerning participants' attitudes to their lives, maps where participants can highlight areas of importance to their lives, and cameras with instructions asking participants to take photos of important objects. Visual methods similar to cultural probes such as photos, videos, and drawings are often used for data collection [123, 124]. The use of cultural probes in diabetes education is a promising method of translating the theoretical concepts of person-centredness and active involvement into practice to support both educators and people with diabetes. One of the early examples of the use of probes was the Conversation Maps tool, which successfully facilitates interactive dialogue among people with diabetes through relationship building, trust, and confidence as well as the sharing of personal stories and experiences [125]. Further examples are the British Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) programme [15] and the Danish NExt EDUcation (NEED), Empowerment, Motivation and Medical Adherence (EMMA), and Involvement in families with Type 2 diabetes (PIFT) programmes [126, 127] (Box 26.2).

Evaluation of diabetes education

Given the potential positive role that DSMES can have on people living with diabetes and their family, perhaps the most important indicator in the evaluation of diabetes education is the availability of and access to diabetes education. Biological outcome measures have for a long time dominated the evaluation of diabetes education, which is unsurprising as they make up essential outcomes in diabetes. In reviews and meta-analyses of diabetes education, the most used outcome measures can be divided into four categories: biological, behavioural, knowledge, and psychosocial outcomes. Most attention has been paid to biological outcomes, particularly HbA_{1c}, and knowledge-based outcomes. Less attention has been placed on behavioural outcomes and least on psychosocial outcomes [131].

An interesting and useful perspective, which is consistent with the complexity of diabetes education, is to examine the mechanisms by which an education programme works [132, 133]. If an education programme is found to be effective, how do we know what to replicate and what to change when we implement the programme somewhere else? Why do some programmes work in one place for one group of participants and not for another? Focusing on mechanisms of effects is complicated, as the education process typically involves multiple interacting components. It is thus difficult to identify the precise mechanisms leading to effects of the various components [134, 135]. Further, outcomes depend on the competencies of educators and the preconditions and motivation of participants as well as organizational conditions, all of which may be difficult to capture in a randomized controlled trial [135]. In response to this, theory-driven forms of evaluation have gained attention, as they can generate knowledge about the effectiveness of an education programme as well as knowledge about the underlying mechanisms of effects [136, 137].

Box 26.2 Examples of dialogue tools to be implemented to facilitate diabetes self-management education and support

The family mirror

The Family Mirror tool (Figure 26.5) aims to allow each member of a family with diabetes to visualize how they experience the effect of diabetes on their everyday life [128]. Each family member makes a figure of themselves and/or another family member, with the goal of being able to look at diabetes and family life from different perspectives. Further, the aspect of sharing the lived experiences of having diabetes in the family allows for all voices of the family to be heard, as well as the creation of transparency and dialogue on the challenging aspects of living with diabetes in the family's everyday life.

Steps in using the Family Mirror:

- The purpose of the Family Mirror is described.
- Each participant collects a stack of cards and a figure representing themselves and sits across from their relatives.
- The participants make a figure of themselves.
- The participants make a new figure of their relative with the help of the cards.
- The figures are presented within the family. The participants explain which cards they have chosen and why.
- The families share reflections and experience.

Balance cards

Balance cards [126, 129] comprise 27 cards with pictures and quotes (Figure 26.6). The aim of the exercise is to assist participants in talking about the imbalances, challenges, and possibilities they experience in their daily lives with diabetes. The exercise can make it easier for participants to express difficult topics and facilitates dialogue among participants about everyday life with diabetes.

My day

The My Day tool [130] aims to establish a good relationship between the person with diabetes and the educator (Figure 26.7). The educator gains insight into the everyday life of the person with diabetes guided by their focus and needs. This includes valuable information about physical activity, medication taking, social relations, etc.

The person with diabetes is encouraged to discuss their everyday life and challenges, particularly when completing the statement 'It is difficult for me to live with diabetes when...'. A shared understanding is achieved between the educator and the person with diabetes about the challenges involved in living with a chronic illness for specifically this person. This insight allows the educator to acknowledge the difficulties the person with diabetes is going through by including these dynamics in their relationship.

Theory-driven evaluation comprises 'an explicit theory or model of how the program causes the intended or observed outcomes and an evaluation that is at least partly guided by this model' [137]. Thus, a core element of theory-driven forms of evaluation is the development and use of theory in the evaluation process. The theory, often referred to as programme theory, specifies relationships between intervention actions and intended outcomes [136].

An education programme is an incarnated theory of change: a theory about how to change problematic conditions or behaviour.

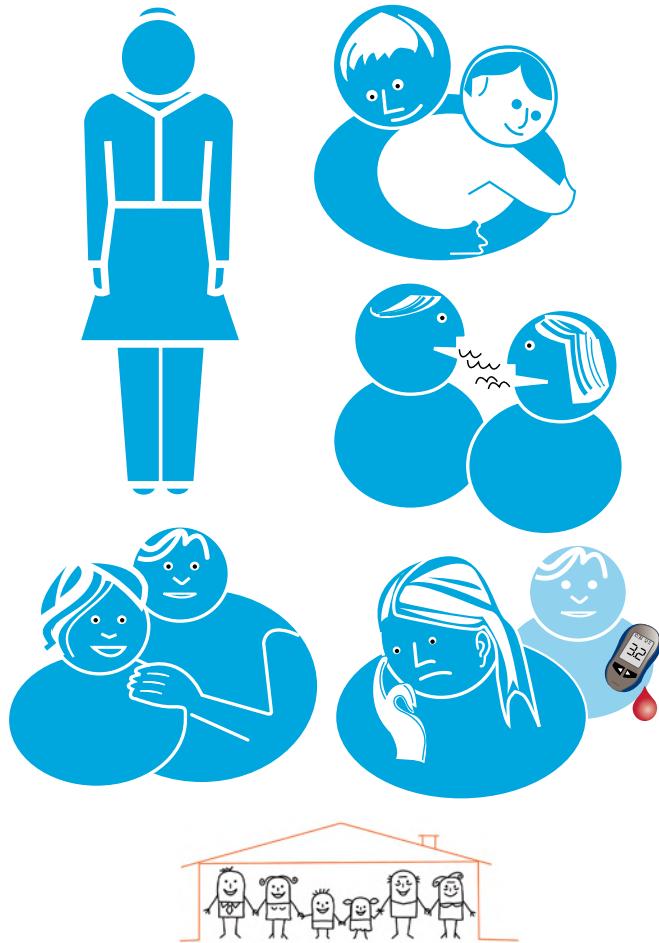


Figure 26.5 The family mirror.



Figure 26.6 Balance cards.

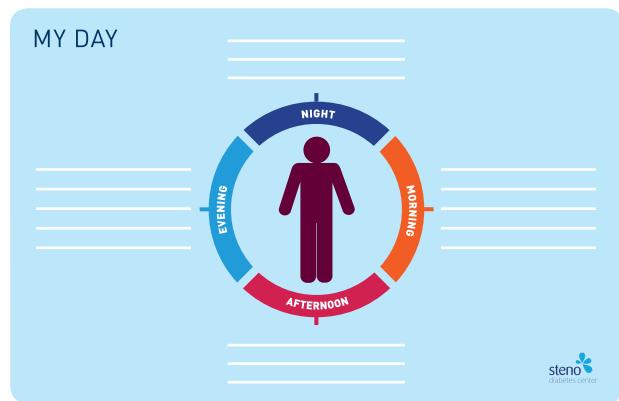


Figure 26.7 My day.

However, this theory is often unrecognized or poorly articulated, perhaps since a programme is an active open system that:

- Is apt to change over time as the programme unfolds.
- Works through the ideas and intentions of those implicated.
- Works differently among different subgroups.

Pawson and Tilley [138] describe the realistic evaluation approach, which focuses on three key concepts for understanding how, for whom, and under what conditions programmes will work: *most effective outcomes*, *mechanisms* through which outcomes occur, and *contexts* where the outcomes potentially will be replicable. Mechanisms refer to the process of how people interpret and act on the intervention to produce outcomes. Mechanisms are not assumed to be fixed, but are contingent on contexts. Thus, the programme theory can be expressed as context–mechanism–outcome configurations (C–M–O configurations). The evaluation implies the development of a theory about how outcomes, mechanisms, and contexts operate and use of this theory to direct empirical work. The evaluation focuses on exploring whether the theory can explain the observational data [138]. In a recent review regarding use of realistic evaluation, the use of C–M–O configurations was found to provide clarity in complex evaluation environments and rich information about what type of interventions work for whom in what context [139].

Table 26.4 shows a programme theory. If a person with diabetes is recruited to the programme and completes it, and if the programme takes a specific educational approach, then the person will attain improved knowledge and skills related to the management of diabetes and increased autonomy and quality of life. Working with programme theory, ideally a second level of data collection and analysis is needed in order to evaluate whether (i) the theory is right but not properly implemented; (ii) the theory should be refined; or (iii) the theory is wrong. Table 26.5 gives the key points in programme theory.

Conclusion

The provision of DSMES based on evidence, values and theories, skills, and tools (Figure 26.1) [35] is a challenging task; however, the evidence base of the beneficial effects of this approach is rapidly increasing. Self-management education is considered a complex intervention [140] with many different components, actors, and settings, leading to challenges in identifying the most effective components. Therefore, it is difficult to assess the effect of a single tool or method, or whether specific combinations of tools and methods or

Table 26.4 Programme theory.

Context	Mechanisms	Outcomes
The specific diabetes education programme or concept is applied: • Involvement, dialogue • Integrates cognitive, emotional, and bodily elements • Facilitates exchange of experience The educator has the skills to juggle, facilitate, and motivate, and is empathic	The participants reflect on their experiences and feelings and share them with other participants and the educator Educator talk ratio <40% on average The participants feel involved in the education process and experience that their individual needs are met	The participants increase their knowledge and confidence in relation to diabetes self-management The participants increase their well-being The participants engage in health-promoting behaviour The participants improve as regards articulated outcomes of the programme

Table 26.5 Key points in programme theory.

- Realistic evaluation is about theory testing and refinement
- Realistic evaluation develops and tests context–mechanism–outcome (C–M–O) configurations (hypotheses) empirically
- Realistic evaluation applies any approaches, tools, and methods that are appropriate to test a programme theory
- Realistic evaluation is potentially time-consuming as there is no independent criteria for closure

the quality or quantity makes interventions effective [141]. However, the Health Foundation in the UK identified effective elements of the implementation of 11 programmes of self-management support and shared decision making in chronic disease, including diabetes [141].

Figure 26.8 summarizes the points made in this chapter. A limiting factor of diabetes education is that it almost always does not include ongoing education and support. Once people with diabetes complete an education programme in its entirety, they are not provided with a component of ongoing support to allow tailoring of the education to their continued diabetes care needs. The ‘once’ education becomes education for life and therefore conclusive, without any opportunity for an information refresher or support mechanism that may be needed to adjust to changes in the perceived needs and preferences of people with diabetes. The lifelong process of diabetes self-management requires continued adjustments in knowledge, skills, motivation, and support. DSMES should be a lifelong process, starting at the point of diagnosis and remaining as an essential component of diabetes care [142].

**Figure 26.8** Principles for effective diabetes education and support. Source: Based on Ahmad et al. 2014 [141].

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27

Dietary Management of Diabetes

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Key points

- Weight loss is a primary mediator of diabetes risk reduction and management of type 2 diabetes in those who have overweight or obesity.
- Calorie content and maintenance of the diet are more important than macronutrient content for successful weight loss maintenance.
- The type and quality of dietary fat and carbohydrate are more important than amounts of these macronutrients for prevention and management of diabetes and its complications.
- Various dietary patterns are effective for weight loss, and for diabetes and cardiovascular risk reduction, and clinicians should consider individual preferences.
- Matching carbohydrate to insulin dose, either as part of multiple daily insulin or continuous subcutaneous insulin regimen, is the most effective approach for the management of glycaemia in type 1 diabetes.
- Women with diabetes planning to become pregnant should take 5 mg of folic acid per day to prevent neural tube defects.
- Calorie restriction to lose weight should not currently be recommended during pregnancy, but limiting weight gain can improve pregnancy outcomes.
- Low-glycaemic index foods may help manage blood glucose concentrations during pregnancy.

Diet plays an important role in the effective management of type 1 diabetes and type 2 diabetes and is fundamental to the prevention of type 2 diabetes. The aim of nutritional management of diabetes is to optimize glycaemic and blood pressure management, correct any lipid abnormalities, and, in doing so, reduce the risk of long-term complications [1–3]. Dietary advice must be evidence based and individualized, taking into account personal and cultural preferences, and ensuring the diet is appropriate and compatible with the person's lifestyle, existing treatment regimen, other comorbidities, and willingness to change [1–3].

Individuals with diabetes are up to four times more likely to develop cardiovascular disease [4,5], with an elevated risk also seen in impaired glucose tolerance [5] compared to individuals with normoglycaemia. Therefore, evidence-based nutritional recommendations for individuals with diabetes are based on the glucose management of the diabetes, reducing the risk of developing cardiovascular disease and the complications of diabetes [1–3]. The strength of evidence for the different nutritional recommendations for both management of diabetes and prevention of cardiovascular disease is graded according to the type and quality of published studies as well as statements from expert committees [2]. The gold standard for evidence-based guidelines is meta-analyses of large, well-controlled trials with long follow-up periods that include fatal or non-fatal clinical endpoints. However, this information is often not available and instead surrogate endpoints, such as glycaemia, body composition, lipoprotein profile, blood pressure, insulin sensitivity, and renal function, are used to determine the potential of dietary modification to influence glycaemic levels and risk of acute and chronic complications of diabetes [1,2].

There are many confounding factors within long-term dietary trials in diabetes, which limit the precision of such trials to establish effectiveness. These include but are not limited to differences in weight loss [2], medication withdrawal [6], and the composition and intensity of the control diet [7]. Adherence to a dietary trial protocol tends to lapse over time, which often means that intended differences in the dietary composition of intervention and control arms diminish in long-term trials [8]. While short-term trials can often achieve better adherence to a dietary intervention [9], the external validity of these trials to understand the long-term effect of diet on chronic disease management is poor. Each of these factors should be considered when interpreting findings from meta-analyses of nutritional interventions.

While nutritional science illuminates the underlying mechanisms of diet on disease risk, in practice nutrients are consumed as foods and as part of dietary patterns. Therefore, throughout this chapter, while reference will be made to the impact of individual macro- and micronutrients on clinical outcomes, it is important to consider how these nutrients form part of an overall healthful dietary pattern for diabetes prevention and management. Tables 27.1 and 27.2 summarize such dietary approaches.

Energy balance and body weight

Weight management is now understood to be the primary strategy for prevention of type 2 diabetes and for glycaemic management in people with type 2 diabetes who have overweight or obesity [1,2]. Weight gain is associated with an increased incidence of type 2 diabetes [10],

Table 27.1 The association of particular dietary components with risk or management of type 2 diabetes, and their inclusion or exclusion in established dietary patterns or guidelines.

Dietary components	Mediterranean	DASH	Diabetes UK	NICE	Effect on diabetes management/risk
Fruit	×	×	×	×	Dietary fibre associated with reduction of risk
Vegetables	×	×	×	×	Dietary fibre associated with reduction of risk
Nuts/seeds	×	×	×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA _{1c} , and insulin resistance Insoluble fibres associated with reduction in risk of diabetes Magnesium associated with reduction in risk of diabetes
Pulses	×	×	×	×	Soluble fibres reduce post-prandial glucose in randomized controlled trials. Low GI is associated with reduction of risk, and reduces HbA _{1c} by 5 mmol/mol (0.5%)
Fish and seafood	×		×	×	No known effects of omega-3 on diabetes management or risk
Increased white to red meat ratio			×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA _{1c} , and insulin resistance
Wholegrains/ cereal fibre	×	×	×	×	Insoluble fibres associated with reduction in risk of diabetes Magnesium associated with reduction of risk of diabetes
Low glycaemic index			×	×	Associated with reduction of risk, and reduces HbA _{1c} by 5 mmol/mol (0.5%)
Olive oil	×				↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA _{1c} , and insulin resistance
Vegetable oil (sunflower, rapeseed oil)			To replace butter and SFA spreads	To replace butter and SFA spreads	↑ PUFA/MUFA to SFA ratio associated with reduction in FPG, HbA _{1c} , and insulin resistance
Low-fat dairy		×	×	×	Dairy intake associated with reduction of risk; milk proteins may lead to reduced glucose concentrations and increased insulin secretion. Vitamin D and calcium associated with reduction of risk
Alcohol	Moderate	↑			Moderate intake associated with reduction of risk
Decreased red or processed meat					Diets high in red, especially processed, meat associated with increased risk of diabetes
Butter	Limited		Replaced with non-SFA spreads	Replaced with non-SFA spreads	↓ PUFA/MUFA to SFA ratio associated with increased risk of diabetes, FPG, HbA _{1c} , and insulin resistance
Sweetened beverages		×	Limit	Limit	Sugar-sweetened beverages associated with increased BMI, leading to increased risk of diabetes
Sodium					No known effects of omega-3 on diabetes management or risk

× = included in dietary pattern.

These data are largely derived from observational studies. Orange indicates components with a protective association; blue indicates components with a deleterious association.

BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; FPG, fasting plasma glucose; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; MUFA, monounsaturated fat; NICE, National Institute for Health and Care Excellence; PUFA, polyunsaturated fat; SFA, saturated fat.

while weight loss reduces insulin resistance and improves glucose handling in people with and without diabetes [11]. A series of large-scale, lifestyle-based randomized controlled trials [12, 13] have conclusively shown that a 5–7% weight loss in people at risk of diabetes reduces risk by up to 66% (Figure 27.1). While these programmes also included other components such as increasing fibre, decreasing total and saturated fat, and increasing physical activity, weight loss was the primary driver of the reduction in risk [14]. A trial testing the independent effect of dietary fibre on type 2 diabetes development did not find that it significantly reduced the risk of type 2 diabetes [15]. Interestingly,

there also appears to be a legacy effect of weight loss on diabetes prevention, such that even three years after the intervention stopped, there was still a 48% risk reduction in the intervention group [16].

Each of the large-scale type 2 diabetes prevention trials tested a similar dietary pattern: low fat, with some of the trials specifying low saturated fat and/or high fibre. One recent multinational trial compared a high- versus low-protein diet and did not find that the protein content influenced the risk of type 2 diabetes [17]. However, prior to randomization to the high- or low-protein groups, all participants had undergone an intensive weight loss intervention and

Table 27.2 The association of particular dietary components with risk of cardiovascular disease, and their inclusion or exclusion in established dietary patterns or guidelines.

Dietary components	Mediterranean	DASH	Diabetes UK	NICE	Effect on cardiovascular disease risk
Fruit	×	×	×	×	Dietary fibre associated with reduction of risk
Vegetables	×	×	×	×	Dietary fibre associated with reduction of risk
Nuts/seeds	×	×	×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk
Pulses	×	×	×	×	Dietary fibre associated with reduction in risk of cardiovascular disease
Fish and seafood	×		×	×	Dietary fibre associated with reduction in risk of cardiovascular disease
Increased white to red meat ratio			×	×	Low glycaemic index associated with reduction in risk
Wholegrains/cereal fibre	×	×	×	×	No known effects of omega-3 on diabetes management or risk
Low glycaemic index			×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk
Olive oil	×				Dietary fibre associated with reduction in risk of cardiovascular disease
Vegetable oil (sunflower, rapeseed oil)			To replace butter and SFA spreads	To replace butter and SFA spreads	Associated with reduction of risk
Low-fat dairy		×	×	×	↑ PUFA/MUFA to SFA ratio associated with reduction in LDL, neutral effect or ↑ HDL, reduction in cardiovascular disease risk
Alcohol	Moderate	↑			No consensus on effect of dairy on cardiovascular disease risk
Decreased red or processed meat					Moderate intake associated with reduction of risk
Butter	Limited		Replaced with non-SFA spreads	Replaced with non-SFA spreads	Diets high in red, especially processed, meat associated with increased risk of diabetes
Sweetened beverages		×	Limit	Limit	↓ PUFA/MUFA to SFA ratio associated with increased LDL concentrations and cardiovascular disease risk
Sodium					Sugar-sweetened beverages associated with increased BMI, leading to increased risk of cardiovascular disease
					Sodium restriction reduces blood pressure and cardiovascular disease risk

× = included in dietary pattern.

Orange indicates components with a protective association; blue indicates components with a deleterious association.

BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fat; NICE, National Institute for Health and Care Excellence.

lost about ~10kg over eight weeks. This type of intervention “reboots” the pancreatic β cells and normalizes blood glucose concentrations in type 2 diabetes [18], and likely would have done the same in people with pre-diabetes. Therefore, at the present time, it is unknown whether the addition (or reduction) of specific nutrients or food groups within a weight loss intervention could optimize type 2 diabetes prevention programmes.

Remission of type 2 diabetes

Remission of type 2 diabetes refers to the normalization of blood glucose concentrations in the absence of anti-diabetes medications, although there is currently no consensus on the exact

definition. While numerous short-term studies have shown that marked caloric restriction can normalize the underlying pathophysiology and hyperglycaemia of type 2 diabetes [19], until recently it was not known how enduring this *normalization* could be. The DiRECT trial (Diabetes Remission Clinical Trial) published in 2017 showed that remission of type 2 diabetes can be long-lasting, but is dependent on both the achievement and maintenance of substantial weight loss, in the order of 10–15 kg [18, 20].

Remission appears to be contingent on the return of the first-phase insulin response [21]. The first-phase insulin response declines along the pathway of type 2 diabetes; it is reduced in newly diagnosed type 2 diabetes and nearly absent in type 2 diabetes of long duration [22]. It appears that return of the first-phase insulin

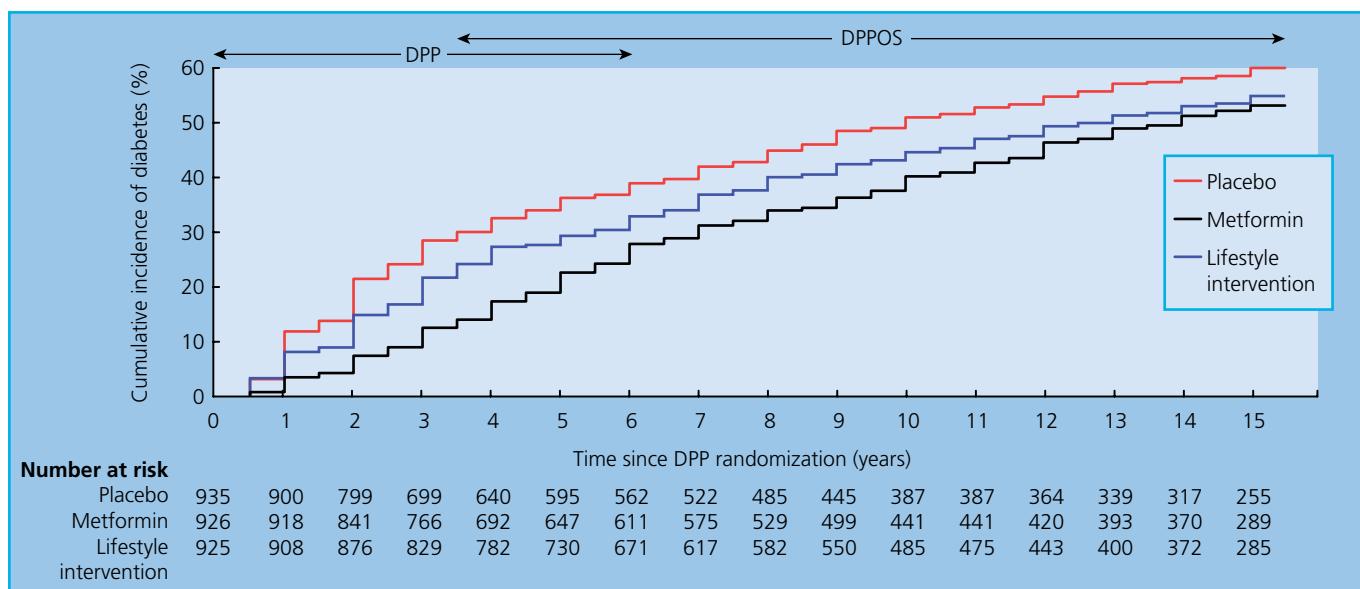


Figure 27.1 Reduction in the incidence of diabetes in the US Diabetes Prevention Program (DPP). This figure shows the data from the DPP itself and data from the follow-on Diabetes Prevention Program Outcomes Study (DPPOS), which followed the same individuals up to 15 years. Source: Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; 3(11):866–875. Copyright 2015 Elsevier.

response can occur in type 2 diabetes of short duration (within approximately 4–6 years of diagnosis), but is much less likely in type 2 diabetes of long duration [21].

As an emerging area of research, there are many unknowns surrounding remission of type 2 diabetes, including whether it can occur with more modest weight loss; and whether other dietary strategies, particularly low carbohydrate, could increase the rate of remission and prevent relapse to type 2 diabetes. Currently available data suggest that ketogenic or high-protein, low-carbohydrate diets could help achieve remission, potentially via mechanisms independent of weight loss [23,24] but longer-term and/or controlled studies are needed to confirm this.

Weight loss also reduces important cardiovascular risk factors, including circulating triglycerides and blood pressure [2]. A systematic review of studies with at least two years' follow-up showed that intentional weight loss in people with type 2 diabetes reduces their mortality risk by 25%, with a higher risk reduction with greater weight loss [25]. The LookAHEAD (Action for Health in Diabetes) study found that an intensive lifestyle for primary prevention of cardiovascular disease did not significantly reduce cardiovascular disease-related morbidity or mortality after nearly 10 years of follow-up [26]. However, this may reflect the limitations of dietary improvements in long-term mortality in people treated aggressively with antihypertensive and lipid medications [27], and does not discount the role of weight loss and dietary change in improving quality of life [27], reducing intensification of medical treatment of diabetes and cardiovascular disease, and greater physical functioning [26,27]. Reductions of 5–10% are effective at reducing cardiovascular risk factors and are achievable and feasible, although greater weight loss may reduce risk further [28].

Weight management has also been considered for people with type 1 diabetes, as the prevalence of overweight and obesity is increasing in type 1 diabetes [29] and the co-presentation of insulin resistance is associated with hyperglycaemia [30]. However, there is little evidence that body weight or weight loss influences glycaemic

levels in people with type 1 diabetes [29]. Furthermore, in both type 1 and type 2 diabetes, caution should be applied to intentional versus unintentional weight loss, as unintended weight loss in people with diabetes may also be an indication of suboptimal medical management or omission or inadequate dosing of medications leading to hyperglycaemia [31].

Therefore, national [32–34] and international guidelines [5] recommend initial weight loss of 5–10% in those with overweight or obesity for the purposes of type 2 diabetes management and prevention of type 2 diabetes and cardiovascular disease.

Currently there is no consensus on the optimal diet to achieve and maintain the recommended weight loss [1]; however, the overall energy content of the diet is more important than macronutrient composition [2,35,36]. Effective strategies for which there is evidence in people with diabetes include low-carbohydrate [37], low-glycaemic index (GI) [38], low-fat [28], or very low-calorie diets [39], and meal replacement [40]. There has been particular interest in low-carbohydrate diets, which appear to be most effective at promoting weight loss over the short term, and may also have beneficial effects on glycaemia independent of body weight [41,42] and greater withdrawal of type 2 diabetes medications [42]. While there is little evidence for superiority over the long term [43,44], practitioners should be open to this approach and individual preference. The primary factor in achieving and maintaining weight loss remains long-term maintenance of the diet, and the best approach is therefore one that fits with a person's lifestyle, habits, and goals [1,2].

Carbohydrate and diabetes

The relationship between carbohydrate intake and glycaemia in type 2 diabetes is not straightforward and currently there is no definitive evidence that carbohydrate reduction *per se* durably lowers

glycaemia. However, carbohydrate intake remains the primary determinant of glycaemic levels in people with type 1 diabetes [1].

Quantity

There is no evidence for a specific quantity of carbohydrate in the diet for the management of type 2 diabetes [1]. The trial evidence is severely limited by varying amounts of carbohydrate being prescribed in the low-carbohydrate arm, the actual carbohydrate amount and type being consumed throughout the trial, whether or not anti-diabetes medications were taken or withdrawn during the trial, the protein content of the dietary arm, and differences in weight loss achieved. Physiological studies [41] and short-term trials [24] indicate that the ketones produced on a very low-carbohydrate (ketogenic) diet could help lower blood glucose independent of weight loss, perhaps by reducing hepatic glucose output [45]. Trial evidence [46, 47] shows that nutritional ketosis is an effective option for the management of type 2 diabetes, but whether it is superior to other approaches requires better controlled trials.

There are no randomized controlled trials investigating ecaloric carbohydrate restriction and risk of diabetes, but epidemiological data suggest there is no relationship between total carbohydrate intake and risk of type 2 diabetes [48]. Based on the currently available evidence, the quality and source of carbohydrate are more important than total amount for the prevention of type 2 diabetes.

In contrast, carbohydrate counting forms the basis of the management of type 1 diabetes, where recommended carbohydrate intake should take account of energy requirements, blood glucose concentrations, and insulin dosing [49, 50]. Carbohydrate counting is a meal planning approach that involves matching 10 g or 15 g carbohydrate portions to a particular bolus insulin dose [49], and is based on the premise that carbohydrate is the primary driver of post-prandial glucose concentrations [51]. As a concept, carbohydrate counting has been around since the 1920s, but has been widely employed since its use in the Diabetes Control and Complications Trial [52]. It is now the dietary strategy of choice in type 1 diabetes. Approaches to carbohydrate counting can vary immensely between country, region, institution, and individual practitioner, but may include the following:

- Carbohydrate awareness.
- Basic carbohydrate counting and label reading.
- Development of the person's skills in monitoring and recording blood glucose levels in relation to food intake, medications, and physical activity.
- Sophisticated matching of carbohydrate to insulin dose. This may include the use of wizard bolus meters or apps to aid in the estimation of carbohydrate intake and insulin requirement.

These techniques should enable the person with type 1 diabetes to add or subtract short- or rapid-acting insulin at meals and snacks to manage and correct blood glucose levels [49, 53]. The heterogeneity in these approaches must be taken into account when interpreting the evidence for carbohydrate counting [54].

Adjustment of insulin to carbohydrate intake

In people with type 1 diabetes treated with multiple daily insulin or continuous subcutaneous insulin infusions, carbohydrate counting with insulin dose adjustment is an effective approach to lower glycated haemoglobin (HbA_{1c}), reduce the occurrence of hypoglycaemic episodes, and improve quality of life and other clinical markers such as body mass index (BMI) and waist circumference [3, 53, 55, 56]. However, there is a need for good-quality education, and appropriate clinical support is necessary to ensure

accurate and consistent insulin dose adjustments [3, 57]. Inaccuracy in carbohydrate counting or dose adjustment is common, and is associated with poorer clinical outcomes [58]. Care must be taken to ensure that carbohydrate counting and dietary advice are not detrimental to an individual's weight management goal. Additional snacks are not automatically required and should be tailored to the individual's needs. Referral to a structured education programme of proven benefit is recommended, such as the DAFNE (Dose Adjustment For Normal Eating) programme, ideally 6–12 months after diagnosis [3]. In individuals with fixed or biphasic insulin regimens, consistency in carbohydrate intake is recommended and is associated with reductions in HbA_{1c} [3, 59, 60].

A small number of recent studies have suggested that the fat and protein content of the meal should also be taken into account when planning an insulin regimen [61, 62]. However, any potential physiological benefits of these approaches need to be balanced with the complexity and burden for the person with diabetes.

Carbohydrate in the treatment of mild to moderate hypoglycaemia

Mild or moderate hypoglycaemia is a common occurrence with insulin treatment in both type 1 diabetes and type 2 diabetes. Glucose is the most effective treatment and should be given immediately [3]. National and international guidelines recommend 15–20 g should be given straight away (Box 27.1), followed by another 15 g if blood glucose does not rise by 4 mmol/l after 15 minutes [49]. A follow-up carbohydrate snack (15–20 g) may be necessary to reduce the risk of further hypoglycaemia, particularly in circumstances where blood glucose is likely to continue to decrease, such as following alcohol consumption or physical activity [49].

Carbohydrate quality

Dietary carbohydrates represent a heterogeneous group of compounds, which include glucose, cellulose, fructose, lactose, starch, resistant starch, sucrose, oligosaccharides, and lignin. The diverse effects of these different structures [63] on diabetes and metabolic risk factors are too numerous to expand on in this chapter, but these factors emphasize the limitations of such terms as a high- or low-carbohydrate diet. Nevertheless, the *quality* of these different carbohydrates can be imperfectly but usefully captured by use of the glycaemic index.

The GI is an indication of the glucose-raising potential of the carbohydrate, and is defined by the incremental area under the blood glucose curve (iAUC) as a percentage of each person's average iAUC for a standard food, usually 50 g glucose or white bread [64]. The glycaemic load, which is the product of the dietary GI and total dietary carbohydrate, may also be used to express the overall quality of carbohydrate in the diet [65].

In people with type 2 diabetes, a Cochrane review of randomized controlled trials suggests adoption of a low-GI diet can lead to

Box 27.1 Foods containing 15–20 g of fast-acting carbohydrate

- Small glass of sugary (non-diet) drink
- At least three glucose tablets
- Five sweets, e.g. jelly babies
- Small carton of pure fruit juice
- Glucose gel

HbA_{1c} reductions of 5 mmol/mol (0.5%) [65]. While data from epidemiological studies suggest low-GI diets are associated with a lower BMI [66], randomized controlled trials have demonstrated a reduction in HbA_{1c} independent of changes in body weight [67,68]. Low-GI diets are associated with a lower risk of type 2 diabetes [69], but there are no controlled trials examining the effect of the GI on type 2 diabetes incidence as a primary outcome.

The evidence of effectiveness of low-GI diets in management of glycaemia of type 1 diabetes is unclear [2] and the latest National Institute for Health and Care Excellence (NICE) guidelines do not recommend their use in people with type 1 diabetes [3].

Low-GI diets may also reduce cardiovascular disease risk by lowering triglyceride and low-density lipoprotein (LDL) cholesterol levels [70]. However, current guidelines do not make specific recommendations regarding GI and cardiovascular disease risk.

Dietary fibre

The indigestible nature of dietary fibres renders them low or non-glycaemic [63,71]. However, dietary fibres themselves and foods high in fibre appear to influence glucose homeostasis beyond their GI [72,73]. Increasing dietary fibre by approximately 18 g/d up to a total intake of 50 g/d leads to a reduction in fasting plasma glucose of 0.7–0.9 mmol/l [72,74] and in HbA_{1c} of 4 mmol/mol (0.3%) [72]. However, according to the American Diabetes Association, there is insufficient evidence to recommend people with diabetes consume fibre in amounts exceeding the current recommended daily allowances (RDA) [75]. Furthermore, the majority of people in Western populations do not meet the minimum recommendations, and targeting this should be a dietary priority.

Dietary fibre is inversely associated with diabetes risk in cohort studies [76]. In the Finnish Diabetes Prevention Study, participants were advised to consume 15 g/1000 kcal of fibre [13], which appeared to reduce diabetes risk, an effect partly independent of its effects on body weight [77]. Current guidelines for diabetes prevention recommend increasing fibre intake to reduce diabetes risk [2].

Epidemiological data support a protective role of dietary fibre against cardiovascular disease, with the data most consistent for wholegrains [78]. There are currently insufficient data from randomized controlled trials, and current guidelines do not make specific recommendations for the role of fibre in cardiovascular disease risk.

Dietary mono- and disaccharides

Sucrose

Despite controversy about the role of sugar in diabetes management, moderate intake of sucrose (10–15% total energy) or other added sugars can be included in the diet of people with diabetes without worsening glycaemic levels or insulin sensitivity [2,60,79–81]; however, care must be taken not to exceed energy requirements [2,60,82]. In a randomized controlled trial, there was no difference in insulin resistance after six weeks of 25% versus 10% of energy from sucrose in healthy people [79]. In contrast, 11 per day of a sucrose-containing beverage increases hepatic lipid deposition compared to isocaloric quantities of milk, water, or aspartame-sweetened beverages [83]. There is no definitive evidence that sucrose *per se* influences cardiovascular disease risk, but the totality of the evidence supports limiting or avoidance of sucrose as a prudent dietary strategy [84]. In summary, recommendations for sucrose intake for people with or at risk of diabetes are based on those for the general population, namely limiting the consumption of energy-dense, nutrient-depleted sucrose.

Fructose

Fructose is a low-GI monosaccharide and isocaloric exchange of fructose for other carbohydrate improves glycaemic levels in people with type 2 diabetes over the short term, even when consumed up to 160 g/day [85]. However, the metabolism of fructose leads to processes detrimental to human metabolism, including increased *de novo* lipogenesis, higher ectopic lipid accumulation, and elevated triglycerides and uric acid, leading to non-alcoholic fatty liver disease and increased cardiovascular risk [86]. While there is a need to identify the optimal quantity of fructose that improves glycaemia without deleterious cardiometabolic effects [87], a variety of fruits and vegetables are to be encouraged as part of an overall dietary pattern [2] (Tables 27.1 and 27.2).

Non-nutritive sweeteners

The non-nutritive sweeteners approved for use in the UK and Europe include aspartame, saccharin, acesulfame potassium, cyclamate, and sucralose [88]. The increased sweetness of these compounds means they are consumed in minuscule amounts in the diet, and recommendations for people at risk of or with diabetes are the same as the general population [89]. These sweeteners do not contribute to energy intake or influence glucose levels [89]. Other sweeteners commonly used are sugar alcohols. While they are moderately glycaemic, sugar alcohols are consumed in such minor amounts that their consumption does not require alterations in insulin adjustment [2].

Dietary fat

The role of dietary fat in diabetes management has been of interest for decades following observations in the 1950s that dietary fat can modify insulin signalling [90] and the association between saturated fat and cardiovascular disease [2,91]. However, there appears to be little association between total fat in the diet and risk of diabetes [90]. Although diabetes prevention programmes have limited total fat [12,13], weight reduction *per se* and not macronutrient composition of the diet was the primary driver of risk reduction [14]. Similarly, there is no consensus on percent calories from fat in relation to diabetes management [2,90]. Instead, the types and sources of fat consumed and total quality of the diet appear to be more important.

Saturated fat

Replacement of saturated fat (SFA) with polyunsaturated fat (PUFA) is associated with a reduction in diabetes risk in multiple cohort studies [90,92]. The evidence is stronger for replacement with PUFAs than monounsaturated fatty acids (MUFAs), but this may reflect the close association of MUFAs with SFAs in Western diets and the availability of biomarkers for PUFA intake in prospective studies [90]. Data from randomized controlled trials do not consistently demonstrate a detrimental effect of SFA on insulin sensitivity [93–95], but methodological differences in these studies, such as sample size, duration, and the macronutrient that replaces SFA, may explain these inconsistencies.

The proposed relationship between SFA and cardiovascular disease largely arose based on early population studies [96]. However, several updated meta-analyses have questioned the conclusion that simply reducing SFA intake will necessarily reduce cardiovascular disease prevalence [97,98]. Instead, replacing the macronutrient

appears to be important: replacement of SFA with refined but not high-quality carbohydrate or unsaturated fat has been linked to worsening of atherosclerotic risk factors including elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and increased concentrations of small, dense LDL particles [97–101], emphasizing the need to consider the quality of the diet as a whole.

Similarly, recent studies have also drawn attention to the heterogeneous nature of dietary fat classes, with short-chain, long-chain, and odd-chain SFAs associated with diabetes risk reduction, and medium-chain SFAs associated with increased risk [102, 103]. Odd-chain fatty acids are predominantly found in dairy products, but whether or not these fatty acids have beneficial effects *per se* or whether these associations reflect other nutrient components found in dairy is currently unclear.

Similarly, SFAs come from a variety of food sources, including red and processed meats, dairy products, nuts, and oils, and a prudent approach is therefore to promote foods associated with healthful dietary patterns such as nuts, seeds, oils, low-fat dairy, fish, and fruit and vegetables, and to limit red (particularly processed) meat and butter (Tables 27.1 and 27.2).

In summary, current guidelines recommend limiting saturated fat to 7% of energy intake, but careful consideration should be given to the replacing macronutrient and overall dietary pattern (Tables 27.1 and 27.2).

Polyunsaturated fat

The most abundant PUFA in the diet is linoleic acid, which is inversely associated with diabetes incidence and cardiovascular disease in prospective cohort studies [90, 92]. The use of long-chain PUFAs as biomarkers for intake strengthens the subjective nature of cohort studies, which typically rely on self-reported dietary intake [90, 104]. Clinical trials evaluating the effect of PUFAs on insulin sensitivity or surrogate markers for diabetes risk have not been consistent [105–107]. The short duration of some of these studies may be important, as PUFAs are believed to act partly via altering membrane fluidity, which may take up to three months [90].

Replacement of saturated fat with PUFAs reduces cardiovascular disease risk, and surrogate risk markers [97–101, 108, 109], and sources of PUFAs such as nuts, seeds, and vegetable oils should be encouraged as part of a healthy diet (Tables 27.1 and 27.2).

Omega-3 fatty acids

There is little evidence from observational and experimental studies that omega-3 fats improve glycaemia in healthy individuals and people with type 2 diabetes [110, 111] or reduce the risk of developing diabetes [107], and high doses of fish oil impair glucose homeostasis [110]. In contrast, the cardioprotective effects of omega-3 fats, such as reducing serum triglycerides and modifying platelet aggregation and thrombogenicity [112], have led to recommendations to include oily fish twice a week to reduce cardiovascular disease [2, 33, 113]. Importantly, *more* is not better, and previous support for omega-3 supplementation for prevention of cardiovascular disease in people with diabetes was withdrawn by NICE [33].

Monounsaturated fat

Recent evidence from the PREDIMED (Prevención con Dieta Mediterránea) and earlier KANWU (Kuopio, Aarhus, Naples, Wollongong and Uppsala) trials suggests MUFAs may improve insulin sensitivity and reduce diabetes risk independent of energy restriction, particularly where MUFAs replace SFAs [93, 114].

There is also good evidence from randomized controlled trials that diets high in MUFAs can reduce glucose concentrations in people with type 2 diabetes [115–117], and can be used to replace carbohydrate without detrimental effects [2, 118]. There are few studies that have specifically examined the effect of MUFAs on glycaemic levels in individuals with type 1 diabetes, and there is insufficient evidence to make firm recommendations.

Replacing SFAs with MUFAs can reduce risk of cardiovascular disease [119, 120], and controlled trials demonstrate that high-MUFA diets can increase HDL cholesterol, lower blood pressure, and improve other surrogate markers of cardiovascular disease risk [98, 105, 108, 121, 122].

MUFA is a significant component of a Mediterranean diet [123], and it is important to consider the confounding effects on clinical risk factors of other aspects of this dietary pattern, including fish, fruits and vegetables, and moderate alcohol. For example, in the PREDIMED trial, extra-virgin olive oil had a greater effect on cardiovascular disease risk reduction than olive oil, despite identical proportions of MUFA, indicating that nutritive and non-nutritive components are also important [124]. Therefore, while MUFAs appear to have independent effects on glucose homeostasis and cardiovascular disease risk, greater risk reduction is likely achieved by following a diet rich in wholegrains, fruit, vegetables, fish, and limited saturated fat [2, 123, 124].

Trans fats

Trans fats occur naturally in foods such as milk or other dairy products as a byproduct of rumination or are produced industrially (partially hydrogenated vegetable oils). There is little evidence that total trans fat in the diet influences glucose homeostasis [125]; however, prospective studies using the dairy fat transpalmitoleic acid as a biomarker have shown that this naturally occurring trans fat is inversely related to diabetes risk [126]. However, it is unclear whether the fat *per se* has beneficial effects on glucose homeostasis, or whether the erstwhile nutrients of dairy mediate this risk reduction. Naturally occurring trans fats are found in minute amounts in dairy foods, whereas industrially produced trans fat can contribute up to 4 g a day in US diets [127].

There is compelling evidence from clinical and epidemiological studies that industrially produced trans fats have a deleterious effect on cardiovascular disease risk [127–129], and national and international guidelines have recommended their reduction or complete elimination in the diet [2, 127, 130].

In practice, these observations support and inform recommendations for a healthy dietary pattern (Table 27.2), with dairy products forming part of approaches, such as the well-researched Dietary Approaches to Stop Hypertension (DASH) diet, and minimizing foods high in hydrogenated vegetable oil, which typically include biscuits, cakes, and other sweet, high-fat goods.

Dietary cholesterol

There is little evidence that dietary cholesterol increases diabetes risk [131]. Instead, recommendations to limit cholesterol intake come from some clinical studies, which have demonstrated that dietary cholesterol can raise LDL cholesterol [132]. This contention has been a subject of considerable debate for many years. A recent meta-analysis of prospective studies examining whether dietary cholesterol ultimately influences risk of cardiovascular disease was inconclusive [133] and the American Heart Association/American

College of Cardiology have raised concerns about the heterogeneity of the data available [127]. However, given the potential impact of dietary cholesterol on LDL cholesterol, the possible increased absorption of dietary cholesterol in people with diabetes [134], and the elevated risk of cardiovascular disease in people with diabetes, any changes to current guidelines to limit dietary cholesterol to 200–300 mg/d are premature [135].

Protein

Given the primary role of weight loss in the prevention and management of type 2 diabetes and prevention of cardiovascular disease, numerous studies have evaluated the effect of higher protein intakes on satiety and weight management in amounts of up to 40% energy from protein [136–139]. However, the concomitant changes in the amount and quality of carbohydrate and fat in these studies make it difficult to draw any firm conclusions. Guidelines therefore reiterate that the most effective weight loss diet is one that takes into account an individual's preferences, beliefs, cultural values, and practical considerations [1, 2, 140].

Protein is also a macronutrient of interest due to its capacity to increase insulin secretion acutely [141]. However, a high protein intake could induce insulin resistance [142], and therefore the long-term effect of high protein on glycaemia [143] or type 2 diabetes risk may be a trade-off between its effect on promoting prandial insulin release while potentially reducing insulin sensitivity [144]. Suggestions that dietary protein may be modestly linked to increased risk of diabetes [145] may reflect sources of protein such as red or processed meats; dietary patterns that provide vegetable sources of protein alongside low-fat meat represent a prudent approach (Table 27.1).

Increasing the protein content of the diet lowers liver fat [146, 147], independent of weight loss. The provision of amino acids protects against hepatic triglyceride deposition under experimental obesogenic conditions [148, 149]. Given the association between liver fat and type 2 diabetes, high-protein diets might therefore be expected to offer protection against the development of type 2 diabetes.

High-protein diets may also have a role to play in managing hypertension. Observational studies [150] and trials in which carbohydrate is replaced with protein [151, 152] indicate that diets high in plant-based protein in particular may help in managing this cardiovascular disease risk factor.

People with diabetes are at higher risk of renal disease, and caution should be employed when recommending changes to protein intake in individuals with chronic kidney disease. In people with stage 3–5 chronic kidney disease not requiring dialysis, a restricted protein intake of 0.6–0.8 g/kg of body weight/d has been recommended by expert panels [153]. Persons with chronic kidney disease on dialysis require 1.0–1.2 g/kg of body weight/d [153].

Micronutrients

Several micronutrients have been specifically linked to diabetes risk in cohort studies; however, very few randomized controlled trials have confirmed these associations. Such micronutrients include magnesium [154], vitamin D [155], calcium [156], and chro-

mium [157]. Similarly, epidemiological trials and *in vitro* data have suggested that antioxidant vitamins and folate (vitamins A, C, E, and beta-carotene) could play a role in modifying cardiovascular disease risk. However, well-designed randomized controlled trials to confirm these associations are lacking [158], and NICE does not recommend such supplementation [159].

Therefore, current guidelines recommend regular consumption of a variety of vegetables, fresh fruit, legumes, dairy products, vegetable oils, nuts, wholegrain breads, and oily fish to ensure that recommended vitamin and mineral requirements are met [1] (Tables 27.1 and 27.2). This message should be reinforced alongside clarification that there is no proven benefit of vitamin or mineral supplements for management of diabetes.

Salt or sodium

Reduced sodium intake can lower blood pressure, and sodium intake should be limited across the population, including individuals at higher risk of cardiovascular disease [160, 161]. A reduction in mean salt intake of 3 g/d for adults (to achieve a target of 6 g/d) would lead to around 14–20 000 fewer deaths per year from cardiovascular disease [162]. Dietary patterns, such as the DASH diet, that are low in sodium and high in potassium, magnesium, and calcium form an effective approach to control hypertension and are appropriate in people with diabetes (Table 27.2).

Sterols and stanols

Plant sterols and stanols have no known effect on glucose homeostasis, but reduce LDL and total cholesterol in people with and without diabetes [163]. Dietary guidelines have recommended 2–3 g/d of fortified foods to lower LDL and total cholesterol irrespective of whether the individual is taking statins [2], but they are not included in the updated NICE guidelines for lipid modification in the prevention of cardiovascular disease in people with diabetes.

Alcohol

In cross-sectional and prospective studies, a modest alcohol intake is associated with a reduced risk of diabetes and cardiovascular disease, while excessive (>30–60 g/d) and chronic intakes appear to raise blood pressure, increase plasma triglycerides, and heighten the risk of cardiovascular disease [164, 165].

In people with diet-treated diabetes, alcohol consumed with carbohydrate may raise glucose levels, but does not appear to affect glucose or insulin concentrations when consumed alone [140]. However, in people treated with insulin or insulin secretagogues, alcohol increases the risk of hypoglycaemia [2, 140]. The risk increases with the quantity of alcohol consumed and may remain elevated the following day [166]. Therefore, in these people, alcohol should be consumed with food.

Finally, alcohol is a source of energy and is associated with increases in BMI and greater waist-to-hip ratio [167]. Therefore, recommendations for prevention and management of diabetes are the same as those for the general population: 2–3 units/d in women;

3–4 units/d in men [2]. One alcohol unit is measured as 10 ml or 8 g of pure alcohol. This equals one 25 ml single measure of whisky (alcohol by volume [ABV] 40%), or a third of a pint of beer (ABV 5–6%), or half a standard (175 ml) glass of red wine (ABV 12%). The new UK Department of Health guidelines recommended only 14 units per week for both men and women [168].

Diet in special circumstances

Diet in pregnancy

Diabetes increases the risk of adverse pregnancy outcomes, and the risk increases with the duration of diabetes (Chapter 71) [169]. Maintenance of HbA_{1c} towards the target of 48 mmol/mol (6.5%) is likely to reduce the risk of congenital malformations, but may be associated with increased episodes of hypoglycaemia. Excess weight gain is associated with worse glycaemic levels [140, 170]. Therefore, women with a BMI of 27 kg/m² should be provided with advice and support to attain a healthy weight prior to pregnancy [170]; however, weight reduction should not be attempted during pregnancy [171]. In the UK there are no specific guidelines on weight gain during pregnancy, though NICE emphasizes that energy needs do not change in the first six months of pregnancy and increase by a modest degree (approximately 200 kcal/d) in the last three months. The Institute of Medicine has more defined guidelines for weight gain over each trimester, which range from 11 to 20 lb (5–9 kg) for mothers who have obesity at conception to 28–40 lb (13–18 kg) for underweight mothers [172]. There is little evidence to support particular dietary approaches during pregnancy. However, a low-GI diet may modestly improve glycaemia [2, 173].

Folic acid requirements increase to 5 mg/d for women with diabetes, as risk of neural tube defects is increased [168]. Folic acid should be taken up to 12 weeks' gestation to prevent neural tube defects. However, in practice, 50% of pregnancies in the UK are unplanned, in which case folic acid supplementation should be commenced immediately [168].

Diet in children with diabetes

Management of type 1 diabetes and type 2 diabetes in children does not differ substantively from that in adults [140, 174, 175]. Children and their families (or carers) should receive education that covers insulin therapy and dosage adjustment; blood glucose monitoring; detecting and managing hypoglycaemia, hyperglycaemia, and ketosis; and the effects of diet, physical activity, and intercurrent illness on blood glucose levels. Additionally, age and maturity, emotional well-being, and life goals should be considered in an individualized approach. As energy requirements change with age, growth rates have to be monitored and the evaluation of a meal plan should be rechecked at least once a year [176].

As in all healthy children, energy and nutrient intakes should be adequate to ensure optimal growth and development. Good nutrition may also contribute to maintaining normal serum lipid values and meeting blood pressure goals. Meal plans must be individualized to accommodate food preferences and the eating pattern of the family [176].

Exercise and insulin-treated diabetes

Physical activity and exercise have numerous benefits for people with diabetes, including improved glucose levels, lower blood pressure, reduced requirements for medications, and lower cardiovascular risk (Chapter 28) [1–3]. However, risk of hypoglycaemia increases with exercise intensity and duration in insulin-treated diabetes, and careful management of glucose is critical [1–3, 177]. Referral to a specialist diabetes dietitian is recommended to advise on optimal management of different modalities, duration, and intensity of exercise [3]. However, general recommendations for insulin-treated diabetes are to adjust insulin dosing for planned exercise, and to provide additional dietary carbohydrate for unplanned exercise [2, 50, 177]. In practice, for the majority of people who engage in moderate physical activity, additional carbohydrate requirements increase only modestly, and an additional 10–15 g/h should be sufficient to maintain blood glucose levels [50].

For more serious exercisers and athletes, the amount of carbohydrate required will be based on the individual, with sufficient carbohydrate prior to exercise in order to maintain glucose levels during the exercise, and replenishment of glycogen stores in the post-exercise period to enhance performance and prevent hypoglycaemia during the next exercise bout, particularly for those who exercise daily [175, 178]. The complexity, both physiological and psychological, of managing glycaemia during exercise has been acknowledged, and individuals with type 1 diabetes may benefit from specialist support [179].

Many exercisers, particularly young men engaged in weight training, have specific questions about protein intake. There is little evidence that excessive protein intake increases muscle growth or mass in most casual exercisers; but for weight lifters or endurance athletes, the American College of Sports Medicine recommends 1.4–1.7 g/kg/d [180, 181]. In general, most athletes or weight-training men will meet this protein requirement through diet alone. For individuals who do not consume sufficient protein, shakes supplemented with proteins such as whey can be consumed. However, careful monitoring of blood glucose is advised, as whey and other proteins lower glucose levels in people with and without diabetes [147, 182]. Although no studies have been carried out in people with type 1 diabetes, whey could theoretically increase the risk of post-exercise hypoglycaemia. In practice, most shakes of this type will contain additional carbohydrate, which may counteract any glucose-lowering effect.

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28

Physical Activities and Diabetes

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Key points

- In people with type 1 diabetes, exercise improves fitness and strength, reduces cardiovascular risk factors, and improves well-being.
- While regular exercise has not conclusively been found to improve glycaemia in type 1 diabetes, it is associated with decreased long-term morbidity and mortality in this population.
- Managing type 1 diabetes in the context of exercise can be complicated by both hypoglycaemia and hyperglycaemia during and after exercise.
- It is recommended that individuals with type 1 diabetes adjust their insulin dose and carbohydrate consumption prior to, during, and/or after exercise to accommodate the type, intensity, and duration of exercise performed.
- Structured, supervised diet and exercise interventions can reduce the risk of developing type 2 diabetes by ~60% in individuals with impaired glucose tolerance.
- Regular exercise improves fitness and strength, reduces cardiovascular risk factors, and improves glycated haemoglobin (HbA_{1c}), and is associated with decreased long-term morbidity and mortality in people with type 2 diabetes.
- People with type 2 diabetes should combine aerobic and resistance exercises for ≥ 150 min/wk to maximize the effect of exercise on glucose levels.
- While regular exercise has not conclusively been found to prevent gestational diabetes, there is emerging evidence that it can improve glycaemia in women with gestational diabetes.

Defining exercise, type of exercise, and intensity

Physical activity, exercise, and physical fitness are terms that describe different concepts. However, they are often confused with one another, and the terms are sometimes used interchangeably. Physical activity is defined as any bodily movements that involve muscle contraction to produce energy expenditures above the basal level. Exercise is a type of physical activity, which is planned, structured, and repetitive, with the objective of improving or maintaining physical fitness [1]. Physical fitness is generally accepted as the ability to carry out daily tasks without undue fatigue. Physical fitness comprises various elements, including health-related and skill-related components.

Physical activity is measured in metabolic equivalent (MET) units that estimate the oxygen consumption of an activity. One MET is equivalent to oxygen consumption of $3.5 \text{ ml O}_2/\text{kg/min}$ in a resting seated adult. Moderate physical activity, which includes leisure cycling, swimming, walking, and general house cleaning, is equivalent to 3–6 METs. Vigorous physical activity is activities equivalent to >6 METs, such as running, rope jumping, and sit-ups.

Physical fitness refers to the circulatory and respiratory systems' ability to supply oxygen during sustained exercise. The intensity of an exercise is typically measured as a percentage of maximal oxygen consumption ($\text{VO}_{2\text{max}}$). Moderate activity is when the body utilizes

40–60% of $\text{VO}_{2\text{max}}$, whereas high-intensity activity reaches 80–90% $\text{VO}_{2\text{max}}$. The volume of exercise is usually measured by the duration of the activity.

Exercise can be categorized into aerobic, anaerobic and resistance training. There are few data to support that one type of exercise is superior to another in terms of general health benefits [2]. However, an exercise that is enjoyable and suitable to the individual is likely to be performed regularly and maintained for a longer period.

Aerobic exercise engages large muscle groups with repetitive and continuous movements for ≥ 10 minutes to produce improved oxygen utilization with the aim of improving cardiovascular and respiratory fitness. Examples include walking, cycling, and jogging.

Anaerobic exercise comprises short, but high-intensity, bursts of physical activity that rely on rapid release of energy produced via glycolysis, rather than being dependent on oxygen consumption. This exercise builds lean muscles, improves muscle and bone strength, and enhances sports performance.

Resistance training enhances muscle strength by working muscles against a resistance load or weight. By altering the combination of weight load and frequency of repetition, this exercise improves muscle endurance and strength as well as increasing the lean muscle mass and metabolic rate.

Aerobic, anaerobic, and resistance training exercises can be used alone or in combination to achieve the desired effect of improving cardiorespiratory fitness, muscle strength, and endurance, as well

as achieving weight loss and its maintenance. The type, intensity, and volume of exercise should be tailored to individual needs to allow maximal adherence and long-term health benefits. Although the benefits greatly outweigh the risks, there are restrictions to exercise for people with certain medical conditions in terms of the type and intensity of physical activity. Gradual increases in exercise intensity and volume are generally advisable, but especially in those who are ordinarily sedentary at the start of an exercise programme.

Type 1 diabetes and exercise

Prevention of type 1 diabetes

Many people view type 1 diabetes as affecting young, otherwise healthy individuals. This together with the disease's autoimmune pathogenesis mean that regular exercise is not typically thought to prevent type 1 diabetes. Evidence is now emerging, however, that exercise may be one of the modifiable factors that interact with genetic predisposition to determine if and when type 1 diabetes develops [3].

Figure 28.1 shows the possible mechanism by which exercise could improve or maintain β -cell mass. Physical activity induces elevations in circulating levels of growth hormone (GH), insulin-like growth factor I (IGF-I), glucagon-like peptide 1 (GLP-1), interleukin 6 (IL-6), and IL-1 receptor agonist (IL-1 RA), all of which increase proliferation of β cells [4–8]. By reducing fat and visceral fat mass, exercise reduces pro-inflammatory adipokines, such as leptin and tumour necrosis factor α (TNF- α), and increases anti-inflammatory adipokines, such as adiponectin, which may help to reduce β -cell death [9]. Exercise may reduce the destructive immune response to the β cell by reducing the Toll-like receptors (TLRs) on monocytes and macrophage immune cells [10]. Finally, exercise improves insulin sensitivity, which in turn helps to normalize plasma glucose [11] and serum lipids [12], which may cause β -cell death when chronically elevated.

In animal models of diabetes, exercise protects the β cell from oxidative stress [13]. In healthy individuals [14], those at risk of type 2 diabetes [15], and people with type 2 diabetes, regular exercise improves β -cell function [16]. However, no human studies have examined whether exercise can delay or prevent individuals at risk from type 1 diabetes from developing the disease. However, the fact that exercise improves insulin resistance, which predicts progression to type 1 diabetes [17], coupled with findings from a cross-sectional study that reported that increased physical activity was associated with better glucose levels, lower insulin needs, and higher C-peptide levels at the onset of type 1 diabetes [18], suggests that more human research is needed in this area.

Treatment of type 1 diabetes

Although the evidence for benefit is less than for type 2 diabetes, there is sufficient to suggest that exercise should be encouraged in people with type 1 diabetes. Figure 28.2 summarizes the benefits that people with type 1 diabetes can expect from exercise.

Physical fitness, cardiovascular disease, and mortality

Although there are only a few small studies of fitness in people with type 1 diabetes, young adults (12–44 years old) with type 1 diabetes are less fit than matched individuals without diabetes, despite similar levels of physical activity [20–24]. Abnormalities in cardiac muscle and autonomic nerve function [25], reduction in skeletal muscle size and power [26], as well as an altered cardiac metabolism that favours non-esterified fatty acids (NEFA) over glucose as a fuel source [27], may contribute to this. Supervised physical activity programmes, however, improve fitness in people with type 1 diabetes [28–30], with increases in $VO_{2\max}$ of up to 27% [22, 30–34].

No large randomized controlled trials (RCTs) have examined whether regular physical activity reduces cardiovascular disease or mortality in type 1 diabetes. A large retrospective study, the Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality study, suggests that regular physical activity may be of benefit. This study demonstrated that in men with

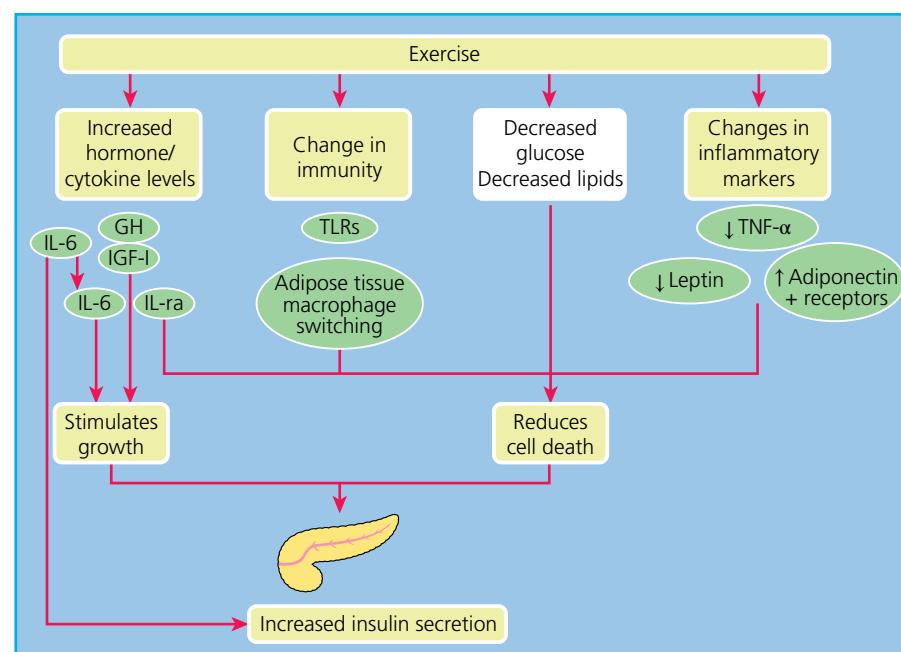


Figure 28.1 Potential mechanisms through which exercise could improve β -cell mass and/or function. GH, growth hormone; GLP-1, glucagon-like peptide 1; IGF-I, insulin-like growth factor I; IL-1 RA, interleukin 1 receptor agonist; IL-6, interleukin 6; TLR, Toll-like receptors; TNF- α , tumour necrosis factor α . Source: Reproduced with permission from Narendran et al. 2015 [3].

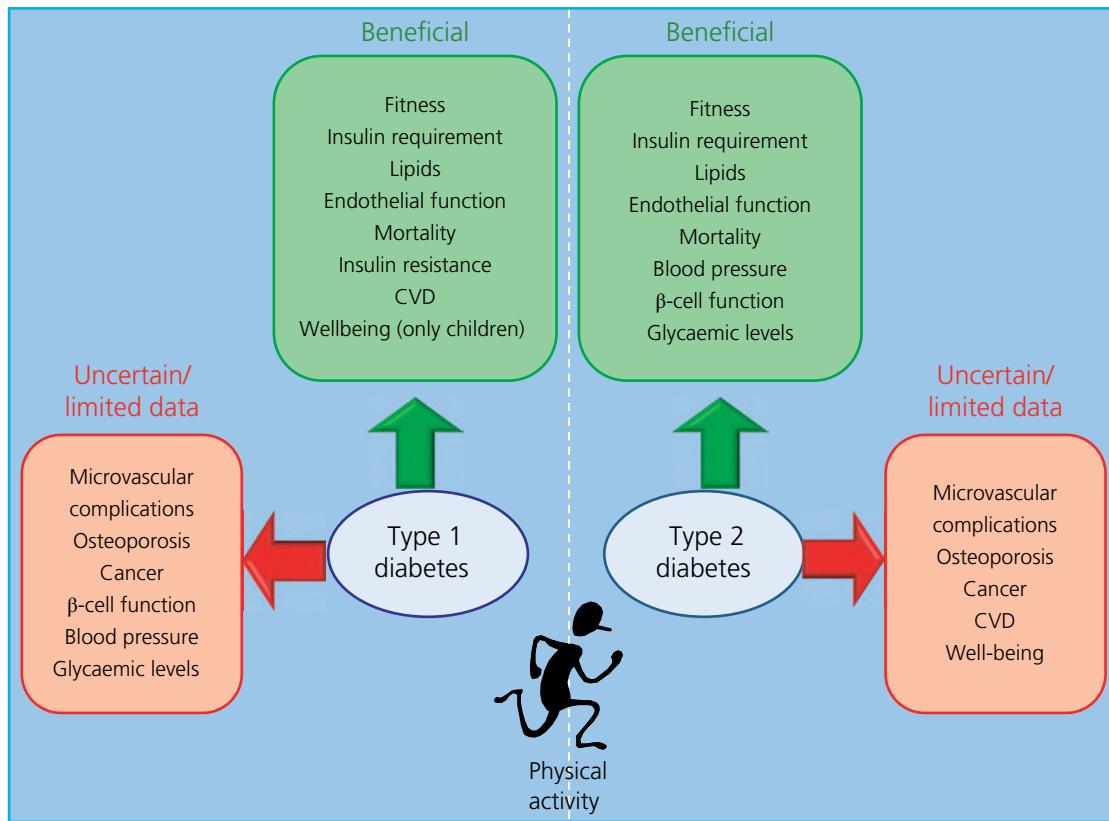


Figure 28.2 Health benefits of physical activity in type 1 diabetes and type 2 diabetes. CVD, cardiovascular disease. Source: Chimen et al. 2011 [19]. Reproduced with permission from Springer.

type 1 diabetes of 25 years' duration, those who had participated in team sports during high school were three times less likely to report macrovascular disease and had mortality rates three times lower than those who did not participate [35]. This pattern was not seen in women, but their participation in team sports was lower (24% reported participation versus 39% in men). The level of physical activity in adulthood (measured using a validated questionnaire) also predicted mortality at six years [20]. Sedentary men were three times more likely to die than active men, and a similar (but again non-significant) effect was seen in women. In the Finnish Diabetic Nephropathy (FinnDiane) study, a prospective and observational study of 2369 individuals with type 1 diabetes who were followed up for a mean of 11.4 ± 3.5 years, exercise was associated with a lower risk of premature all-cause and cardiovascular mortality in both men and women with type 1 diabetes. This study also demonstrated that physical activity is associated with a lower risk of mortality in those with type 1 diabetes and chronic kidney disease [36].

Glycaemic levels and insulin requirements

The effect of physical activity on glycaemia in people with type 1 diabetes is unclear, with some studies showing benefit but the majority showing no benefit. Table 28.1 lists the intervention studies where the controls have type 1 diabetes and Table 28.2 lists other studies.

The intervention studies have tended to use supervised exercise programmes of short duration (1–3 months), have involved small numbers of participants (all but one had fewer than 60), and predominantly involved adolescents or young adults. There have been several meta-analyses of the effect of exercise on glycated haemo-

globin (HbA_{1c}) in type 1 diabetes. Kennedy et al. only included studies in which there was a non-intervention group of participants with type 1 diabetes [80]. They found no glycaemic benefit of exercise in people with type 1 diabetes. However, subanalyses suggested that exercise may confer glycaemic benefit in the young, and when undertaken for longer periods. They also stated that exercise can be carried out by people with type 1 diabetes without significant risk of hypoglycaemia. This is important because some studies have reported that hypoglycaemia is a barrier to exercise in those with type 1 diabetes [81,82].

Tonoli et al. [83] used less stringent criteria, including trials with no control groups, but excluded some of the studies used in the Kennedy analysis. Exercise overall resulted in a small but statistically significant reduction in HbA_{1c} (0.3%; 3 mmol/mol). When exercise was analysed by type, aerobic exercise reduced HbA_{1c} by 0.2% (2 mmol/mol), strength training did not lower HbA_{1c} , and combined aerobic exercise and strength training showed a statistically significant reduction in HbA_{1c} of –1.6% (17 mmol/mol).

In the meta-analysis by Wu et al. [84], studies were included if they were RCTs, quasi-experimental trials, and crossover trials and the exercise intervention comprised supervised or unsupervised aerobic, resistance, or combined physical activity for ≥ 4 weeks. The study identified 21 studies that met these criteria and had HbA_{1c} before and after the intervention, with 7 having adult participants and 17 children and adolescents. Overall HbA_{1c} fell by 0.45% (5 mmol/mol) in the exercise group compared to control. When broken down by age, children and adolescents saw a fall of 0.6% (6 mmol/mol), but no effect was seen in adults. Subgroup analysis showed that combined exercise was the only form of exercise that

Table 28.1 Intervention studies evaluating the effect of physical activity on glycated haemoglobin (HbA_{1c}) in people with type 1 diabetes.

Study	n (Control/type 1 diabetes)	Mean age \pm SD/age range (years)	RCT (yes/no)	Duration	Type of physical activity	Type 1 diabetes control group		Type 1 diabetes intervention group	
						HbA_{1c} before (%) (mmol/mol)	HbA_{1c} after (%) (mmol/mol)	HbA_{1c} before (%) (mmol/mol)	HbA_{1c} after (%) (mmol/mol)
No HbA_{1c} effect									
Yki-Jarvinen et al. [30]	6/7	NA	No	6 wk	Supervised aerobic physical activity	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)
Landt et al. [32]	6/9	14–16	No	12 wk	Supervised aerobic physical activity	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)
Wallberg-Henriksson et al. [34]	7/6	25–45	No	5 mo	Non-supervised aerobic physical activity	10.6 ± 0.6 (92 ± 7)	10.4 ± 0.6 (90 ± 7)	10.4 ± 0.6 (90 ± 7)	10.5 ± 0.6 (91 ± 7)
Huttunen et al. [37]	16/16	8.2–16.9	No	3 mo	Supervised aerobic physical activity	9.4 ± 2.1 (79 ± 23)	9.7 ± 2.2 (83 ± 24)	9.8 ± 2.3 (84 ± 25)	10.5 ± 2.5 (91 ± 28)
Laaksonen et al. [28]	28/28	32.5 ± 5.7	Yes	12–16 wk	Supervised aerobic physical activity	8.2 ± 1.1 (66 ± 12)	8.2 ± 1.0 (66 ± 11)	8.3 ± 1.3 (67 ± 14)	8.5 ± 1.6 (69 ± 18)
Fuchsberger-Mayrl et al. [31]	8/18	42 ± 10	No	4 mo	Supervised aerobic physical activity	7.4 ± 0.4 (57 ± 6)	7.2 ± 0.2 (55 ± 2)	7.3 ± 0.2 (56 ± 2)	7.5 ± 0.3 (58 ± 4)
Newton et al. [38]	40/38	14 ± 2	Yes	12 wk	Non-supervised aerobic physical activity	8.5 ± 2.8 (69 ± 31)	8.5 ± 2.8 (69 ± 31)	8.0 ± 1.8 (64 ± 20)	8.3 ± 1.8 (67 ± 20)
D'Hooge et al. [39]	8/8	10–17	Yes	20 wk	Supervised aerobic and resistance training	8.8 ± 2.0 (73 ± 22)	8.6 ± 2.2 (71 ± 24)	7.9 ± 2.5 (63 ± 27)	7.8 ± 2.4 (62 ± 26)
Wong et al. [40]	11/12	12 ± 3	Yes	3 mo	Home-based aerobic exercise	8.3 ± 1.4 (67 ± 16)	8.3 ± 1.3 (67 ± 14)	8.1 ± 1.0 (65 ± 11)	8.2 ± 1.0 (66 ± 9)
Tunar et al. [41]	14/17	14 ± 2	Yes	3 mo	Supervised Pilates class	8.9 ± 1.6 (74 ± 17)	8.8 ± 1.5 (73 ± 16)	9.2 ± 2.1 (77 ± 23)	8.7 ± 1.8 (72 ± 19)
Brazeau et al. [42]	23/25	45 ± 14	Yes	12 mo	Non-supervised aerobic physical activity	7.9 ± 1.0 (63 ± 10)	7.9 ± 1.1 (63 ± 12)	8.1 ± 1.3 (65 ± 14)	8.2 ± 1.2 (66 ± 13)
Narendran et al. [43]	28/30	32 ± 11	Yes	12 mo	Non-supervised aerobic physical activity	9.0 ± 4.4 (75 ± 50)	7.3 ± 2.4 (56 ± 27)	9.0 ± 4.4 (75 ± 50)	7.4 ± 2.4 (56 ± 28)
Gusso et al. [44]	15/38	16 ± 1	Yes	20 wk	Supervised aerobic physical activity	8.6 ± 1.5 (70 ± 16)	8.7 ± 1.2 (71 ± 13)	8.8 ± 2.2 (73 ± 16)	8.5 ± 1.1 (69 ± 13)
Mohammed et al. [45]	10/10	9–13	Yes	12 wk	1.5 hr of football twice per week	10.5 ± 2.4 (91 ± 27)	11.0 ± 2.1 (97 ± 23)	11.5 ± 2.7 (102 ± 30)	11.2 ± 2.3 (99 ± 25)
HbA_{1c} improvement									
Dahl-Jorgensen et al. [46]	8/14	5–11	No	5 mo	Supervised aerobic physical activity	13.4 ± 1.9 (123 ± 21)	12.9 ± 1.6 (117 ± 18)	15.1 ± 2.2 (142 ± 49)	13.8 ± 1.9 (127 ± 21)
Campaigne et al. [47]	9/10	9 ± 0.47	Yes	12 wk	Supervised vigorous physical activity	13.9 ± 0.61 (128 ± 8)	13.3 ± 0.54 (122 ± 6)	12.5 ± 0.65 (113 ± 7)	11.3 ± 0.5 (100 ± 5)
Stratton et al. [48]	8/8	15 ± 1	Yes	8 wk	Supervised aerobic physical activity	11.7 ± 2.9 (104 ± 32)	11.4 ± 2.9 (101 ± 32)	10.1 ± 2.2 (87 ± 23)	9.9 ± 2.2 (85 ± 23)

(continued)

Table 28.1 (Continued)

Study	n (Control/type 1 diabetes)	Mean age \pm SD/age range (years)	RCT (yes/no)	Duration	Type of physical activity	Type 1 diabetes control group		Type 1 diabetes intervention group	
						HbA _{1c} before (%) (mmol/mol)	HbA _{1c} after (%) (mmol/mol)	HbA _{1c} before (%) (mmol/mol)	HbA _{1c} after (%) (mmol/mol)
Durak et al. [49]	8/8 (crossover)	31 \pm 3.5	Yes	10 wk	Supervised heavy resistance training	6.9 \pm 1.4 (52 \pm 15)	6.9 \pm 1.4 (52 \pm 15)	6.9 \pm 1.4 (52 \pm 15)	5.8 \pm 0.9 (40 \pm 10)
Perry et al. [50]	30/31	20–69	Yes	6 mo	Non-supervised aerobic physical activity	8.7 \pm 2.0 (72 \pm 21)	8.8 \pm 2.3 (73 \pm 25)	8.9 \pm 2.6 (74 \pm 28)	8.6 \pm 2.1 (70 \pm 23)
Salem et al. [51]	48/Moderate 75/ Intensive 73	14.5 \pm 2.4	Yes	6 mo	Supervised aerobic and resistance physical activity	8.3 \pm 2.1 (67 \pm 23)	8.9 \pm 1.4 (74 \pm 15)	Moderate: 8.9 \pm 1.4 (74 \pm 15) Intensive: 8.9 \pm 1.6 (74 \pm 17)	Moderate: 8.1 \pm 1.1 (65 \pm 12) Intensive: 7.8 \pm 1.0 (62 \pm 11)
Aouadi et al. [52]	11/11 two times per week/11 three times per week	12–14	No	6 mo	Supervised aerobic physical activity	9.5 \pm 2.5 (80 \pm 38)	9.7 \pm 1.1 (83 \pm 12)	Two times per week: 8.6 \pm 2.2 (71 \pm 24) Four times per week: 8.2 \pm 1.5 (66 \pm 17)	Two times per week: 8.2 \pm 1.3 (66 \pm 14) Four times per week: 6.8 \pm 1.1 (51 \pm 12)
Lee et al. [53]	15/15	44 \pm 10	Yes	12 wk	High-intensity interval training	8.4 \pm 0.7 (68 \pm 8)	8.2 \pm 1.0 (67 \pm 10)	8.6 \pm 0.7 (71 \pm 7)	8.1 \pm 1.0 (65 \pm 11)
Petschnig et al. [54]	14/15	9–13	Yes	32 wk	Supervised strength training	7.8 \pm 1.4 (62 \pm 14)	8.7 \pm 1.3 (72 \pm 14)	8.8 \pm 1.4 (72 \pm 14)	8.0 \pm 1.3 (64 \pm 14)

All studies quoted have included people with type 1 diabetes in both the intervention and control groups. The studies are listed in chronological order according to whether or not physical activity improved HbA_{1c}. RCT, randomized controlled trial; SD, standard deviation.

Source: Adapted with permission from Chimen et al. 2011 [19].

Table 28.2 Interventional and observational studies evaluating the effect of physical activity on glycated haemoglobin (HbA_{1c}) in people with type 1 diabetes.

Study	n (Type 1 diabetes)	Mean age (years)	Design	Duration	Type of exercise	$\text{VO}_{2\text{max}}$	HbA_{1c} before (%), mmol/mol	HbA_{1c} after (%), mmol/mol
No HbA_{1c} effect								
Wallberg-Henriksson et al. [27]	9	NA	Case series	16 wk, 1 h, 2–3 times/wk	Aerobic exercise: jogging, running, ball games, and gymnastics	↗ 8%	10.4 ± 0.7 88 ± 8	11.3 ± 0.5 97 ± 5
Wallberg-Henriksson et al. [55]	10	NA	Control trial	8 wk, 45 min, 3 times/wk	Aerobic exercise: running	↗ 13%	NA	NA
Zinman et al. [56]	13	30 ± 1.8	Control trial	12 wk, 45 min, 3 times/wk	Aerobic exercise: cycling	↗ 8%	10.7 ± 0.3 91 ± 3	10.3 ± 0.8 87 ± 9
Baevre et al. [57]	6	14 to 17	Case series	6 mo	Aerobic exercise	NA		
Selam et al. [58]	50	NA	Cross-sectional study	Weekly energy expenditure	Total physical activity index (questionnaire)	NA	NA	NA
Lehmann et al. [59]	20	NA	Case series	3 mo, ≥135 min/wk	Endurance training	↗	7.6 60	NA
Ligtenberg et al. [60]	221	31.7	Cross-sectional study	Measurement of physical activity for past year	Total physical activity index (questionnaire)	NA	No correlation between total physical activity and HbA_{1c}	NA
Rigla et al. [61]	14	25.5 ± 6	Case series	3 mo, 1 h min, 3 times/wk	Aerobic activity at 60–75% $\text{VO}_{2\text{max}}$: treadmill, bicycle	↗ 5%	6.5 ± 0.8 48 ± 9	6.7 ± 1 50 ± 11
Rigla et al. [61]	14	25.5 ± 6	Control trial	3 mo, 1 h, 3 times/wk	Aerobic exercise: running, cycling	↗	6.5 ± 0.8 48 ± 9	6.7 ± 1 50 ± 11
Roberts et al. [62]	24	Adolescent	Case series	24 wk	Supervised training	↗ 17% in aerobic capacity	NA	NA
Sarnblad et al. [63]	26	15.7 ± 2.1	Cohort study	7 days	Measurement of physical activity	NA	No association between time spent exercising and HbA_{1c} : 7.6 ± 1.4 60 ± 15	NA
Mittermayer et al. [64]	11	44 ± 3	Control trial	4 mo, 50 min, 2–3 times/wk	Supervised aerobic exercise: cycling	NA	7.2 ± 0.2 55 ± 2	7.6 ± 0.3 59 ± 3
Haider et al. [65]	18	42 ± 10	Control trial	4 mo, 1 h, 2–3 times/wk	Supervised aerobic exercise	NA	7.3 ± 0.9 56 ± 10	7.5 ± 1 58 ± 11
Ramalho et al. [66]	13	13–30	Case series	12 wk, 40 min, 3 times/wk	Aerobic vs resistance	NA	Aerobic: 8.7 ± 1.6 71 ± 17 Resistance: 8.2 ± 2.9 66 ± 31	Aerobic: 9.8 ± 1.8 84 ± 19 Resistance: 7.6 ± 1.6 59 ± 17
Harmer et al. [67]	8	25 ± 4	Control trial	7 wk, 3 times/wk	Supervised aerobic exercise: intense cycling	NA	8.6 ± 0.8 70 ± 9	8.1 ± 0.6 65 ± 7
Aman et al. [68]	NA	11–18	Cross-sectional study	NA	Measurement of leisure time activity	NA	No association of physical activity	NA
Edmunds et al. [69]	46	12.8 ± 2.1	Cross-sectional study	Measurement of physical activity for 2 weeks	Moderate and vigorous activity (questionnaire)	NA	No association between time spent exercising and HbA_{1c}	NA
Minnebeck et al. [70]	11	41 ± 14	Cohort study	4 wk	High-intensity interval training	NA	7.5 ± 0.5 58 ± 5 7.3 ± 0.9	7.3 ± 0.4 56 ± 4 7.3 ± 0.9
	11	42 ± 15		11 BMI 29 ± 2 kg/m ² 11 BMI 23 ± 1 kg/m ²			56 ± 10	56 ± 10

(continued)

Table 28.2 (Continued)

Study	n (Type 1 diabetes)	Mean age (years)	Design	Duration	Type of exercise	VO _{2max}	HbA _{1c} before (%, mmol/mol)	HbA _{1c} after (%, mmol/mol)
HbA_{1c} deterioration								
Woo et al. [71]	10	11.21 ± 0.97	Control trial	12 wk, 3 times/wk	Aerobic exercise: treadmill	→	8.09 ± 0.5 65 ± 5	8.33 ± 0.8 65 ± 8
HbA_{1c} improvement								
Marrero et al. [72]	10	12–14	Case series	12 wk, 45 min, 3 times/wk	Aerobic fitness programme	↗	11.41 ± 4.47 101 ± 45	10.01 ± 3.21 86 ± 33
Bak et al. [73]	7	27.9 ± 7.1	Control trial	6 wk	Physical training	↗	7.9 ± 1.4 63 ± 15	7.7 ± 1.5 61 ± 16
Mosher et al. [22]	10	17.2 ± 2.9	Control trial	12 wk, 45 min, 3 times/wk	Aerobic exercise: circuit training	↗ 4%	7.72 ± 1.26 61 ± 14	6.76 ± 1.07 50 ± 11
Zoppini et al. [74]	53	NA	Cross-sectional study	Measurement of physical activity	30 regular exercise, 23 sedentary exercise	NA	7 ± 1 in regular exerciser group 53 ± 11	7.8 ± 1.2 in sedentary group 62 ± 13
Salvatoni et al. [75]	69	8.98 ± 3.9	Cross-sectional study	Measurement of physical activity for 1 wk	3 ± 2.9 h/wk	NA	6.3 ± 0.3 in group ≥7 h exercise/wk 45 ± 3	7.7 in group 2–4 h exercise/wk 61
Sideraviciute et al. [76]	19	14–19	Control trial	14 wk, 45 min, 2 times/wk	Aerobic exercise: swimming	↗	8.5 ± 0.4 69 ± 4	7.8 ± 0.3 62 ± 3
Herbst et al. [77]	19143	12.9–14	Cross-sectional study	0, or 1–2, or ≥3 times/wk	Measurement of regular physical activity	NA	8.4 ± 1.9 in 0 time/wk group 68 ± 20	8.0 ± 1.6 in 1–2 and ≥3 times/wk group 64 ± 17
Herbst et al. [78]	23251	12.7 ± 4.3 to 13.9 ± 3.1	Cross-sectional study	0, or 1–2, or ≥3 times/wk	Measurement of regular physical activity	NA	8.1 ± 1.9 in 0 time/wk group 65 ± 20	7.8 ± 1.6 in 1–2 and ≥3 times/wk group 62 ± 17
Ruzic et al. [79]	20	12.81 ± 2.14	Case series	2 wk intense exercise programme, 5 days of at least 1 h of exercise	Aerobic exercise: swimming, cycling, running	NA	8.28 ± 1.3 67 ± 14	7.92 ± 1.42 (but increase 2 mo after camp) 64 ± 15

All studies quoted have included people with type 1 diabetes in the intervention group, but the control group has either not been present or has included people without diabetes. The studies are listed in chronological order according to physical activity effect on HbA_{1c}.

BMI, body mass index; NA, not available.

Source: Adapted with permission from Chimen et al. 2011 [19].

significantly lowered HbA_{1c} (-0.71% ; 8 mmol/mol). It also suggested that people needed to exercise more than three times a week and for longer than 12 weeks to see an effect on HbA_{1c}.

Studies in people with type 1 diabetes that have examined the effect of exercise on plasma glucose have not shown a consistent benefit on fasting glucose [28, 33, 69, 70]. However, these studies have shown, as seen with healthy individuals [50], that blood glucose decreases (without hypoglycaemia) around the time of exercise [37, 71]. The lack of glycaemic benefit as assessed by HbA_{1c} may result from rebound hyperglycaemia immediately following exercise, and better management of this may be beneficial.

Two main factors may account for the poor effect of exercise on HbA_{1c}. Many individuals with type 1 diabetes consume energy when physical active, either as a fuel source or to manage hypoglycaemia, and this may counteract any glucose-lowering effect of physical activity [50]. Similarly, people with type 1 diabetes who exercise regularly reduce their daily insulin dosages by 6–15% [28, 29, 48]. While this may be required to manage hypoglycaemia, these reductions may mask improvements in HbA_{1c}.

Vascular risk factors other than glucose

People with type 1 diabetes commonly have hypertension and dyslipidaemia that are associated with increased risk of vascular disease [85]. Most studies suggest that physical activity in people with type 1 diabetes improves lipid profile [22, 28, 30, 31, 33, 59]. These studies were of short duration (generally ≤ 4 months) and showed similar benefits to those seen in individuals without diabetes. High-density lipoprotein (HDL) cholesterol increased by 8–30%, while low-density lipoprotein (LDL) cholesterol and triglycerides decreased by 8–14% and 13–15%, respectively. Exercise also reduces apolipoprotein B, which is pro-atherogenic and is associated with premature mortality in type 1 diabetes [86], and increases the anti-atherogenic apolipoprotein A-I [28]. These benefits are independent of changes in glycaemia and weight and most pronounced in those with an adverse lipid profile.

Only four studies have examined the effect of physical activity on blood pressure in type 1 diabetes. All four studied young adults and used similar supervised exercise programmes. Two showed no benefits in systolic or diastolic blood pressure [31, 33] and two showed a 2–3% reduction in blood pressure [51, 59]. Three studies were small: 26, 14, and 20 participants, respectively [31, 33, 59]. The remaining study was larger and included 196 participants and was one of the studies to show a benefit [51].

People with type 1 diabetes have clear evidence of endothelial dysfunction and this is worse if microalbuminuria is present [21]. Regular exercise can reverse endothelial dysfunction [87] and improve vascular function, but this improvement is not as great as that seen in individuals without diabetes [31, 88]. Improved vascular function is also seen in vascular beds not supplying exercising muscles, suggesting that this is a global rather than local benefit of exercise. Benefits only persist while people are exercising regularly and cease soon after regular activity is stopped.

Although less insulin resistant than those with type 2 diabetes, people with type 1 diabetes are more insulin resistant than matched individuals without diabetes [21, 30]. This insulin resistance can be improved by up to 23% by both resistance and endurance exercises [29–31, 66].

The beneficial effects of physical activity on insulin resistance, as well as on lipid levels and endothelial function, suggest that physical activity should reduce vascular complications in type 1 diabetes.

Microvascular complications

Increased physical activity is associated with fewer diabetes-related complications in individuals with type 1 diabetes [89]. In the Pittsburgh IDDM Morbidity and Mortality study [90], in men but not women activity levels were inversely associated with the risk of nephropathy and neuropathy, but not retinopathy. However, a retrospective analysis of baseline physical activity in the Diabetes Control and Complication (DCCT) trial found that rates of development or progression of diabetic retinopathy, nephropathy, and neuropathy were unaltered by physical activity after a mean follow-up of 6.5 years [91].

Other studies have shown an inverse association between physical activity and the severity of several complications in type 1 diabetes [89, 92]. A follow-up study involving 1945 individuals with type 1 diabetes reported that those involved in either little leisure-time physical activity or low-intensity activity were more likely to have impaired renal function and more proteinuria as well as greater rates of retinopathy and cardiovascular disease when compared to their more frequently and more vigorously active counterparts [89]. Balducci et al. randomized 78 people (21 with type 1 diabetes and 57 with type 2 diabetes) without signs and symptoms of peripheral diabetic neuropathy to either supervised exercise or a control group [92]. The percentage of people with diabetes who developed motor and sensory neuropathy during the four-year study was significantly higher in the control than the exercise group, 17.0% vs 0.0% and 29.8% vs 6.4%, respectively. Thus, long-term aerobic exercise training seems to prevent the onset or modify the natural history of diabetes neuropathy [92].

More recently, a cross-sectional multicentre study of 18028 people with type 1 diabetes reported that frequencies of retinopathy and microalbuminuria were lower in active compared with inactive people [93]. However, due to the cross-sectional design, no causality can be inferred. It remains unclear whether the presence of comorbidities affected people's ability to exercise or whether being physically active decreased the risk of developing these complications.

β -cell function

Type 1 diabetes is a chronic inflammatory autoimmune disease characterized by destruction of insulin-producing β cells and subsequent insulin deficiency [94]. This loss of β cells is gradual and at the time of diagnosis of type 1 diabetes significant β -cell function remains [95]. While it is generally assumed that the remaining β cells are completely destroyed soon after diagnosis, studies now indicate that these cells can persist for many years [96].

The preservation of these remaining β cells has important clinical benefits. A meal-stimulated C-peptide value of $>200 \text{ pmol/l}$ is associated with improved glucose levels for the first four years after diagnosis, a reduced risk of developing retinopathy and nephropathy, and a $>50\%$ reduction in hypoglycaemia rates [97]. Thus, interventions that have the potential to preserve β -cell function are worth striving for.

In diabetes animal models [13], healthy individuals [14], and people with type 2 diabetes, physical activity preserves β -cell function [15]. In a two-year prospective study of 125 children diagnosed with type 1 diabetes, those who were physically active had higher rates of partial remission compared to the inactive group [98]. Similarly, in a case-controlled study of adults recently diagnosed with type 1 diabetes, the honeymoon period was more than five times longer in men undertaking high levels of physical exercise, compared with age-, sex-, and body mass index (BMI)-matched sedentary controls [99]. In a pilot RCT of adults with newly diagnosed type 1 diabetes, β -cell

function, corrected for improved insulin sensitivity, was preserved by exercise [43]. A large RCT is needed to confirm these findings.

Bone density

People with type 1 diabetes have reduced bone mineral density and osteoporosis and increased risk of fracture [100]. A systematic review identified two RCTs and twelve observational (ten cross-sectional and two longitudinal) studies that had reported associations between physical activity and skeletal outcomes [101]. The two RCTs reported a beneficial effect of physical activity interventions on bone accrual in children. Results of the observational studies were mixed, with four finding a positive association with a measure of activity and a skeletal outcome and eight finding no effect. No studies have examined whether physical activity reduces fracture risk in people with type 1 diabetes.

Cancer

Whether people with type 1 diabetes are at increased risk of cancer is unknown [102]. Physical activity appears to protect the general population from cancer and improve outcomes in those who develop cancer (surgical outcome, side effects of chemotherapy, subsequent prevention of recurrence). Again, this has not been examined in type 1 diabetes.

Well-being

People with type 1 diabetes are two to three times more likely to have depression than the general population [85]. In young adults, physical activity is associated with significantly greater satisfaction with life and well-being [74], but these associations were not found in the one study that examined this in children [81].

Type 2 diabetes and exercise

Prevention of type 2 diabetes

Prospective observational studies

The earliest evidence that indicated that exercise might play a role in prevention of diabetes came from large prospective cohort studies. In these studies, higher levels of physical activity and/or cardiorespiratory fitness were consistently associated with reduced risk of developing type 2 diabetes [103–115]. After adjustment for confounding variables, the most active participants had a 25–60% lower risk of subsequent diabetes compared to those who were most sedentary. This reduction was seen regardless of the presence or absence of additional diabetes risk factors such as hypertension, parental history of diabetes, and obesity. In addition, similar magnitudes of risk reduction were seen with walking compared to more vigorous activity, when total energy expenditures were similar [111].

Non-randomized studies

The first large study to assess the effectiveness of lifestyle modification in preventing and treating diabetes was the Malmö study [116]. In this non-randomized study, 41 participants with type 2 diabetes and 181 with impaired glucose tolerance accepted enrolment into a 6–12-month intervention in which they were given advice to reduce energy intake and increase physical activity. The control group comprised 114 healthy individuals and 79 with impaired glucose tolerance who declined the intervention. At six-year follow-up, 10.6% of those with impaired glucose tolerance in the intervention

group had progressed to type 2 diabetes, compared with 28.6% in the control group, a risk reduction of 63% [16]. Over 12 years, mortality among the controls was 14.0 per 1000 person-years, but only 6.5 per 1000 person-years in the intervention group [117]. This seminal study led on to several RCTs that have assessed the effect of lifestyle programmes in preventing type 2 diabetes.

Randomized studies

Table 28.3 summarizes the RCTs that have assessed whether lifestyle can prevent type 2 diabetes.

The China Da Qing Diabetes Prevention Outcome Study included 577 participants with impaired glucose tolerance who were randomized by centre into four arms – diet only, exercise only, diet and exercise, or control – and followed for six years [118]. The cumulative incidence of type 2 diabetes was 68% in controls, but only 44%, 41%, and 46% in the diet, exercise, and diet and exercise groups, respectively. The long-term follow-up is even more encouraging and indicates that the benefits from these lifestyle interventions continue for many years after completing *active treatment*; the so-called *legacy effect*. After 20 years' follow-up, 14 years after leaving the study, those in the interventional groups had 43% lower incidence and spent on average 3.6 fewer years with diabetes compared to the control group [119].

In the Finnish Diabetes Prevention Study, 522 people with impaired glucose tolerance were randomized to an exercise and diet intervention or control [120]. The intervention was intense and included individualized exercise plans, thrice-weekly supervised facility-based aerobic and resistance exercise, and seven one-hour meetings with a dietitian focusing on weight reduction, reduced fat intake, and reduced total caloric intake. Participants in the control group had one meeting per year. At four years, 22% of the control group and only 10% of the intervention group had developed diabetes, a 58% risk reduction. Again, a legacy effect was seen, with participants in the intervention arm having a 43% lower risk of developing diabetes three years after leaving the study [121].

In the American Diabetes Prevention Program [122], 3234 men and women with impaired glucose tolerance were randomly assigned to placebo, metformin, or a lifestyle-modification programme. Again, the lifestyle intervention was intense, with the participants provided with 16 lessons in the first 24 weeks. These lessons were delivered individually and covered diet, exercise, and behaviour modification. A minimum of two supervised exercise sessions per week and at least monthly contact with the study personnel were maintained thereafter. Cumulative incidences of type 2 diabetes were 11.0/100 person-years in the placebo group, 7.8 per 100 person-years in the metformin group, and only 4.8 per 100 person-years in the intensive lifestyle group. The risk of type 2 diabetes was 58% lower in the lifestyle group than in the placebo group, and 39% lower than in the metformin group [123].

The India Diabetes study randomized 421 men and 110 women with impaired glucose tolerance (mean age 45.9 ± 5.7 years, BMI $25.8 \pm 3.5 \text{ kg/m}^2$) into four groups [125]. Group 1 was the control, Group 2 was given advice on lifestyle modification, Group 3 was treated with metformin, and Group 4 was given lifestyle modification plus metformin. The lifestyle advice was less intense than that given in the American and Finnish prevention studies. Participants in the lifestyle-modification group were asked to increase their activity to 30 minutes per day; if they were already achieving this goal, they were asked to maintain this level of activity. Exercise was not supervised. Diet modification was advised for each participant

Table 28.3 Controlled studies that have examined the prevention of type 2 diabetes.

Name	Number of participants	Design of study	Study participants	Detail of intervention	Duration	Outcome
Malmo Study [116, 117]	222	Non-RCT	C: 114 healthy and 79 individuals with IGT; LSM: 41 individuals with type 2 diabetes and 181 individuals with IGT	Individuals were given advice to reduce energy intake and increase physical activity. Intervention lasted for 0.5–1 yr	6 yr	Progression to type 2 diabetes: 10.6% vs 28.6% for LSM vs C group. A 63% risk reduction for the development of type 2 diabetes. Over 12 years, mortality was 14 vs. 6.5 per 1000 person-years in the C and LSM groups, respectively
China Da Qing Diabetes Prevention Outcome Study [118, 119]	577	RCT	Individuals with IGT randomized into four arms, D, E, D + E, or C	D: received prescribed diet, advice on healthy eating and caloric reduction; E: taught exercise with increased exercise intensity; D + E: include both diet and exercise instructions as D and E groups. All intervention groups received regular counselling sessions	6 yr, and follow-up at 20 yr	Cumulative incidence of type 2 diabetes was 44%, 41%, 46%, 68% in D, E, D + E, C groups, respectively. Legacy effect: D, E, and D + E groups had 43% lower incidence and spent average 3.6 fewer yr with type 2 diabetes compared to C group
Finish Diabetes Prevention Study [120, 121]	522	RCT	Individuals with IGT randomized into two arms: LSM and C	LSM: individualized exercise plans, thrice-weekly supervised facility-based aerobic and resistance exercise, and seven 1 h meetings with a dietitian focusing on weight reduction, reduced fat intake, and reduced total caloric intake	4 yr and follow-up at 7 yr	Development of type 2 diabetes 10% in LSM compared to C group. Risk reduction 58%. Legacy effect: 43% lower risk in intervention arm
American Diabetes Prevention Program [122, 123]	3234	RCT	Individuals with IGT randomized into three arms: placebo, MET, or an LSM programme	LSM included intense 16 lessons in first 24 wk, delivered 1 to 1 and covering diet, exercise, and behaviour modification. A minimum of two supervised exercise sessions per week and at least monthly contact with the study personnel were maintained thereafter	Average 2.8 yr	Cumulative incidences of type 2 diabetes were 11, 7.8, and 4.8 per 100 person-years in the placebo, metformin, and lifestyle groups respectively
Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males [124]	458	RCT	Men with IGT randomized into two arms in ratio 4:1: control (356) and LSM (102)	Control: if $BMI \geq 24 \text{ kg/m}^2$ advised to have 5–10% smaller meals, increase physical activity, and lose weight. If $BMI < 24 \text{ kg/m}^2$ told to avoid gaining weight. Seen every 6 months. LSM: $BMI \geq 22 \text{ kg/m}^2$ advised how to lose weight and increase weight. If $BMI < 22 \text{ kg/m}^2$ advice how to maintain weight by diet and exercise. Seen every 4 mo	4 yr	Cumulative 4 yr incidence of diabetes 9.3% in control group, versus 3.0% in LSM group, and reduction in risk of diabetes 67.4% ($p < 0.001$)

(continued)

Table 28.3 (Continued)

Name	Number of participants	Design of study	Study participants	Detail of intervention	Duration	Outcome
Indian Diabetes study [125]	531	RCT	Individuals with IGT randomized into four arms: C, LSM, MET, and LSM plus MET	LSM: asked to increase or maintain their activity to 30 min per day. Non-supervised exercise. Diet modification included reduction in total calories, refined carbohydrates, and fats, avoidance of sugar, and inclusion of fibre-rich foods. Individuals with LSM were contacted monthly by telephone and seen 6-monthly during the study	2.5yr	3 yr cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in control, LSM, MET, and LSM + MET, respectively. Relative risk reduction 28.5% with LSM, 26.4% with MET, and 28.2% with LSM + MET compared with control group
European Diabetes Prevention RCT [126]	102	RCT	Individuals with IGT over age of 40 and BMI 25 kg/m ² randomized into two arms, LSM and C	C: standard diet and exercise advice. LSM: individual motivational interviewing aimed at weight reduction, increase in physical activity, fibre and carbohydrate intake, and reduction of fat intake	Mean follow-up of 3.1 yr	Absolute incidence of type 2 diabetes 32.7 per 1000 person-years LSE and 67.1 C. Incidence of diabetes reduced by 55% in LSM compared with C
Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes [127]	137	RCT	Individuals with IGT randomized into four arms: C, AT, RT, or AT + RT	Control: continue activity as normal. AT: 60 min 3 times/wk. RT: 60 min all major muscles 3 times/wk. Combined: 30 min AT + 30 min RT 3 times/wk	2yr	Incidence of diabetes adjusted by sex and age significantly decreased by 74% (combined), 65% (AT), and 72% (RT) compared with control group

AT, aerobic training; BMI, body mass index; C, control; D, diet; E, exercise; IGT, impaired glucose tolerance; LSM, lifestyle modification; MET, metformin; RCT, randomized controlled trial; RT, resistance training.

and included reduction in total calories, refined carbohydrates, and fats; avoidance of sugar; and inclusion of fibre-rich foods. To support the lifestyle modification, people were contacted monthly by telephone and seen six-monthly during the study. The median follow-up period was 30 months, and the three-year cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in Groups 1–4, respectively. The relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin, and 28.2% with combine lifestyle modification and metformin compared with the control group.

In these prevention studies, weight loss seems to be the main factor in reducing diabetes incidence. In the US Diabetes Prevention Program, among those in the intervention arm for every kilogram in weight loss a 16% reduction in diabetes was seen, when adjustment for changes in diet and lifestyle were made [128]. Results from a meta-analysis also suggest that the effectiveness of these lifestyles programmes may be greater in those who are more overweight.

Weight loss, however, does not explain all the intervention effects. In the Indian Diabetes Prevention Programme, a 28.5% reduction in diabetes incidence was achieved without weight loss or reduction in waist circumference [125]. In the exercise intervention arm of the Da Qing study, a 46% reduction in diabetes incidence was achieved without weight loss [118]. These factors

suggest that some aspects of diet as well as physical activity, not necessarily related to weight loss, may be involved in mediating the beneficial effect of lifestyle modification in the prevention of type 2 diabetes.

A recent study has examined the effect of exercise alone on preventing type 2 diabetes in people with impaired glucose tolerance [127]. In this study 137 people with impaired glucose tolerance were randomized into four groups. Group 1 was the control and continued normal activity. Group 2 did 60 minutes of aerobic exercise (dance) three times per week, Group 3 did 60 minutes of resistance training three times a week, and Group 4 did combined aerobic and resistance training for 60 minutes three times per week. After 24 months the incidence of diabetes was 69%, 22%, 26%, and 22% in Groups 1–4, respectively. The relative risk reduction was 72% with aerobic exercise, 65% with resistance training, and 74% with combined exercise compared with the control group.

Treatment of type 2 diabetes

There is very clear evidence that exercise alone has profound benefits in people with established type 2 diabetes. Figure 28.2 summarizes the benefits that people with type 2 diabetes can expect to see with exercise.

Physical fitness, cardiovascular disease, and mortality

People with type 2 diabetes have a significantly lower $\text{VO}_{2\text{max}}$ than healthy age-, BMI-, and activity-matched participants without diabetes [129]. Meta-analysis of nine RCTs involving 266 people with type 2 diabetes, comparing exercise and control, shows that regular exercise, at least 50% of $\text{VO}_{2\text{Max}}$, improved overall $\text{VO}_{2\text{Max}}$ by 11.8% in the exercise group versus a reduction of 1% in the control group. Additionally, higher-intensity exercise produces even larger improvements in cardiorespiratory fitness [130].

Observational studies have shown that increased physical activity improves cardiorespiratory fitness and lowers mortality rate in participants without diabetes [131,132], while prospective studies in people with diabetes report that even walking for two hours a week is associated with less cardiovascular mortality; however, the effect is greater with three to four hours of walking a week [133]. No RCT has assessed the effect of improved physical fitness on mortality in type 2 diabetes.

Glycaemic management

Supervised exercise training

Structured exercise training is normally defined as an intervention in which people engage in a planned, individualized, and supervised exercise programme. The most recent meta-analysis that examined the effect of structured exercise training on $\text{HbA}_{1\text{c}}$ in type 2 diabetes reported in 2011 [134] (Figure 28.3). This included 23 RCTs with 1533 participants. Studies had to be RCTs of ≥ 12 weeks' duration and had a control group of people with type 2 diabetes. Overall, structured exercise reduced $\text{HbA}_{1\text{c}}$ by 0.7% (7 mmol/mol) compared to control participants. When dividing the studies into exercise type, 18 studies with 848 people demonstrated that structured aerobic exercise training reduced $\text{HbA}_{1\text{c}}$ by 0.7% (7 mmol/mol), 4 studies with 261 people showed that structured resistance exercise training reduced $\text{HbA}_{1\text{c}}$ by 0.6% (6 mmol/mol), and 7 studies with 404 people demonstrated

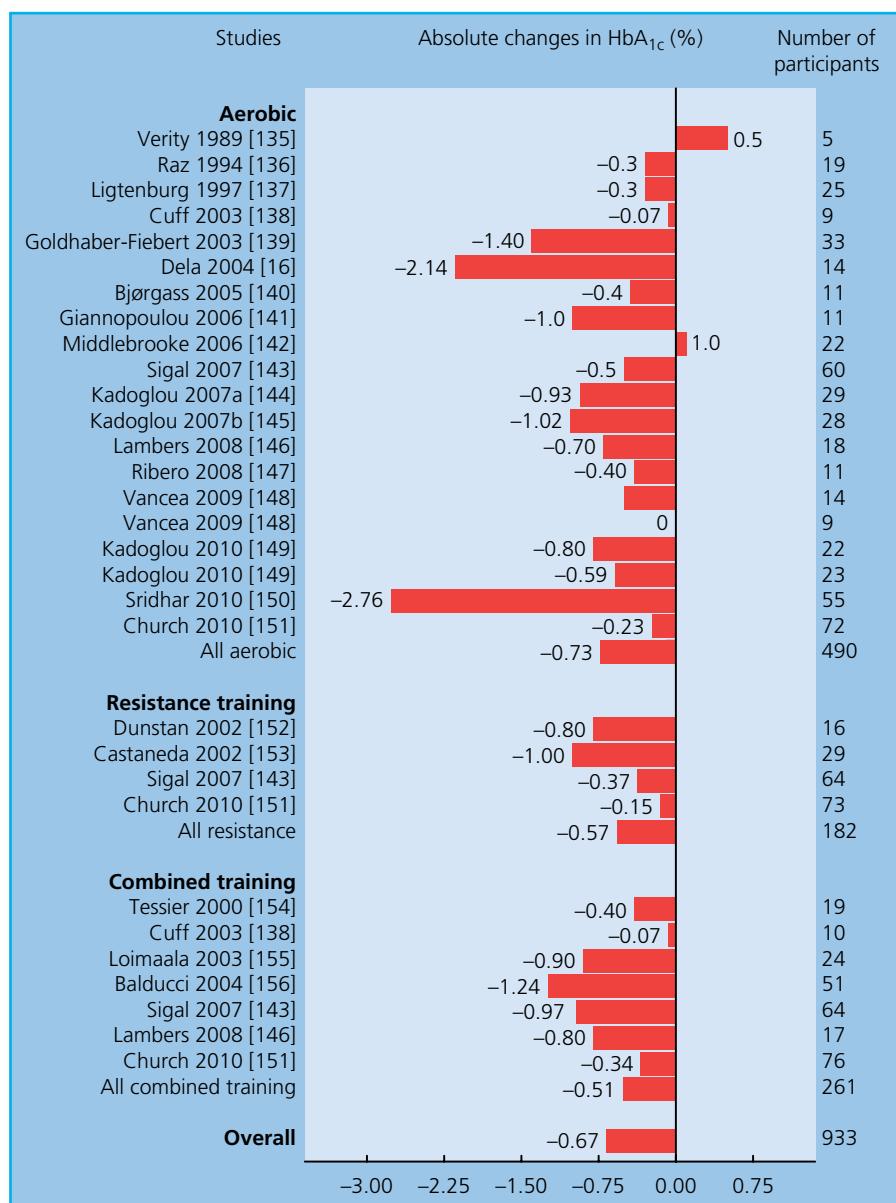


Figure 28.3 Absolute changes in glycated haemoglobin ($\text{HbA}_{1\text{c}}$) of individual studies of structured exercise training versus no intervention. Number of participants in each exercise regimen is shown in the box in white. Source: Adapted from Umpierre et al. 2011 [134].

that the combined aerobic and resistance exercise reduced HbA_{1c} by 0.5% (5 mmol/mol). This meta-analysis also showed that structured exercise duration of ≥150 minutes per week was associated with greater benefit than structured exercise duration of ≤150 minutes (0.9% vs 0.4%; 9 mmol/mol vs 4 mmol/mol reduction, respectively).

Using a meta-regression analysis, Umpierre et al. assessed the association between intensity and volume of supervised exercise training (aerobic, resistance, or combined) and HbA_{1c} changes in type 2 diabetes [157]. Higher baseline HbA_{1c} was associated with greater HbA_{1c} reduction with training. For supervised aerobic training and combined aerobic/resistance training, higher volume of exercise was associated with greater HbA_{1c} reduction. For example, each set of aerobic exercise added within the exercise week produced a 0.4% (4 mmol/mol) HbA_{1c} reduction. No exercise variables were found to be possible candidates to explain the effects of supervised resistance training.

A meta-analysis of RCTs that compared supervised resistant exercise with aerobic exercise in people with type 2 diabetes sought to clarify whether there was an optimum type of exercise for treating type 2 diabetes [158, 159]. The 12 included studies of 626 participants were RCTs of ≥8 weeks' duration that compared supervised resistant exercise with supervised aerobic exercise. Although there was a greater reduction of HbA_{1c} with supervised aerobic exercise compared to supervised resistant exercise, the difference was only 0.2% (2 mmol/mol) and not clinically significant.

Two RCTs have compared the three commonly used types of supervised exercise for treating type 2 diabetes, namely aerobic, resistance training, or a combination [143, 151] (Figure 28.4). In the Diabetes Aerobic and Resistance Exercise (DARE) trial [143], 251 previously sedentary individuals with type 2 diabetes were randomized into four arms: aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training, or a non-exercising control group. Compared to the control group, HbA_{1c} decreased significantly in the aerobic group by 0.5% (5 mmol/mol) and the resistance group by 0.4% (4 mmol/mol). In the combined exercise group, HbA_{1c} fell by an additional 0.5% (5 mmol/mol) compared with the aerobic group and 0.6% (6 mmol/mol) compared with the resistance group. In people with HbA_{1c} ≤7.5% (48 mmol/mol), HbA_{1c} only decreased significantly in the combined exercise training group.

Church et al. [151] randomized 262 sedentary people with type 2 diabetes to four groups: aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training, or a non-exercising control group. Compared with the control group, neither the resistance nor aerobic training produced a significant change in HbA_{1c}. For the combination training exercise group, a fall in HbA_{1c} of 0.3% (3 mmol/mol) was seen compared to the control group.

High-intensity interval training (HIIT) is the newest form of exercise to be tried in the management of type 2 diabetes, as it takes less time to perform and can produce similar physiological effects to longer duration of standard exercises. Recently a meta-analysis of ten small studies that aimed to quantify the effects of HIIT on markers of glucose regulation with control conditions or continuous training has reported [158]. Compared with control conditions, in people with type 2 diabetes HIIT did not produce a significant reduction in HbA_{1c}, but was superior to continuous training with a 0.37% (4 mmol/mol) HbA_{1c} reduction.

Physical activity advice

Although structured exercise training may be available to some people with type 2 diabetes, physical activity advice may be more feasible. Physical activity advice is normally defined as formal instructions to exercise regularly with or without an individualized exercise prescription. The most recent meta-analysis that assessed the effect of physical advice on HbA_{1c} in people with type 2 diabetes reported in 2011 [134] (Figure 28.5). This included 24 studies with 7025 participants. Overall physical activity advice produces a 0.4% (4 mmol/mol) decrease in HbA_{1c} compared to control. When the studies were broken down to those that included dietary advice, it was seen that physical activity advice in combination with dietary advice (12 studies, 6313 people) was associated with a 0.6% HbA_{1c} reduction (6 mmol/mol) compared with control, but physical activity advice alone (14 studies, 712 people) was not associated with HbA_{1c} changes.

Structured exercise training versus physical activity advice

The Italian Diabetes and Exercise Study [184] compared structured exercise training to physical activity advice. In the study, 606 individuals with type 2 diabetes were randomized to a full year of either physical activity advice alone, or supervised facility-based combined aerobic and resistance exercise training twice weekly plus physical activity advice. HbA_{1c} fell to a greater extent in the

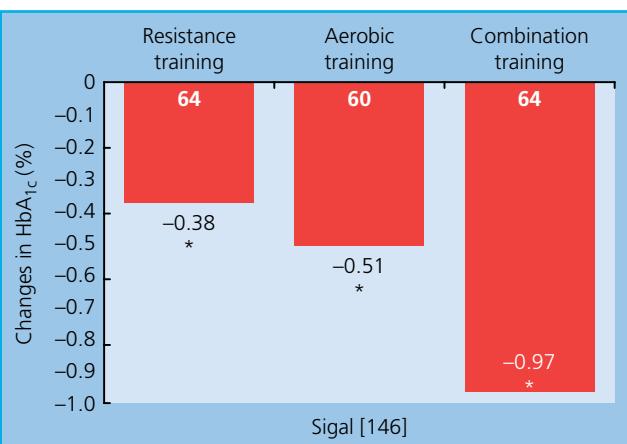
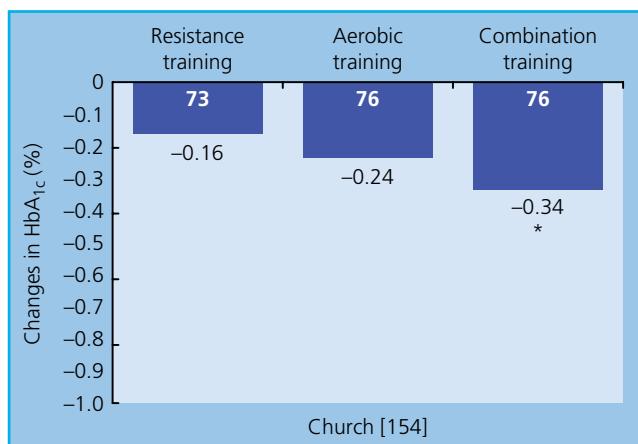


Figure 28.4 Reduction in glycated haemoglobin (HbA_{1c}) seen with different exercise regimens compared to control group in two studies, Church [150] and Sigal [143]. Number of participants in each exercise regimen is shown in the box in white. A star denotes significant improvement compared to control group.

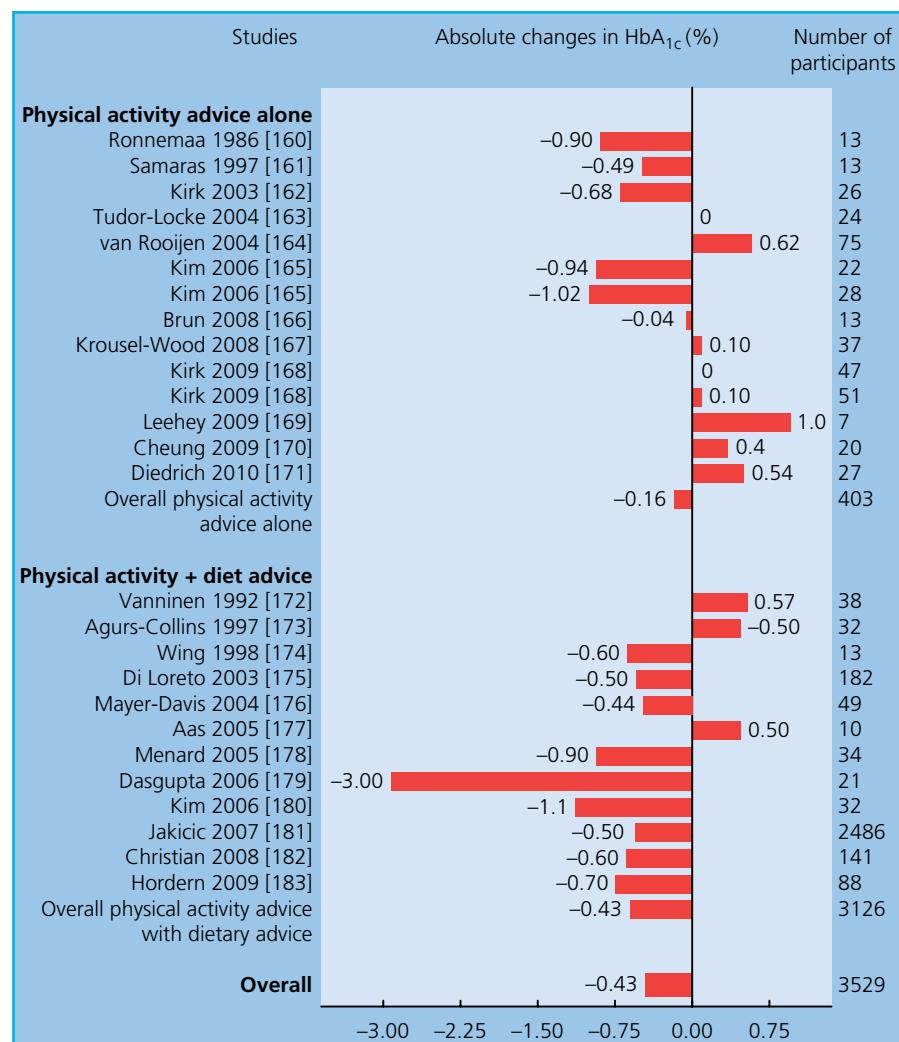


Figure 28.5 Absolute changes in glycated haemoglobin (HbA_{1c}) of individual studies of physical activity advice versus no intervention. Number of participants in each exercise regime is shown in the box in white.

Source: Adapted from Umpierre et al. 2011 [134].

supervised exercise group (0.4%; 4 mmol/mol) than the advice group (0.1%; 1 mmol/mol). This study suggests that supervised exercise programmes are more effective than physical activity advice.

Vascular risk factors other than glucose

In healthy people, aerobic and resistance training lower both systolic and diastolic blood pressure, whereas combined training only lowers diastolic blood pressure [185]. In 2014 Figueira et al. conducted a meta-analysis to assess the effect of physical activity advice alone or structured exercise training on blood pressure in type 2 diabetes [186]. They identified 30 RCTs (2217 participants) of structured exercise training and 21 RCTs (7323 participants) of physical activity advice alone. Overall, structured exercise reduced systolic blood pressure by 4 mmHg and diastolic blood pressure by 2 mmHg compared to controls. Greater reductions in blood pressure were seen when exercise duration was ≥ 150 minutes and when the intensity of the exercise was higher. When exercise training was broken down into exercise type, compared to control, aerobic exercise training reduced systolic blood pressure by 5 mmHg and diastolic blood pressure by 2 mmHg, and resistant exercise training reduced systolic blood pressure by 4 mmHg and diastolic blood pressure by 3 mmHg. Combined exercise training was not associated with a reduction in blood pressure. Physical activity advice

alone produced a 3 mmHg reduction in systolic blood pressure and a 1 mmHg reduction in diastolic blood pressure.

Several studies have examined the effect of aerobic and combined aerobic and resistance supervised exercise on lipids in type 2 diabetes. In a meta-analysis, both reduced triglycerides by 0.3 mmol/l but had no effect on HDL cholesterol or LDL cholesterol [187]. Only one study has assessed the effect of resistance training and found no effect on total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides [176].

People with type 2 diabetes have impaired endothelial function [188, 189], which is a powerful and independent predictor of long-term cardiovascular events [190, 191]. Only a few small studies have assessed the effect of exercise on endothelium function in type 2 diabetes, but a meta-analysis of 5 studies including 217 participants reported that supervised exercise improved endothelium function [191].

Insulin resistance is one of the hallmarks of type 2 diabetes and is involved in the pathogenesis of hypertension and cardiovascular disease. Both aerobic and resistance training improve insulin resistance in type 2 diabetes [138]. Although in healthy individuals resistance exercise has a greater effect on insulin sensitivity than aerobic exercise, there is insufficient evidence to confirm whether this is the case in type 2 diabetes [192].

Microvascular complications

The fact that exercise improves HbA_{1c} and blood pressure, the two key risk factors in the development of diabetic microvascular complications, suggests that regular exercise should protect against microvascular complications. Few studies have examined whether this is the case. Impaired exercise capacity is associated with diabetic nephropathy and retinopathy [193]. In retrospective and prospective cohort studies, regular physical activity was associated with reduced progression and development of diabetic kidney disease [194, 195]. In the Look Ahead study, people randomized to the intervention arm (diet, exercise, and weight loss) were less likely to develop retinopathy or neuropathy [196]. In contrast, in the Japan Diabetes Complications Study in which 2033 participants were randomized to a lifestyle intervention (diet and exercise) or usual care, there was no difference in incident retinopathy or nephropathy between groups at eight years' follow-up [197]. No RCTs have examined the effect of exercise alone on microvascular risk in people with type 2 diabetes.

β-cell function

In the UK Prospective Diabetes Study, progressive decline of β-cell function was associated with worsening of glycaemic levels in people with type 2 diabetes, irrespective of treatment strategy [198]. Thus, maintenance of β-cell function is important to meet glucose targets in people with type 2 diabetes. Several studies have shown that aerobic exercise of varying intensity improves insulin secretion in type 2 diabetes [199–202].

Bone mineral density

People with type 2 diabetes are at increased risk of fractures despite normal, or even increased, bone mineral density [203]. This increase in fracture risk may be due to altered bone architecture or an increased risk of falling due to neuropathy. No studies has assessed the effect of physical activity on bone mineral density or fracture risk in type 2 diabetes.

Cancer

Type 2 diabetes is associated with an increased risk of developing cancer [203]. In the general population regular physical activity reduces cancer risk and improves outcomes in those who develop it. Again, no studies have examined whether this holds true for people with type 2 diabetes.

Well-being

People with type 2 diabetes have a higher chance of developing depression [204, 205]. They also have a poorer quality of life [206] and a higher prevalence of general anxiety disorder (14%) than the general population [207]. The effects of exercise training on quality of life, symptoms of depression and anxiety, and emotional well-being in type 2 diabetes were reviewed in 2014 [208], with two further studies since then [215, 225]. A summary of all studies is shown in Table 28.4. No form of exercise improved quality of life and emotional well-being, while depressive symptoms were only improved by resistant training and anxiety symptoms were only improved by aerobic training.

Table 28.4 Effect of exercise on well-being.

		Number of studies	Length of interventions (wk)	Number of participants	Results
Quality of life	Aerobic	5	8, 16, 16 and 52, 12 and 12	18, 50, 44, 29, 38	4 found no effect [146, 208–211] and 1 found effect on physical health and sleep subscales but not other subscales [212]
	Resistance	5	16, 16, 12 and 26, 16 and 12	58, 48, 110, 37, 30	3 found no difference [213–215], 1 found a significant effect [216], and 1 found effects on general health subscale [170] but no effect on other subscales
	Combined	11	24, 52, 16 and 52, 12 and 26, 8, 12, 26, 12, 16, 16	84, 606, 64, 109, 36, 77, 43, 28, 38, 29	6 found no effect [146, 154, 167, 210, 213, 217]. 4 found improvement across all measures of quality of life [218–221]. Remaining 1 found improvement in emotional role, mental health, and vitality, but not for other subscales [222]
Well-being	Aerobic	3	6, 8, 8	58, 40, 20	2 showed improvement [223, 224] and 1 no improvement [225]
	Resistance	2	8, 12 and 26	20, 110	One showed improvement [225], the other did not [213]
	Combined	1	12 and 26	109	No effect [213]
Depression	Aerobic	2	6 and 8	78, 58	Both showed no effect [223, 226]
	Resistance	1	16	58	Improved [216]
	Combined	1	8	36	No effect [222]
Anxiety	Aerobic	1	6	58	Reduced anxiety [223]
	Resistance	—			
	Combined	—			

Physical activity and gestational diabetes

Prevention of gestational diabetes

Gestational diabetes (GDM) is a condition in which women without a previous diagnosis of diabetes develop glucose intolerance during pregnancy (Chapter 71) [227]. The prevalence of GDM ranges from 1% to 14% depending on the diagnostic criteria used and the population being studied [228]. It is associated with adverse maternal and fetal outcomes; women with GDM have an increased risk of developing GDM in subsequent pregnancies and type 2 diabetes. Offspring of mothers with GDM are at high risk of macrosomia [229] and as adults are more likely to develop obesity [230] and type 2 diabetes [231]. Preventing GDM is therefore a clinical priority.

Several prospective studies have shown that low physical activity is associated with the development of GDM. In the largest of these studies, including 21 765 women, Zhang et al. found that when comparing the highest with the lowest quintiles of vigorous activity there was a relative risk reduction of 0.77 [232]. Among women who did not engage in vigorous activities, women who briskly walked ≥ 30 minutes or climbed ≥ 15 flights of stairs daily also had a lower risk of GDM [232].

Two recent systematic reviews have examined whether prenatal physical activity prevents GDM. Sanabria-Martinez et al. reviewed RCTs of sedentary healthy women or those with low levels of physical activity (exercising <20 minutes on <3 days per week) with uncomplicated and singleton pregnancies [233]. In their review, 13 RCTs with 2873 pregnant women met the inclusion criteria, of which only 3 reported ethnicity and involved white women. Exercise reduced the risk of GDM by 31%, with this increasing to 36% if started early in pregnancy. Davenport et al. identified 46 RCTs with 14 923 pregnant women and found that prenatal exercise was associated with 24% lower odds of developing GDM compared with no exercise [234]. Both reviews felt that larger, better-quality studies were needed to confirm or refute these findings.

Treatment of gestational diabetes

Regular exercise during pregnancy is associated with many benefits, including improved cardiorespiratory fitness, less low back pain, reduced urinary incontinence, reduced depressive symptoms [235], and less weight gain in pregnancy [236]. Although diet and exercise are recommended as the first step in managing GDM, there is debate about whether there is clear evidence about the effectiveness of exercise. A 2006 Cochrane review concluded that 'there is insufficient evidence to recommend, or advise against, diabetic pregnant women to enrol in exercise programs. Further trials, with larger sample size, involving women with gestational diabetes, and possibly type 1 and 2 diabetes, are needed to evaluate this intervention' [237]. A systematic review identified seven studies that examined the effect of exercise in managing GDM [238]. Five studies found improvements in glycaemic levels and/or a limitation in insulin use [239–243], but two reported no effect [244,245].

Exercise advice for people with type 1 diabetes or type 2 diabetes

Exercise guidelines

The American Diabetes Association has published recommendations and guidelines for exercise in individuals with diabetes [246]. These and other guidelines are summarized in Table 28.5.

Table 28.5 Exercise guidelines for adults and children with type 1 diabetes and type 2 diabetes and pregnant women with diabetes.

Categories	Physical activity recommendations
Adults with type 1 diabetes and type 2 diabetes	At least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic physical activity, or equivalent combination of the two. This should be spread over 3 d with no more than 2 consecutive days without exercise Additionally, muscle-strengthening activities that involve all major muscle groups should be performed on 2 or more days of the week Reduction in sedentary time is also recommended [206] Flexibility training and balance training are recommended 2–3 times/wk for older adults with diabetes
Children and teens with type 1 diabetes and type 2 diabetes	At least 60 min of physical activity daily, which should include vigorous-intensity aerobic activity, muscle-strengthening activities, and bone-strengthening activities at least 3 d of the week [206]
Pregnancy in women with diabetes	At least 30 min or more of moderate exercise daily if there are no medical or obstetric complications [206]

Source: Adapted from Colberg et al. 2016 [246].

Where possible, advice should be tailored to the individual, taking into account their interests, level of fitness, possible contraindications, and personal goals. There are many examples of people with diabetes competing at the highest level, so diabetes should not interfere with an individual's sporting goal and treatment should be adjusted according to the demands of the activity. For activities and competitions considered to be high risk for individuals with diabetes (e.g. car racing, flying, diving), individual governing bodies should be consulted regarding restrictions in competition. It is also important to note that the use of insulin is prohibited by the World Anti-Doping Agency, and elite-level athletes with diabetes will require a Therapeutic Use Exemption (TUE) certificate prior to competition.

Most guidelines recommend ≥ 150 minutes of moderate aerobic activity, and/or ≥ 90 minutes of vigorous aerobic exercise every week, and that this activity be spread over at least three days [246]. A day's activity need not occur in a single session, but may be accumulated in bouts of ≥ 10 minutes at a time, performed throughout the day. Performing ≥ 150 minutes of moderate activity is associated with greater benefit, so if an individual has reached the target of 150 minutes they should be encouraged to do more if possible.

In addition to aerobic exercise, many guidelines also suggest that resistance training should be carried out at least twice per week, as combining aerobic exercise with resistance training has the greatest effect on HbA_{1c}. Ideally at least three sets of resistance exercise should be performed at each session, as the resistance exercise studies that have used ≥ 3 sets have shown the greatest reduction in HbA_{1c} [49,152,247]. Weight lifting is safe in people with cardiac disease [248] and is not associated with increased proliferative retinopathy risk [248].

The guidelines recommend that people with diabetes should also reduce their sedentary time [246]. This is because higher sedentary

time is associated with a poorer metabolic profile in type 2 diabetes and reduced sedentary time improves metabolic profile [249].

Minimizing risk of exercise-related adverse events

Assessment

There is often concern about the safety of exercise for people with diabetes, although for most people the benefits of exercise will outweigh the risks. Prior to starting exercise for the first time or when beginning a programme of vigorous physical activity, people with diabetes should be assessed for conditions that might increase risks associated with certain types of exercise or predispose them to injury. Table 28.6 provides guidance on what pre-exercise assessment should be undertaken.

Specific exercise considerations for people with type 1 diabetes

In healthy individuals without diabetes, changes in insulin and counter-regulatory hormone secretion during exercise are dependent on the type of exercise being performed [250]. These changes facilitate an increase in liver glucose production to match skeletal muscle glucose uptake [162]. A change in the secretion of these hormones is also seen post-exercise to facilitate recovery and adaptation to exercise. As a result, blood glucose levels remain relatively stable before, during, and after exercise.

In people with type 1 diabetes, because insulin lies in subcutaneous depots and is not under regulation, insulin levels do not change in a physiological manner during exercise, thus they cannot fall in response to exercise and there may be impaired secre-

tion or action of counter-regulatory hormones. This impairs normal fuel regulation [251]. The inability of the pancreas to modulate insulin and counter-regulatory hormones (in particular glucagon) following exercise can also hamper recovery and adaptation to exercise. This increases the risk of hypoglycaemia both during and following exercise. Furthermore, hyperglycaemia prior to and following some types of exercise can be problematic [252]. Consequently, people with type 1 diabetes have three main problems when exercising:

- Problems controlling their blood glucose during and immediately following exercise.
- Unexplained severe hypoglycaemia, particularly at night.
- Reduced performance through excessive fatigue and reduced muscle strength.

To help overcome these problems, people need to understand how different exercises affect glucose, know when it is safe to exercise, and have strategies to manage glucose during and after exercise.

How different exercise affects blood glucose

Both intensity and exercise type will determine what happens to blood glucose concentrations (Figure 28.6). The most rapid drop in blood glucose occurs during aerobic or endurance exercise, when circulating insulin suppresses metabolic fuel production and increases muscle glucose uptake. With intermittent high-intensity exercise, there is a mixture of both aerobic and anaerobic exercise, which is characteristic of team sports and children's play; blood glucose is either stable or falls slowly [253]. High-intensity or anaerobic exercise tends to raise blood glucose, as a result of the increased catecholamines that are normally seen with these exercises [254].

When it is safe to exercise

Hypoglycaemia in the 24 hours preceding exercise blunts the counter-regulatory hormone response to exercise-induced hypoglycaemia, placing an individual at greater risk of exercise-induced

Table 28.6 Pre-exercise assessment and advice for people with diabetes complications.

Complication	Advice
Cardiovascular disease	Symptoms of cardiovascular disease should be asked about and where there is concern referral to a cardiologist for further assessment is indicated There is no evidence for screening of asymptomatic individuals Cardiovascular assessment is recommended for individuals with diabetic autonomic neuropathy
Peripheral neuropathy	It is vital to ensure that appropriate footwear is worn and feet are examined regularly, particularly if peripheral neuropathy is present Weight-bearing exercise should be avoided in those with active foot disease Walking does not increase the risk of ulceration in individuals with peripheral neuropathy Exercise delays the progress of neuropathy and so should be encouraged
Retinopathy	When proliferative or severe non-proliferative retinopathy is present, it may be sensible to avoid vigorous activity (both aerobic and resistance) because of the possible increased risk of vitreous haemorrhage or retinal detachment
Nephropathy	No evidence for restriction of any type of exercise in individuals with diabetic kidney disease Exercise can reduce progression and so should be encouraged

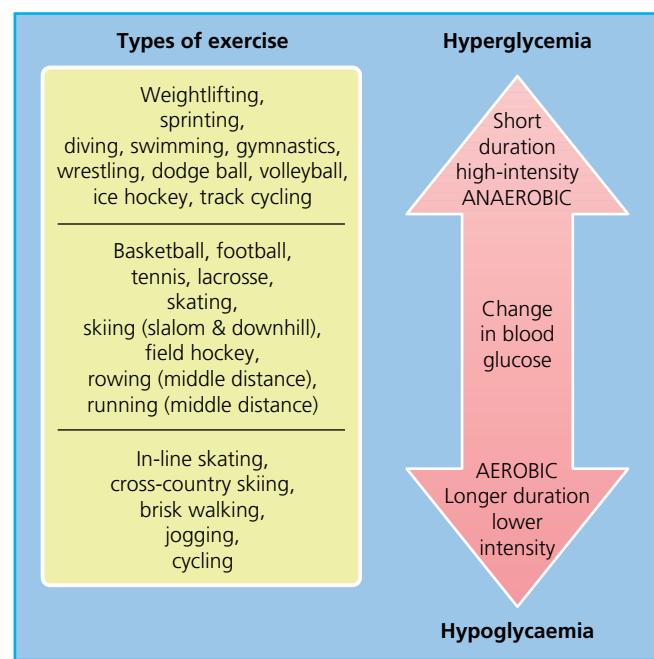


Figure 28.6 Effects of different sports on blood glucose concentrations.

Table 28.7 Insulin dose adjustment table for exercise.

	Duration	Intensity		
		Low (<50 MHR % or Borg scale 10)	Medium (50–75% MHR or Borg scale 10–15)	High (>75% MHR or Borg scale >15)
% Dose reduction	<30 min	10–20%	20–45%	40–60%
	30–60 min	20–30%	30–55%	50–75%
	>60 min	30–50%	45–70%	100%

MHR, maximum heart rate. Borg scale is based on the Borg rating of perceived exertion (see [265]).

hypoglycaemia. This risk is proportional to the severity of the preceding hypoglycaemia, with the effect starting at 3.9 mmol/l [255]. There is currently no evidence to guide individuals as to when it is safe to exercise following a hypoglycaemic episode. However, a consensus document suggests the following [256]:

- Not to exercise within 24 hours of severe hypoglycaemia requiring third-party assistance.
- Not to exercise within one hour of self-treated hypoglycaemia. If an individual insists on doing so, they should treat the hypoglycaemia and wait 45–60 minutes once the glucose is stable before commencing activity.
- Take extra precautions when there has been an episode of self-treated hypoglycaemia within the previous 24 hours. This would include more frequent glucose testing, exercising with an informed partner, and, if possible, including an anaerobic component to their training, because this will tend to raise their blood glucose.

If there is hypoglycaemia during exercise, exercise should be discontinued and the hypoglycaemia treated. The individual should wait at least 45 minutes before recommencing activity (or until blood glucose is stable). If an episode of severe hypoglycaemia occurs during exercise, then the activity should be stopped altogether because of the high risk of further hypoglycaemia.

When the blood glucose level is ≥ 15 mmol/l before exercise, the presence of ketones (capillary or urine) should be assessed [256]. If ketones are present, exercise is contraindicated and supplemental insulin should be considered (1 unit for 2–3 mmol/l glucose reduction). Exercise should only be commenced when ketone free and blood glucose is < 15 mmol/l [257]. Where the blood glucose level is ≥ 15 mmol/l and ketones are not present, advice depends on timing of the last meal (and, therefore, last quick-acting insulin dose). If a meal has been eaten in the last 1–2 hours, exercise may be commenced with close blood glucose monitoring. If the last meal was eaten ≥ 2 hours ago, then 30% of the usual correction dose should be given.

Strategies to manage glucose during exercise

An initial strategy for managing blood glucose during exercise is to replace the carbohydrate that will be used during exercise orally. In its simplest form, this is a fixed carbohydrate replacement regimen. In adults, we initially recommend 15 g of carbohydrate for every 30 minutes of exercise [258]. Although activities vary widely in terms of fuel requirements, this range represents a safe starting point for most people beginning moderate-intensity exercise. Estimates of carbohydrate requirement based on body mass can be used in preference to fixed-dose carbohydrate replacement. For

moderate and intensive activity, 0.5 g/kg/hr and 1 g/kg/hr, respectively, may be used [259].

An alternative approach that adjusts for the variable fuel requirements of different exercises is using standardized tables. These have been devised to help athletes of different body weight estimate carbohydrate requirements for different exercise intensities [260]. The maximum rate of enteral glucose absorption is 1 g/min. Therefore, carbohydrate requirement exceeding 60 g of glucose per hour would need to comprise a combination of glucose and fructose. In general, once carbohydrate requirements for exercise exceed 60 g/hr, we recommend altering insulin doses.

Several studies have examined insulin dose reductions for exercises of different intensities. This has enabled the development of dose reduction tables (Table 28.7). These tables tend to refer to changes to fast-acting insulin and therefore relate to exercise undertaken within two hours of eating (three hours if on soluble human insulin). To gain the most from these reductions, exercise is best conducted within 30 minutes after eating, and the meal or snack should predominantly contain low glycaemic index carbohydrate [261]. Reduction in basal insulin can, however, be helpful if people are undertaking prolonged exercise in the morning, or in the afternoon two hours after their meal.

Strategies to manage glucose post-exercise

Following exercise, carbohydrate is required to replenish muscle and liver glycogen stores. Protein is also needed for post-exercise muscle repair and synthesis. Failure to provide this increases the risk of hypoglycaemia in the subsequent hours, and fatigue in subsequent exercise sessions. Initially individuals should be advised to take snacks equivalent to 1 g/kg body weight of carbohydrate and 0.3 g/kg of protein [262]. This snack should be taken with insulin, as this increases carbohydrate storage in the exercising muscles and liver [263]. Initially we recommend a third of their normal insulin-to-carbohydrate ratio.

There is a risk of hypoglycaemia several hours after exercise through an increase in insulin sensitivity. If individuals have exercised during the morning or early afternoon, they should monitor their blood glucose and take extra carbohydrate as needed. If exercise has been undertaken in the late afternoon or evening, this may lead to nocturnal hypoglycaemia. To prevent this, people should reduce their evening basal insulin by 20% or take extra carbohydrates before going to bed.

High-intensity aerobic and anaerobic exercise can lead to post-exercise hyperglycaemia through increased hepatic glucose output

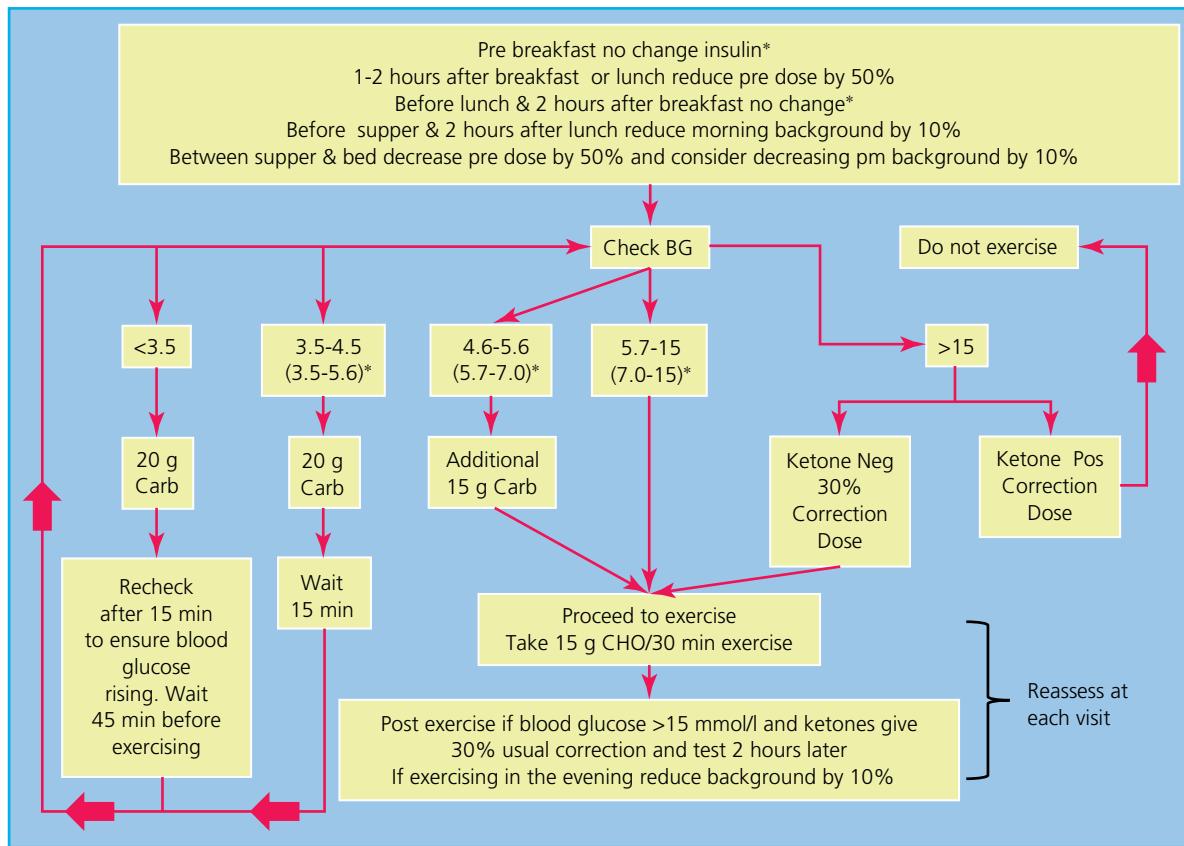


Figure 28.7 Algorithm for people with type 1 diabetes suggesting changes to insulin and carbohydrate (CHO) intake when exercising. Note that different blood glucose (BG) levels are used in this algorithm if exercising before breakfast or when exercising two hours after breakfast and before lunch, when no changes in insulin dosages are made – this is denoted by a star. Blood glucose values are given in mmol/l. To convert to mg/dl, these should be multiplied by 18.018.

and muscle insulin resistance, brought on by increased production of counter-regulatory hormones [264]. This means that additional insulin may be needed post-exercise. While there is currently no evidence to guide insulin correction dose, we recommend starting with 30% of the usual correction dose for blood glucoses ≥ 14 mmol/l post-exercise. Figure 28.7 shows a simple algorithm that brings together all this advice.

Specific considerations for people with type 2 diabetes

In people with type 2 diabetes, exercise does not typically cause hypoglycaemia and so carbohydrate supplementation is usually unnecessary. If blood glucose declines rapidly during exercise, as may occur in individuals taking oral anti-diabetes agents or insulin, the drug dosage should be reduced or withheld on exercising days.

Conclusion

Exercise improves well-being and reduces the risk of heart disease, cancer, and type 2 diabetes in the general population. In individuals with established type 1 diabetes or type 2 diabetes, regular exercise improves cardiovascular risk factors such as blood pressure and lipids and is associated with decreased mortality and decreased frequency and severity of diabetes-related complications. For individuals with type 2 diabetes, regular exercise improves metabolic management, as demonstrated by decreases in HbA_{1c}. This chapter has summarized the existing evidence about the effects of exercise in type 1 diabetes, type 2 diabetes, and gestational diabetes. A summary of current exercise recommendations is provided, along with practical advice on managing exercise training in individuals with both type 1 diabetes and type 2 diabetes.

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29

Monitoring Diabetes

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Key points

- Glycated haemoglobin ($\text{HbA}_{1\text{c}}$) is now used for both the long-term monitoring of people with diabetes and the diagnosis of type 2 diabetes. $\text{HbA}_{1\text{c}}$ and blood glucose remain the mainstay for monitoring glycaemic levels.
- $\text{HbA}_{1\text{c}}$ values are reported in SI units (mmol/mol) and derived % units using a stable master equation. All methods for $\text{HbA}_{1\text{c}}$ should now be standardized to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference measurement procedure.
- People with type 1 diabetes should have $\text{HbA}_{1\text{c}}$ monitored every 2–6 months, depending on the level and stability of blood glucose and change in therapy.
- People with type 1 diabetes should be encouraged to self-monitor blood glucose with capillary blood glucose meters or continuous glucose monitoring systems. With treatment regimens intended to produce intensive glycaemic management, testing should be frequent (e.g. four or more times a day).
- For people with type 2 diabetes, glycaemic levels should be monitored using high-precision methods for measurement of $\text{HbA}_{1\text{c}}$ every 3–6 months, depending on the level and stability of blood glucose and change in therapy.

Why monitor?

The field of diabetes care has advanced significantly over the past 50 years and people with diabetes can expect to achieve optimal glycaemic levels through multiple pharmacological and non-pharmacological approaches. Coupled with the advances in treatment of the disease, methods for detecting diabetes and its complications have also advanced. Without accurate and precise measures of blood glucose and glycated haemoglobin ($\text{HbA}_{1\text{c}}$) to monitor the efficacy of any intervention, tight glycaemic levels would not be achievable in a safe manner. Therefore, it is essential that people with diabetes have a clear regimen for monitoring their diabetes and are supported with education programmes to understand the role that testing plays in their care.

The aim of monitoring in diabetes includes:

- Allowing people with diabetes to understand the nature of their disorder.
- Determining the optimum times for initiating therapeutic intervention.
- Guiding the day-to-day adjustment of treatment.

Choosing the optimal target for monitoring and which assay is important ensures the best outcomes not only for an individual, but also at a population level, where small differences between the performance of tests, the frequencies with which they are carried out, and their costs may lead to important differences in outcomes and overall costs of care.

$\text{HbA}_{1\text{c}}$ and blood glucose are the two most frequently used measures of glycaemia in current practice. $\text{HbA}_{1\text{c}}$ provides information

about overall glucose levels in the previous 6–8 weeks, allowing assessment of the need for therapy and therapeutic response with minimal within-person variation in measurement. Blood glucose measurements provide information about the day-to-day levels, variation in levels, and response to therapeutic intervention. This chapter will describe the tests for $\text{HbA}_{1\text{c}}$ and glucose levels, the characteristics of these tests, the technology used in measuring their levels, and their clinical application in type 1 diabetes and type 2 diabetes. Additionally it will explore the role of other glycated proteins and the increasing role of point-of-care testing in diabetes monitoring. Newer and emerging technologies to assess glycaemia, including continuous glucose monitoring (CGM), are covered in Chapter 32.

Tests and their characteristics

Glycated haemoglobin

$\text{HbA}_{1\text{c}}$ measurement plays a pivotal role in the management of people with diabetes and in the diagnosis of people with type 2 diabetes. $\text{HbA}_{1\text{c}}$ levels are associated with the response to treatment and the risk of developing complications, and therefore provide an evidence-based marker with which to judge the impact of glucose-lowering treatment and prognosis. The outcomes of trials such as the UK Prospective Diabetes Study (UKPDS), the Diabetes Control and Complications Trial (DCCT), and Epidemiology of Diabetes Interventions and Complications (EDIC) clearly demonstrate the association between improved glycaemic levels and microvascular and, to a lesser extent, macrovascular complications of diabetes.

Glycohaemoglobin, glycosylated haemoglobin, glycated haemoglobin, glucosylated haemoglobin, fast haemoglobins, HbA₁, HbA_{1a+b}, HbA_{1c} and total glycohaemoglobin have all been used to refer to haemoglobin with the addition of glucose. However, with the introduction of standardization of HbA_{1c} testing, many of these terms are no longer in use and the term HbA_{1c} (sometimes abbreviated to A_{1c}) is the commonly accepted term.

HbA_{1c} is reported in SI units (from the French Système International d'Unités) of mmol/mol (mmol HbA_{1c}/mol Hb A₀+HbA_{1c}). While this is the internationally recognized unit for HbA_{1c}, it is still common to see the former units of % (the proportion of glycated to total levels of haemoglobin) used in many texts [1]. There are numerous conversion tables available to convert between the two units.

HbA_{1c} is formed by the binding of glucose to the β chain of haemoglobin in circulating red blood cells. The reaction between circulating glucose and haemoglobin is spontaneous and non-enzymatic, therefore HbA_{1c} formation is dependent on glucose concentration and duration of exposure. HbA_{1c} is formed slowly and continuously throughout the ~120-day lifespan of the red cell; however, due to the continual turnover of red cells in circulation, the most recent 60 days account for up to 75% of the influence on HbA_{1c} concentration.

Glucose, in the open-chain format, binds to the N-terminal valine of the β chain of haemoglobin A₀ [2] to form an aldimine (Schiff base), before undergoing an Amadori rearrangement to form a more stable ketoamine [3, 4] (Figure 29.1). This is a non-enzymatic process that occurs continuously *in vivo* [4]. Glycation of haemoglobin is atypical, because the reaction occurs predominantly between glucose and the N-terminal valine of the β chain of haemoglobin to

form HbA_{1c} [5]. Although this is the favoured reaction *in vivo*, other aldoses (galactose, maltose, lactose) may form haemoglobin adducts and other amino groups (α-chain N-terminal, various ε-amino groups on both the α and β chains) can be glycated [6]; these adducts contribute to the measurement of total HbA_{1c}.

Clinical drivers for standardization of HbA_{1c}

Early studies indicated that monitoring of HbA_{1c} allowed changes in therapy and subsequent reduction of measured HbA_{1c}, but did not categorically show that these changes improved overall outcomes [7]. The lack of standardization, both in terms of analytical performance and clinical utility, meant there were no uniform HbA_{1c} target values for maintaining blood glucose; accordingly, there was no consensus on whether strict glucose targets were of benefit in improving outcomes. This changed, however, with the publication of the DCCT and UKPDS studies [8, 9]. These large longitudinal studies, involving people with type 1 diabetes and type 2 diabetes, respectively, addressed the question of whether tight management of glucose levels resulted in a decrease in complication rates.

The DCCT study was a multicentre, randomized clinical trial in people with type 1 diabetes. The study was designed to assess if intensive therapy could be used to prevent or delay the progression of early vascular or neurological complications, using retinopathy as the primary study outcome. The treatment goal for the conventional therapy group was an absence of symptoms attributable to glycosuria or hyperglycaemia, whereas the intensive therapy group targets were near-normal glucose levels. The primary outcome measure of the study was a sustained change in levels of retinopathy; over the mean follow-up period of six years, the intensive therapy reduced the adjusted mean risk by 76% ($p < 0.001$).

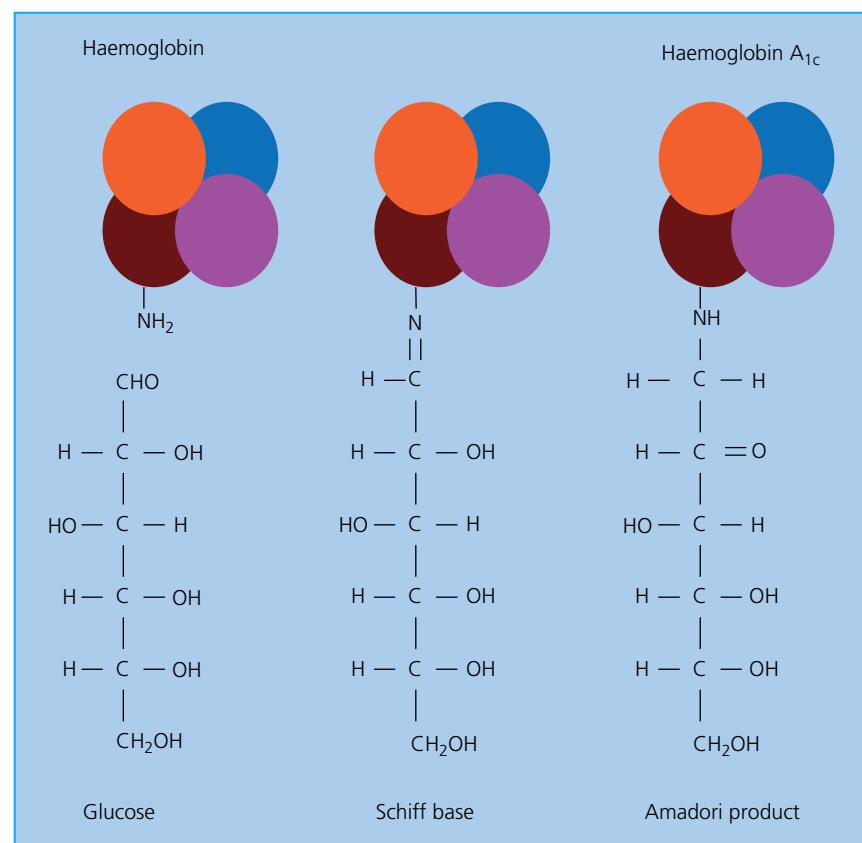


Figure 29.1 The Amadori reaction.

The EDIC study followed the individuals enrolled in the DCCT study for a further 20 years, with no attempt to formally continue the original therapy regimens of the DCCT study. Mean HbA_{1c} values converged between the two groups as a result of the changes in clinical practice brought about by the results of the original trial. The EDIC follow-on study showed that the reduction in risk for any fatal and non-fatal cardiovascular disease event (including confirmed angina, or the need for coronary artery revascularization) was 42% in intensive versus conventional treatment groups and 5% in fatal and non-fatal myocardial infarction and stroke [10].

The UKPDS study recruited individuals with newly diagnosed type 2 diabetes who were randomized by weight, then into conventional and intensive therapy regimens [9]. The conventional regimen aimed to avoid marked hyperglycaemia (fasting plasma glucose >15 mmol/l and/or symptoms of hyperglycaemia) and was primarily based on diet and lifestyle advice alone. The intensive therapy group aimed to achieve a fasting plasma glucose <6.0 mmol/l with treatment using insulin or sulfonylureas. Unlike the DCCT study, a target value of HbA_{1c} was not assigned in either of the therapy groups. In regard to the study endpoints, the reduction in microvascular complications was the most significant with a reduction of 25% in the intensive therapy group, predominantly attributable to retinopathy (two-stage progression of disease).

After the completion of the UKPDS, the individuals continued to be monitored in a follow-up study to determine if there were longer-term effects of the therapy regimens [11]. The follow-up showed a 24% risk reduction in microvascular complications, 15% risk reduction in myocardial infarction, and 13% risk reduction for all-cause mortality. This risk reduction, despite the loss in differences of HbA_{1c}, has been termed the *legacy effect*. When the relative risk profiles for micro- and macrovascular complications are compared, they show a significantly different profile: higher HbA_{1c} values contribute to a greater proportional risk in cases of microvascular disease, but a wider range of HbA_{1c} (including lower ‘non-diabetic’) values contribute to increased risk in macrovascular disease.

These two seminal trials showed that early, intensive therapy could significantly reduce the risk of a range of complications, even after the initial therapy has been discontinued. Accordingly, these studies established precise target HbA_{1c} values for treatment goals. This led to the urgent need for standardization of HbA_{1c} measurement for treatment targets to be globally applicable.

The lack of international standardization led to the development of national schemes for harmonization of HbA_{1c} results. The most commonly known is the US National Glycohemoglobin Standardization Program (NGSP), which uses the method utilized during the DCCT as a primary reference method. While this allowed reference to DCCT values, it suffered from interferences from non-HbA_{1c} components and there is no primary reference material.

In 1995 the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a working group with the remit of achieving uniform international standardization of HbA_{1c} [12]. In 1997 an international network of reference laboratories was formed to implement the newly devised reference measurement procedure for HbA_{1c}. Inter-comparison studies demonstrated a stable relationship between the IFCC reference measurement procedure and national harmonization schemes, allowing for the development of master equations to allow conversion between the more accurate IFCC values and national harmonization schemes such as the NGSP [13]. Due to difference in values between the systems, the decision was also made to adopt SI

units for HbA_{1c} to avoid confusion of apparently lower HbA_{1c} values and subsequent risk of misinterpretation of results, with the introduction of standardized values. The change of units also reduced potential confusion between reports of blood glucose levels in mmol/l and HbA_{1c} measurements. By contrast, in countries that still use mg/dl, the potential for confusion increased and this is one of the reasons why the American Diabetes Association (ADA) has not adopted the new units. Nevertheless, there is an ongoing need for a considerable education initiative to inform both people with diabetes and clinicians of the change.

The international reference network for HbA_{1c} standardization has now been established for nearly two decades and is the only recognized international system to which all manufacturers of HbA_{1c} test devices should be calibrated. Many of the secondary reference methods used by the IFCC network for assigning values to calibrator materials are also the NGSP secondary reference methods; this ensures that the master equation between the two systems remains stable and that measured HbA_{1c} values can be converted from SI units to % for those who still wish to understand the values in DCCT/UKPDS terms. Master equations for the conversion between IFCC and NGSP units are as follows:

$$\text{NGSP}(\%) = [0.0915 \times \text{IFCC}(\text{mmol/mol})] + 2.15$$

$$\text{IFCC}(\text{mmol/mol}) = [10.93 \times \text{NGSP}(\%)] - 23.50$$

The global consensus statement on HbA_{1c} states that HbA_{1c} results are to be reported by clinical laboratories worldwide in SI units (mmol/mol – no decimals) and derived NGSP units (% – one decimal), using the IFCC–NGSP master equation (DCCT units) [1]. The conversion equation is available on numerous websites and in other publicly available resources.

Diagnosis of type 2 diabetes using HbA_{1c}

The successful implementation of standardization of HbA_{1c} measurement paved the way for HbA_{1c} to be introduced for the diagnosis of type 2 diabetes [14]. An International Expert Committee, appointed by the ADA, the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD), published a report in 2009 recommending the use of HbA_{1c} for the diagnosis of diabetes [15]. Based on the evidence that HbA_{1c} level correlates with adverse disease outcomes and the fact that HbA_{1c} targets are used for individual treatment, use of HbA_{1c} as a diagnostic tool seemed a logical progression. The committee proposed a diagnostic cut point of 48 mmol/mol (6.5%) HbA_{1c}. In 2011 the World Health Organization (WHO) also endorsed the use of HbA_{1c} for the diagnosis of type 2 diabetes, stating:

HbA_{1c} can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. [14]

Assays for measurement of HbA_{1c}

There are a wide range of methods used for the routine analysis of HbA_{1c}. They can be divided into methods that are based on charge differences, including cation-exchange high-performance liquid chromatography (HPLC) and capillary electrophoresis, and those that separate based on structural differences such as enzymatic, immunoassay, and boronate affinity separation methods. The analytical

performance goals for all methods have been defined and are based on sigma metrics. This allows both analytical imprecision and bias to be considered together, through a measure of total analytical error [16]. Quality targets are necessary for HbA_{1c} measurement, as the difference between HbA_{1c} values considered low risk for diabetes and the level diagnostic of diabetes is very small. In some countries this range is as low as 42–48 mmol/mol, meaning that relatively small levels of bias and imprecision can have a significant impact on a clinical diagnosis. For example, if a person's true HbA_{1c} value were 45 mmol/mol, a positive or negative bias of 2 mmol/mol and imprecision of 3% could easily generate values in the diagnostic range for diabetes or the low-risk range, respectively. Since the publication of these goals, there has been annual monitoring of laboratories around the world through national External Quality Assessment (EQA) schemes. The number of laboratories that participate in the EurA_{1c} trial is steadily growing, with >5000 participants within five years of the study commencing. The data generated give an overview of performance by country and by manufacturer, allowing targeted quality improvement measures to be devised and implemented [17].

Point-of-care HbA_{1c}

Point-of-care test devices are often considered a valuable addition to a clinician's armament in managing diabetes. They play an increasingly important role in wide range of clinical settings and there is increasing desire from clinicians to have access to more point-of-care tests [18]. Point-of-care testing is promoted as enabling faster clinical decision making, increased rapport with people with diabetes, and reduced referrals to secondary care and subsequent healthcare costs. However, there are also perceived barriers to implementation of point-of-care testing, including test accuracy, impact on individual pathways, and cost of testing [19].

Evidence of clinical utility for point-of-care testing for HbA_{1c} is mixed with some analyses suggesting a clear benefit, while others found an absence of clinical evidence for the use of point-of-care tests in clinical care [20, 21]. It is clear that there is a potential role for point-of-care testing; however, the accuracy, clinical utility, impact on care pathways, and cost of point-of-care testing should be considered before implementation.

The availability of point-of-care test devices for HbA_{1c} is rapidly expanding and while a small number of manufacturers currently hold market share, the number of providers is set to grow. Several studies have studied the accuracy of point-of-care test devices for HbA_{1c} and there are mixed results in performance [22]. Some devices have been extensively evaluated and can perform to the same level as laboratory devices. In future, pre-qualification of HbA_{1c} point-of-care test devices by the WHO will aid in decision making about the use of these devices more widely in clinical practice.

Factors affecting HbA_{1c} measurement

Both analytical and biological factors affect the measurement of HbA_{1c}. The importance of standardization and excellent analytical performance has already been described; however, there are a number of other factors that may lead to erroneous results in HbA_{1c} measurement (Table 29.1).

Accurate interpretation of HbA_{1c} requires a normal lifespan of erythrocytes. The presence of a shortened lifespan, for example with haemolytic disease or blood loss, can lead to underestimates of the true value. By contrast, iron-deficiency anaemia, which is associated with a longer lifespan, can be associated with an overestimate of the true value [23].

Table 29.1 Conditions that can affect the measurement of glycated haemoglobin (HbA_{1c}).

Haemoglobinopathies
Iron deficiency
Chronic kidney disease stage 4 and above
Ethnicity
Blood transfusion
Haemolysis (haemolytic anaemia)
Polycythaemia
A wide range of drugs including those used to treat HIV infection

Approximately 7% of the global population has a haemoglobin variant and these present both biological and analytical issues. The most common haemoglobin variants, in descending order of prevalence, are HbS, HbE, HbC, and HbD. Heterozygous carriers of these variants are often asymptomatic and generally have normal red-cell lifespans. There is no clear evidence on whether the structural changes in haemoglobin, due to the variants, directly affect glycation of the β chain at the N-terminal valine (to form HbA_{1c}); however, it is reasonable to assume that substitutions at the glycation site could alter the rate of glycation. Caution should be used when interpreting HbA_{1c} results from individuals with HbSS, HbCC, and HbSC, as the pathology of these diseases leads to anaemia, increased red-cell turnover, and transfusion requirements, which have adverse impacts on HbA_{1c} as a marker of long-term glycaemic levels. Alternative tests such as glycated serum protein (fructosamine) or glycated albumin should be considered for these individuals.

Some methods, such as ion-exchange chromatography and capillary electrophoresis, are capable of identifying the presence of a haemoglobin variant while others do not. Some methods are affected by haemoglobin variants and will give erroneous results. There is no set rule as to which method will or will not be affected by each variant, although the NGSP provides an updated list of methods and how they perform with common variants [24]. Some laboratories routinely report the identification of new variants; it is important to liaise with your local laboratory to assess the impact of potential variants on the local clinical population.

Chronic kidney disease affects 9% of the global population and has historically been cited as a cause of erroneous HbA_{1c} results due to the increased carbamylation of haemoglobin from urea. Modern HbA_{1c} methods are generally not affected by increased carbamylated haemoglobin and thus this is no longer a clinical issue. However, there is still a statistically significant divergence between HbA_{1c} values and fasting plasma glucose with increasing chronic kidney disease stages. Diabetes is a leading cause of chronic kidney disease and the two are often present concomitantly.

Studies so far suggest that chronic kidney disease stages 1–2 appear not to have a significant impact on HbA_{1c}, but chronic kidney disease stages 4–5 are consistently reported to influence HbA_{1c}, thus limiting its use in these stages. Most studies show that HbA_{1c} is underestimated compared to other markers of glycaemia either before or after the use of erythropoiesis-stimulating agents. Likewise, underestimation of HbA_{1c} is observed in individuals on dialysis, either haemodialysis or peritoneal dialysis. Nonetheless, despite the high prevalence of chronic kidney disease, little evidence of the effect of chronic kidney disease stages 3–4 on HbA_{1c} is available and, in particular, on the role of anaemia, which is a common

comorbidity. Individuals with diabetes and chronic kidney disease often develop anaemia, which can lead to increased HbA_{1c} values due to erythropoietin deficiency and iron-deficiency anaemia (through elongation of the erythrocyte lifespan) or decreased HbA_{1c} caused by reduced red blood cell survival, increased erythrocyte turnover, or administration of erythropoietin. Non-iron-deficiency anaemia, if present, may falsely decrease HbA_{1c} levels. Health professionals should be aware of these erroneous results when monitoring glycaemic levels or when using HbA_{1c} for diagnosis of type 1 diabetes.

Several studies report an increase in HbA_{1c} with increasing age, with mixed opinion as to whether this is a glucose-dependent or -independent process. Increases in HbA_{1c} may simply reflect a decline in glycaemia over time; however, there is evidence to suggest that the change in HbA_{1c} is not simply related to a change in glycaemia alone and that HbA_{1c} increases with age independent of glycaemia. The discordance between glucose and HbA_{1c} is more apparent between the two-hour glucose of an oral glucose tolerance test. While the overall increase in HbA_{1c} per decade is small, when considering this over a range of 70 years the absolute difference can be clinically meaningful.

Since the introduction of HbA_{1c} for the diagnosis of type 2 diabetes, there have been numerous studies that have shown that HbA_{1c} and fasting plasma glucose identify different populations. While there is considerable overlap between the two groups, there are still people who will be diagnosed with type 2 diabetes with one method but not the other. Some of the discrepancy is due to differences in ethnicity. A recent random effects meta-analysis of multiple studies demonstrated that HbA_{1c} ranged from 1.1 to 3.0 mmol/mol lower in White populations compared to Hispanic, East Asian, Black, and South Asian populations. However, it remains unclear whether there should be differentiated HbA_{1c} diagnostic thresholds for type 2 diabetes for different ethnic groups based on risk of clinical complications. Policy makers and clinicians should be aware of the evidence indicating racial or ethnic differences when delivering a more personalized medicine approach.

Fructosamine and glycated albumin

Fructosamine is the generic name for plasma protein ketoamines. Albumin is the predominant plasma protein and constitutes a significant proportion of the fructosamine value. Fructosamine reflects the average glycaemic exposure of the preceding 1–3 weeks. It may be useful in individuals where the measurement of HbA_{1c} is precluded, for example in pregnancy where glucose levels change rapidly, or in the preconception period where motivation to improve glycaemia is high and the changes can be evaluated at shorter intervals. Fructosamine measurement is not appropriate for routine use because the assay is markedly affected by excessive turnover or excretion of albumin in, for example, renal disease. Data are currently limited on the correlation between fructosamine and HbA_{1c}, with wide confidence intervals around the diagnostic cut point of 48 mmol/mol and no direct outcome data linking fructosamine and diabetes-related complications [25]. Indirect linkage via comparison with HbA_{1c} is of limited value at this stage and further work is needed to improve its clinical utility.

Glycated albumin is the most abundant glycated serum protein and has been advocated as a more sensitive marker of glycaemia than fructosamine due the reduced heterogeneity of the lifespan of the protein. While fructosamine levels tend to decrease in the third

trimester of pregnancy, due to the dilutional effects of an increased blood volume, glycated albumin levels tend to remain relatively constant in women without diabetes, because it is measured as a ratio of glycated to total serum albumin.

Albumin has a shorter lifespan in comparison to erythrocytes (~20 days). Therefore, glycated albumin is a better measure of shorter-term glycaemic levels than HbA_{1c} and is more likely to be affected by rapid fluctuations in blood glucose levels; this means that it may better reflect post-prandial increases in plasma glucose in comparison to HbA_{1c}. To date there is increasing evidence of the correlation of glycated albumin and HbA_{1c} values especially in diabetes, but there is currently limited translation of this into a marker of complications. As such, glycated albumin may be a useful marker in individuals where HbA_{1c} cannot be used. Methods for glycated albumin have now been harmonized and are relatively well characterized, meaning they may become an increasingly useful tool in the management of people with diabetes.

Measurement of blood glucose

The measurement of glucose is used for both diagnosis and monitoring of diabetes. Glucose measurement can enable the diagnosis of diabetes, impaired glucose tolerance, or impaired fasting glycaemia; the latter two are intermediate states of abnormal glucose metabolism that exist between normal glucose homeostasis and the overt hyperglycaemia of diabetes. Analysis of glucose in a blood sample is performed either in a clinical laboratory or by point-of-care testing (either by people with diabetes themselves or by healthcare professionals at the bedside or in clinic). Blood glucose measurement is a term that is frequently used without precise definition. Measurement of glucose levels is usually carried out on either capillary or venous specimens of blood; serum analysis is less common. Under usual circumstances, the concentration of glucose in whole blood is ~10–15% lower than in plasma. This is because a given volume of red blood cells contains less water than the same volume of plasma. Capillary blood glucose concentrations are very similar to venous blood levels in the fasting state; however, after a glucose load capillary samples may be up to 25% higher than simultaneously drawn venous blood samples [26]. Table 29.2 shows the equivalent measurements from the different sample types.

Blood glucose levels are expressed in SI units as millimoles/l (mmol/l). The traditional unit for measuring blood glucose is milligrams/decilitre (mg/dl), although use of these units is now largely confined to the USA. To convert mmol/l glucose to mg/dl, multiply by 18 (Table 29.2). Blood specimens for analysis of glucose levels need to be taken under controlled conditions as they are subject to

Table 29.2 Differences in blood glucose values dependent on sample type.

Time of measurement	Glucose concentration (mmol/l) ^a			
	Plasma		Whole blood	
	Venous	Capillary	Venous	Capillary
Fasting	≥7.0	≥7.0	≥6.1	≥6.1
2 h after a glucose load	≥11.1	≥12.2	≥10.0	≥11.1

^a 1 mmol/l = 18 mg/dl.

continuing glycolysis by red blood cells, which is enhanced by the presence of leucocytosis. The continuing glycolysis should be avoided by collection onto ice, rapid centrifugation, and analysis within 30 minutes [27]; however, this is impractical in many routine clinical settings. The use of blood collection tubes containing sodium fluoride inhibits further glucose metabolism, although there is still some loss of glucose for the first two hours post-collection, when the amount of glucose lost could be as much as 15% of the original concentration. If an individual has an intravenous line *in situ*, blood should be drawn from the arm opposite to the one with the line to prevent contamination of the sample from any infusion. Clinicians should be aware of these potential limitations of blood glucose measurement.

There are three basic approaches to the laboratory measurement of blood glucose concentration: reducing methods, condensation methods, and enzymatic methods. Most laboratories utilize hexokinase and glucose oxidase enzymatic methods, with only a small proportion of laboratories using glucose dehydrogenase methods. Reducing methods and condensation methods are cheaper than enzymatic methods, but they are more prone to interferences from strong reducing agents or other sugars.

Point-of-care test devices for blood glucose

Glucose oxidase and glucose dehydrogenase methods are those most commonly used in handheld point-of-care test devices. Most systems include strips that contain all the reagents necessary for analysis in a single-use disposable unit. Blood is applied to the end of the strip either directly or through capillary action by touching the strip to the blood droplet being analysed.

Some meters additionally incorporate the facility to measure blood ketone levels, of particular importance for people with type 1 diabetes. Other meters have the facility to calculate insulin bolus requirements or to download blood glucose results for evaluation of the pattern of glucose levels over time.

Most of the currently marketed handheld capillary blood glucose meters give results as an equivalent to venous plasma glucose, but this is not always the case. The same type of handheld meter may be calibrated to report whole blood glucose in one country and plasma values in another. The calibration of a meter should be checked and the thresholds for action set accordingly. Factors that affect the accuracy of point-of-care test devices for blood glucose are shown in Table 29.3.

Table 29.3 Factors that affect the accuracy of point-of-care test devices for blood glucose.

- Direct chemical interferences with substances such as acetaminophen and ascorbate (vitamin C)
- Blood oxygen concentrations in systems using glucose oxidase
- Changes in blood viscosity and haematocrit
 - Oedema
 - Dehydration
 - Hyperosmolar hyperglycaemia syndrome
 - Sepsis
 - Poor sampling by massaging sample site
- Errors arising from transcription errors (when not electronically linked)
- Impact of environmental conditions
 - Temperature
 - Humidity
 - Altitude

Point-of-care testing, utilizing capillary blood glucose measurement, can be used to replace venepuncture in many settings, with greater comfort and more rapidly available results for monitoring individuals in an acute situation. Standards have been laid down to ensure that bedside glucose determinations can be made accurately and include the need for well-defined policies, which incorporate adequate training, quality control procedures, and regular maintenance of equipment [28]. This guidance differs from that provided for devices that are intended for self-monitoring of blood glucose by individuals with diabetes.

Self-monitoring blood glucose devices

Devices used for self-monitoring of blood glucose must meet ISO 15197:2013 standards; in addition other standards may be dictated by national or local guidance. It is of note that people with diabetes often assume that their devices are accurate because they meet the standards prescribed or carry approval from the US Food and Drug Administration (FDA) or the European Conformité Européenne (CE) mark, although this is not always the case and education plays a key role in supporting people with diabetes to identify incorrect data from their device [29]. Despite their imprecision, blood glucose meters remain particularly helpful at higher blood glucose values, where, for example, it is of less importance to distinguish a plasma glucose of 11 mmol/l (198 mg/dl) from one of 14 mmol/l (252 mg/dl). In such circumstances, the aim of management is to achieve a substantial reduction in plasma glucose. At lower plasma glucose levels, however, the consequences of imprecision of 15% are much greater.

Accuracy of devices is dependent on both the user and the device, therefore evaluation of the individual's technique when using their device is advised at regular intervals. Correct sampling for self-monitoring of blood glucose devices is important for accurate results and is detailed in information for users for each device, as well as in publications such as the WHO Guidelines on Drawing Blood (Figure 29.2) [30]. The most common site of sampling is the pad of the finger; alternative sites for sampling include the base of the thumb, forearm, and thigh. Pre-meal readings will be the same between sites, but at times of rapid glucose change



Figure 29.2 The correct technique for self-monitoring of blood glucose improves the accuracy of testing.

(in the post-prandial period or during hypoglycaemia), forearm and thigh results will be different from fingertip results, because glucose changes lag behind the fingertip results.

Newer devices can store and upload data to mobile devices or computers, may allow reapplication of blood to the sample strip if the first sample is insufficient, and utilize very small volumes of blood. This allows for smaller, thinner lancets to be used, which reduces discomfort for the individual and encourages ongoing testing. Calibration and issues such as erroneous readings when test strips are incorrectly inserted have largely been ameliorated with updates in technology and thus further reduce the risk of errors.

Continuous glucose monitoring

CGM devices use a broad range of analytical techniques to assess glucose levels. The development of these devices has arisen from the increasing awareness of the need for individuals to have optimal glycaemic levels. CGM devices use a range of techniques, from predominantly non-invasive through to invasive methods. All of these devices work on the sampling of interstitial fluids on the basis that this correlates with blood glucose levels. For further details refer to Chapter 32.

Estimated average glucose

Estimated average glucose (eAG) values have been derived from the correlation between mean HbA_{1c} levels and mean blood glucose levels in the A_{1C}-Derived Average Glucose (ADAG) study [31,32]. The mean glucose levels were determined from self-monitoring of blood glucose and CGM measurements and calculated by combining weighted results from at least two days of CGM performed four times, with seven-point daily self-monitoring of capillary glucose performed at least three days per week. Numerous calculators are available online for the calculation of estimated average glucose from HbA_{1c}. The ADA and the American Association for Clinical Chemistry have determined that the correlation in the ADAG data is strong enough to justify inclusion in the Standards of Medical Care in Diabetes [33]; however, this is not a universally accepted calculation due to the wide range in glucose levels reported for each HbA_{1c} level.

Measurement of glucose in urine

The presence of glycosuria can be identified by semi-quantitative or quantitative glucose methods. The use of dry reagent test strips for urine dipstick analysis allows cheap, rapid, and portable urine analysis. Urine specimens should be analysed immediately, preserved at pH<5 to inhibit bacterial metabolism or stored at 4°C. Chemical reactions and subsequent visual assessment of the colour against a printed colour chart yield a semi-quantitative result. As a consequence of their condition, many people with diabetes are prone to visual difficulties and this has been a major operator-dependent step with visually monitored systems, in particular distinguishing the small variations in blues and blue-green colours produced by many of the test strips. Automated urinalysis machines are now available that can accurately determine colour changes in samples, making them a cheap and rapid method for screening large numbers of samples. Quantitative methods utilize hexokinase or glucose dehydrogenase methods.

The clinical utility of urine glucose measurement is limited, as it does not reflect the changing levels of hyperglycaemia with any accuracy. In addition, the renal threshold above which glucose is excreted in the urine varies between individuals and during pregnancy and with ageing. Nevertheless, it may have a role in resource-poor settings where identification and treatment of individuals with suboptimally managed diabetes are the highest priority.

Measurement of ketones

Diabetic ketoacidosis (DKA) is a commonly encountered diabetes-related emergency with appreciable morbidity and mortality. Reports of euglycaemic DKA in people with diabetes using sodium-glucose cotransporter 2 (SGLT-2) inhibitors means that clinicians and people with diabetes should be aware of the possible testing options [34]. Ketone bodies are derived from the catabolism of free fatty acids to form acetoacetate, acetone, and β-hydroxybutyrate. Acetoacetate and β-hydroxybutyrate are normally present in equimolar concentrations; however, due to increased levels of nicotinamide adenine dinucleotide + hydrogen (NADH) present in severe diabetes, the ratio may shift towards β-hydroxybutyrate up to 6:1, and thus methods for ketones that only detect acetoacetate may significantly underestimate the degree of ketosis. Therefore, methods that measure β-hydroxybutyrate are preferable in the monitoring of individuals with DKA. Like all laboratory and point-of-care testing methods, rigorous quality assurance procedures should be in place, along with training of users to understand the limitations of the devices and where to seek help and advice in their use.

Clinical approaches to monitoring in diabetes

Effective monitoring of glycaemia requires a partnership between healthcare professionals and the person with diabetes. Optimal testing intervals and the balance between use of laboratory testing and self-monitoring require consideration of a range of factors, extending from wholly clinician-directed testing (e.g. during acute illness in a hospital setting) to self-monitoring by a person with diabetes in the community who is otherwise well. The approach to this discussion with people with diabetes should be person centred and communication should be strength based, with a focus on active listening to ensure that the individual's beliefs, abilities, and barriers to care can be fully considered. As well as person-centred communication, care should be offered from multidisciplinary teams to present a holistic approach to treatment.

Self-monitoring of blood glucose

Self-monitoring of blood glucose, in conjunction with diabetes self-management education and support, is an integral part of self-care for people with type 1 diabetes to maintain levels of blood glucose that minimize risks of complications. In addition, it is required for people with type 2 diabetes using insulin, and for some people with type 2 diabetes who have specific indications [35,36]. When correctly done, glucose monitoring enables people with diabetes to assess their individual response to therapy and provide insight into their achievement of their target goals. The ability to accurately record data from self-monitoring of blood glucose devices in the

individual's records enables more effective diabetes management and guides medical nutrition therapy, physical activity, identification of risk of hypoglycaemia, and adjustment of medications (particularly prandial insulin doses). The individual's specific needs, capabilities, and goals should dictate the frequency of self-monitoring of blood glucose and timing or the consideration of CGM use. For further detail on testing using CGM including frequency, refer to Chapter 32.

is a representative example. Blood glucose levels for critically ill individuals should be maintained between 7.8 and 10.0 mmol/l (140 and 180 mg/dl), although a lower target of 6.1–7.8 mmol/l (110–140 mg/dl) may be aimed at, provided that there is no increase in the incidence of severe hypoglycaemia [40]. Self-management of diabetes in the hospital setting may be appropriate where adult individuals are alert, able to self-manage their diabetes at home, and have stable requirements for insulin. This may also offer an opportunity for providing support in learning techniques of insulin adjustment in line with carbohydrate intake.

Monitoring in type 1 diabetes

Glycaemia should be assessed using HbA_{1c} measurement in all adults with type 1 diabetes every 3–6 months. This could be increased if a person's blood glucose is thought to be rapidly changing due to treatment changes or when they are not meeting their treatment goals [33, 37]. As detailed in the previous sections, HbA_{1c} methods should be calibrated to the IFCC standardization and enrolment in an EQA scheme is strongly recommended. In the USA and some other countries, methods are also expected to be certified by the NGSP. Targets for HbA_{1c} vary between different guidelines and are dependent on multiple factors. Goals are set to minimize risk of long-term complications, but individualized targets should be agreed based on lifestyle and previous experience of hypoglycaemia. HbA_{1c} values of 48 or 53 mmol/mol (6.5% or 7.0%) are common goals, although these may differ in older adults and those with multiple comorbidities [33, 37].

Adults with type 1 diabetes should also be encouraged and supported to routinely undertake self-monitoring of blood glucose, and test at least four times a day (including before each meal and before bed). This may be increased to up to ten times a day when treatment goals are not being reached, when hypoglycaemic episodes are increasing in frequency, when the individual's employment or legal restrictions require it, during increased activity, or during periods of illness. The use of CGM devices for monitoring is becoming increasingly common.

Education is an essential tool to empower individuals with diabetes to monitor their blood glucose, and they should be taught how to use the blood glucose data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. However, tight glucose levels bring with them the risk of hypoglycaemia, which in turn may occur more frequently in people with suboptimally managed diabetes [38]. Additional checks on blood glucose levels should be made in relation to the risk of hypoglycaemia, for example before exercise or driving and in the presence of symptoms that may indicate hypoglycaemia.

Targets for blood glucose level vary between different guidelines. The ADA guidance recommends pre-prandial capillary plasma glucose of 4.4–7.2 mmol/l (80–130 mg/dl) and peak post-prandial capillary plasma glucose of 10.0 mmol/l (<180 mg/dl) [33].

Children and young adults with type 1 diabetes and their caregivers should be given age-related and culturally appropriate education for self-monitoring of blood glucose. Guidance on frequency varies from a minimum to five times a day and upwards; CGM is also advocated [39]. Glucose concentration targets are similar to those of adults; however, HbA_{1c} targets vary more widely depending on the source of the guidelines.

Guidance for monitoring diabetes in a hospital setting varies depending on the guideline and the resources available; the following

Monitoring in type 2 diabetes

For people with type 2 diabetes, the overall level of glycaemia should be monitored using HbA_{1c} every 3–6 months until stable and there is no change in therapy. For those with stable blood glucose levels and no changes in therapy, every 6 months is sufficient. The majority of HbA_{1c} values are still provided via centralized laboratories; however, there is increasing interest in the use of point-of-care test devices to enhance community-based care pathways. Currently there is no guidance that actively supports routine use of point-of-care HbA_{1c} for diagnosis of diabetes, although there are examples of effective use of point-of-care HbA_{1c} in the community-based care of people with type 2 diabetes, such as the Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus) system [41].

Setting HbA_{1c} targets for people with type 2 diabetes is important to guide decisions about treatment and to provide feedback to the individual and clinician about the effectiveness of treatment. The level at which targets should be set for an individual remains widely debated. Although guidelines provide advice about generally accepted targets, individuals need to be involved in decisions about their own HbA_{1c} target. Once available, the results of tests should be used to encourage people to achieve and maintain their target unless they develop hypoglycaemia.

If HbA_{1c} measurement is unavailable, then a fasting plasma glucose measurement can be used to indicate need for, or response to, a treatment that leads to a reduction in fasting hyperglycaemia (e.g. metformin or a sulfonylurea). A fasting capillary plasma glucose level of 3.9–7.2 mmol/l is recommended as a target.

The approach to self-monitoring of blood glucose in people with non-insulin-treated type 2 diabetes is mixed. Guidelines for treatment of people with type 2 diabetes draw attention to the lack of evidence for effectiveness and cost-effectiveness of routine use of self-monitoring of blood glucose and recommend that it should not be routinely used. Although there is some evidence that testing may improve glycaemic levels in some people, there is similarly evidence that data are frequently not acted on and that the benefit does not outweigh the cost. It continues to have a place where there are concerns about hypoglycaemia (e.g. use of sulfonylurea) or HbA_{1c} measurements are not possible or do not provide an accurate measure of glycaemia.

For people with type 2 diabetes who are using insulin, self-monitoring of blood glucose is needed to adjust insulin dose and check that glucose levels are maintained, although optimal use remains to be established. Frequency and targets are similar to those with type 1 diabetes.

Diabetes in pregnancy

Diabetes in pregnancy and gestational diabetes (diabetes first identified during pregnancy) are rising in prevalence. Pre-conception care for women with diabetes is important, with glycaemic targets as near normal as possible ($\text{HbA}_{1c} < 48 \text{ mmol/mol} (< 6.5\%)$) to reduce the risk of complications during pregnancy and birth, including macrosomia, pre-eclampsia, and congenital abnormalities. The results of the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) demonstrated that the use of CGM was associated with improved neonatal outcomes and led to the recommendation that all pregnant women with type 1 diabetes, or those without type 1 diabetes but on intensive insulin therapy, be offered CGM [42]. Further details are provided in Chapter 71.

Monitoring of diabetes in special situations

Bariatric surgery

Bariatric surgery is being increasingly used in the management of people with type 2 diabetes and obesity. Post-surgery, blood glucose levels may return to near-normal levels for prolonged periods of time, with HbA_{1c} values within the normal range. These individuals are determined to have diabetes in remission. While each of the measures used to diagnose diabetes is valid, the preferred test for identification of diabetes remission is HbA_{1c} at $< 48 \text{ mmol/mol} (< 6.5\%)$ for three months or more with no glucose-lowering pharmacological intervention; the same caveats to the use of HbA_{1c} for diagnosis and monitoring apply to this situation. As implied by the term *remission*, there is a need for ongoing monitoring of these people for complications of diabetes, including retinal screening, renal function, foot evaluation, and measurement of blood pressure and weight, in addition to ongoing monitoring of HbA_{1c} . The frequency of HbA_{1c} measurement should not be more often than every three months nor less frequent than yearly to confirm continuation of the remission, in line with monitoring of stable type 2 diabetes [43].

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Low-resource settings

While data and guidance advocate timelines and tests for monitoring of diabetes, the management of diabetes is very costly. Estimates of test costs vary immensely, but it is unlikely that the cost of prescribed monitoring can be met in many low-resource settings. The myriad of different environmental and economic factors around the use of diabetes testing mean that testing is often suboptimal. While urine dipsticks for glucose are inexpensive and portable, they are non-specific, non-quantitative, and not sensitive to small changes in blood glucose levels. Blood glucose testing necessitates adequate fasting and temperature-sensitive reagents, and CGM devices are very expensive. HbA_{1c} is a preferred monitoring test as fasting is not required and it is a longer-term marker of glycaemic levels, but point-of-care test devices are still quite cumbersome and not yet truly adapted for the low-income setting. WHO and other non-governmental organizations are actively engaged with the development and assessment of point-of-care devices for diabetes testing, and this is an area that is likely to see significant investment, research, and improvement in the future.

Conclusion

Glycaemic levels should be monitored regularly for all people with diabetes. The optimal method of determining risk of long-term complications is through HbA_{1c} measurement, although if this is not available then examination of a series of blood glucose measurements, including fasting tests, may provide guidance. HbA_{1c} methods should be standardized to the IFCC reference measurement procedure and units of reporting are the SI units mmol/mol, with derived percentage units in brackets. The role of CGM in diabetes monitoring is increasing and is likely to become a prominent feature of diabetes care in the future. New considerations for diabetes monitoring, such as in the remission of diabetes post-surgical intervention, will continue to be identified, and there is a critical need for investment and research into low-cost, robust, and accurate testing for low-resource settings.

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31 Insulin and Insulin Treatment

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Key points

- Insulin is a peptide hormone essential for life. It is released by the pancreatic β cells in the fasting state to limit catabolism. Post-prandially, insulin secretion is increased to ensure energy storage as carbohydrates, proteins, and lipids, and to stop endogenous glucose production.
- Insulin therapy is necessary in absolute insulin deficiency, as in type 1 diabetes or post-pancreatectomy; however, insulin therapy is also used frequently in states of relative deficiency of endogenous insulin due to insulin resistance, such as type 2 diabetes or gestational diabetes.
- The challenge of insulin replacement therapy is to reproduce a normal physiological insulin profile with low burden to the person with diabetes.
- In 1993, the Diabetes Control and Complications trial showed that intensive insulin therapy can reduce chronic complications of hyperglycaemia, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, in people with type 1 diabetes. The UK Prospective Diabetes Study demonstrated a reduction of diabetes-related complications through tight glycaemic management in people with type 2 diabetes. However, the risk of hypoglycaemia and insulin-induced weight gain remains a major barrier for treatment intensification.
- Early insulins were extracted from the pancreases of pigs and cows, but optimal glycaemia was difficult to achieve due to impurities in the preparation. Newer and purer insulins, and later synthetic human insulins and insulin analogues, are better tolerated and more predictable in terms of their glucose-lowering effect.
- A range of modern insulin preparations with differing durations of actions are available. These include rapid- and ultra-rapid-acting insulin analogues (duration of action ~2–3 hours), soluble insulin (~6–8 hours), neutral protamine Hagedorn (NPH) insulin (12–18 hours), long-acting insulin analogues (~24 hours), and ultra-long-acting insulin analogues (~40 hours).
- Current recommendations for the injection of insulin are to use the abdomen, upper buttocks, upper arms, and upper thighs, and to rotate injection sites to avoid lipohypertrophy. The needle should be injected at right angles to the skin and left there for 10 seconds before removing the needle. Injection needle lengths should be as short as possible to minimize trauma and to avoid intramuscular delivery. For those using insulin pens, 4 mm needles are available. Syringe needles remain at 8 mm. Alternative routes of insulin delivery such as continuous subcutaneous insulin infusion can also be highly effective.
- Multiple-dose insulin (MDI) therapy is an appropriate initial approach to reproduce the physiological insulin profile in people with absolute insulin deficiency such as those with type 1 diabetes. This comprises a long-acting insulin preparation administered usually once a day to meet the basal insulin requirement, with the injection of a short-acting insulin preparation with each meal.
- Novel technologies, such as insulin pumps that administer rapid-acting insulin continuously through a subcutaneous catheter, provide more flexibility for people with type 1 diabetes. Sensor-augmented smart pump therapy, with automated delivery adapted by an algorithm, reduces the combined rate of severe and moderate hypoglycaemia in people with type 1 diabetes.
- Different insulin injection regimens are available for people with varying degrees of residual endogenous insulin production and insulin resistance, including those with type 2 diabetes, who may already be treated with non-insulin-based therapies. These include a once-daily injection of a long-acting insulin, twice-daily injections of insulin mixtures, or a combination of mealtime short-acting and once-daily long-acting insulins. In addition, insulin can be administered in a co-formulation with other injectables such as glucagon-like peptide 1 receptor agonists.

Discovery and early days of insulin therapy

Insulin is a potent anabolic hormone, and its absence induces a profound catabolic state that affects fat, carbohydrate, and protein stores. Absolute insulin deficiency, as in type 1 diabetes, will result in death if left untreated. In the pre-insulin era, the most effective therapy appeared to be severe nutritional restriction, perhaps most popularly

expounded by Frederick Allen from the Rockefeller Institute in New York [1]. This, however, was a difficult regimen that did not appear to prolong life expectancy significantly, and when death came it was unclear whether it was the result of diabetes or starvation.

The relevance and therapeutic potential of insulin arose from the seminal experiments of Frederick Grant Banting and his student Charles Best, although there had been several previous attempts at

identifying a pancreatic agent that could regulate blood glucose, most notably by the Romanian physiologist Nicolas Paulescu. With the logistical support of John Macleod and help from biochemist James Collip, Banting and Best succeeded in the isolation and purification of an *internal pancreatic secretion* that could normalize glycaemia in pancreatectomized dogs (Figure 31.1). For this work, Banting and Macleod shared the Nobel Prize in Medicine in 1923. In recognition of the essential contributions of the team members, Banting split his prize money with Best, and Macleod shared his portion with Collip. Banting, Best, and Collip shared the patent for insulin, which they sold to the University of Toronto for one Canadian dollar [2]. This remarkable scientific progress took place 100 years ago, and the first dose of insulin was administered to a person with diabetes on 23 January 1922.

Commercially available insulin was initially extracted from porcine and bovine pancreases. This procedure resulted in insulin with a purity of 80–90%, the contaminants largely being pancreatic polypeptides and glucagon. Though this insulin was effective, its use was often complicated by immune-mediated side effects, in particular lipoatrophy and antibody-mediated insulin resistance [3], both of which could profoundly influence the kinetics of insulin action. It was not until 1980 with the introduction of recombinant DNA technology that human insulin therapy became widely available, with purification achieving 99.5–99.9% insulin purity, thus virtually eliminating problems associated with immune-mediated side effects [4].



Figure 31.1 Charles Best and Frederick Banting on the roof of the medical building at the University of Toronto, Summer 1921.

Both beef- and pork-derived insulin remain available in many countries, but leading insulin manufacturers have phased out animal insulins in favour of modern recombinant human insulins. A meta-analysis of 45 randomized controlled trials involving 2156 participants comparing animal and human insulin did not show a significant difference in achieved glucose levels between these two therapies [5].

Advances in insulin manufacturing involved the manipulation of the insulin molecule, resulting in the design and production of shorter- and longer-acting insulin analogues [6]. Analogue insulins are currently favoured due to the closer mimicry of the physiological insulin profile and reduced risk of hypoglycaemia, although generally they are more expensive than human insulin. While those responsible for healthcare budgets seek persuasive clinical trial data on improved overall glycaemic levels, it is most unlikely that we will ever see direct head-to-head studies that provide incontrovertible data one way or another. Most of the benefits of the insulin analogues lie in the increased flexibility and protection against hypoglycaemia, and although some of the individual benefits appear small, collectively they are likely to have an impact on many people with diabetes [7].

Modern insulin formulations to reproduce physiological insulin delivery

Insulin is a peptide hormone of 51 amino acids that is secreted by the pancreatic β cells within a narrow physiological range. In the fasting state, insulin circulates at a concentration of 15–20 mU/l to limit catabolism. Post-prandially, insulin secretion increases to 60–80 mU/l to ensure energy storage of nutrients as carbohydrates, proteins, and lipids, and to stop endogenous glucose production (Figure 31.2). The secretion and action of insulin are covered in more detail in Chapters 7 and 9, respectively.

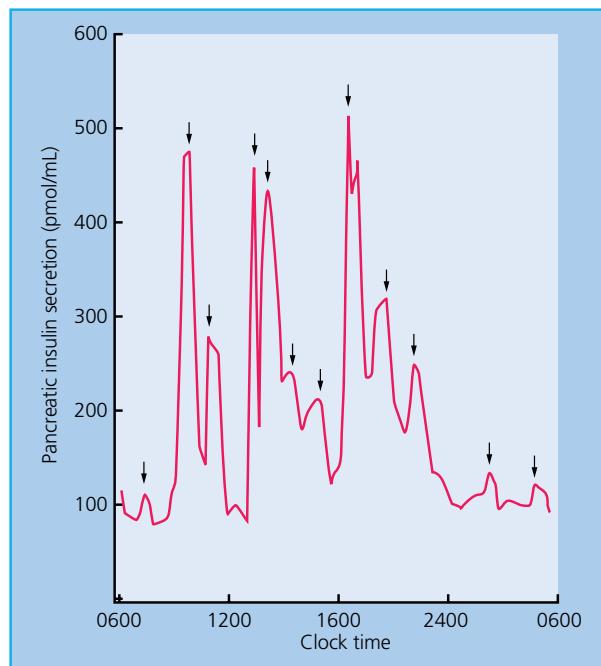


Figure 31.2 Pancreatic insulin secretion in healthy individual with normal body weight. Meals were consumed at 09.00, 13.00, and 18.00. Statistically significant pulses of secretion are shown by the arrows. Source: Polonsky et al. 1988 [8]. Reproduced with permission from the American Society for Clinical Investigation.

Insulin is stored in the β cells as hexamers stabilized by zinc ions (Figure 31.3). When secreted, the zinc-insulin hexamers are diluted in the bloodstream, disassembling into monomers, the active state of insulin. In exogenous insulin administration, hexamer formation can be induced by additives to form stable solutions for vials and cartridges. Classic additives are zinc, a phenolic preservative (m-cresol and/or phenol) that serves a dual purpose as an antibacterial agent and a hexameric stabilizer, and a buffer to maintain the correct pH. Following injection, fluid is drawn into the injected insulin depot through osmosis. This leads to dilution of the insulin and dissociation of the insulin molecules; this is a spontaneous but gradual process that must occur before insulin crosses the capillary walls as monomers into the blood circulation [10]. People with diabetes are therefore advised to inject their soluble insulin 15–20 minutes before a meal to ensure that circulating insulin levels are optimal at the time their meal is being absorbed. A significant proportion of people with diabetes find it hard to follow this advice because of the planning required. Even when they do, the calculated doses may be inaccurate, particularly if the preparation and presentation of the meal are not under the individual's control.

In order to mimic the endogenous insulin response as closely as possible, the time-action profiles of insulins and formulations have

been modified over time with the creation of insulin analogues (Figure 31.3). To reproduce the basal and post-prandial insulin secretion, a combination of short-acting and intermediate or long-acting insulin formulations is used [9].

Short-acting formulations

The biological action of soluble human insulin lasts 5–6 hours. The first rapid-acting insulin analogues were designed to form less stable insulin hexamers, ensuring that the insulins would more readily become monomeric, thus moving into the bloodstream more rapidly after subcutaneous injection. These changes result in faster absorption of insulin into the bloodstream and allow it to be injected closer to the mealtime, often just before starting to eat.

One way to reduce the association between insulin molecules is to change the amino acid sequence, usually focusing on the B28–29 amino acids [11]. To date, three such rapid-acting analogues have become available. Insulin lispro (Humalog®, Eli Lilly, Indianapolis, IN, USA) differs from human insulin at position B28 where the amino acid proline is replaced by lysine, and the lysine in position B29 is replaced by proline. Insulin aspart (NovoRapid®, Novo Nordisk, Bagsvaerd, Denmark) also has a substitution at B28, with proline replaced with

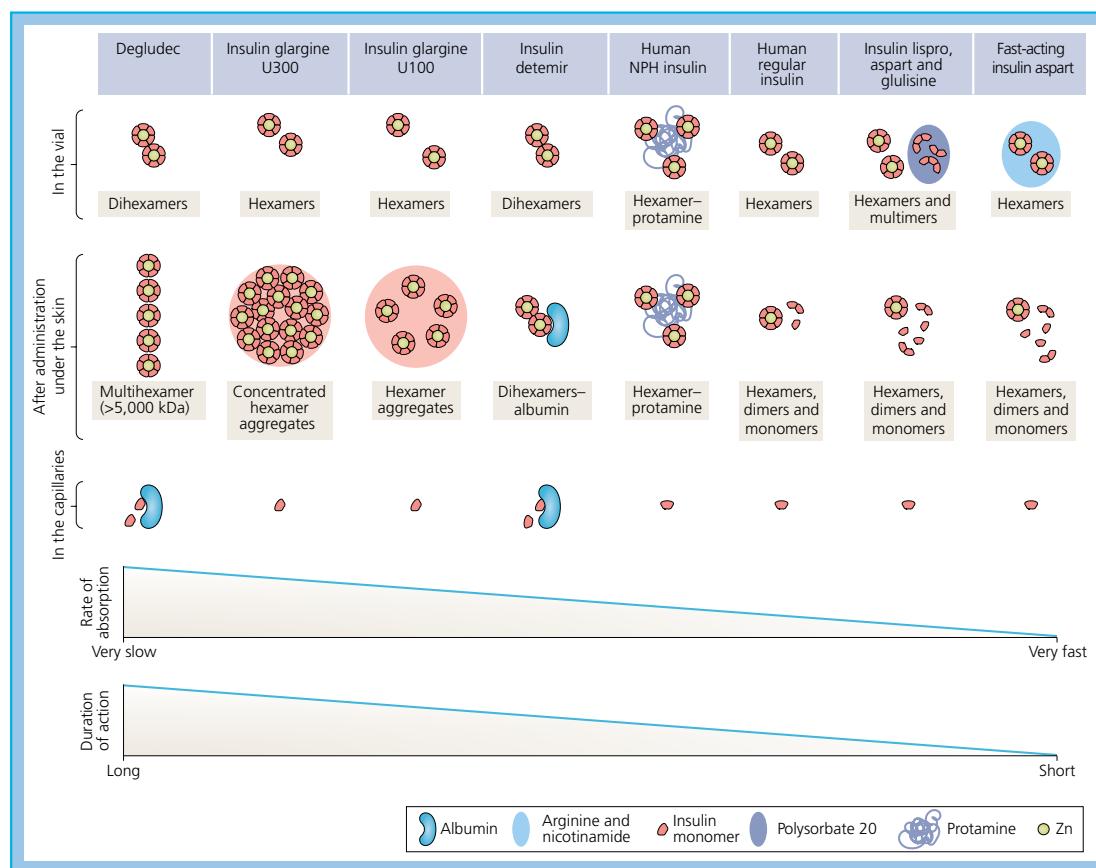


Figure 31.3 Different determinants of absorption and duration of action of human and analogue insulins. Degludec forms weak hexamers in solution in the vial and stable multihexamers after administration at the injection depot, thereby slowing its absorption. Reversible binding to albumin in the circulation further prolongs its action. Insulin glargine U300 precipitates at physiological pH, forming compact aggregates at the injection depot, leading to a reduced surface area from which absorption can occur, causing slow absorption and prolonged duration of action. Insulin glargine U100 also precipitates at physiological pH but is less compact than insulin glargine U300. Insulin detemir forms weak dihexamers in the vial and strong dihexamers at the injection depot. Reversible binding to albumin, both at the injection depot and in circulation, further slows the absorption rate and prolongs the duration of action. Neutral protamine Hagedorn (NPH) insulin co-crystallizes with protamine, both in the pharmaceutical preparation and at the injection site, slowing absorption and action. The classic rapid-acting insulin analogues (lispro, aspart and glulisine) dissociate into dimers and monomers more rapidly than does human regular insulin, causing a more rapid absorption and shorter duration of action. For glulisine, polysorbate 20 is used as a stabilizing agent, and formation of hexamers is prevented by absence of zinc (Zn). More rapid absorption and earlier action of fast-acting insulin aspart is caused by addition of arginine and nicotinamide to the formulation, thereby increasing the rate of formation of monomers at the injection depot and increasing the rate of absorption.

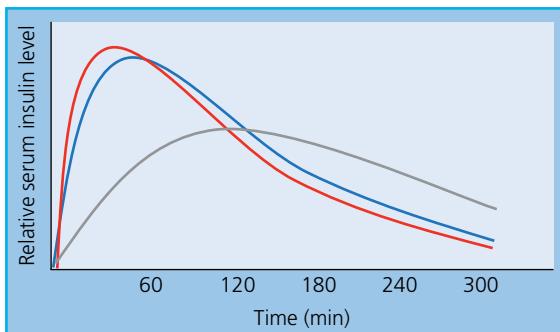


Figure 31.4 Time-action profiles of short-acting insulin formulations. Pharmacokinetic profile of human regular insulin (depicted in grey), rapid-acting insulin analogues (insulin lispro, aspart, glulisine; blue), and ultra-rapid-acting insulin analogues (faster insulin aspart and ultra-rapid lispro; red).

aspartic acid. For insulin glulisine (Apidra®, Sanofi, Paris, France), the lysine at position B29 is replaced by glutamic acid, and asparagine at position B3 is replaced by lysine. These analogues act more quickly (within 10–20 min) and have a shorter duration of action (3–5 h) than soluble insulin (30–60 min and 6–8 h, respectively) [12] (Figure 31.4).

Numerous studies have demonstrated the safety of rapid-acting analogues in both type 1 diabetes and type 2 diabetes, as either part of a *basal-bolus* insulin injection regimen combined with intermediate-acting insulins, or in continuous subcutaneous insulin infusion [13]. The time-action profile of rapid-acting analogues is well suited to mimicking the requirement at mealtimes, and therefore they probably control post-prandial hyperglycaemia more effectively than soluble insulin. As a result, individuals can achieve better glycaemic levels and fewer episodes of hypoglycaemia with rapid-acting analogues than with soluble insulin. The benefits of rapid-acting analogues over soluble insulin appear to be clearer in studies involving people with type 1 diabetes than type 2 diabetes, and when using insulin pumps rather than multiple-dose injections [12].

Recently, the addition of excipients to expedite absorption from the subcutaneous space has led to novel formulations of ultra-rapid-acting insulin analogues. Faster insulin aspart (FIASP®, Novo Nordisk) contains L-arginine as a stabilizer and niacinamide to increase absorption by increasing subcutaneous blood flow. Similarly, ultra-rapid lispro (Lyumjev®, Eli Lilly) contains additional citrate to increase absorption by enhancing local vascular permeability and treprostinil to increase local vasodilatation [14]. While both formulations reach peak insulin levels a few minutes earlier, have an earlier offset of action, and achieve a greater reduction in post-prandial glucose compared with rapid-acting insulin analogues, the added value for clinical practice is unproven, and their use in pumps and compatibility with pump catheters need to be studied further.

Intermediate and long-acting formulations

To avoid the frequent painful injections of early insulin preparations, attempts were made in the 1920s and 1930s to provide the daily insulin requirement in just one injection. Modifying agents such as lecithin, oil, and cholesterol were used [15], but the duration of action varied significantly from injection to injection, which limited their clinical utility. In 1936, a method was reported incorporating the addition to insulin of protamine, a highly basic protein derived from the sperm of salmon or trout, to form a poorly soluble complex, thus slowing its absorption [16]. This technique was later refined by adding protamine and zinc in stoichiometric proportions (so that there was no free protamine or zinc) to form isophane or

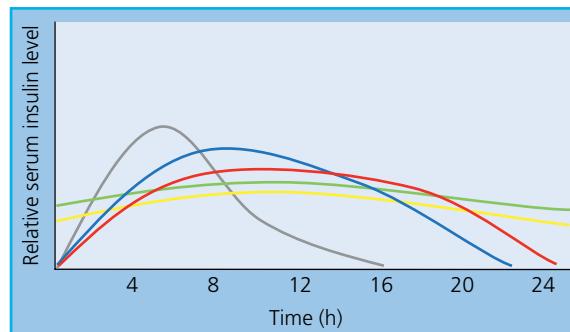


Figure 31.5 Time-action profiles of intermediate and long-acting insulin formulations. Pharmacokinetics profile in steady state of neutral protamine Hagedorn (NPH) insulin (depicted in grey), insulin glargine U100 (red), insulin detemir (blue), insulin glargine U300 (yellow), and insulin degludec (green). Care must be taken when interpreting the curves as the experimental setting in which the data were gathered differed among studies.

neutral protamine Hagedorn (NPH) insulin. Though the action of NPH insulin is delayed and can cover a 12–24-hour period, significant variation in duration of action and absorption persisted [17]. Consequently, attempts at stringent glucose management using these formulations as basal insulin are associated with an increased risk of hypoglycaemia.

As for rapid-acting analogues, modification of the insulin molecule primary amino acid sequence can also result in a longer and more reproducible duration of action. There are currently three such insulin analogues. Glargine (Lantus®, Sanofi) achieves prolonged insulin action through amino acid substitutions that make the insulin molecule less soluble. Glargine insulin forms microcrystals following subcutaneous injection that dissolve slowly over an 18–26-hour period (Figure 31.5) [18]. In non-inferiority studies, insulin glargine achieves similar glycaemic levels as isophane insulin, but does so with less hypoglycaemia [19]. Insulin detemir (Levemir®, Novo Nordisk) has a fatty acid side chain addition to the insulin molecule that promotes binding to circulating albumin, which then slowly dissociates, giving it a duration of action just a little short of glargine insulin. Detemir is as efficient as isophane insulin at improving glycaemic levels, but again does so with less hypoglycaemia and interestingly less weight gain [20].

The most recent commercially available addition to the long-acting insulin analogues has been insulin degludec (Tresiba®, Novo Nordisk). Degludec also has a fatty acid side chain, but structured in such a way as to encourage it to form long multihexamer chains following subcutaneous injection. This chain disassembles very slowly and gives degludec a very long duration of action (half-life exceeding 25 h), such that it has been termed an ultra-long-acting insulin analogue [21]. This long duration of action allows a very flat insulin profile and a more reproducible duration of action that is not significantly affected by variations in the time of day-to-day administration. Non-inferiority studies have shown that insulin degludec achieves similar glycaemic levels to insulin glargine, but with less overall and nocturnal hypoglycaemia [22].

Comparative studies of the long-acting analogue insulins have been designed to demonstrate equivalence rather than superiority in terms of glycaemia [23]. They do, however, demonstrate that the same level of glycaemia can be achieved with less hypoglycaemia, and some with less weight gain (detemir). These benefits come to date at a cost, with insulin analogues costing more than double the price of NPH insulin.

Biosimilars

Several patent protections for insulin analogue preparations have expired, and the pharmaceutical industry has explored these opportunities to develop *copycat* insulins to compete with original formulations. Because insulins are currently produced biologically (i.e. through expression in living cells), they are more correctly termed *biological* or *biosimilar* drugs than generic drugs. Biosimilars (such as peptide hormones and monoclonal antibodies) are already in clinical practice and are required to undergo more rigorous testing than standard generic drugs. This testing includes direct comparison of the biological activity, pharmacology, clinical safety, and efficacy of the biosimilar with the reference insulin. While the development costs of biosimilars are higher than those for other generic drugs, they are not as expensive as developing the original insulin, and any cost savings will likely be magnified through long-term prescription. Therefore, these insulins will likely be cheaper, thus expanding market competition and increasing availability for people with diabetes. Currently, several biosimilars of insulin have been approved by various regulatory agencies: glargine (Abasaglar®, Eli Lilly) by the European Medicines Agency (EMA; 2014) and US Food and Drug Administration (FDA; 2015); Basalin® (Gan & Lee, Beijing, China) by China (2005); Semglee® (Biocon Biologics/Mylan, Bangalore, India/Canonsburg, PA, USA) by Australia (2018); and insulin lispro (Admelog®, Sanofi) by the FDA (2017) [24].

Concentration

Insulin *units* were introduced to address and compare the blood glucose-lowering potency of insulin preparations. One unit of insulin generally has the potential to drop blood glucose by 50 mg/dl (2.8 mmol/l), although it can range from 30 to 100 mg/dl (1.7–5.6 mmol/l), depending on individual insulin sensitivity. Injecting large volumes of insulin, as is required in those who are insulin resistant, slows absorption kinetics and reduces the effectiveness of the insulin. Furthermore, it can be more painful. Splitting the dose across different injection sites can reduce the volume. However, in some people the use of more concentrated insulin is more appropriate. Insulin preparations are currently standardized to 100 U; that is, 100 units of biological activity per ml of insulin. Concentrating human insulin, however, typically leads to a protraction of its action [25] and ultra-concentrated human insulin (for example, human regular insulin U500) has a pharmacokinetic profile that is intermediate between U100 and NPH [26].

Concentrated formulations of analogue insulins are available for clinical use and have been demonstrated to be clinically effective [27–29]. While the U100 and U200 formulations of short-acting lispro and long-acting degludec have bioequivalence, for one insulin analogue hyperconcentration from U100 to U300 has led to the ‘creation’ of a new commercial entity (U300 glargine, Toujeo®, Sanofi). U300 glargine has a protracted action exceeding that of U100 glargine, with a duration of action of 25 hours. In clinical trials comparing U100 and U300 glargine, similar glycaemic levels were demonstrated, with a reduced risk of (nocturnal) hypoglycaemia in those using the U300 formulation.

Insulin administration

The early experiments of Frederick Banting quickly revealed that the oral route of insulin administration was not an effective means of insulin delivery, as the insulin molecule is functionally degraded by gut peptides. Subcutaneous injection of insulin has become the most popular route of insulin delivery, because of its relatively reproducible kinetics of absorption and the ease with which it can be administered, but it is worth considering some of the other routes.

Subcutaneous insulin injections

Subcutaneous insulin injections are the most used insulin therapy. The recommended sites for injection are the abdomen, upper arms below the deltoid region, upper thighs, and upper buttocks (Figure 31.6). The area should be clean and free from signs of infection or lipohypertrophy.

Insulin can be directly dialled up on a pen device or drawn up using a disposable syringe. If the insulin preparation is cloudy (e.g. NPH), it should be gently rolled and inverted 10 times. This will allow the insulin crystals to disperse and for the mixture to turn to a milky-white suspension. If using a pen device for insulin delivery, the device should be properly primed and a drop of insulin should be visible at the tip of the needle. Similarly, if an insulin syringe is being used, the barrel should be tapped and any air excluded by squeezing the plunger. These manoeuvres ensure that air is not contributing to the volume of insulin that has been dialled or drawn, and that an accurate dose of insulin is delivered.

The needle should enter the skin at right angles to the surface in a smooth process, the plunger squeezed gradually and completely, and left there for 10 seconds to allow the insulin to enter the tissue.

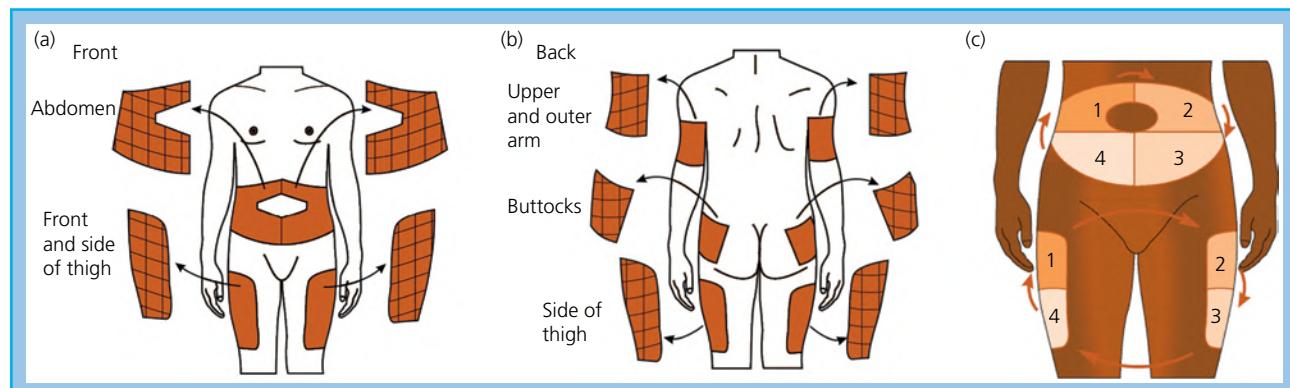


Figure 31.6 Insulin injection sites and rotation of insulin injection sites. The areas recommended for insulin injections as viewed from the front (a) and back (b). They may be divided up into smaller areas, so that each area is injected not more than once a day. (c) A method that can be adopted to rotate insulin injections. Source: Adapted from Bahendeka et al. 2019 [30].

Disposable syringes should be replaced at each injection; for pens it is considered good practice to change the needle for every injection, but this should be done at least once daily. Rubbing of the skin following injection is discouraged because this increases the rate of insulin absorption and may increase the risk of hypoglycaemia.

Syringe needle lengths are currently restricted to 8 mm. Pen needles come in a variety of lengths, including 4, 5, 6, and 8 mm. There is no indication to use needles longer than 8 mm because longer needles increase the risk of intra-muscular injection, with the associated rapid absorption and risk of hypoglycaemia. Currently 4 mm needles are recommended for many adults and most children, and these can often be used without the need to lift skin folds. Injecting into lifted skin folds is appropriate in children, slim adults, and when there is a risk of injecting into muscle. The correct technique for lifting skin folds needs to be taught; it should not lift up underlying muscle, nor be so tight as to cause blanching of the skin (Figure 31.7). The use of lifted skin folds is recommended for all people who use 8 mm needles. Injecting through clothing is discouraged because as needle lengths get shorter, there is a risk of intradermal injection.

Studies of absorption of subcutaneously administered insulin have used various techniques, including measuring the rate of loss of I^{125} -labeled insulin from the site of injection using a gamma counter [32]. They show that the rate can vary significantly between individuals, but also from one injection to another within the same individual [17]. Absorption rates in individuals with obesity are slower than in people without obesity, and there do not appear to be any clear differences in the rate of absorption between the different injection sites. In lean individuals, the absorption of insulin analogues (both rapid- and long-acting) does not appear to vary by injection site [33,34]. However, in these individuals absorption of human insulin from the abdomen appears to be faster than from the arm or leg [35], and the upper abdomen faster than the lower abdomen [36]. This difference can be utilized to good effect, for example injecting NPH insulin into the thigh or buttock ensures slower absorption, and soluble mealtime insulin in the abdomen more rapid absorption.

Repeated injection of insulin at the same site leads to local hypertrophy of adipose tissue, resulting in slower and more erratic insulin absorption. People with diabetes should always be advised to rotate their insulin injection sites to avoid this complication and should be shown an easy-to-follow rotation scheme (Figure 31.6). Other local factors such as oedema or local inflammation can influence rates of absorption. Exercise results in greater blood flow to the skin and can lead to faster uptake of insulin, particularly when that is injected into an area close to the muscle groups being exercised. Individuals who are planning to run, for example, should be advised that injection

into the leg may be less favourable than injecting into the arm or abdomen [37]. Similarly, temperature influences cutaneous blood flow and can affect insulin absorption [38]. Hot climates or sitting in the sauna may result in a rapid surge in insulin levels, whereas the converse, travelling to cooler climates, can result in a slower uptake. There are also reports that hypoglycaemia and smoking can reduce the rate of insulin absorption [39,40].

Standard insulin preparations have a shelf life of 4–6 weeks when stored at under 25 °C. Storage for longer periods will require that they be kept in a fridge (4 °C), which then allows them to be stored until their expiry date. Exposure of insulin to high temperatures or to microwaves can render it inactive.

Continuous subcutaneous insulin infusion

Next to delivery by pen or disposable syringes, insulin can be administered to the subcutaneous space using a pump device, which is discussed in detail in Chapter 33.

Alternative routes of insulin administration

Intramuscular injection is more painful, and absorption more rapid, than subcutaneous injection and is not recommended for any insulin formulation [41]. However, this route can be useful in the emergency situation when intravenous access is difficult. Inadvertent intramuscular administration should be considered in lean individuals who complain of pain on insulin injection, and who may experience erratic glucose levels and hypoglycaemia. The correct choice of insulin needles can help address this problem.

The delivery of insulin directly into the peritoneal space, for example, with implantable pumps or directly via a port [42] mimics physiological insulin secretion, in that insulin bypasses the systemic circulation and directly enters the portal circulation. The theoretical advantages of portal delivery include rapid insulin absorption, near physiological carbohydrate and lipid metabolism, and avoiding peripheral hyperinsulinaemia [43]. The clinical advantages of intra-peritoneal insulin delivery have been explored in a number of clinical trials [44]. While some evidence exists for improved glycated haemoglobin (HbA_1c) and quality of life in selected people with type 1 diabetes [45], the use of this delivery method is limited. However, research is ongoing and the role of implantable pumps in the development of a true artificial β cell remains appealing.

Insulin administration via the respiratory mucosal surface avoids degradation by gut peptides and can be an effective route for insulin delivery, particularly for those who have needle phobia [46]. Inhaled insulin was made available in Europe (Exubera[®], Pfizer, New York, USA) in 2006, but was withdrawn within a year due to poor uptake

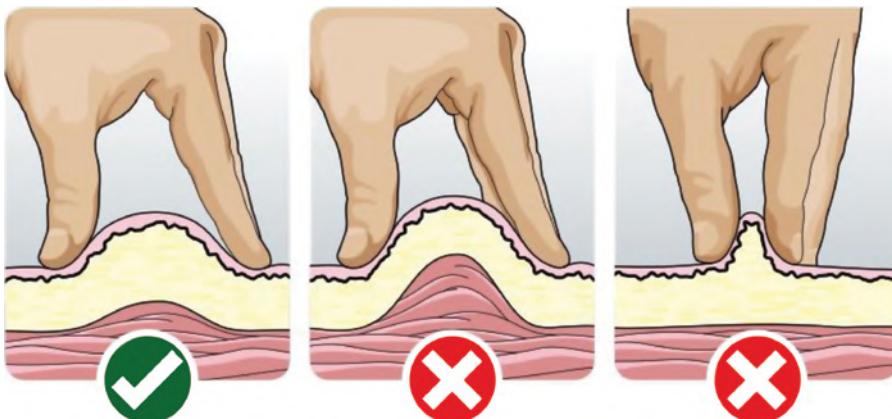


Figure 31.7 The recommended technique for lifting skin folds for subcutaneous injection of insulin.

Source: FIT UK Forum for Injection Technique 2016 [31]. Reproduced with kind permission of BD Medical Diabetes Care.

by people with diabetes and healthcare professionals. In 2015, Technosphere insulin, a dry-powder formulation of human regular insulin adsorbed onto microparticles that are inhaled, was approved in the USA for use as a mealtime rapid-acting insulin (Afrezza®, MannKind, Westlake Village, CA, USA). With both formulations, there is a reduction in lung function that reverses when the therapy is stopped, and there is the potential risk of lung cancer in heavy smokers. Afrezza is not recommended in people who are current smokers, or in those with reactive airway diseases such as asthma or chronic obstructive pulmonary disease. While trials of newer inhaled insulins are awaited, systematic reviews of previous formulations suggest they are as clinically effective, but not as cost-effective, as short-acting injectable insulin in unselected people with diabetes [47].

Complications of subcutaneous insulin therapy

The major and most feared complication of insulin injections, which affects most people using insulin, is hypoglycaemia. The causes, avoidance, consequences, and management of hypoglycaemia are discussed in Chapter 40. The fear of hypoglycaemia may be a major barrier to insulin initiation and intensification.

Insulin not only restores fat and muscle mass in newly or suboptimally treated people requiring insulin, but can lead to excessive weight gain [48]. This remains a major concern for many people, particularly those with type 2 diabetes who already have overweight and can no longer be managed with oral anti-diabetes agents. Weight gain is also becoming a growing issue for people with type 1 diabetes, limiting the appeal of intensive insulin therapy [49]. Weight gain can be reduced by concomitant dietary advice and an insulin regimen tailored to the requirement of the individual, which wherever possible provides most insulin when needed; that is, at mealtimes. Overaggressive insulin titration regimens leading to low blood glucose and stimulation in appetite can lead to excessive weight gain. The management of diabetes for some people, particularly but not exclusively young women, can be challenging when insulin doses are reduced to suboptimal levels to manipulate body weight (Chapter 65).

Immune responses to the older animal insulins have been well reported, but such responses to current human and analogue insu-

lins are less common [50]. Allergies may rarely develop in response to the insulin molecule (this may become a more common issue with the introduction of biosimilar insulins where folding may differ) or to components of the insulin preparation (such as protamine or metacresol). Most commonly, allergic reactions manifest as local acute urticarial reactions. These are best managed with intradermal skin testing of 1:20 dilutions of different insulin preparations, and then switching to that which is best tolerated [51]. Antihistamines may be of benefit, as too may high-dose steroids in exceptional circumstances. More rarely, widespread systemic reactions develop as a reaction to the insulin and these individuals may benefit from referral to clinical immunology services.

Local complications of insulin therapy include lipoatrophy and lipohypertrophy. Lipoatrophy, in which subcutaneous tissue at the site of injection disappears or atrophies, is an allergic response predominantly with the older animal insulins and is rarely seen today. In contrast, lipohypertrophy occurs commonly. It is not an allergic response, but develops because of a trophic response of adipose tissue to insulin. It is most commonly seen in those with a poor injection technique and usually in people who do not rotate their insulin injection sites. Sustained injections into sites of hypertrophy can lead to poor and delayed insulin absorption, with consequent effects on blood glucose levels [52]. Lipohypertrophy generally resolves within two months if injecting into the affected area is avoided. Occasionally mild ulceration, pitting, and, more commonly, bruising can occur at injection sites. Rotating injection to another site and selecting a shorter needle may be indicated.

Importance of education and assessment of glycaemia

Diabetes self-management education and support is a central component of diabetes therapy for all those living with diabetes [53]. Education should target lifestyle and complication prevention, but in the case of those treated with insulin, glucose monitoring, adaptation of insulin doses, overall nutritional advice, and specifically carbohydrate assessment and glucose monitoring should be central (Chapter 26) (Figure 31.8).

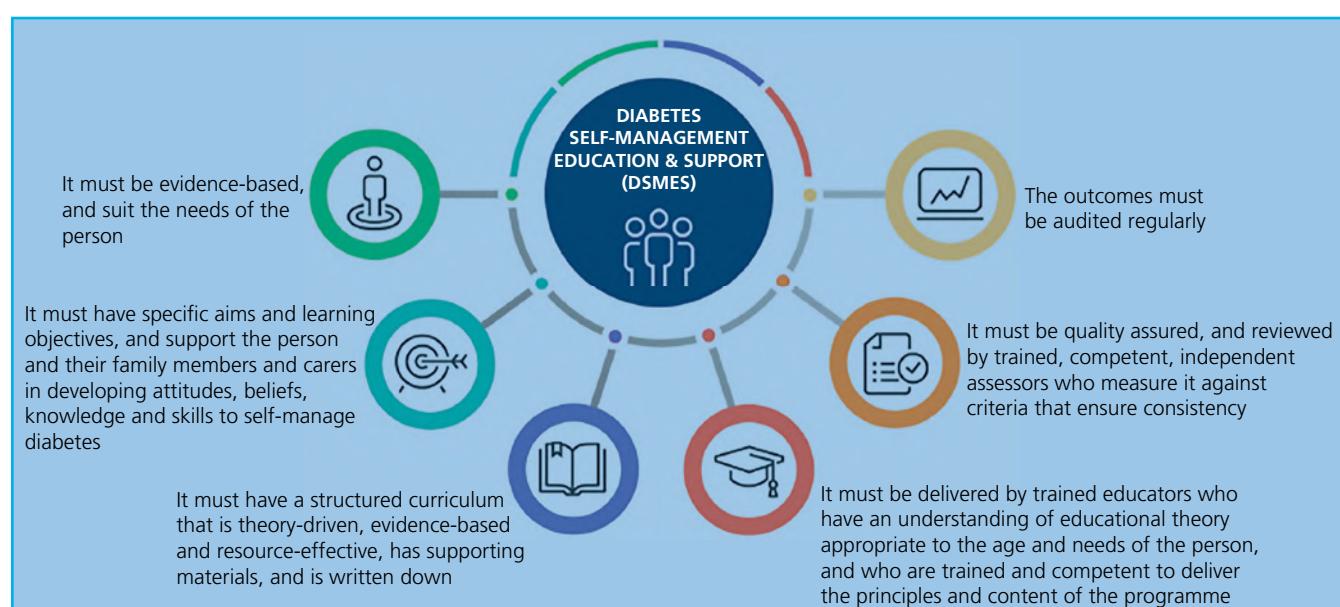


Figure 31.8 A pictorial representation of the standards for diabetes self-management and structured education programmes for people with type 2 diabetes (in the UK). Source: Adapted from Hadjiconstantinou et al. 2021 [53].

While national and international guidelines have made recommendations on glycaemic targets based predominantly on HbA_{1c} [54], self-monitoring of blood glucose not only helps people with diabetes achieve HbA_{1c} targets by adjustment of insulin doses, but also helps them better understand their own diabetes and blood glucose levels (Chapters 29 and 32).

People with insulin-dependent forms of diabetes, including type 1 diabetes and pancreatic forms, who are treated with intensive insulin therapy, should monitor their glucose levels intensively, to assess glucose levels and take them into account when deciding on insulin doses, taking into account exercise and meal carbohydrate content. More and more continuous glucose monitoring systems (intermittent scanning or continuous glucose monitoring devices) are being used, and time in range (TIR) (Chapter 32) is rapidly becoming the standard to assess overall glucose levels.

To achieve strict glycaemic targets and avoid long-term hyperglycaemic complications, as supported in the Diabetes Control and Complications trial for type 1 diabetes [48] and later in the UK Prospective Diabetes Study for type 2 diabetes [55], pre-meal blood glucose readings should range between 4 and 7 mmol/l and post-meal levels from 4 to 10 mmol/l, with a value >7 mmol/l before bed. While individual specialists often follow their own dose adjustment algorithms, in general terms a change in dose of 2 units or 10% of a dose (whichever is the greater) is a sensible adjustment for most people taking insulin. A TIR (70–180 mg/dl; 4–10 mmol/l) of 70% is the target in most people living with type 1 diabetes [56].

Similar targets may be sought for people with type 2 diabetes, although trials based on achieving very tight HbA_{1c} targets, with some aiming for <6% (42 mmol/mol), serve to highlight the dangers of hypoglycaemia [57]. The frequency of blood glucose testing is extremely variable, with people being recommended to test anything from seven times a day down to four or five tests a week.

The most important aspect of regular self-monitoring by people on insulin is that the test result should be used as part of a management plan to help decide prospectively on insulin dose. There are, however, other points that should be considered when advising on when to self-test, including times of intercurrent illness to adjust insulin dose, symptoms and treatment of hypoglycaemia, driving, and foreign travel [58].

Place of insulin therapy in people with different types of diabetes

Insulin deficiency leads to hyperglycaemia, the hallmark of diabetes mellitus. Diabetes mellitus, however, comprises a heterogeneous group of diseases with regard to clinical presentation and progression. The classification of diabetes into type 1 diabetes and type 2 diabetes, which relies primarily on the presence or absence of auto-antibodies against pancreatic islet β-cell antigens and age at diagnosis (younger for type 1 diabetes), is making room for a paradigm with a more individual assessment of remaining endogenous insulin production and insulin resistance [59].

Absence of endogenous insulin secretion, including type 1 diabetes

In people who are no longer producing endogenous insulin at levels that suffice to maintain normoglycaemia, such as people with type 1 diabetes or after total pancreatectomy, the administration of exogenous insulin is necessary to provide 24 h background and

meal-time coverage, unless they are in the early stages of type 1 diabetes, have some residual β-cell function, or have been fortunate to become insulin independent following a pancreas or islet cell transplant. For many this coverage is provided by the *basal bolus regimen*, involving a combination of short- and long-acting insulin preparations. The advantage of such an approach is that it is generally better at providing a more physiological insulin replacement with a greater degree of 24 h flexibility than premix insulins injected once or twice daily. While it has the disadvantage of involving more daily insulin injections and requiring more frequent blood glucose monitoring, it provides a much greater degree of flexibility throughout the day. Importantly, for example, it allows the individual to vary the mealtime and size during the day to accommodate different daily activities and meal sizes. For some, this freedom is less important and the administration of only two injections a day sways them towards an insulin premix.

Insulin pumps can provide even more flexibility and responsiveness regarding glycaemia throughout the day and night. In case of pronounced diurnal variation in insulin sensitivity such as the *dawn effect* or related to intensive physical exercise, basal insulin infusion rates can be set and modified per hour, so that a more physiological insulin profile can be mimicked more closely than with the stable release of long-acting basal insulins. In specific circumstances, for example for children or for women attempting to become pregnant or who are pregnant, insulin pumps are becoming increasingly popular as a tool to achieve tight glycaemic levels. Furthermore, several novel *closed-loop* and *smart pump* devices enable automated reduction or increase in basal insulin delivery rate depending on the glucose level recorded by a coupled sensor; these devices have proven to be especially useful during the night [60, 61]. In addition, pumps may be more convenient to administer inter-meal correction bolus insulin or titrate the mealtime bolus to the anticipated carbohydrate load using the incorporated bolus calculators. The need to observe and react more directly with pump systems, however, requires more active involvement of the person with diabetes, while some people do not wish to have an external device and/or catheter attached to their body. Furthermore, pumps systems are more expensive (Chapter 33).

Insulin resistance and relative insulin deficiency, including type 2 diabetes

Exogenous insulin administration also has a place in the diabetes management of people with remaining, but insufficient, endogenous insulin production to cope with growing insulin resistance, such as those with type 2 diabetes or gestational diabetes. Insulin may be used with other anti-diabetes agents. Given the pandemic prevalence of type 2 diabetes, more people with type 2 diabetes use insulin than people with type 1 diabetes [62].

The recent European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) consensus statement for type 2 diabetes treatment recommends choosing second-line therapies after metformin based on the presence of cardiovascular- and/or kidney-related comorbidities, risk of weight gain and hypoglycaemia, and cost [54]. Most guidelines worldwide recommend that people with established atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure should be treated with a sodium glucose cotransporter 2 (SGLT-2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1 RA). Consequently, the use of insulin in people with type 2 diabetes has been moved to later stages of the disease, as add-on therapy to other anti-diabetes agents. However, in case of obvious signs of catabolism, such as

unintentional weight loss, an HbA_{1c} higher than 10% (86 mmol/mol), or glucose levels higher than 300 mg/dl (16.7 mmol/l), insulin should be considered without delay.

Despite all guidelines giving clear indications on the importance of tight glycaemic levels, clinical inertia resulting in the delayed management of type 2 diabetes with insulin has been noted for decades. This clinical inertia involves not only the initiation of insulin therapy in people with type 2 diabetes and elevated HbA_{1c} despite other therapies, but also the intensification of insulin therapy [63]. For example, a real-world analysis of 6054 individuals with type 2 diabetes noted that insulin therapy was initiated at a mean HbA_{1c} of 10.1% (87 mmol/mol) [64]. In African American and Hispanic individuals with diabetes, the delay in insulin initiation might be even longer than in non-Hispanic white individuals [65]. In contrast, prompt intensive insulin therapy at the time of initial type 2 diabetes diagnosis when HbA_{1c} levels are higher than 9.0% (75 mmol/mol) might even improve β-cell function [66].

Often as type 2 diabetes progresses, the transition from oral anti-diabetes agents to insulin can be a time of stress and anxiety for many people for various reasons, including [67]:

- A sense of personal failure about being unable to control blood glucose levels with lifestyle, diet, and oral therapy.
- A feeling that the diabetes is much more serious than previously because it now requires injections rather than tablets.
- Apprehensions, fears, and very occasionally real phobias over the need to self-inject a treatment.
- Worries of hypoglycaemia leading to coma and death.
- Concerns over weight gain.
- Concerns that insulin may severely affect the individual's occupation and certain lifestyle activities.

With the increasing use of GLP-1 RAs, many people are now acquainted with injection therapy before exogenous insulin is needed. The advantages of injectable GLP-1 therapy are low risk of hypoglycaemia and less frequent, often only once-weekly, injection, which allows the person to become accustomed to the idea and technique of self-injection in a less frightening way. Nonetheless, we remain aware of the many anxieties insulin injections can induce.

Selecting the most appropriate insulin regimen: towards a personalized approach

Most people who have had either type 1 diabetes or type 2 diabetes try a number of treatment regimens throughout their lives. There are many factors that influence the decision to opt for a specific regimen and ultimately the most important is individual choice built on evidence from clinical trials. As insulin preparations have evolved from the early animal insulins to both human and analogue insulins, we have also seen the development of more versatile and indeed flexible treatment regimens that enable the doctor and nurse to provide the person with diabetes requiring insulin with a bespoke treatment that fits in better with their individual needs and lifestyle (Figure 31.9).

Intensive insulin therapy, combining mealtime and basal insulin preparations or pump therapy, is the standard of care in people with type 1 diabetes [68]. While in some people with type 2 diabetes insulin requirements are similar to those with type 1 diabetes, for many with type 2 diabetes insulin initiation and intensification is a more gradual process. Views differ on the insulin of choice for initiation, particularly as an add-on to other anti-diabetes agents. Supported by clinical trials, once-daily long-acting basal insulins are now recommended in type 2 diabetes treatment guidelines and have found significant popularity, particularly in the community as a means of introducing the person with type 2 diabetes to insulin [54]. Choosing basal insulin analogues over NPH is a matter of debate, mainly because of the higher costs that use of basal analogue insulins entails, despite the fact that clinical trials demonstrated lower rates of hypoglycaemia with long-acting basal analogues as an add-on to existing oral therapy compared to NPH insulin [69]. However, while basal insulin is a popular way of starting insulin, many people with diabetes do not achieve satisfactory glycaemic targets with this regimen and will require a second insulin injection with a mealtime component within 6–12 months [70].

In areas of the world with high carbohydrate intakes, starting insulin therapy with a combination of a basal and prandial component (often as basal plus, or as premix insulins), or even a prandial

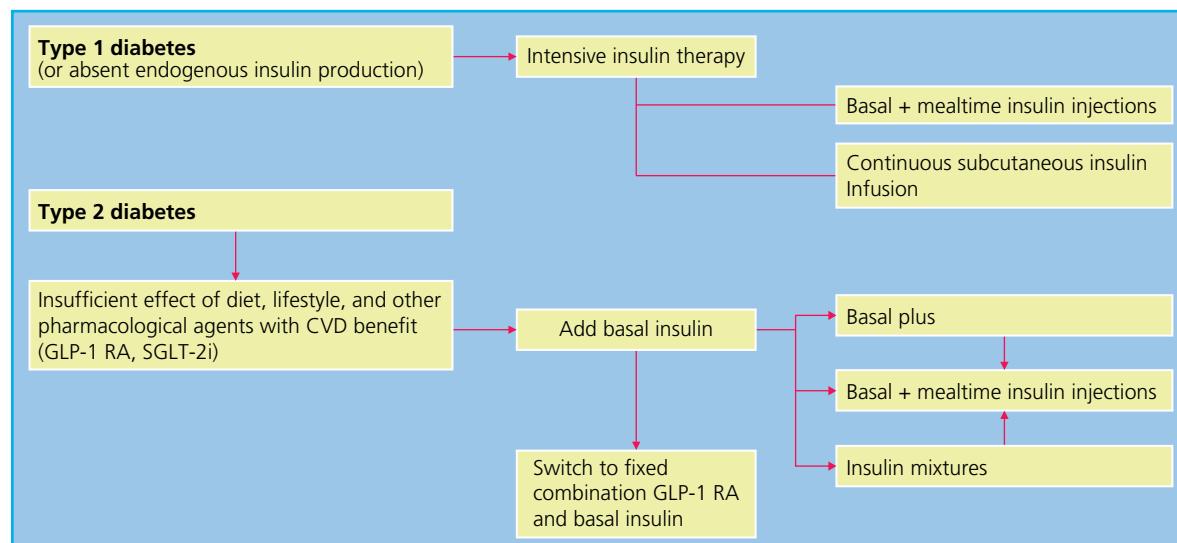


Figure 31.9 Suggested approach to selecting an insulin regimen in people with type 1 diabetes and 2 diabetes. CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, sodium glucose cotransporter 2 inhibitor.

insulin regimen only, is popular. The relative merits of basal only, prandial only, and premix insulin have been evaluated [70,71]. Clearly there are advantages and disadvantages associated with each approach.

A pragmatic response is to consider the person with diabetes and their lifestyle, social circumstances, and comorbidities and take account of their likely long-term insulin needs. If it seems likely that the person will remain on a basal insulin as a single injection or as part of a future basal-bolus regimen, the basal insulin may be the best option. However, if it seems probable that the individual will be switched to a premixed insulin if a long-acting bolus does not achieve target, then initiating with a premixed insulin is a sensible alternative.

Basal only

One way in which insulin injections can be introduced to people with type 2 diabetes who are no longer able to manage their blood glucose with diet, lifestyle, and non-insulin anti-diabetes pharmaceutical therapies is to start with only one injection of insulin a day. This is usually added on to existing agents such as metformin, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT-2 inhibitors, or GLP-1 RAs rather than as a replacement therapy. National and international guidelines in the UK, Europe, and the USA as well as the recent ADA/EASD consensus on glucose-lowering therapies in type 2 diabetes also recommend the use of a basal insulin with oral therapy as a way of initiating insulin in people with type 2 diabetes [54]. The initiation of insulin therapy, whether in the hospital or now more commonly in the community, should only take place within a structured programme employing active insulin dose titration. The program should include appropriate education; ongoing telephone, text, or email support; the use of glucose monitoring to inform dose titration to an agreed target; an understanding of diet; avoidance and management of hypoglycaemia; and support from appropriately trained and experienced healthcare professionals. Use of structured diabetes self-management education and support systems has proven to be very effective [53].

Some guidelines continue to recommend initiation with a human NPH insulin taken once or twice a day according to need [72]. However, many healthcare professionals are opting for long-acting insulin analogues, considering the reduced risk of (nocturnal) hypoglycaemia with these analogues. Also practicalities drive the preference for using basal insulin analogues with longer action profiles, particularly in people who require assistance with injections from a carer or healthcare professional and where the use of an analogue would reduce the number of injections from twice to once a day [23]. Similarly, indications for switching from NPH insulin to a long-acting basal analogue include not reaching an agreed HbA_{1c} target because of hypoglycaemia regardless of HbA_{1c}.

Most basal insulins are best administered before bedtime to reach the maximal effect during the night, thus achieving the primary goal of basal insulin, which is suppression of nocturnal hepatic glucose output and maintaining fasting glycaemia in an optimal way. When using the ultra-long insulin analogues, like U300 glargine or degludec, the timing of insulin administration is less crucial. Starting insulin doses can be calculated based on body weight (e.g. 0.1 unit/kg) or be standard (e.g. 10 units).

Once a basal insulin is started, it is important to adjust insulin doses appropriately to achieve an agreed target. Whereas the goal is to improve overall glycaemia, as measured by HbA_{1c}, the target to be used by individuals with diabetes and healthcare professionals to

adapt the basal insulin dose is self-measured fasting glycaemia. Several algorithms have been developed to assist with this, almost all based on fasting blood glucose measured in the community and usually by the person with diabetes themselves [73–75]. Clinical inertia needs to be avoided and a reasonable, simple, but strict titration regimen should be agreed with the person with diabetes, in order to reach optimal glycaemic levels within an acceptable time-frame (e.g. titration twice a week). However, *over-basalization*, namely the blind up-titration of basal insulin doses without result, should be avoided. Indeed, once doses exceed 0.5 U/kg, the effects on glucose levels of increasing the insulin dose further are minimal, whereas their effect on weight gain continue. As a rule of thumb, when fasting glycaemia is within target but HbA_{1c} is not with basal insulin only, it is time to add mealtime insulin.

Basal plus

The addition of a fast-acting human insulin or rapid-acting insulin analogue prior to the main meal of the day can be a useful next step in intensification after starting a basal insulin in people with type 2 diabetes [76,77]. Increasingly healthcare professionals are prescribing rapid-acting insulin analogues over fast-acting human insulins [78,79]. The individual's dietary intake will determine which is the main meal and, therefore, with which meal the single injection of fast-/rapid-acting insulin will be given. Once again, it is important to titrate the prandial insulin to a glucose target. The ideal time to assess the impact of the prandial insulin, and certainly a rapid-acting insulin analogue, is 90–120 min after the meal. As with basal insulin adjustment, it is advisable not to change the insulin dose too frequently, ideally no less than twice a week. The person with diabetes may vary the amount of insulin administered based on the size of the meal, although as the insulin is given with the main meal of the day, the dose is usually fairly stable from one day to another. As glycaemic targets become more difficult to achieve, a second prandial insulin injection may be necessary, taken before the second main meal of the day using a similar dose titration procedure to that for the single prandial injection [80].

Insulin mixtures: premix insulins, combination insulins

As an alternative to the basal plus regimen, people with type 2 diabetes can change from a basal insulin to a mixed insulin formulation, which is given traditionally twice a day, with breakfast and the evening meal. This concept of premix insulins originated as a means of replacing the self-reconstituted combinations of regular insulin and NPH insulin and to cover the insulin needs for a typical Western diet with only two injections (30% regular insulin and 70% insulin NPH) [81]. However, such an approach does not mimic normal insulin physiology, and therefore increases the risk of hypoglycaemia [82]. Two types of pharmaceutical preparation have been developed to allow people with type 2 diabetes to harness the benefits of basal insulin action with other products, without increasing the risk of hypoglycaemia. The first is a combination of a basal and ultra-rapid insulin analogue (degludec and faster-acting insulin aspart, Rysodeg®, Novo Nordisk) and the second a combination of a basal insulin analogue and a GLP-1 RA (U100 glargin/lisixenatide, Suliqua®, Sanofi; degludec/liraglutide, Xultophy®, Novo Nordisk). In the case of the degludec/faster-acting insulin aspart combination, the advantage of the combination of a basal insulin and a mealtime insulin is maintained, with a lower risk of hypoglycaemia compared to standard premix insulins using NPH as the basal component. The combination of a basal insulin analogue and a GLP-1

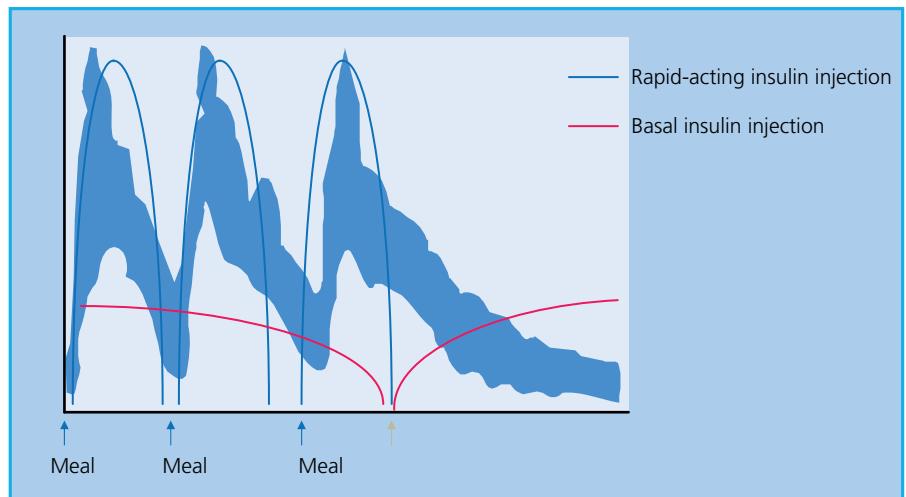


Figure 31.10 Schematic representation of the attempt to mimic physiological insulin release following three main meals using a basal-bolus regimen.

RA not only provides better overall glycaemic levels than basal-only insulins, but does so at a lower risk of hypoglycaemia and with less weight gain [83].

Basal bolus

Basal bolus is the most commonly used form of intensive insulin therapy in people with type 1 diabetes, but is also a popular regimen in people with type 2 diabetes where both mealtime and basal insulin components are needed.

The use of the basal bolus regimen in people with type 1 diabetes and type 2 diabetes attempts to mimic as closely as possible the normal physiological secretion of insulin by providing a background 24 h coverage of insulin by a basal insulin along with bolus injections at each meal (Figure 31.10). In most people with diabetes, with the development of long-acting analogue insulins the basal injection is administered once a day. However, based on the results of pre-meal self-monitored blood glucose values, some people may require two basal injections ~12 h apart to achieve satisfactory pre-meal glucose values without hypoglycaemia. Traditionally with NPH, basal injections are given in the evening, often before bed. However, this is less important with the basal insulin analogues and many people prefer to take their once-daily basal injection at the same time each morning. It is important that insulin doses are adequately titrated to achieve target glucose and HbA_{1c} values; for the basal bolus regimen the dose of the basal insulin is determined by measurement of fasting (pre-meal) glucose values, and the most appropriate fast human or rapid-acting analogue insulin dose is best determined by two-hour post-prandial glucose values.

More practical tips on starting and titrating insulin

In the past, particularly for people with type 1 diabetes, insulin initiation was conducted either as an inpatient or as a day case in a hospital diabetes centre. As confidence grew with the development of purer animal insulins and most recently with human and analogue insulins and the introduction of disposable syringes, pen injectors, and needles, more insulin starts are performed as an outpatient. Lately, with an increased emphasis on community-based diabetes care, insulin initiation, particularly in people with type 2

diabetes, is taking place in health centres and general practitioner surgeries [84]. While older algorithms for helping to decide when and where insulin should be initiated have been published, national and local guidelines now seem more appropriate as varying levels of expertise, infrastructure, and service delivery are present in different areas of the world.

In order to achieve a successful insulin initiation, it is vital that a good insulin initiation programme is in place, with a qualified and competent diabetes nurse specialist. Several programmes are available, most with appropriate training courses for healthcare professionals. Insulin initiation involves much more than teaching someone how to use a needle and syringe, and the process of starting and successfully stabilizing them on insulin will require several structured contacts with the nurse and also a 24 h emergency contact number for any urgent problems that may arise (Table 31.1).

For those presenting acutely ill with nausea and vomiting with or without ketosis, admission to hospital for insulin initiation and, where needed, intravenous fluids is a necessity.

Future perspectives: route, hepatoselectivity, glucose-dependent action

From the early days of insulin, alternatives to the classical parenteral route of insulin administration have been explored. Although inhaled insulin is available, the quest for oral insulin has never stopped. Structural modification and the use of innovative pharmaceutical formulations such as nanoparticles encapsulating the insulin to engender resistance to degradation have been investigated [85]. In 2019, a long-acting, basal insulin analogue formulated in a tablet with the absorption-enhancer sodium caprate, called oral insulin 338, was found to improve glycaemic levels in insulin-naïve individuals similar to subcutaneously administered insulin glargine [86]. Further development of this particular oral insulin project was discontinued because the doses were high, and therefore production for wide public use was deemed not commercially viable. Recent encouraging developments in oral peptide hormone administration in the GLP-1 RA arena (oral semaglutide using salcaprozate sodium [SNAC] technology) have boosted the research efforts towards

Table 31.1 An example of an outpatient/community pathway for people starting insulin for the first time.

<p>Session 1</p> <p>The need for insulin has already been discussed with the person with diabetes by a doctor or diabetes nurse specialist and the person with diabetes has been seen by a dietitian</p> <p>A regimen has been agreed and the first prescription has been obtained by the person with diabetes</p> <p>A review usually takes place of what diabetes is, including what insulin does and the need for insulin injections</p> <p>A nurse demonstrates the basics and use of an insulin injection device and the person with diabetes gives the first injection</p> <p>Further discussions including:</p> <ul style="list-style-type: none"> • sites for injection/site rotation • timing of injections • where and how to obtain equipment (insulin, pens, needles, self-monitoring equipment, sharps disposal equipment) • recognition and management of hypoglycaemia and hyperglycaemia (in type 1 diabetes importance of ketones) • self-blood glucose monitoring • driving and legal issues surrounding insulin • 24 h contact details provided <p>Session 2 (around 2 wk after insulin initiation)</p> <p>Prior to session 2, the person with diabetes and the nurse will usually have had telephone contact over insulin injections and blood glucose readings</p> <p>Review of information provided in session 1</p> <p>Review of insulin injection technique</p> <p>Session 3 (around 4 wk after insulin initiation)</p> <p>Review of sessions 1 and 2</p> <p>Further information provided about:</p> <ul style="list-style-type: none"> • insulin on holiday and when travelling • insulin injections when travelling through time zones (e.g. transatlantic travel) • insulin management during periods of acute sickness • foot care, other diabetes-related complications, and, in women of child-bearing potential, pregnancy <p>Session 4 (around 10 wk after insulin initiation)</p> <p>Review of previous sessions</p> <p>Assessment of glycaemic control and need for further doctor/nurse follow-up</p> <p>Book follow-up clinic/surgery appointment</p>	<p>the development of oral insulin preparations [87]. However, the hurdles remain numerous, such as low bioavailability, interference with food intake, and in particular the narrow dosing range of insulin.</p> <p>Another unmet need in insulin therapy is the hepatoselectivity of the preparations. It is important to appreciate that in health, pancreatic-derived insulin acts directly on the liver via the portal circulation. In the fasting state, a major function of insulin is to suppress hepatic glucose production. Between 50% and 80% of the insulin is metabolized by the liver [88], such that much lower and tightly regulated insulin levels enter the systemic circulation. Peripheral tissues such as muscle also take up glucose at higher insulin concentrations, which tend to occur predominantly postprandially. The administration of insulin by subcutaneous injection delivers it to the systemic circulation, with relatively lower levels reaching the liver. Therefore, glucose uptake by muscle and adipose tissue is preferential to liver. The lower exposure of the liver to insulin also results in greater hepatic glucose production, making the management of blood glucose and body weight even more challenging.</p> <p>An initial approach to targeting insulin action to the liver was through the development of hepatoselective insulins [89], including the technique of making the insulin molecule larger through PEGylation to favour its leaving the circulation at the hepatic sinusoids. The first trials with insulin peglispro resulted in a reduction of HbA_{1c} and body weight [90]. However, insulin peglispro also caused elevated transaminase and triglyceride levels, resulting in the early termination of its development [91]. Currently, other approaches such as an insulin analogue with a C20 fatty diacid attached at position A22K (NNC0123-0327) is under investigation; this insulin has a high affinity for serum albumin and reduced trans-endothelial transport from plasma to periphery, which could result in high clearance via the hepatic insulin receptors [92]. Safety will have to be proven, particularly regarding steatohepatitis and hypoglycaemia, before these products could gain market access.</p> <p>Finally, the ultimate dream of insulin development is the realization of a glucose-dependent insulin action. Several paths are explored, ranging from glucose-responsive polymer encapsulation of insulin to molecule modifications [93].</p>
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35

Oral Glucose-Lowering Agents

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Key points

- Treatment of hyperglycaemia is a fundamental part of the management of type 2 diabetes in order to address acute symptoms and to prevent, defer, or reduce the severity of chronic microvascular and macrovascular complications.
- Treating type 2 diabetes is complicated by the multivariable and progressive natural history of the disease. Insulin resistance, a progressive decline in β -cell function, and defects of other gluco-regulatory hormones and of nutrient metabolism give rise to continually changing manifestations of the disease that require therapy to be adjusted accordingly. People with diabetes often have overweight or obesity, exhibit substantial comorbidity and elevated cardiovascular and renal risk, and receive many other medications that may further complicate treatment.
- Care plans and treatment programmes should be tailored to fit the prevailing circumstances of the individual. Lifestyle management (diet and exercise) should be emphasized from the time of diagnosis and reinforced thereafter. Drug treatment should be undertaken promptly if lifestyle intervention does not achieve adequate glycaemic levels.
- Choice of drug therapy should ideally address underlying pathophysiology, but any safe means of restraining the escalating hyperglycaemia may be appropriate. Combinations of differently acting agents are frequently required to provide additive efficacy, and single-tablet, fixed-dose combinations are available to facilitate therapy. Contraindications and precautions associated with each component of pharmacotherapy must be respected.
- The biguanide metformin is often selected as initial oral glucose-lowering therapy. It counters insulin resistance and lowers blood glucose through several insulin-dependent and -independent mechanisms, notably reducing hepatic glucose production, increasing intestinal glucose-lactate turnover, and increasing glucose uptake by skeletal muscle. It does not stimulate insulin secretion, carries a low risk of hypoglycaemia, and does not cause weight gain. Metformin also exerts several potentially beneficial effects on cardiovascular risk factors independently of glycaemic levels, with evidence of improved long-term cardiovascular outcomes. Metformin may be conveniently combined with other classes of anti-diabetes drugs. Gastrointestinal side effects including diarrhoea limit the use of metformin in some people. The rare but serious adverse effect of lactic acidosis precludes use of the drug in people with severe renal insufficiency, advanced liver disease, or any condition predisposing to hypoxia or hypoperfusion, including decompensated heart failure or respiratory failure.
- Sulfonylureas (e.g. gliclazide, glimepiride, glibenclamide/glyburide, glipizide) act on the pancreatic β cells to stimulate insulin secretion. They bind to the transmembranal complex of sulfonylurea receptors SUR1 with ATP-sensitive Kir6.2 potassium efflux channels. This closes the channels, depolarizes the membrane, opens voltage-dependent calcium channels, and raises intracellular free calcium concentrations. This in turn activates proteins that regulate insulin secretion. The efficacy of sulfonylureas depends on adequate residual β -cell function. Hypoglycaemia is the most serious adverse effect, particularly with longer-acting sulfonylureas and in older people. Caution with hepatic and/or renal insufficiency is warranted in accordance with the metabolism and elimination of individual preparations, and interactions with other protein-bound drugs can occur.
- Meglitinides (repaglinide and nateglinide), also known as prandial insulin releasers, are rapid- and short-acting insulin secretagogues taken before meals to boost insulin levels during digestion, thereby reducing prandial hyperglycaemia and decreasing the risk of inter-prandial hypoglycaemia. They act in a similar manner to sulfonylureas by binding to a benzamido site on the SUR1–Kir6.2 complex. They are conveniently used in combination with an agent that reduces insulin resistance.
- Dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin), also termed gliptins, act predominantly as prandial insulin secretagogues by raising the circulating concentrations of endogenous incretin hormones, notably glucagon-like peptide 1 (GLP-1). This enhances the ‘incretin’ effect of endogenous GLP-1 to potentiate nutrient-stimulated insulin secretion and reduce excess glucagon secretion. DPP-4 inhibitors are weight neutral and, as monotherapy, they carry a low risk of inter-prandial hypoglycaemia. They are often used in combination with metformin or a thiazolidinedione.
- Sodium–glucose cotransporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) increase the elimination of excess glucose in the urine (glucosuria) by reducing glucose reabsorption

from the renal filtrate. They carry a low risk of hypoglycaemia and the glucosuria facilitates weight loss. Their action is independent of insulin, enabling use with other glucose-lowering agents irrespective of the extent of insulin resistance or β -cell dysfunction, but their efficacy requires adequate renal function. The glucosuria can increase the risk of mycotic genital infection, although an associated osmotic diuresis may assist in blood pressure control. SGLT-2 inhibitors reduce the onset and progression of heart failure and exert renal protective effects independently of their glucose-lowering efficacy. Reductions in cardiovascular and all-cause mortality have been reported in cardiovascular outcome trials of some agents in this class.

- An oral formulation of the GLP-1 receptor agonist semaglutide is available in some regions. It mimics the incretin effect to potentiate nutrient-stimulated insulin secretion and suppress excess glucagon secretion with low risk of hypoglycaemia: it also delays gastric emptying and exerts a satiety effect, typically facilitating weight loss. The GLP-1 receptor agonist class has improved outcome measures of atherosclerotic cardiovascular disease and albuminuria in trials in type 2 diabetes.
- Thiazolidinediones (e.g. pioglitazone) produce a slow-onset glucose-lowering effect, attributed mainly to increased insulin sensitivity. They alter the expression of certain insulin-sensitive genes by stimulating the transcription factor peroxisome proliferator-activated receptor γ , increasing adipogenesis, and rebalancing the glucose–fatty acid (Randle) cycle. Thiazolidinediones can be used as monotherapy or in combination

with other classes of glucose-lowering agents. They have a low risk of hypoglycaemia but often cause weight gain. The potential for fluid retention and an attendant risk of congestive heart failure should be borne in mind, especially in combination with insulin. Thiazolidinediones are not recommended for individuals at high risk for cardiac decompensation or women with reduced bone density, and members of this class have been discontinued in some countries.

- α -Glucosidase inhibitors (acarbose, miglitol, voglibose) slow the digestion of carbohydrates by competitive inhibition of intestinal α -glucosidase enzymes. This delays glucose absorption and reduces post-prandial glucose excursions without stimulating insulin secretion. These agents must be used in conjunction with meals rich in digestible complex carbohydrate. They do not cause weight gain or hypoglycaemia as monotherapy and can be used alongside any other glucose-lowering agents.
- The dopamine D2 receptor agonist bromocriptine and the bile sequestrant colestevam have an indication for the treatment of type 2 diabetes in some countries. Their glucose-lowering mechanisms are unclear, but they do not cause weight gain and carry a low risk of hypoglycaemia.
- As type 2 diabetes advances, combinations of glucose-lowering agents with different modes of action are often required. Eventually β -cell function can become too severely compromised to support the continued use of oral agents alone and/or other non-insulin treatments. Insulin therapy should then be initiated, continuing one or more other agents where appropriate.

Treatment of hyperglycaemia is fundamental to the management of type 2 diabetes. It is required to prevent and relieve acute symptoms and complications of hyperglycaemia; prevent, defer, and reduce the severity of microvascular complications; and afford some benefits against macrovascular complications (Table 35.1) [1]. Correction of the hyperglycaemia is an integral part of individualized care that takes account of coexisting diseases and personal circumstances, offers suitable advice on lifestyle and diet, includes other measures to address modifiable cardiovascular risk, selects realistic targets, and facilitates patient education and empowerment. This chapter focuses on the role of oral blood glucose-lowering agents (other anti-diabetes therapies are addressed in Chapters 36 and 37) in the treatment of type 2 diabetes [2–5].

Table 35.1 Aims of appropriate glycaemic management in type 2 diabetes.

Purpose	Complications
Prevent acute symptoms of hyperglycaemia	Dehydration, thirst, polyuria, blurred vision, increased infections
Prevent acute complications	Hyperosmolar non-ketotic state
Prevent, defer, or reduce severity of chronic complications	Microvascular and neuropathic: retinopathy, nephropathy, neuropathy Macrovascular: coronary, cerebrovascular, peripheral vascular disease

Pathophysiological considerations

The interdependent multiplicity of genetic and environmental factors underlying type 2 diabetes gives rise to a highly heterogeneous and progressive natural history [1,6,7]. The pathophysiology typically involves defects of insulin secretion *and* insulin action. Obesity, especially visceral adiposity, and abnormalities of glucagon secretion, incretin hormone action, the microbiome, inflammation, and neurotransmitters contribute to the disease process, while cellular disturbances of nutrient metabolism participate as both causes and consequences of glucotoxicity and lipotoxicity [6,7]. An ideal approach to therapy might therefore address the basic endocrine defects, but any other safe means of ameliorating the hyperglycaemia and attendant biochemical disruptions should provide clinical benefits.

The progressive nature of type 2 diabetes was well illustrated by the UK Prospective Diabetes Study (UKPDS), a randomized trial of 5102 individuals with newly diagnosed type 2 diabetes followed for a median of 10 years while receiving either conventional (diet) therapy or intensive therapy with various oral glucose-lowering agents or insulin (Figure 35.1). Note that insulin was introduced earlier than is usual in clinical practice, and insulin was also used as necessary when oral agents were deemed inadequate. Although the glycated haemoglobin (HbA_{1c}) level deteriorated with time irrespective of the treatment, the improvement in glycaemic indices afforded by intensive therapy (median HbA_{1c} reduced by 0.9% [10 mmol/mol]) was associated with a 12% reduction in overall diabetes-related endpoints and a 25% reduction in microvascular endpoints [8]. An epidemiological analysis showed that benefits of intensive therapy continued to accrue until glucose levels were

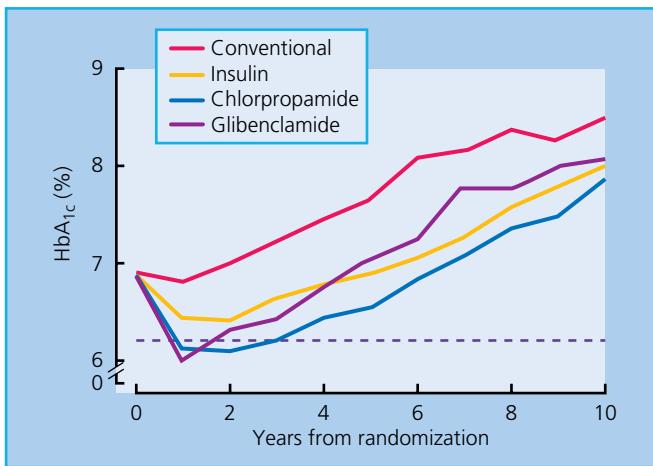


Figure 35.1 The UK Prospective Diabetes Study (UKPDS) shows the progressive rise in glycated haemoglobin ($\text{HbA}_{1\text{c}}$) occurring with time in groups receiving conventional (diet) therapy and intensive therapy with various glucose-lowering drugs (two sulfonylureas – chlorpropamide and glibenclamide – and insulin). Source: Data from UK Prospective Study (UKPDS) Group 1998 [8].

returned to the normal range [9]. Moreover, the benefits of earlier intensive management were continued during an unrandomized post-trial follow-up (median 8.5 years) during which glycaemic differences between the former groups were not maintained [10]. This illustrates the glycaemic *legacy effect*, in which early intensive glycaemic management confers an extended reduction in complications, even when glycaemia deteriorates at later stages in the disease process.

Other large randomized trials [11–13] have confirmed fewer microvascular complications among those receiving more intensive glycaemic management (Table 35.2). One such study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, noted increased mortality during highly intensified (5% mortality, 257/5128) versus standard (4% mortality, 205/5123) glycaemic management. Although the cause of the increased mortality associated with highly intensified management remains uncertain, deaths were more common among those individuals who continued to have hyperglycaemia [14]. In this context, it is noteworthy that an acceptable $\text{HbA}_{1\text{c}}$ value does not exclude excessive daily fluctuations in blood glucose with hyperglycaemic excursions and hypoglycaemic troughs, the latter often unrecognized nocturnally. Survival following a myocardial event appears to be reduced by both hypo- and hyperglycaemia [15].

Guidelines and algorithms

Factors to consider when selecting a glycaemic target for a particular individual are deliberated in detail in Chapter 37, but it is pertinent to reiterate here that the general principle is to return glycaemia safely as close to normal as practicable, while avoiding hypoglycaemia, minimizing adverse effects on body weight and potential drug interactions, and observing other necessary cautions and contraindications. An individualized approach is recommended. Current treatment algorithms [3, 4] provide a framework for initiating and intensifying therapy, but clinical judgement should be applied to harmonize this with the circumstances of the people with diabetes.

Thus, a younger, newly diagnosed individual without comorbidity who is responsive to therapy might be expected to meet a more rigorous target, whereas an older, frail individual with comorbidity or a long history of problems with diabetes management may require a less rigorous target. Management of hyperglycaemia should always be part of a comprehensive management programme to address coexisting disease and modifiable cardiovascular risk factors.

It is emphasized that diet, exercise, and other lifestyle measures should be introduced at diagnosis and reinforced at every appropriate opportunity thereafter. These measures can provide valuable blood glucose-lowering efficacy and may initially enable the desired glycaemic target to be achieved. However, even when lifestyle advice is successfully implemented, the progressive natural history of the disease dictates that the majority of people with type 2 diabetes will later require pharmacological therapy, and this should be introduced promptly if the glycaemic target is not met or maintained. Choice of agent is often limited by comorbidities and driven by the need to address obesity, cardiovascular or renal disease, and avoid the risk of hypoglycaemia [3, 4]. To date, precision medicine approaches that could provide more personalized pharmacotherapy for people with type 2 diabetes remain underdeveloped. In part, this reflects a deficit of clinically useful biomarkers, for example for insulin action and/or deficiency, together with the limited practical utility of relevant pharmacogenomics. This said, evidence of cardio-renal protective effects of some sodium–glucose cotransporter-2 (SGLT-2) inhibitors and some glucagon-like peptide-1 (GLP-1) receptor agonists has prompted recommendations to refine the treatment algorithm for individuals with type 2 diabetes to consider earlier use of agents with such benefits in individuals at high risk of cardiovascular disease [1, 3, 4].

The main classes of oral glucose-lowering drugs and their principal modes of action are listed in Table 35.3. Not all agents are available in all countries and prescribing information may vary between countries. The main tissues through which agents exert their glucose-lowering effects are illustrated in Figure 35.2, and the main cautions and contraindications are listed in Table 35.4. Although there are several different classes from which to choose, many dilemmas continue to impinge on both strategy and individualization of treatment. For example, an increase in fasting glycaemia usually accounts for the majority of the total burden of hyperglycaemia in type 2 diabetes; ideally, therefore, this should be adequately addressed using appropriate therapy [16]. It is also pertinent to note the link between post-prandial hyperglycaemic excursions and cardiovascular risk, which mandates the need also to address this component of the hyperglycaemic day profile [17]. Additionally, consideration should be given to the improvements in glycaemic measures that can be achieved through the treatment of obesity [18]. By the time of diagnosis, insulin resistance is usually well established and typically shows only a modest further increase with extended duration of the disease [6, 7]. Nevertheless, the association between insulin resistance and cardiovascular risk warrants the amelioration of insulin resistance as a valued therapeutic strategy. The ongoing deterioration in glycaemic measures after diagnosis is considered to be largely attributable to a further progressive decline in β -cell function [6, 7]. Thus, preserving β -cell function and mass are important considerations in the quest to maintain long-term glycaemic targets. If β -cell function deteriorates beyond the capacity of oral agents and non-insulin injectable agents (GLP-1 receptor agonists) to provide adequate glycaemic levels, then the introduction of insulin should not be delayed [19]. Incorporating

Table 35.2 Trials comparing intensive with standard (conventional) glycaemic management in type 2 diabetes.

Trial	No.	Duration of follow-up (years)	Age (years)	Duration of diabetes (years)	Baseline HbA _{1c} (%)	Intensive HbA _{1c} %	Conventional HbA _{1c}	Relative risk reduction			
								Microvascular		Macrovascular	
								(%)	p	%	p
UKPDS	3867 ^a	10	53	New	7.1 ^b	7.0	vs 7.9	↓ 25	0.009	↓ 16 ^c	0.052 ^d
UKPDS (post-trial follow-up)	2998	8.5	63	10	—	—	—	↓ 24	0.001	↓ 15 ^c	0.014
ADVANCE	11140	5	66	8	7.5	6.5	vs 7.3	↓ 14	0.01	↓ 6	0.32 ^b
ACCORD ^e	10251	3.5 ^e	62	10	8.3	6.4 ^e	vs 7.5	↓ 33	0.005 ^f	↓ 10	0.16 ^b
VADT	1791	5.6	60	11.5	9.4	6.9	vs 8.4	↓ 2.5 ^g	0.05	↓ 12	0.14 ^b

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial. HbA_{1c}, glycated haemoglobin.

↓, decrease.

To convert HbA_{1c} % to IFCC mmol/mol, the following formula should be used: IFCC mmol/mol = 10.93 DCCT% - 23.5 mmol/mol.

^a Participants without obesity.

^b After a 3 mo dietary run-in.

^c Myocardial infarction.

^d Non-significant.

^e Intensive therapy discontinued at median 3.5 years because of increased deaths in the intensive (257/5128; 5%) vs conventional (203/5123; 4%) group.

^f Reduction in new or worsening nephropathy. No effect on incidence of progression of retinopathy.

^g Any increase in albuminuria.

Part 6 Treatment of Diabetes

Table 35.3 Classes of oral glucose-lowering drugs and their main modes of action.

Class with examples	Main mode of glucose-lowering action	Main cellular mechanism of action
Biguanide Metformin	Counter insulin resistance (especially decrease hepatic glucose output)	Enhance various insulin-dependent and -independent actions including effects on AMPK, mitochondrial respiratory chain, and insulin receptor signalling
Sulfonylureas Glimepiride, glicazide, glipizide, glyburide (=glibenclamide) ^a	Stimulate insulin secretion (typically 6–24 h)	Bind to SUR1 sulfonylurea receptors on pancreatic β cells, which closes ATP-sensitive Kir6.2 potassium channels
Meglitinides Repaglinide, nateglinide	Stimulate insulin secretion (faster onset and shorter duration of action than sulfonylureas)	Bind to benzamido site on SUR1 receptors on pancreatic β cells, which closes ATP-sensitive Kir6.2 potassium channels
DPP-4 inhibitors (gliptins) Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin	Increase prandial insulin secretion	Inhibit DPP-4 enzyme, resulting in increased plasma half-life of incretin hormones, notably GLP-1
Thiazolidinediones (PPAR-γ agonists) Pioglitazone, rosiglitazone ^b	Increase insulin sensitivity (especially increase peripheral glucose utilization)	Activate nuclear receptor PPAR-γ mainly in adipose tissue, which affects insulin action and glucose–fatty acid cycle
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Increase elimination of glucose in the urine	Inhibit SGLT-2 transporters in renal proximal tubules
α-Glucosidase inhibitors Acarbose, miglitol, voglibose	Slow rate of carbohydrate digestion	Competitive inhibition of intestinal α-glucosidase enzymes
Dopamine agonist Bromocriptine ^b	Reduce hepatic glucose production	Central dopaminergic effect
Bile acid sequestrant Colesevelam ^b	Not established	Not established
Glucagon-like peptide-1 (GLP-1) receptor agonist Semaglutide	Increase prandial insulin secretion and reduce glucagon secretion, delay gastric emptying, and exert central effects on increased satiety	Activate GLP-1 receptors on pancreatic β and α cells and in other tissues including upper gastrointestinal tract, portal system, and brain

AMPK, adenosine 5'-monophosphate-activated protein kinase; ATP, adenosine triphosphate; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; PPAR-γ, peroxisome proliferator-activated receptor γ; SGLT-2, sodium–glucose cotransporter-2.

^a Glyburide is the same active compound as glibenclamide.

^b Rosiglitazone has been withdrawn in many countries, pioglitazone is no longer available in some countries, and bromocriptine and colesevelam are not widely used for the treatment of type 2 diabetes.

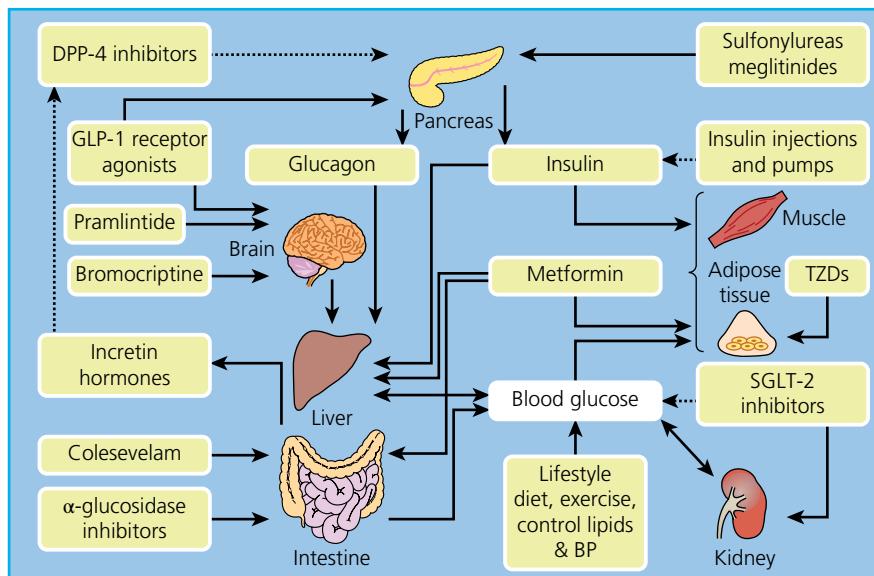


Figure 35.2 Main tissues through which oral glucose-lowering agents exert their glucose-lowering effects. BP, blood pressure; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium–glucose cotransporter-2; TZD, thiazolidinedione.

Table 35.4 General features of the more widely used oral blood glucose-lowering treatments for type 2 diabetes including the main cautions and contraindications.

Feature	Metformin	Sulfonylureas	Meglitinides	Thiazolidinediones	SGLT-2 inhibitors	DPP-4 inhibitors	α -Glucosidase inhibitors	GLP-1 receptor agonist
HbA _{1c} (%)	↓ 1–2	↓ 1–2	↓ 0.5–1.5 ^f	↓ 0.5–1.5	↓ 0.5–1.5	↓ 0.5–1.5	↓ 0.5–1	↓ 1–1.5
HbA _{1c} (mmol/mol)	↓ 11–22	↓ 11–22	↓ 6–17 ^f	↓ 6–17	↓ 6–17	↓ 6–17	↓ 6–11	↓ 11–17
Body weight	-/↓	↑	↑/-	↑	↓	—	—	↓
Lipids	-/+	—	—	+/-/x	-/+	—	-/+	-/+
Blood pressure	—	—	—	↓/-	↓	—	—	↓
Tolerability	GI ^a	Hypo ^d	Hypo ^g	Fluid retention	Mycotic infection	—	GI ^a	GI ^a
Safety	Lactic acidosis ^b	Hypo ^d	Hypo ^g	Oedema ^h	Dehydration ⁱ	Pancreatitis ^j	—	Pancreatitis ^j
				Anaemia				
				Heart failure ^j				
				Fractures				
Cautions	Renal Liver Hypoxaemia ^c	Liver Renal ^e	Liver Renal ^e	CV ⁱ	Renal ^k	Liver ^m	GI ^a	GI ^a

^a Gastrointestinal side effects.^b Lactic acidosis is rare.^c Check for adequate renal and hepatic function, avoid in conditions with heightened risk of hypoxaemia.^d Risk of hypoglycaemia, occasionally severe.^e Check liver and/or renal function relevant to mode of metabolism/elimination.^f Mostly act to lower post-prandial hyperglycaemia; lesser impact on fasting glycaemia and on HbA_{1c}.^g Lesser risk of severe hypoglycaemia than sulfonylurea.^h Fluid retention, anaemia, increased risk of heart failure in susceptible individuals.ⁱ Check for pre-existing cardiovascular disease or developing signs of heart disease; controversy regarding possible early increase in myocardial infarction with rosiglitazone not confirmed in long-term prospective studies.^j Rare reports of ketoacidosis.^k Ensure adequate renal function.^l Possible risk of acute pancreatitis.^m Monitoring of liver function with vildagliptin.[↑], Increased; ↓, decreased; —, neutral; +, benefit; x, impair. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated haemoglobin (1% ≈ 11 mmol/mol); Hypo, hypoglycaemia; SGLT-2, sodium–glucose cotransporter-2.

Table 35.5 Drug interactions with oral glucose-lowering agents that may affect their glucose-lowering effects.

Agent	Increase glucose-lowering effect	Decrease glucose-lowering effect
Any	Combination with other glucose-lowering drugs Minor insulin releasers (e.g. aspirin) Minor insulin sensitivity enhancers (e.g. ACE inhibitors, magnesium or chromium supplements)	Agents that impair insulin action (e.g. glucocorticoids, some antipsychotics, minor effects of diuretics, β -blockers, some β_2 -agonists) Impair insulin secretion (e.g. octreotide, some calcium channel blockers)
Metformin	Renal cation secretion competition by cimetidine Minor PK interaction with furosemide and nifedipine	—
Sulfonylureas	Reduce hepatic metabolism (e.g. some antifungals and MAOIs) Displace plasma protein binding (e.g. coumarins, NSAIDs, sulfonamides) Decrease excretion (e.g. probenecid) Reduce hepatic metabolism (e.g. gemfibrozil) Potentially displace plasma protein binding	K ⁺ -ATP channel openers (e.g. diazoxide) Metabolism secondary to enzyme induction (e.g. rifampicin)
Meglitinides	Reduce hepatic metabolism, gemfibrozil Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g. rifampicin, barbiturates, carbamazepine)
Thiazolidinediones	Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g. rifampicin)
SGLT-2 inhibitors	—	Impaired renal function
DPP-4 inhibitors	Potential interactions with liver and renal metabolism and plasma protein binding	—
GLP-1 receptor agonist	—	If not taken on an empty stomach
α -Glucosidase inhibitors	Slow gut motility (e.g. cholestyramine)	Potentially with agents that increase gut motility

ACE, angiotensin-converting enzyme; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; MAOI, mono oxidase inhibitor; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic; SGLT-2, sodium–glucose cotransporter-2.

some or all of these into the treatment process is inevitably a challenge, and the need to explore suitable combinations of therapies to accommodate the changing status of the disease is common practice [3, 4].

The increasing prevalence of type 2 diabetes among children, adolescents, and young adults adds an extra long-term dimension to risk–benefit considerations [20]. Although initial adequate intervention remains paramount, there is limited experience with oral glucose-lowering agents in children and adolescents; metformin has been used safely in paediatric practice from 10 years of age; and sulfonylureas have been used in paediatric presentations of certain monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY). Treating type 2 diabetes in women who are of childbearing age carries the risk of unplanned pregnancy while receiving oral glucose-lowering agents. Treatment with metformin or a sulfonylurea at the time of conception and during the first trimester has not been shown to have any adverse effects on mother or fetus, and judicious use of metformin may reduce miscarriage and gestational diabetes. Insulin remains the preferred glucose-lowering medication in pregnancy, as there is a substantial evidence base for the safety and flexibility of insulin in gestational diabetes. A paucity of evidence, allied with animal toxicity data or theoretical considerations for some classes, contraindicates thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists during pregnancy and lactation.

Older people are more vulnerable to most of the cautions and contraindications for glucose-lowering drugs, and a deterioration in pathophysiological status can occur rapidly, necessitating more frequent monitoring [21]. Hypoglycaemia is a particular concern in this age group. Although safety must be judged on an individual drug–patient basis, it is noteworthy that several commonly used concomitant medications can impair glucose levels (e.g. glucocorticoids, certain antipsychotics, diuretics, and β -blockers), whereas

others may have their own minor glucose-lowering effect (e.g. aspirin, some angiotensin-converting enzyme [ACE] inhibitors, and mineral supplements; Chapter 21). The most frequent interactions with glucose-lowering drugs are summarized in Table 35.5.

Descriptive terminology applied to glucose-lowering drugs may simplify the use of the different agents. Hypoglycaemic agents have the capacity to lower blood glucose below normal to the extent of frank hypoglycaemia (e.g. sulfonylureas, meglitinides, and insulin). Anti-hyperglycaemic agents can reduce hyperglycaemia, but when acting alone they do not usually have the capability to lower blood glucose below normoglycaemia to the extent of frank hypoglycaemia (e.g. metformin, DPP-4 inhibitors, thiazolidinediones, SGLT-2 inhibitors, GLP-1 receptor agonists, α -glucosidase inhibitors, bromocriptine, and colesvelam).

Biguanides

Metformin (dimethylbiguanide) is the only biguanide currently used in most countries (Figure 35.3). The history of biguanides stems from a guanidine-rich herb, *Galega officinalis* (goat's rue or French lilac), which was used as a traditional treatment in Europe [22]. Guanidine has a glucose-lowering effect, and several guanidine derivatives were adopted for the treatment of diabetes in the 1920s. These agents all but disappeared as insulin became available, but three biguanides – metformin, phenformin, and buformin – were introduced in the late 1950s. Phenformin and buformin were withdrawn in many countries in the late 1970s because of a high incidence of lactic acidosis. Metformin remained and was introduced into the United States in 1995 [23], and it has since become the most prescribed glucose-lowering agent worldwide [24].

Mode of action

Metformin exerts a range of actions that counter insulin resistance and lower blood glucose; the drug also offers some protection against vascular complications independently of its anti-hyperglycaemic effect (Table 35.6) [25, 26]. At the cellular level, metformin exerts insulin-dependent and -independent effects on glucose metabolism that vary with the concentration of metformin to which the tissue is exposed and the prevailing gluco-regulatory mechanisms in that tissue (Figure 35.4). For example, high concentrations of metformin in the intestinal wall can suppress the mitochondrial respiratory chain at complex 1 independently of insulin and promote anaerobic glycolysis to lactate. The conversion of lactate to glucose in other tissues (increased glucose turnover as part of the Cori cycle) may help to prevent weight gain. Lower concentrations

of metformin can suppress mitochondrial glycerol-phosphate dehydrogenase and modestly improve insulin sensitivity in liver and muscle, in part by enhancing post-receptor signalling pathways for insulin, and also by effects on nutrient metabolism and energy

Table 35.6 Diverse metabolic and vascular effects of metformin.

Features associated with diabetes	Effects of metformin	
Hyperglycaemia	↓	↓ HGP, ↑ peripheral glucose uptake, ↑ glucose turnover
Insulin resistance	↓	↑ Receptor-postreceptor insulin signals
Hyperinsulinaemia	↓	↓ Fasting and often post-prandial insulin
Obesity	↓/–	↓ Or stabilizes body weight
IGT	↓	↓ Progression to type 2 diabetes
Dyslipidaemia	↓/–	Modest benefits if abnormal ↓ VLDL-TG, ↓ LDL, ↑ HDL May decrease FA oxidation
Blood pressure	–	No significant effect
Pro-coagulant state	↓	Antithrombotic (↓ fibrinogen, ↓PAI-1, ↓ platelet aggregation)
Endothelial function	↑	↓ Vascular adhesion molecules
Atherosclerosis	↓	↓ MI, ↓ stroke, ↑ vascular reactivity, ↓ cIMT, ↑ life expectancy, anti-atherogenic in animals

↑, Increase; ↓, decrease; –, no significant effect.

cIMT, carotid intima-media thickness; FA, fatty acid; HDL, high-density lipoprotein cholesterol; HGP, hepatic glucose production; IGT, impaired glucose tolerance; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PAI-1, plasminogen-activator inhibitor-1; VLDL-TG, very low-density lipoprotein triglyceride.

Figure 35.3 Chemical structures of guanidine and metformin.

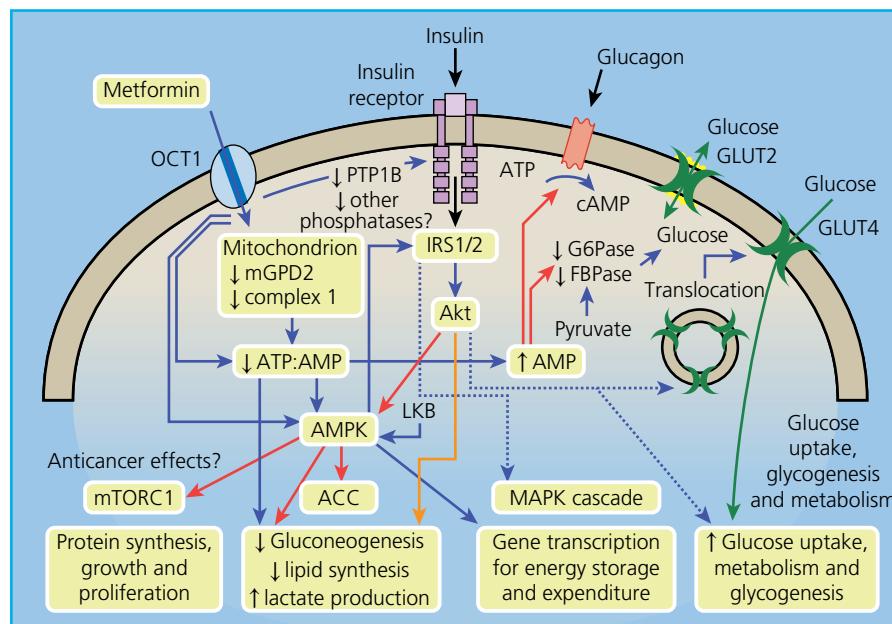


Figure 35.4 Multiple cellular actions of metformin involve insulin-dependent and -independent effects and vary according to the tissue and the level of exposure to metformin. For example, very high exposure to metformin in the intestine can reduce oxidative phosphorylation and promote anaerobic metabolism. Lower concentrations of metformin can improve insulin sensitivity in liver and muscle via effects on insulin receptor signalling and post-receptor signalling pathways of insulin action. Metformin can influence cellular nutrient metabolism and energy production independently of insulin via activation of adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK). ACC, acetyl-CoA carboxylase; Akt, protein kinase

B (PKB); AMPK, adenosine monophosphate-activated protein kinase; FBPase, fructose 1,6-bisphosphatase; G6Pase, glucose 6-phosphatase; GLUT, glucose transporter isofrom; IRS, insulin receptor substrate; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; mGPD, mitochondrial glycerol-phosphate dehydrogenase; mTORC1, mammalian target of rapamycin complex 1; OCT1, organic cation transporter 1; PTP, protein tyrosine phosphatase. Blue lines indicate positive effects; red lines indicate negative effects; dashed lines indicate multistep pathways; up arrows indicate positive effect; down arrows indicate negative effect.
Source: Adapted from Bailey 2012 [27].

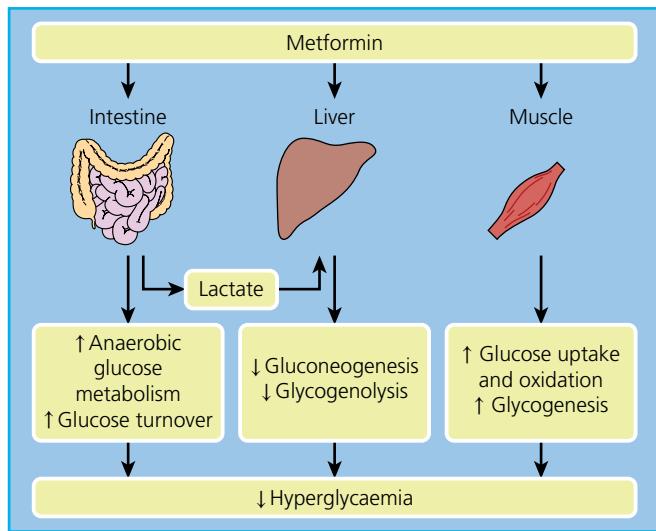


Figure 35.5 Main sites of action of metformin contributing to glucose-lowering effect.

production independently of insulin via activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) [28].

The glucose-lowering efficacy of metformin requires the presence of at least some insulin, because metformin does not mimic or activate the genomic effects of insulin. Also, metformin does not stimulate insulin release; its main glucose-lowering effect appears to be a reduction of hepatic glucose production by suppressing gluconeogenesis and glycogenolysis, but not sufficiently to cause frank hypoglycaemia when used as monotherapy. Metformin reduces gluconeogenesis by increasing hepatic insulin sensitivity, reducing hepatic glucagon receptor signalling, and decreasing hepatic extraction of some gluconeogenic substrates such as lactate (Figure 35.5). Metformin can enhance insulin-stimulated glucose uptake in skeletal muscle by increasing the translocation of insulin-sensitive glucose transporters (GLUT4) into the cell membrane and increasing the activity of glycogen synthase, which promotes glycogen synthesis.

Pharmacokinetics

Metformin is rapidly but incompletely absorbed, shows little binding to plasma proteins, and is not metabolized, and so it does not interfere with co-administered drugs. Metformin is widely distributed at concentrations similar to plasma (about 10^{-5} mol/l), but much higher concentrations are retained in the walls of the gastrointestinal tract. The plasma half-life ($t_{1/2}$) is about 6 hours with elimination of unchanged drug in the urine, mostly within 12 hours [29]. Although renal clearance is achieved more by tubular secretion than glomerular filtration, metformin is contraindicated for people with significant impairment of glomerular filtration. Cimetidine is the only drug known to compete for clearance sufficiently to cause a clinically significant increase in plasma metformin concentrations.

Indications and contraindications

Because metformin does not cause weight gain, it is often preferred for people who have overweight or obesity and type 2 diabetes, although it shows similar anti-hyperglycaemic efficacy in individuals with normal weight [30]. To preclude drug accumulation, patient suitability and dose should be considered very carefully if

there is evidence of impaired renal function (e.g. creatinine clearance is <60 ml/min). Starting metformin is not encouraged if the estimated glomerular filtration rate (eGFR) is <45 ml/min/1.73 m², although reduced doses of the drug are permitted in most countries down to an eGFR of 30 ml/min/1.73 m². Further contraindications include significant cardiac or respiratory insufficiency, or any other condition predisposing to hypoxia or reduced tissue perfusion (e.g. hypotension, septicaemia), and also significant liver disease, alcohol abuse, or a history of metabolic acidosis. Because the potential for acute deterioration in renal, cardiopulmonary, and hepatic function should be considered, it is difficult to identify precise cut-offs for starting or stopping metformin therapy. With this in mind, metformin can be used in older people provided that renal insufficiency and other exclusions are not present. Ovulation can resume in women with anovulatory polycystic ovary syndrome (PCOS), which is an unlicensed purpose for which the drug has been used in the absence of diabetes [31]. Metformin is also under investigation for a possible inhibitory effect on tumour formation and progression in some tissues.

A standard (so-called immediate release, IR) tablet or liquid formulation of metformin should be taken with meals or immediately before meals to minimize possible gastrointestinal side effects. Treatment should start with 500 or 850 mg once daily, or 500 mg twice daily (divided between the morning and evening meals). The dosage is increased slowly – one tablet at a time – at intervals of about 1–2 weeks until the target level of blood glucose is attained. If the target is not attained and an additional dose produces no further improvement, the previous dose should be resumed. In the case of monotherapy, combination therapy can be considered by adding a differently acting agent (e.g. an insulin-releasing drug, SGLT-2 inhibitor, or thiazolidinedione). The maximal effective dosage of metformin is about 2000 mg/day, taken in divided doses with meals, and the maximum is 2550 or 3000 mg/day in different countries [30].

Slow-release formulations (XR/SR/ER) of metformin are available in most countries; they can be taken once daily in the morning, or if necessary morning and evening. Metformin can also be used in combination with any other class of glucose-lowering agent, including insulin, and an extensive range of fixed-dose combination tablets is available in which metformin is combined with either a sulfonylurea, SGLT-2 inhibitor, DPP-4 inhibitor, or thiazolidinedione (see later). It should be noted that although metformin alone is unlikely to cause serious hypoglycaemia, it can occur when metformin is used in combination with an insulin-releasing agent or insulin.

During long-term use of metformin, it is advisable to check at least annually for the emergence of contraindications, particularly renal. Metformin can reduce gastrointestinal absorption of vitamin B₁₂, and although this is rarely a cause of frank anaemia, an annual haemoglobin measurement is recommended, especially for individuals with known or suspected nutritional deficiencies. Metformin should be stopped temporarily when using intravenous radiographic contrast media, or during surgery with general anaesthesia or other intercurrent situations in which the exclusion criteria could be invoked. Substitution with insulin may be appropriate at such times [30].

Efficacy

As monotherapy in people whose diabetes is not adequately managed by lifestyle modification, optimally titrated metformin typically reduces fasting plasma glucose by 2–4 mmol/l, corresponding

to a decrease in HbA_{1c} by ~1–2% (11–22 mmol/mol) [23, 24, 29, 30]. This is largely independent of body weight, age, and duration of diabetes, provided that some β-cell function is still present. To accommodate the progressive nature of type 2 diabetes, it is likely that uptitration of dosage and addition of a second agent will be required to maintain glycaemic targets in the long term.

Metformin carries minimal risk of significant hypoglycaemia or weight gain when used as monotherapy. It may lead to a decrease in basal insulin concentrations, notably in people with hyperinsulinaemia, which should help to improve insulin sensitivity. Minor improvements in the blood lipid profile have been observed during metformin therapy, mostly in those with hyperlipidaemia: plasma concentrations of triglycerides, fatty acids, and low-density lipoprotein (LDL) cholesterol tend to fall, whereas that of high-density lipoprotein (HDL) cholesterol tends to rise [24, 30]. These effects appear to be independent of the anti-hyperglycaemic effect, although a lowering of triglyceride and free fatty acids is likely to help improve insulin sensitivity and benefit the glucose–fatty acid (Randle) cycle.

In the UKPDS, individuals with overweight who started oral glucose-lowering therapy with metformin showed a 39% reduced risk of myocardial infarction (MI) compared with conventional treatment ($p = 0.01$) [32]. There was no obvious relationship with metformin dosage, suggesting that people who can tolerate only a low dose of metformin may benefit from continuing the drug, even when other agents are required to meet adequate glycaemic targets. The decrease in MI was not related to the extent of the glucose-lowering effect of metformin, or effects on classic cardiovascular risk factors such as blood pressure or plasma lipids. Reported benefits of metformin on various atherothrombotic risk markers and factors have been reported, including reduced carotid intima-media thickness (cIMT), increased fibrinolysis, and reduced concentrations of the anti-thrombolytic factor plasminogen activator inhibitor-1 (PAI-1) (Table 35.6) [24, 25, 30].

When metformin is added to the regimens of people receiving insulin therapy, a reduction of insulin dosage is often required, consistent with the ability of metformin to improve insulin sensitivity. Similarly, addition of insulin in people already receiving metformin usually requires lower dosages of insulin and results in less weight gain. Lower amounts of insulin are also associated with fewer and less severe episodes of hypoglycaemia [24, 30]. In some regions of the world metformin is indicated for the prevention of diabetes: the US Diabetes Prevention Program found metformin to reduce the incidence of new cases of diabetes in participants who had overweight or obesity with impaired glucose tolerance (IGT) by 33%, compared with a reduced risk of 58% using an intensive regimen of diet and exercise [33, 34]. The preventive effect of metformin was most evident among individuals who were younger or with a higher level of obesity.

Adverse effects

The main tolerability issue with metformin is abdominal discomfort and other gastrointestinal adverse effects, including diarrhoea. These are often transient and can be ameliorated by taking the drug with meals and titrating the dose slowly. Symptoms may remit if the dose is reduced, but around 10% of people cannot tolerate the drug at any dose. The most serious adverse event associated with metformin is lactic acidosis; it is rare (probably about 0.03–0.06 cases per 1000 patient-years), but about half of cases are fatal [35]. Because the background incidence of lactic acidosis among people with type 2 diabetes has not been established, it is possible that some cases previously attributed to metformin were caused by other factors.

Most reported cases of lactic acidosis in people receiving metformin have been caused by inappropriate prescription, particularly overlooking renal insufficiency. The resulting accumulation of metformin is likely to increase lactate production, and increasing lactate will be aggravated by any hypoxic condition or impaired liver function. Hyperlactataemia occurs in cardiogenic shock and other illnesses that decrease tissue perfusion, and so metformin may be only an incidental factor in some cases. Nevertheless, metformin should be stopped immediately in all cases of suspected or proven lactic acidosis, regardless of cause.

Lactic acidosis is typically characterized by a raised blood lactate concentration (e.g. >5 mmol/l), decreased arterial pH, and/or bicarbonate concentration with an increased anion gap ($[Na^+] - [Cl^- + HCO_3^-] > 15 \text{ mmol/l}$). Presenting symptoms are generally non-specific, but often include hyperventilation, malaise, and abdominal discomfort. Treatment should be commenced promptly without waiting to determine whether metformin is a cause; bicarbonate remains the usual therapy, but evidence of its efficacy is limited. Haemodialysis to remove excess metformin can be helpful, and may assist restoration of fluid and electrolyte balance during treatment with high-dose intravenous bicarbonate.

Sulfonylureas

Since their introduction in the 1950s, sulfonylureas have been used extensively as insulin secretagogues for the treatment of type 2 diabetes. Sulfonylureas were developed as structural variants of sulfonamides after the latter were reported to cause hypoglycaemia [36]. Early sulfonylureas such as carbutamide, tolbutamide, acetohexamide, tolazamide, and chlorpropamide are often referred to as *first-generation* compounds. These have been largely superseded by more potent *second-generation* sulfonylureas, notably glibenclamide (=glyburide), gliclazide, glipizide, and glimepiride (Figure 35.6).

Mode of action

Sulfonylureas act directly on the β cells of the islets of Langerhans to stimulate insulin secretion (Figure 35.7). They enter the β cell and bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), which forms part of the transmembrane complex of ATP-sensitive Kir6.2 potassium channels (K⁺ATP channels) (Figure 35.8) [37]. Binding of a sulfonylurea closes the K⁺ATP channel, reducing the efflux of potassium and enabling membrane depolarization. Localized membrane depolarization opens adjacent voltage-dependent L-type calcium channels, increasing calcium influx and raising the cytosolic free calcium concentration. This activates calcium-dependent signalling proteins that control the contractility of microtubules and microfilaments that mediate the exocytotic release of insulin granules. Preformed insulin granules adjacent to the plasma membrane are promptly released (*first-phase* insulin release), followed by a protracted (*second-phase*) period of insulin release that begins about 10 minutes later [38]. The second phase of insulin release involves translocation of preformed and newly formed insulin granules to the plasma membrane for secretion. Sulfonylureas continue to stimulate insulin release while they are bound to the SUR1 provided that the β cells are functionally competent. Some desensitization, however, occurs during repeated and protracted stimulation [39]. Because sulfonylureas can stimulate insulin release when glucose concentrations are below the normal

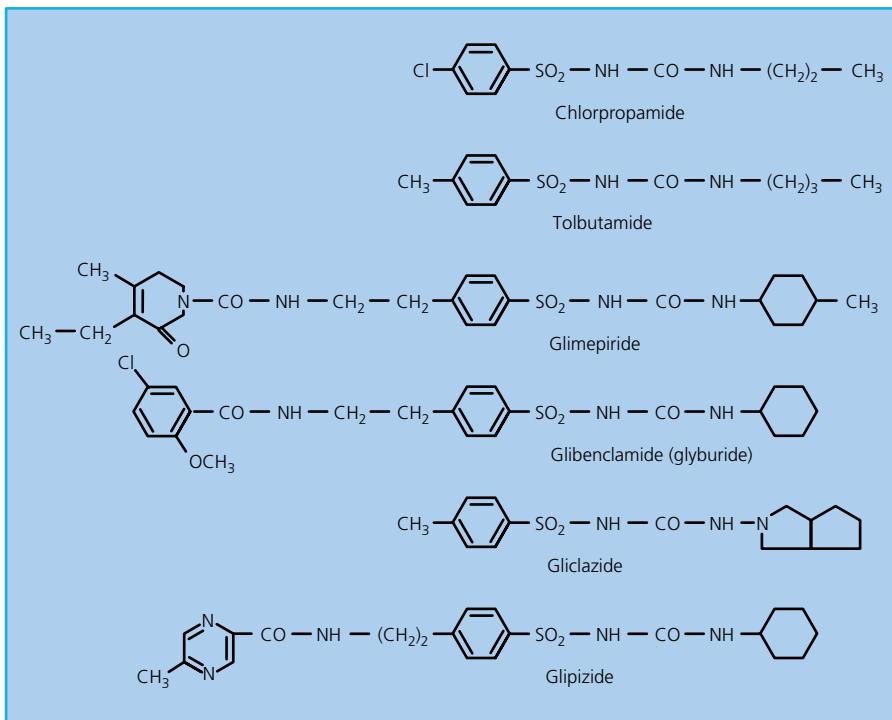


Figure 35.6 Chemical structures of sulfonylureas.

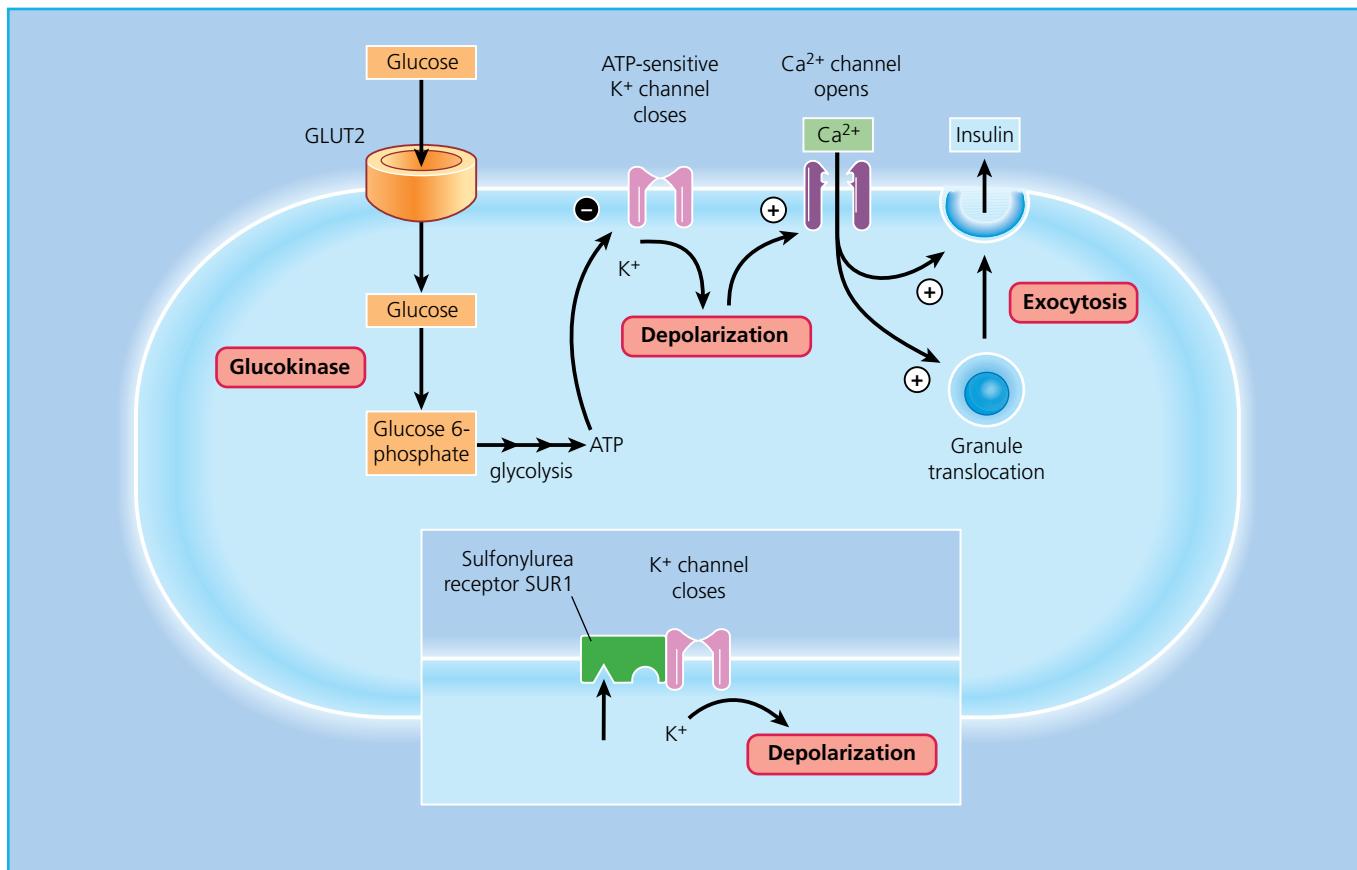


Figure 35.7 Sulfonylureas act on the pancreatic β cell to stimulate insulin secretion. They bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), causing closure of ATP-sensitive Kir6.2 potassium channels, depolarizing the plasma membrane, opening calcium channels, and activating calcium-dependent signalling proteins that control insulin exocytosis.

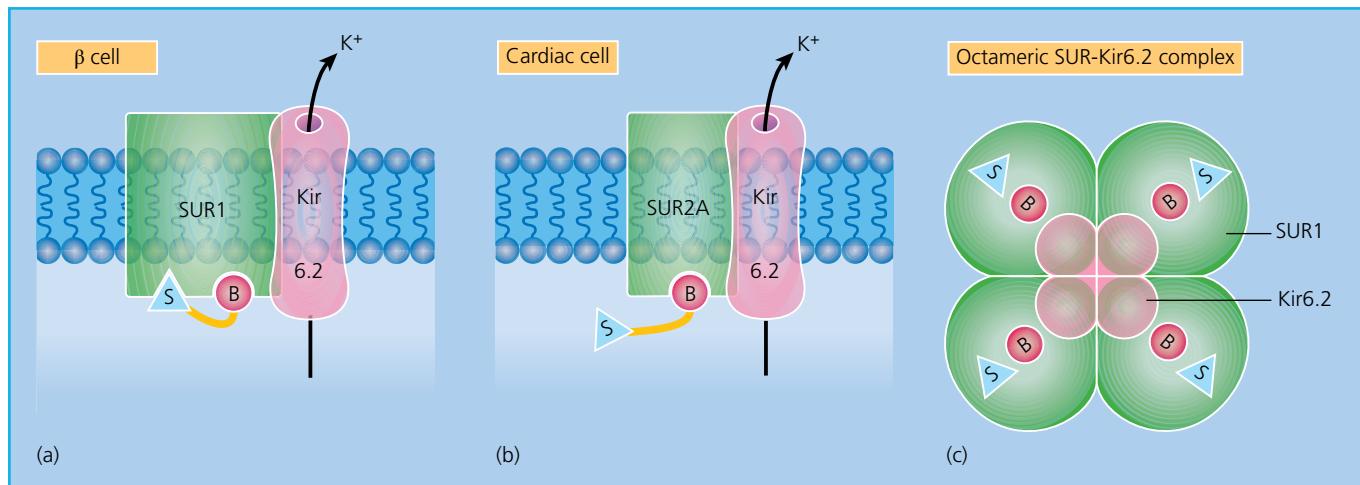


Figure 35.8 (a) The transmembrane complex of the SUR1 sulfonylurea receptor and the ATP-sensitive Kir6.2 potassium efflux channel on the pancreatic β cells. Each SUR1 has a cytosolic sulfonylurea (S) binding site and a benzamido (B) binding site. (b) SUR2A on cardiac muscle cells (and SUR2B on vascular smooth muscle cells) does not have a sulfonylurea binding site. (c) The SUR1–Kir6.2 complex is a non-covalently bonded octamer comprising 4 \times SUR1 and 4 \times Kir6.2, illustrated from the cytosolic surface to show the sulfonylurea and benzamido binding sites. The Kir6.2 components are located at the centre and form the K^+ efflux pore. The Kir6.2 channel has a cytosolic binding region for ADP/ATP.

Table 35.7 Sulfonylureas.

Agent ^a	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Tolbutamide	500–2000	6–10	Inactive	Urine 100%
Glipizide	2.5–20	6–16	Inactive	Urine ~70%
Gliclazide	40–320	12–20	Inactive	Urine ~65%
Gliclazide MR	30–120	18–24	Inactive	Urine ~65%
Glimepiride	1.0–6.0	12–>24	Active	Urine ~60%
Glibenclamide ^b	1.25–15	12–>24	Active	Bile >50%
Chlorpropamide ^c	100–500	24–50	Active	Urine >90%

MR, modified release.

^a People with newly diagnosed type 2 diabetes are not usually started on first-generation sulfonylureas (tolbutamide, chlorpropamide).

^b Glibenclamide is also known as glyburide in some countries.

^c Chlorpropamide is no longer available in many countries.

threshold for glucose-stimulated insulin release (~ 5 mmol/l), they are capable of causing hypoglycaemia, mainly through insulin-induced suppression of hepatic glucose production.

Sulfonylureas may exert minor glucose-lowering effects independently of increased insulin secretion [40, 41]. A small reduction in glucagon concentrations, increased peripheral glucose transport, and increased hepatic glucose deposition have been reported, but these effects are not considered to be of sufficient magnitude to be clinically relevant.

Pharmacokinetics

Sulfonylureas vary considerably in their pharmacokinetic properties (Table 35.7), which in turn affects their clinical suitability for different individuals [40–42]. They are generally well absorbed, and reach peak plasma concentration in 2–4 hours. Sulfonylureas are highly bound to plasma proteins, which can lead to interactions with other protein-bound drugs such as salicylates, sulfonamides, and warfarin. Also, displacement of protein-bound sulfonylurea

can increase the risk of hypoglycaemia (Table 35.5). Sulfonylureas are metabolized in the liver to varying extents to a range of active and inactive metabolites that are eliminated along with unchanged drug via the bile and urine. Longer-acting sulfonylureas can be given once daily but carry a greater risk of hypoglycaemia, especially with active metabolites. Sites and rates of metabolism and elimination are also important considerations, especially in older people and individuals with coexisting liver or kidney disease or taking several other medications.

The formulation of some sulfonylureas has been altered to modify the duration of action. For example, a micronized formulation of glibenclamide (termed glyburide) in the USA increases the rate of gastrointestinal absorption for earlier onset of action. A longer-acting (extended-release) formulation of glipizide and a modified-release (MR) formulation of gliclazide have been introduced for once-daily dosing. Interestingly, the 30 mg preparation of gliclazide MR gives similar efficacy to 80 mg of unmodified gliclazide and reduces the risk of severe hypoglycaemia [43].

Indications and contraindications

Sulfonylureas are widely used as monotherapy and in combination with metformin or a thiazolidinedione. They can also be used with an α -glucosidase inhibitor or SGLT-2 inhibitor, and there are individuals who can benefit from a combination of a sulfonylurea with an incretin agent or insulin. Combination of a sulfonylurea with a different type of glucose-lowering agent usually affords approximately additive glucose-lowering efficacy, at least initially, but there is an increased risk of hypoglycaemia. The additive efficacy of a sulfonylurea with another type of insulin secretagogue is dependent on different modes of action on the β cell.

The pharmacological theory of adding a sulfonylurea (or other insulin secretagogue) to insulin therapy for people with type 2 diabetes is that subcutaneous insulin injections do not mimic the normal endogenous delivery of more insulin to the liver than to the periphery. Thus, where there is residual endogenous β -cell function, a stimulus to increase delivery of endogenous insulin to the liver should assist in reducing hepatic glucose production,

particularly during digestion of a meal. Hence daytime sulfonylurea is sometimes given with bedtime insulin, and this can substantially, if only temporarily, reduce the required insulin dose [40, 42]. Guidelines generally include sulfonylureas as alternative first-line oral therapy where metformin is not appropriate or not tolerated, although DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists are generally favoured in recent guidelines. Because sulfonylurea therapy is associated with weight gain, these agents have customarily been preferred for people who are not overweight.

Sulfonylurea therapy is begun with a low dose, preferably with self-monitoring of blood glucose by the individual at least once daily during the first few weeks. This is especially recommended where there are strong concerns about the potential consequences of hypoglycaemia (e.g. in older individuals and those living alone, operating machinery, or driving). In general, people who have responded to some extent (but still inadequately) with lifestyle measures and have less marked fasting hyperglycaemia are more likely to incur hypoglycaemia with a sulfonylurea. The dosage is uptitrated at 2–4-week intervals as required. Hypoglycaemia or early hypoglycaemic symptoms are the main limitation to dose escalation of sulfonylureas. If evidence of hypoglycaemia occurs before the glycaemic target is achieved, or if a dosage increment produces no further glycaemic benefit, it is advisable to return to the previous dose. Adjustment of the administration regimen may assist or an alternative class of insulin secretagogue may be more suitable. Where the sulfonylurea is taken as monotherapy and the glycaemic target is not achieved, then addition of an agent to reduce insulin resistance or an SGLT-2 inhibitor or an α -glucosidase inhibitor is the usual recourse. Note that the maximal blood glucose-lowering effect of a sulfonylurea is usually achieved at a dose that is well below the recommended maximum, indicating that maximal stimulation of insulin secretion has already been achieved.

Efficacy

As monotherapy in people whose diabetes is inadequately managed by lifestyle measures, sulfonylureas can be expected to reduce fasting plasma glucose by about 2–4 mmol/l, equating to a decrease in HbA_{1c} of 1–2% (11–22 mmol/mol) [2, 5, 40–43]. The glucose-lowering effect of sulfonylureas is immediate, and they are particularly effective in the short term. Efficacy is dependent, however, on sufficient reserve of β -cell function, and this is set against the inevitable decline in β -cell function as the natural history of type 2 diabetes proceeds. Hence it is expected that the dose will need to be escalated to counter the progressive loss of β -cell function, which can reduce the durability of the glucose-lowering efficacy. A rapid deterioration of glycaemic indices during sulfonylurea therapy (sometimes termed *secondary sulfonylurea failure*) occurs in ~5–10% of people per annum. Although this may possibly vary between compounds, it largely reflects the progression of β -cell failure [2, 5, 40–43]. Early intervention in people with a greater reserve of β -cell function usually produces a better and longer response to sulfonylureas, although not without risk of hypoglycaemia, whereas late intervention in those with severely compromised β -cell function is less effective.

Sulfonylureas generally have little effect on blood lipids. Occasionally, their use will cause a small decrease in plasma triglyceride or increase in HDL cholesterol.

Adverse effects

Weight gain, typically in the range 1–4 kg, is common after initiation of sulfonylurea therapy; it stabilizes by about six months [40–42]. The weight gain probably reflects the anabolic effects of increased

plasma insulin concentrations together with reduced loss of glucose in the urine.

Hypoglycaemia is a common and potentially the most serious adverse effect of sulfonylurea therapy. Although it is only rarely life threatening in people with type 2 diabetes, even mild impairment of neural or motor function can endanger the individual and others, and may predispose to a poor prognosis after a myocardial infarction [44]. People treated with sulfonylureas should be given instruction on the prevention and recognition of hypoglycaemia and the prompt actions required. In the UKPDS, ~20% of sulfonylurea-treated participants reported one or more episodes of hypoglycaemic symptoms annually. Other studies have suggested similar rates [9, 12, 42]. Severe hypoglycaemia (requiring third-party assistance) during sulfonylurea therapy occurred in ~1% of participants annually in the UKPDS, and lower rates (~0.2–2.5 episodes per 1000 patient-years) have been reported elsewhere. The mortality risk from sulfonylurea-induced hypoglycaemia is reported to be 0.014–0.033 per 1000 patient-years [44]. Longer-acting sulfonylureas, irregular meals, combination with other glucose-lowering drugs, especially insulin, excessive alcohol consumption, already near-normal fasting glycaemia, old age, and interacting drugs can predispose to an increased risk of hypoglycaemia.

Sulfonylurea-induced hypoglycaemia requires prompt admission to hospital. Treatment with glucose by continuous intravenous infusion, probably for more than one day, is applied to guard against the tendency for a recurrence of hypoglycaemia where long-acting sulfonylureas are concerned. If accumulation of chlorpropamide is suspected, renal elimination may be enhanced by forced alkaline diuresis. The vasodilator diazoxide and the somatostatin analogue octreotide have been used successfully (but with extreme caution) to inhibit insulin secretion in severe sulfonylurea-induced hypoglycaemia. Use of glucagon in people with type 2 diabetes should be avoided as this is itself an insulin secretagogue.

Very occasionally, sulfonylureas produce sensitivity reactions, usually transient cutaneous rashes. Erythema multiforme is rare. Fever, jaundice, acute porphyria, photosensitivity, and blood dyscrasias are also rare. Chlorpropamide (no longer in common use) was known for its propensity to cause facial flushing with alcohol and increasing renal sensitivity to antidiuretic hormones, occasionally causing water retention and hyponatraemia. Glibenclamide is claimed to have a mild diuretic action.

Although the efficacy of sulfonylureas depends on the stimulation of insulin secretion, this seldom raises plasma insulin concentrations beyond the range of normal individuals without diabetes and those with IGT. The suggestion emanating from the University Group Diabetes Program study in the 1960s that tolbutamide-induced hyperinsulinaemia might have a detrimental effect on the cardiovascular system remains unsubstantiated.

Further studies on the cardiovascular safety of sulfonylureas were prompted by the finding that two isoforms of the sulfonylurea receptor, SUR2A and SUR2B, are expressed in cardiac muscle and vascular smooth muscle, respectively. These isoforms lack the sulfonylurea binding site, but they retain the benzamido binding site (Figure 35.8). Therefore, SUR2A/B can only bind those sulfonylureas that contain a benzamido group (glibenclamide, glipizide, glimepiride) [37]. Sulfonylureas without a benzamido group (e.g. tolbutamide, chlorpropamide, gliclazide) show very little interaction with the cardiac and vascular SUR receptors. The effects of the K⁺ATP channel opener nicorandil (an anti-anginal drug with cardioprotective properties) are blocked by sulfonylureas that have a benzamido group. Compounds with a benzamido group could

theoretically interfere with ischaemic preconditioning and increase vascular contractility at a time when this might be undesirable (e.g. severe myocardial ischaemia). However, there is no clear evidence that therapeutic concentrations of sulfonylureas exert such an effect. Indeed, hyperglycaemic states appear to obviate ischaemic preconditioning, but some authorities continue to advocate that the use of sulfonylureas is kept to a minimum in people with overt coronary artery disease [41, 45].

Meglitinides (short-acting prandial insulin releasers)

Meglitinide analogues (sometimes termed glinides) were evaluated as potential glucose-lowering agents after an observation in the 1980s that meglitinide – the non-sulfonylurea moiety of glibenclamide that contains the benzamido group – could stimulate insulin secretion similarly to a sulfonylurea [46]. The pharmacokinetic properties of these compounds favoured a rapid but short-lived insulin secretory effect that suited administration with meals to promote prandial insulin release. By generating a prompt increase of insulin to coincide with meal digestion, these agents help to restore partially the first-phase glucose-induced insulin response

that is lost in type 2 diabetes. Specifically targeting post-prandial hyperglycaemia might also address the vascular risk attributed to prandial glucose excursions and reduce the risk of inter-prandial hypoglycaemia [47]. Two agents, the meglitinide derivative repaglinide and the structurally related phenylalanine derivative nateglinide, were introduced in 1998 and 2001, respectively, as *prandial insulin releasers* (Figure 35.9). Although acting mainly during the prandial and early post-prandial periods, their effects extend sufficiently to produce some reduction of fasting hyperglycaemia, particularly with repaglinide.

Mode of action

Prandial insulin releasers bind to the benzamido site on the sulfonylurea receptor SUR1 in the plasma membrane of the islet β cells (Figure 35.8). This site is distinct from the sulfonylurea site, but the response to binding is the same as for sulfonylureas, causing closure of the K^+ ATP channel. Thus, there is usually no therapeutically additive advantage of using the two types of agents together.

Pharmacokinetics

Repaglinide is almost completely and rapidly absorbed with peak plasma concentrations after about one hour. It is quickly metabolized in the liver to inactive metabolites, which are mostly excreted in the bile (Table 35.8). Taken about 15 minutes before a meal,

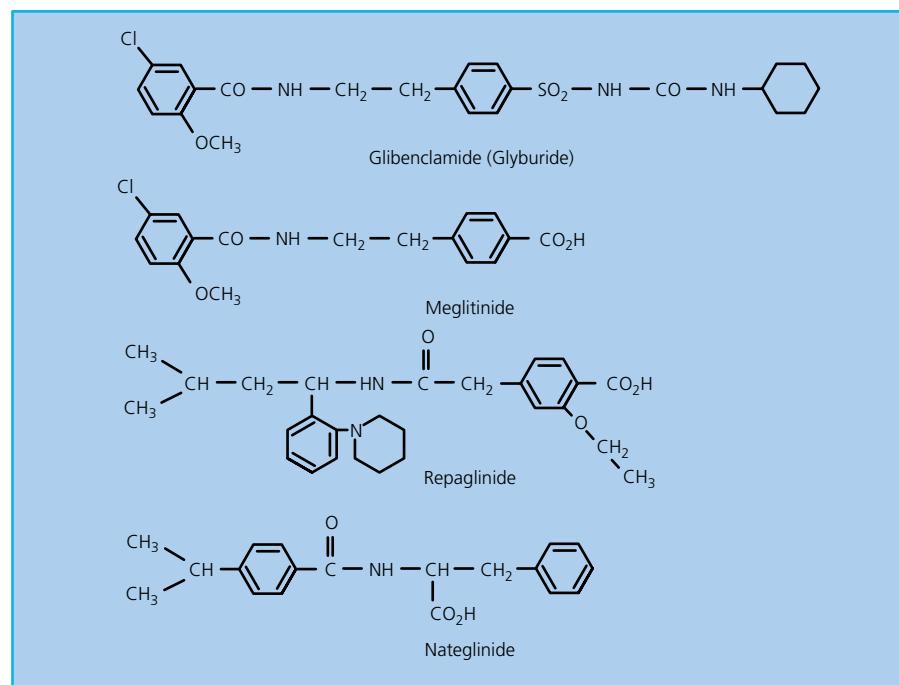


Figure 35.9 Chemical structures of meglitinide and the prandial insulin releasers repaglinide and nateglinide compared with glibenclamide (glyburide).

Table 35.8 The meglitinides: repaglinide and nateglinide.

Agent	Dose range (mg/meal)	Maximum daily dose (mg)	Duration of action (h)	Metabolites	Elimination
Repaglinide	0.5–4.0	16	4–6	Inactive	Bile ~90%
Nateglinide	60–180	540	3–5	One slightly active	Urine ~80%

repaglinide produces a prompt insulin response that lasts about three hours, coinciding with the duration of meal digestion. Nateglinide has a slightly faster onset and shorter duration of action [47].

Indications and contraindications

Prandial insulin releasers can be used as monotherapy in people whose diabetes is inadequately managed by non-pharmacological measures. They are perhaps most suited for individuals who exhibit post-prandial glycaemic excursions while retaining near-normal fasting glycaemia. As rapid-acting insulin releasers, they can be helpful to individuals with irregular lifestyles with unpredictable or missed meals. The lower risk of hypoglycaemia also provides a useful option for some older individuals, particularly if other agents are contraindicated, although the need for multiple daily dosages may be a disincentive.

Repaglinide is ideally taken 15–30 minutes before a meal. Therapy is introduced with a low dose (e.g. 0.5 mg) and glycaemic levels are monitored during titration every two weeks up to a maximum of 4 mg before each main meal. When a meal is not consumed, the corresponding dose of repaglinide should be omitted. With appropriate caution and monitoring, repaglinide can be given to those with moderate renal impairment where some sulfonylureas and metformin are contraindicated.

Nateglinide can be used as monotherapy in much the same way as repaglinide, although nateglinide tends to be faster and shorter acting and requires caution in people with hepatic disease. Note that in some countries, such as the UK, nateglinide is not licensed for use as monotherapy, only for combination therapy.

If the desired glycaemic target is not met with a prandial insulin releaser, early introduction of combination therapy (e.g. with an agent to reduce insulin resistance) can be considered. Prandial insulin releasers can also be useful add-ons to monotherapy with metformin or a thiazolidinedione.

Efficacy

Consistent with their use to boost prandial insulin secretion, repaglinide (0.5–4 mg) and nateglinide (60–180 mg) taken before meals produce dose-dependent increases in insulin concentrations and reduce post-prandial hyperglycaemia. There is usually a small reduction in fasting hyperglycaemia. Reductions in HbA_{1c} are similar to or smaller than with sulfonylureas, as predicted by their shorter duration of action. As an add-on to metformin, they can reduce HbA_{1c} by an additional 0.5–1.5% (6–17 mmol/mol).

Adverse effects

Hypoglycaemic episodes are fewer and less severe with prandial insulin releasers than with sulfonylureas. Sensitivity reactions, usually transient, are uncommon. Plasma levels of repaglinide may be increased during co-administration with gemfibrozil. Prandial insulin releasers may cause a small increase in body weight when started as initial monotherapy, but body weight is little affected among people switched from a sulfonylurea or when a prandial insulin releaser is combined with metformin.

Thiazolidinediones

The glucose-lowering activity of a thiazolidinedione (ciglitazone) was reported in the early 1980s. In the early 1990s, the peroxisome proliferator-activated receptor (PPAR) family was identified as part

of the nuclear receptor superfamily 1, and it became evident that thiazolidinediones were potent agonists of PPAR- γ [48]. The PPAR- γ -mediated transcriptional effects of thiazolidinediones improved whole-body insulin sensitivity, and troglitazone became the first thiazolidinedione to enter routine clinical use, introduced in the USA in 1997. The drug, however, was associated with fatal cases of idiosyncratic hepatotoxicity and was withdrawn in 2000. Troglitazone was available for only a few weeks in 1997 in the UK. Two other thiazolidinediones, rosiglitazone and pioglitazone (Figure 35.10), which did not show hepatotoxicity, were introduced in the USA in 1999 and in Europe in 2000. Fixed-dose combinations of each agent with metformin also became available.

By 2007, meta-analyses of safety data for rosiglitazone were indicating increased risks of heart failure, myocardial infarction, and cardiovascular death, resulting in withdrawal of rosiglitazone in Europe in 2010 and restricted use in the USA (placement on Risk Evaluation and Mitigation Strategy, REMS) [49]. However, evaluation of a large prospective cardiovascular outcome study with rosiglitazone (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes, RECORD) did not confirm the increased risk of myocardial infarction and cardiovascular death, and the REMS restriction in the USA was lifted in 2013. An earlier study in 2007 with pioglitazone (Prospective Pioglitazone Clinical Trial in Macrovascular Events, PROactive) had not shown increased risk of myocardial infarction or cardiovascular death, and pioglitazone has since been shown to reduce risk of stroke [50,51]. However, concerns regarding weight gain, oedema, risk of bone fracture, and other potential cautions have limited the use of pioglitazone in some countries [5].

Mode of action

Most of the glucose-lowering efficacy of thiazolidinediones appears to be achieved through stimulation of PPAR- γ , leading to increased insulin sensitivity [5, 48, 52]. PPAR- γ is highly expressed in adipose tissue, and to a lesser extent in muscle and liver. When activated it forms a heterodimeric complex with the retinoid X receptor and binds to a nucleotide sequence (AGGTCAAGGTCA) termed the peroxisome proliferator response element (PPRE) located in the promoter regions of PPAR-responsive genes. In conjunction with co-activators such as PGC-1, this alters the transcriptional activity of a range of insulin-sensitive and other genes (Table 35.9). Many of these genes participate in lipid and carbohydrate metabolism (Figure 35.11). Stimulation of PPAR- γ by a thiazolidinedione promotes differentiation of pre-adipocytes into mature adipocytes; these new small adipocytes, mostly in subcutaneous depots, are particularly sensitive to insulin, and show increased uptake of fatty acids with increased lipogenesis. This in turn reduces circulating

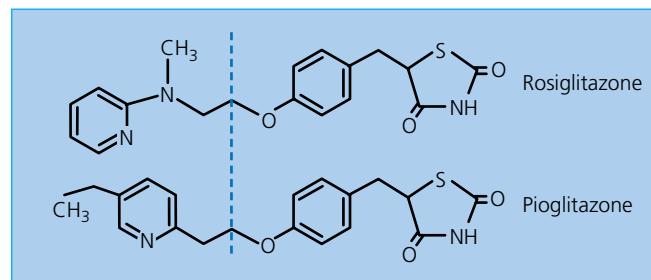


Figure 35.10 Chemical structures of thiazolidinediones rosiglitazone and pioglitazone.

Table 35.9 Examples of key genes activated by thiazolidinediones via stimulation of the peroxisome proliferator-activated receptor γ (PPAR- γ).

- ↑ Lipoprotein lipase
- ↑ Fatty acid transporter protein (FATP/CD36)
- ↑ Adipocyte fatty acid-binding protein (aP2)
- ↑ Acyl-CoA synthetase
- ↑ Malic enzyme
- ↑ Glycerol kinase (in adipocytes?)
- ↑ PEPCK (adipocytes), ↑ perilipin
- ↑ GLUT4 (by derepression), ↑ GLUT2 (islet β cells)
- ↓ 11 β -Hydroxysteroid dehydrogenase-1
- ↓ Resistin, ↓ RBP 4
- ↑ Adiponectin (↑ leptin?)
- ↓ TNF- α , ↓ IL-6
- ↓ CRP and some proinflammatory cytokines, ↓ NF κ B
- ↓ PAI-1, ↓ MMP-9
- ↑ UCP-1 (?)

Not all genes appear to be activated in all tissues due in part to the involvement of different coactivators in different tissues. The main effects are in adipose tissue.

↑, Increase expression; ↓, decrease expression; ?, unconfirmed. CRP, C-reactive protein; GLUT, glucose transporter; IL-6, interleukin 6; MMP-9, matrix metalloproteinase 9; NF κ B, nuclear factor κ B; PAI-1, plasminogen activator inhibitor 1; PEPCK, phosphoenolpyruvate carboxy kinase; RBP, retinol-binding protein; TNF- α , tumour necrosis factor α ; UCP-1, uncoupling protein 1.

non-esterified (free) fatty acids, which rebalances the glucose–fatty acid (Randle) cycle, facilitating glucose utilization and restricting fatty acid availability as an energy source for hepatic gluconeogenesis. By reducing circulating fatty acids, ectopic lipid deposition in muscle and liver is reduced, which further contributes to improvements of glucose metabolism. Thiazolidinediones also increase mitochondrial biogenesis, but may act directly on mitochondria to reduce respiratory function.

Thiazolidinediones increase glucose uptake into adipose tissue and skeletal muscle via increased availability of GLUT4 glucose transporters. Improvements in insulin sensitivity are likely to be assisted by reduced production of several adipocyte-derived proinflammatory cytokines, notably tumour necrosis factor α (TNF- α), which is implicated in muscle insulin resistance. Thiazolidinediones also increase the production of adiponectin, which enhances insulin action and exerts potentially beneficial effects on vascular reactivity. Because PPAR- γ is expressed to a small extent in many tissues, thiazolidinediones can affect responsive genes at these locations, and this has given rise to the tag *pleiotropic effects* [52, 53].

Thiazolidinediones, like metformin, require the presence of sufficient insulin to generate their blood glucose-lowering effect. Plasma insulin concentrations are typically lowered by thiazolidinediones, and long-term viability of islet β cells might be improved [53].

Pharmacokinetics

Absorption of rosiglitazone and pioglitazone is rapid and almost complete, with peak concentrations at 1–2 hours, but slightly delayed when taken with food. Both drugs are metabolized extensively by the liver. Pioglitazone is metabolized predominantly by CYP2C8 and CYP3A4 to active metabolites that are eliminated in the bile (Table 35.10). Pioglitazone does not cause any clinically significant reductions in plasma concentrations of other drugs metabolized by CYP3A4, such as oral contraceptives. Both thiazolidinediones are almost completely bound to plasma proteins, but their concentrations are not sufficient to interfere with other protein-bound drugs.

Indications and contraindications

Thiazolidinediones can be used as monotherapy in individuals with type 2 diabetes with and without obesity in whom lifestyle does not afford adequate glycaemic levels. Various treatment algorithms ascribe different positions for thiazolidinediones, but in general they can be used as monotherapy if metformin is inappropriate or not tolerated, and as an add-on to metformin for those in whom weight gain is not an issue and an insulin secretagogue is not favoured. Because of their slow onset of action, it is not straightforward to substitute a thiazolidinedione for another class of glucose-lowering agent without a temporary deterioration in glycaemic levels. Combination of a thiazolidinedione with insulin can improve

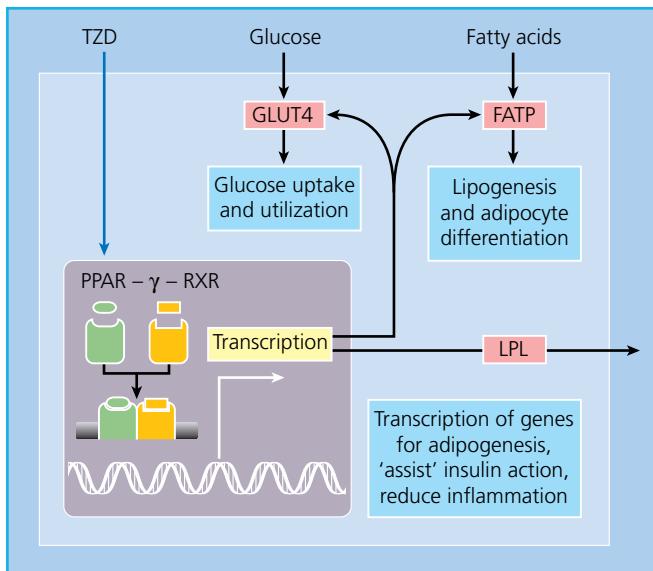


Figure 35.11 Mechanism of action of thiazolidinediones. Most actions of a thiazolidinedione (TZD) are mediated via stimulation of the nuclear peroxisome proliferator-activated receptor γ (PPAR- γ), which is highly expressed in adipose tissue. When stimulated, PPAR- γ forms a heterodimeric complex with the retinoid X receptor (RXR). The complex binds to the peroxisome proliferator response element (PPRE) nucleotide sequence (AGGTCAAGGTCA) in the promoter regions of certain genes, recruits co-activators, and alters the transcriptional activity of these genes. This modifies nutrient uptake and metabolism, and also the other functions of the cell.

Table 35.10 The thiazolidinediones: pioglitazone and rosiglitazone.

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Pioglitazone	15–45	~24	Active	Bile >60%
Rosiglitazone	4–8	~24	Inactive	Urine ~64%

glycaemic indices while reducing insulin dosages, especially in individuals with obesity, but requires extra caution as peripheral oedema is more common [53].

The propensity for fluid retention with thiazolidinediones, which can increase plasma volume by up to 500 ml, reduce haematocrit, and decrease the haemoglobin concentration up to 1 g/dl, contraindicates these agents for people with evidence of heart failure. The exclusion criteria, based on cardiac status, vary between countries; for example, New York Heart Association classes I–IV are exclusions in Europe, whereas classes III and IV are exclusions in the USA [5]. Appropriate clinical monitoring is important, especially for people considered at higher risk for cardiac failure and those showing marked initial weight gain. Despite an increased fluid volume, thiazolidinediones do not increase, and usually slightly decrease, blood pressure.

The troglitazone experience of idiosyncratic hepatotoxicity prompted vigilance with liver function by measuring serum alanine aminotransferase (ALT) before starting rosiglitazone and pioglitazone therapy, and periodically thereafter. Pre-existing liver disease, development of clinical hepatic dysfunction, or elevated ALT levels >2.5 times the upper limit of normal are contraindications to thiazolidinediones. Interestingly, because of the effects of thiazolidinediones to reduce hepatic fat, recent studies have suggested that this class of drug might be useful for the treatment of non-alcoholic steatohepatitis [53].

If there are no contraindications, a thiazolidinedione can be used in older people. A thiazolidinedione can also be considered for individuals with mild renal impairment, while appreciating the potential for oedema. Use of a thiazolidinedione in women with anovulatory PCOS can cause ovulation to resume, but thiazolidinediones should not be continued in pregnancy.

Efficacy

Thiazolidinediones produce a slowly generated anti-hyperglycaemic effect, which usually requires 2–3 months to reach maximum effect [52, 53]. This tends to prolong the dose titration process, and because the therapeutic response can vary considerably between individuals, it is appropriate to consider the individual as a non-responder and to switch to another treatment if there is no clinically meaningful effect after three months. Thiazolidinediones reduce HbA_{1c} by around 0.5–1.5% (6–17 mmol/mol). In a long-term monotherapy comparison with metformin or a sulfonylurea (A Diabetes Outcome Progression Trial, the ADOPT study), rosiglitazone showed a slower onset but more durable glucose-lowering effect over more than three years [54]. The effect of thiazolidinediones may be better in people with greater β-cell reserve and in more overweight individuals, but a clear indicator of the best responders has not been established. Thiazolidinediones do not cause hypoglycaemia as monotherapy.

Thiazolidinediones substantially reduce circulating non-esterified (free) fatty acids, but effects on other components of the plasma lipid profile have been the subject of debate. Rosiglitazone tends to cause a small rise in the total cholesterol concentration, which stabilizes by about three months, although this may be mitigated by adequate statin therapy. The effect appears to reflect a rise in both LDL and HDL cholesterol, leaving the LDL-to-HDL cholesterol ratio and the total-to-HDL cholesterol ratio little changed or slightly improved. Pioglitazone generally appears to have little effect on total cholesterol, and has frequently reduced triglyceride concentrations in clinical trials. Both thiazolidinediones reduce the proportion of the smaller, denser (more atherogenic) LDL particles [53].

Weight gain, similar in magnitude to sulfonylurea therapy (typically 1–4 kg) and stabilizing over 6–12 months, is usually observed after initiation of thiazolidinedione therapy. Several studies indicate that the distribution of body fat is altered; the visceral adipose depot is little changed or reduced, while the subcutaneous depot is increased as new small, insulin-sensitive adipocytes are formed [53].

Thiazolidinediones exert beneficial effects on a selection of atherothrombotic risk markers, indices of vascular reactivity, and components of the metabolic syndrome. For example, thiazolidinediones downregulate PAI-1 expression, decrease urinary albumin excretion to a greater extent than expected for the improvement in glycaemic levels, reduce cIMT and coronary restenosis, and reduce circulating markers of chronic low-grade inflammation [53]. However, a recent pragmatic trial (Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents. Intervention Trial, TOASCA.IT) noted that the incidence of cardiovascular events was similar when either pioglitazone or a sulfonylurea was added to metformin [55]. Thiazolidinediones also reduce the occurrence of new-onset diabetes in individuals with IGT or those with a history of gestational diabetes [53].

Adverse effects

Despite improvements in several atherothrombotic risk factors, the main concerns over thiazolidinediones have focused on the cardiovascular impact of oedema, reduced haemoglobin levels, and congestive heart disease. Although long-term cardiovascular events were reduced during a large prospective study with pioglitazone (PROactive), the cardiovascular safety issues raised over rosiglitazone reduced confidence in the class, and the TOSCA.IT pragmatic study indicated no overall cardiovascular benefit of pioglitazone [49, 50, 53, 55].

Recent studies have noted an approximate doubling of the risk of a bone fracture with use of a thiazolidinedione, mainly at distal sites and among postmenopausal women [53]. This has been attributed at least in part to a reduction in bone mineral density. Stimulation of PPAR-γ in colonic cells has been reported both to increase and to decrease the risk of tumours in animals and cell models; thus, familial polyposis coli is a contraindication to thiazolidinediones on theoretical grounds. There has been debate concerning a possible increased risk of bladder cancer with pioglitazone, and the drug is not recommended for people with active bladder disease or a history of bladder disease. However, long-term safety analyses have not confirmed a significant increase in risk of bladder cancer with pioglitazone [53].

Hypoglycaemia may occur several weeks after adding a thiazolidinedione to a sulfonylurea; self-monitoring of blood glucose can be helpful to identify when the dosage of the sulfonylurea should be reduced.

Dipeptidyl peptidase 4 inhibitors

DPP-4 inhibitors (often termed gliptins) inhibit the enzyme DPP-4, which is responsible for the rapid degradation of two key incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). Thus DPP-4 inhibitors enhance endogenous incretin activity by preventing the rapid degradation of these incretin hormones. The history, structure, and function of incretin hormones, and the therapeutic role of subcutaneously injected GLP-1 receptor agonists such as exenatide,

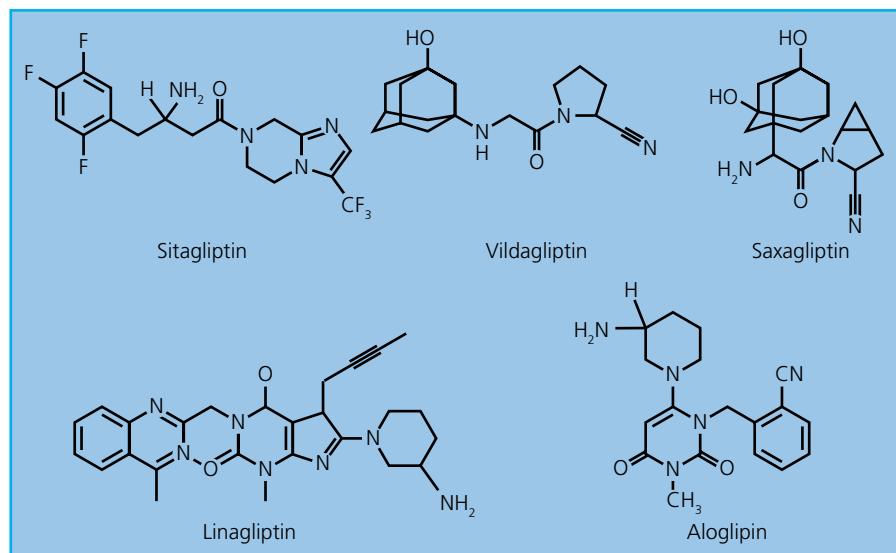


Figure 35.12 Chemical structures of the dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

liraglutide, lixisenatide, and dulaglutide, are covered in Chapter 36. Briefly, incretin hormones are secreted from the intestine in response to meal digestion; one of their main actions is to increase glucose-induced insulin secretion by the pancreatic islet β cells, thereby reducing prandial glucose excursions [5, 56, 57]. GLP-1 also suppresses glucagon secretion from the islet α cells, exerts a satiety effect, and delays gastric emptying.

It was noted in the 1980s that the incretin effect is reduced in type 2 diabetes, and subsequent studies have shown that this is largely due to reduced activity of GLP-1 [58, 59], suggesting that administration of extra GLP-1 might be therapeutically useful. Because GLP-1 is rapidly degraded ($t_{1/2} < 2$ minutes) by DPP-4, the potential of DPP-4 inhibitors was investigated in the 1990s, giving rise to the introduction of several specific inhibitors [60], notably sitagliptin (2007), vildagliptin (2008), saxagliptin (2008), linagliptin (2011), and alogliptin (2013) (Figure 35.12).

Mode of action

DPP-4 inhibitors act to prevent the aminopeptidase activity of DPP-4; the enzyme is found free in the circulation and tethered to endothelia and other epithelial cells in most tissues, especially in the intestinal mucosa [61]. DPP-4 cleaves the N-terminal dipeptide from peptides that have either an alanine or a proline residue penultimate to the N-terminus. The incretins GLP-1 and GIP are prime targets for DPP-4, and DPP-4 inhibitors more than double their circulating concentrations (although this is not as high as the concentrations of subcutaneously administered GLP-1 receptor agonists) [58]. Raised endogenous incretin concentrations enhance nutrient-induced insulin secretion. Increased insulin biosynthesis and increased β -cell mass have also been noted in some animal studies, but these effects have not been confirmed in clinical studies (Table 35.11). Increased GLP-1 concentrations also suppress excessive glucagon secretion. Because these effects are glucose dependent, there is a low risk of inducing significant hypoglycaemia, and this is a key reason for the increased use of DPP-4 inhibitors in preference to sulfonylureas. The elevation of GLP-1 levels produced by DPP-4 inhibitors is not generally sufficient to create a measurable satiety effect or sufficient to delay gastric emptying, hence avoiding any nausea. Body weight is usually little changed or slightly reduced by DPP-4 inhibitors (Figure 35.13).

Table 35.11 Effects of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) on glucose homeostasis.

	GLP-1	GIP
Effects on pancreatic islets		
Increase nutrient-induced insulin secretion	✓	✓
Increase insulin biosynthesis ^a	✓	✓
Increase β -cell mass ^a	✓	✓
Suppress glucagon secretion	✓	–
Increase somatostatin secretion	✓	–
Extrapancreatic effects		
Slow/delay gastric emptying	✓	–
Decrease gastric acid secretion	–	✓
Promote satiety and weight reduction	✓	–
Promote lipogenesis	–	✓

✓, Yes; –, no effect.

^a Effect observed in animal studies but not confirmed by clinical studies in type 2 diabetes.

Because the incretin-mediated effect of DPP-4 inhibitors potentiates glucose-dependent insulin secretion, the activity period of these agents is mostly prandial. Although they are particularly effective in lowering post-prandial hyperglycaemia, there is a substantial carryover effect to benefit inter-prandial glycaemia [58, 60, 61]. By contrast, DPP-4 inhibitors do not initiate insulin secretion and so they do not increase basal insulin secretion. Also, they only suppress glucagon secretion in the hyperglycaemic state, and so there is a low risk of inter-prandial overshoot into hypoglycaemia.

Pharmacokinetics

The pharmacokinetic properties of DPP-4 inhibitors are summarized in Table 35.12. DPP-4 inhibitors are selective, competitive, and reversible inhibitors of DPP-4 (IC_{50} in the lower nmol/l range). They mimic the N-terminal dipeptide structure of the incretins, which enables them to block the catalytic site of DPP-4 through either covalent (vildagliptin and saxagliptin) or non-covalent

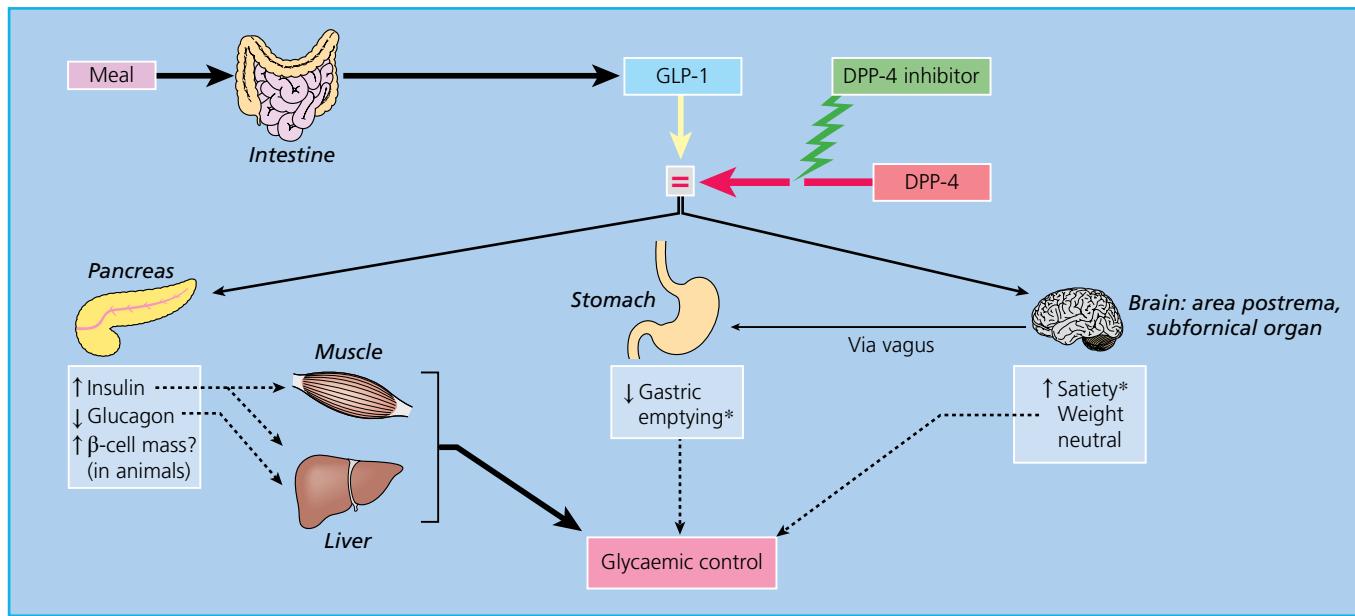


Figure 35.13 Sites of action of dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins). Incretin hormones such as glucagon-like peptide-1 (GLP-1) are released in response to a meal. These hormones are normally degraded rapidly by the enzyme DPP-4. Inhibiting DPP-4 allows the normal effects of the incretin hormones to be enhanced. The main site of the enhanced incretin effect is on the pancreas to increase nutrient-induced insulin secretion. GLP-1 also reduces glucagon secretion. *Potential effects to slow gastric emptying and increase satiety probably contribute little to the therapeutic efficacy of DPP-4 inhibitors.

Table 35.12 Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins): sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

Agent	od/bd ^a	Dose (mg/d)	t _{1/2} (h)	IC ₅₀ (nM) ^b	Selectivity for DPP4 ^c	Metabolism	Excretion
Sitagliptin	od	100	8–24	19	>2500	Unchanged	Urine ~80%
Vildagliptin	bd	50	1.5–4.5	62	32–270	Inactive metabolites	Urine ~80% ^d
Saxagliptin	od	5	2–7 ^e	50	77–390	Active metabolites	Urine ~60% ^d
Linagliptin	od	5	10–40	1	>10 000	Mostly unchanged	Bile ~80%
Alogliptin	od	25	12–21	24	>14 000	Mostly unchanged	Urine >70%

^a od, once daily; bd, twice daily.

^b Concentration causing 50% inhibition of DPP-4 activity.

^c Fold selectivity for inhibition of DPP-4 versus inhibition of DPP-8 and DPP-9.

^d Unchanged drug.

^e Includes metabolites.

(sitagliptin, linagliptin, and alogliptin) interactions. DPP-4 inhibitors are absorbed rapidly, with onset of activity in <10 minutes of administration and t_{max} achieved mostly within 2 hours. They produce >90% inhibition of DPP-4 activity for most of a 24-hour period, although the shorter elimination half-life of vildagliptin requires twice-daily administration compared with once daily for other agents in the class. Two DPP-4 inhibitors are substantially metabolized (vildagliptin to inactive metabolites and saxagliptin to active metabolites), whereas the others undergo little metabolism. Linagliptin is eliminated mostly via the bile into the faeces and can be used without dose adjustment in people with moderate to severe renal impairment. Other members of the class are eliminated in the urine, necessitating dose reduction in people with moderate renal impairment (typically an eGFR <50 ml/min) [60, 60].

Indications and contraindications

DPP-4 inhibitors can be used as monotherapy in people whose type 2 diabetes has responded inadequately to lifestyle measures, and as add-on therapy when metformin or a thiazolidinedione alone has not brought the glucose levels into the target range. DPP-4 inhibitors could be used with other classes of oral agent or insulin, as their mode of action on the β cell is different from that of sulphonylureas and meglitinides, and their ability to reduce glucagon levels might be useful as add-on therapy to insulin even without β -cell function. In practice, however, full efficacy in type 2 diabetes requires adequate β -cell reserve, and there is usually little additional efficacy if a DPP-4 inhibitor is added to a GLP-1 receptor agonist. Lack of weight gain makes DPP-4 inhibitors suitable for individuals with overweight or obesity, and the low risk of hypoglycaemia when used as monotherapy (and

when used with non-insulin-releasing agents) favours their use in people who have only slightly raised basal glycaemia, are close to glycaemic target, or have unpredictable meal times [60,61].

Efficacy

The anti-hyperglycaemic effect of DPP-4 inhibitors is quickly generated, with HbA_{1c} values typically reduced by ~0.7–1.0% (8–11 mmol/mol). Post-prandial glucose excursions are reduced by ~3 mmol/l and basal glycaemia by ~1–1.5 mmol/l. The glucose-dependent mode of action (i.e. DPP-4 inhibitors only potentiate insulin secretion when glucose concentrations are raised) reduces the risk of any significant hypoglycaemia, lowering concern over missed meals. Thus, there is no dose titration, but it is recommended that fasting and post-prandial glycaemia are reviewed after about two weeks of therapy, especially when added as a second agent. The incretin-raising effects of DPP-4 inhibitors do not appear to be sufficient to reduce gastric emptying or produce a measurable satiety effect. Accordingly, DPP-4 inhibitors do not cause weight gain and may assist with slight weight loss [61–63].

Adverse effects

Substantial clinical experience with DPP-4 inhibitors has indicated a good safety profile to date. In clinical trials (typically 6–12 months), measures of tolerability and adverse events were generally similar to those with placebo or comparator. Owing to their glucose-dependent action on the pancreas, DPP-4 inhibitors carry a low risk of serious hypoglycaemia unless administered along with an agent that itself carries significant risk of hypoglycaemia. Thus, when a DPP-4 inhibitor is used in combination with a sulfonylurea or with insulin, it may be appropriate initially to lower the dose of the sulfonylurea or insulin, especially for those who are only modestly hyperglycaemic and more vulnerable to hypoglycaemia. DPP-4 inhibition has been associated with some hyperplasia of the exocrine pancreas, and there is evidence from several prospective and retrospective clinical studies that DPP-4 inhibition can increase the risk of acute pancreatitis in type 2 diabetes. Although this has not been consistently observed, or numerical data have not been statistically significant, appropriate caution is recommended and a DPP-4 inhibitor should be stopped if pancreatitis is suspected, and alternative therapy sought for people with a history of pancreatitis. Long-term cardiovascular safety studies have raised the possibility of an increased risk of angina during use of some DPP-4 inhibitors, but the evidence is equivocal, and there is lingering concern from these studies that saxagliptin and possibly alogliptin could carry a small increased risk of heart failure [62–64].

In addition to GLP-1 and GIP, there are many natural substrates for DPP-4, including bradykinin, enkephalins, neuropeptide Y, peptide YY1–36, gastrin-releasing polypeptide, substance P, insulin-like growth factor I, the α chains of thyrotropin, luteinizing hormone, and chorionic gonadotropin, and several chemokines such as monocyte chemotactic protein 1 (MCP-1). Hence DPP-4 inhibitors have the potential to influence the hunger–satiety system, gastrointestinal motility, growth, vascular reactivity, and immune mechanisms, but there is little evidence of any clinically significant changes in these physiological processes [61,63]. DPP-4 is also the CD26 T-cell activation antigen, but neither CD26 knockout mice nor the DPP-4-specific inhibitors used in animals or humans have shown any significant untoward immune-related effects. The importance of selective DPP-4 inhibition is also noted because inhibition of related enzymes such as DPP-8 and DPP-9 has

produced blood dyscrasias and skin lesions in some species, although not in clinical use. No significant drug interactions have been noted with DPP-4 inhibitors, but evidence of reproductive toxicity in animals warrants discontinuation in pregnancy.

Sodium–glucose cotransporter-2 inhibitors

SGLT-2 is highly expressed in the first segment of the proximal tubules of the kidneys, where it is responsible for the reabsorption of ~90% of glucose in the glomerular filtrate. Partial inhibition of SGLT-2 provides a non-insulin-dependent mechanism to reduce glucose reabsorption, eliminate excess glucose in the urine, and so reduce hyperglycaemia [65]. Studies in the 1980s showed that phlorizin, a naturally occurring inhibitor of sodium–glucose transporters found in apple tree bark, could reduce hyperglycaemia in partially pancreatectomized rodents with diabetes. Phlorizin was degraded too rapidly in the intestine to be used therapeutically, but chemical modifications to minimize intestinal breakdown and increase selectivity against SGLT-2 have given rise to a class of selective SGLT-2 inhibitors represented by canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (Figure 35.14).

Mode of action

SGLT-2 is a high-capacity secondary active cotransporter that transfers one sodium ion with one glucose molecule down an electrochemical gradient for sodium, generated by, for example, the activity of an Na⁺–K⁺ ATPase pump [65,66]. SGLT-2 inhibitors interact with SGLT-2 transporters located at the luminal surface of the epithelium lining the initial region of the renal proximal tubules (Figure 35.15). They competitively inhibit the transporter, reducing glucose reabsorption and thereby lowering the renal threshold for glucosuria. In this way, SGLT-2 inhibitors enable ~20–30% of filtered glucose (about 50–100 g glucose/d) to be eliminated in the urine of people with type 2 diabetes [66,68,69]. As the blood glucose concentration declines, both the amount of filtered glucose and the glucosuria decline, minimizing the effect of SGLT-2 inhibition in the euglycaemic range and avoiding frank hypoglycaemia. Because the mechanism is independent of insulin, it will continue to operate under conditions of insulin resistance and β -cell failure, but requires adequate kidney function to filter sufficient glucose for partial SGLT-2 inhibition to create enough glucosuria to impact the hyperglycaemia. The glucosuria induced by SGLT-2 inhibition can assist weight loss and generate a mild osmotic diuresis that may contribute to a small reduction in blood pressure [5,70–73].

SGLT-2 inhibitors can weakly suppress the activity of SGLT-1 transporters (transfer two sodium ions with one glucose or galactose). SGLT-1 is abundant in the intestine and accounts for the absorption of glucose; it is also expressed in the third (straight descending) segment of the proximal tubules, where it is responsible for ~10% of glucose reabsorption. Canagliflozin may interact with SGLT-1 to defer intestinal glucose absorption slightly more distally along the intestinal tract, but it is uncertain whether the concentration of the drug in the renal tubule is sufficient to exert any meaningful inhibition SGLT-1 activity in the kidney [70]. Sotagliflozin is a stronger inhibitor of SGLT-1 and also inhibits SGLT-2; at the time of writing studies in individuals with type 2 diabetes are ongoing.

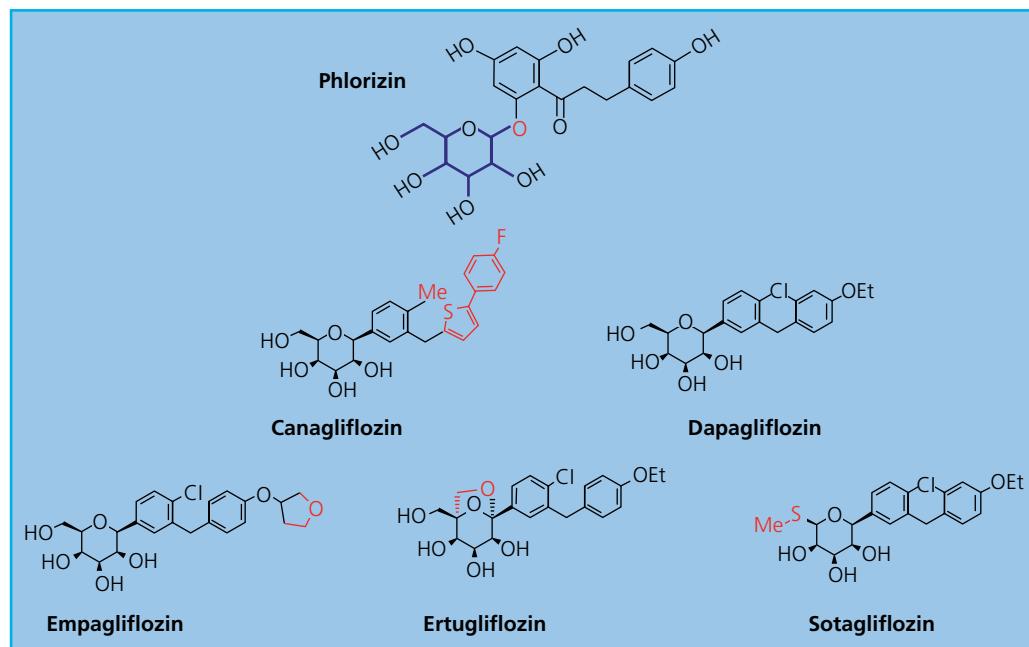


Figure 35.14 Structures of sodium–glucose cotransporter (SGLT) inhibitors. Phlorizin is a naturally occurring inhibitor of SGLT-1 and SGLT-2. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are selective inhibitors of SGLT-2, and sotagliflozin is an inhibitor of SGLT-1 and SGLT-2.

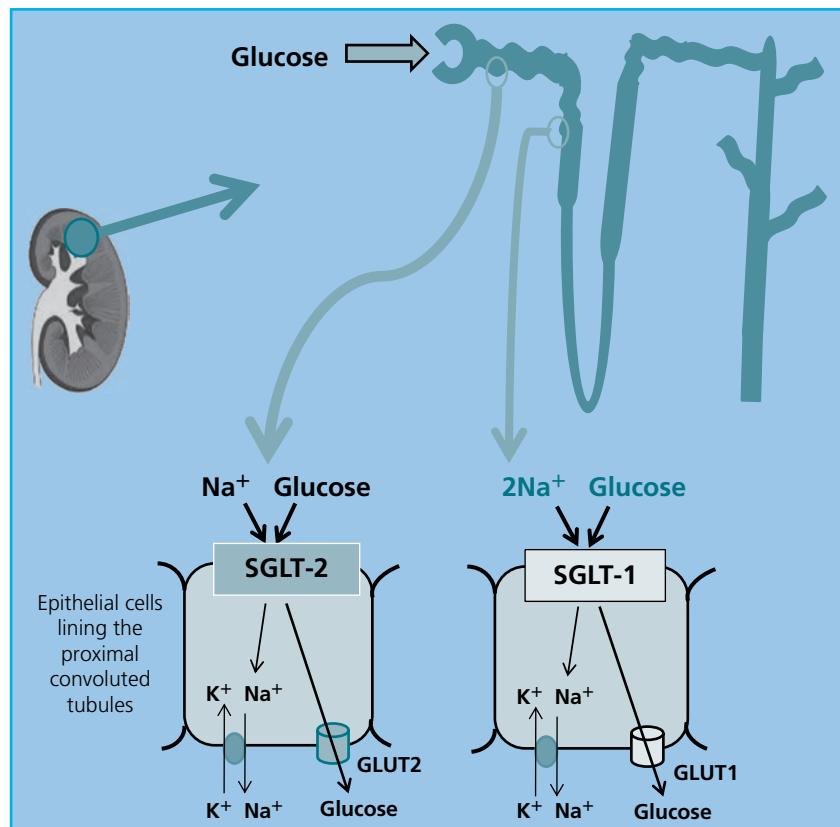


Figure 35.15 Renal sodium–glucose cotransporters (SGLT) reabsorb glucose from the renal proximal tubules. Glucose is filtered at the glomerulus into the proximal tubule and mostly reabsorbed from the initial region of the proximal tubule via the high-capacity transporter SGLT-2. Remaining glucose is reabsorbed more distally along the proximal tubule via the low-capacity transporter SGLT-1. Source: Bailey 2015 [67]. Reproduced by permission.

Table 35.13 Sodium–glucose cotransporter-2 (SGLT-2) inhibitors: dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin.

Agent	Dose (mg/d)	IC ₅₀ SGLT2 vs SGLT1 (nM)	t _{max} (h)	C _{max}	t _{1/2} (h)
Dapagliflozin	5–10	1.1 vs 1390	1–2	~160 µg/l	~13
Canagliflozin	100–300	2.2 vs 910	1–2	~1–5 mg/l	~13
Empagliflozin	10–25	3.1 vs 8300	~1.5	~250–700 nmol/l	~13
Ertugliflozin	5–15	0.9 vs 1960	~1	~260 µg/l	~17

Pharmacokinetics

The pharmacokinetic properties of SGLT-2 inhibitors are summarized in Table 35.13. They reversibly inhibit SGLT-2 at low nmol/l concentrations by blocking the glucose site for several minutes. SGLT-2 inhibitors are taken as once-daily tablets; they are rapidly absorbed with high bioavailability. In plasma they are mostly protein bound and are degraded mainly through glucuronidation by uridine diphosphoglucuronosyltransferases to inactive metabolites. They show little or no inhibition by or induction of P450 isoforms that metabolize other common medications, and no clinically significant drug interactions have been noted [74].

Indications and contraindications

SGLT-2 inhibitors can be used as monotherapy in people whose type 2 diabetes has not responded adequately to lifestyle measures, although they are more often used as add-on therapy in those whose diabetes is inadequately managed by metformin or another glucose-lowering agent. In principle, an SGLT-2 inhibitor can be used with any other class of oral agent or insulin, as the mode of action is different from those of all other classes of glucose-lowering agents. Body weight reduction makes an SGLT-2 inhibitor suitable for individuals with overweight or obesity, and the low risk of hypoglycaemia renders this class of agent suitable for people with glucose values close to target. Modest reductions of blood pressure in individuals with hypertension can also be expected [71].

Adequate renal function is an important consideration for use of an SGLT-2 inhibitor to enable glucosuric efficacy. Recommendations vary between countries, but an SGLT-2 inhibitor can be used at full daily dosage for eGFR >60 ml/min/1.73 m². Although SGLT-2 inhibitors have evident reno-protective effects in clinical trials, current product labels suggest a reduced dose for people with an eGFR value persistently <45 ml/min/1.73 m² [75]. Treated individuals with diabetes should be informed about the need to remain hydrated and the risk of initial nocturia and mycotic genital infections. People with insulin-treated type 2 diabetes should ensure that they maintain an adequate insulin dose, since insulin is required for many more physiological purposes than glucose regulation. At the time of writing, some SGLT-2 inhibitors are approved for use as adjunctive therapy with insulin in type 1 diabetes mellitus; again, the importance of maintaining adequate insulin is emphasized to avoid diabetic ketoacidosis. SGLT-2 inhibitors should be discontinued in pregnancy.

Efficacy

The glucose-lowering efficacy of SGLT-2 inhibitors in type 2 diabetes has been confirmed in prospective randomized clinical trials during use as monotherapy and in combination with other glucose-lowering therapies including insulin [71–73]. There is a rapid onset of action to reduce post-prandial and basal hyperglycaemia. HbA_{1c} is typically reduced by ~0.6–1.2% (7–13 mmol/mol), although larger reductions may be seen in people with severe hyperglycaemia and those with good renal function [76]. Efficacy during trials has extended over several years and risk of hypoglycaemia has been low unless SGLT-2 inhibitors are used in combination with an agent that can itself cause hypoglycaemia (such as a sulfonylurea or insulin). Most people achieve a weight loss of ~2–4 kg, which typically levels out by 6–12 months, possibly reflecting an increase in metabolic efficiency or some increase in food intake as the glucose level declines. The weight loss is predominantly a decrease in fat mass, notably from the visceral adipose depot. In clinical trials involving participants with insulin-treated type 2 diabetes, glycaemic indices are often improved while the insulin dose is slightly lowered, and the improvement is maintained over time without insulin dose escalation. Combination of an SGLT-2 inhibitor with insulin can also reduce the weight gain normally associated with insulin therapy.

Randomized controlled cardiovascular outcome trials in individuals with type 2 diabetes have consistently confirmed that SGLT-2 inhibitors reduce systolic and diastolic blood pressure by about 3–5 and 2–3 mmHg, respectively, without dipping into hypotension. These trials have also noted that use of SGLT-2 inhibitors is associated with a reduced occurrence of new-onset heart failure and less worsening of established heart failure, with about 30% fewer hospitalizations for heart failure, mainly among individuals with reduced ejection fraction [77, 78]. Fewer cardiovascular deaths have also been recorded with use of SGLT-2 inhibitors in some trials, but this has not been a consistent finding. The reductions in blood pressure and risk of heart failure appear to be independent of the glucose-lowering and weight-lowering effects of SGLT2 inhibitors; indeed, similar reductions in blood pressure and heart failure have been noted in people without diabetes [79]. The cardiovascular effects of SGLT-2 inhibitors are also independent of age, prior history of cardiovascular disease, or treatments for hypertension and heart failure, and occur irrespective of normal or impaired renal function.

Several possible mechanisms appear to contribute to these potentially cardioprotective effects of SGLT-2 inhibitors. Lower blood pressure may initially result in part from the osmotic diuresis and reduction in plasma volume, and be assisted in the longer term by reductions in body weight, glucotoxicity, insulin resistance, and uric acid. The myocardium could also benefit from reduced plasma volume, reduced vascular resistance, and increased availability of ketones as an energy source from whole-body fatty acid metabolism. Additionally, SGLT-2 inhibitors have been reported to improve myocardial energetics by increasing myocardial catabolism of branched-chain amino acids and inhibiting the Na⁺/H⁺ exchanger [80].

SGLT-2 inhibitors often cause an initial temporary drop in eGFR by ~5 ml/min/1.73 m², which usually recovers by 3–6 months. Thereafter, use of an SGLT-2 inhibitor slows the long-term decline in eGFR, accompanied by reductions in the onset and progression of micro- and macroalbuminuria. These effects, which preserve

renal function, are independent of the glucose-lowering and weight-lowering effects of SGLT-2 inhibitors and are also evident in people without diabetes. The effects are also independent of age, baseline eGFR, prior or existing cardiovascular disease, or antihypertensive therapies. One postulated mechanism is the effect of SGLT-2 inhibition to increase sodium retention within the lumen of the nephron. The raised luminal sodium concentration carries through to the ascending limb of the loop of Henle, where it is sensed by the macula densa. This increases the tubulo-glomerular feedback of adenosine to constrict the afferent glomerular arterioles, which reduces intra-glomerular pressure [81]. Additional potential reno-protective effects of SGLT-2 inhibitors may include localized reductions of oxidative stress and inflammation within the kidney.

Adverse effects

The glucosuric effect of SGLT-2 inhibitors increases the risk of genital infections, particularly vulvovaginal mycotic infections in women during the initial months of therapy, and there has also been a small increase in the risk of urinary tract infections in some studies. The occurrence and severity of these infections can be reduced by appropriate advice when starting therapy and most of these infections respond to standard treatments, often by self-management. The osmotic diuresis generated by the glucosuria (usually <500 ml/d) requires patient attention to adequate hydration, especially in hot climates, and should be emphasized when initiating therapy. Because the eGFR may temporarily decline after introduction of an SGLT-2 inhibitor, extra caution is recommended for people receiving diuretic therapy, although electrolyte imbalances have not been seen in clinical trials [75].

Accounts of atypical ketoacidosis in individuals treated with an SGLT-2 inhibitor have described a hyperosmolar ketoacidosis with only modest hyperglycaemia. Many of these people had type 1 diabetes or were insulin-treated individuals of unclear diagnosis in whom the insulin dose had been over-reduced because the hyperglycaemia was reduced by the SGLT-2 inhibitor. Basal insulin should be maintained in insulinopenic individuals, as this reduces lipolysis (thereby reducing the supply of fatty acids for ketogenesis) and is required for other physiological purposes beyond glycaemic management. SGLT-2 inhibition may also reduce renal clearance of ketones and may cause a compensatory increase in glucagon release, especially at low glucose levels, which can promote ketogenesis [82]. Thus, people with a history of ketotic episodes are unlikely to be appropriate for SGLT-2 inhibitor therapy.

Because SGLT-2 inhibitors do not interfere with P450 isoenzymes, they do not appear to have any clinically meaningful drug interactions. Minor changes in the circulating lipid profile have been reported with SGLT-2 inhibitors, notably some increases in LDL and HDL cholesterol, but without altering the LDL-to-HDL ratio. During clinical trials, the numbers of major adverse cardiovascular events have generally been similar to or fewer than with comparator therapies, leaving uncertainty regarding any significant class effects on atherosclerotic disease.

Oral glucagon-like peptide-1 receptor agonist

As noted in the section on DPP-4 inhibitors and considered in detail in Chapter 36, GLP-1 is an incretin hormone secreted from intestinal L cells during meal digestion. It potentiates nutrient-induced

insulin secretion, suppresses excess glucagon secretion, exerts a satiety effect, and delays gastric emptying. Several subcutaneously injected analogues of GLP-1 that mimic the effects of the native hormone are established therapies for type 2 diabetes. Recently introduced (2019) is an oral formulation of the GLP-1 receptor agonist semaglutide [83].

Semaglutide is structurally similar to native GLP-1: it has a substitution of alanine to aminoisobutyric acid at position 8 (N2 of the active peptide) to prevent degradation by DPP-4. There is a C18 fatty di-acid chain attached to the lysine at position 26 to enable binding to albumin to prolong circulation time, and a lysine to arginine substitution at position 34 to ensure fatty acid linkage only at position 26. To facilitate absorption across the gastric epithelium, semaglutide is formulated into a tablet with the absorption enhancer sodium hydroxybenzoylaminocaprylate (SNAC), which protects the peptide from proteolytic degradation by raising the pH around the peptide and assisting transcellular absorption. Oral semaglutide is taken on an empty stomach, usually in the morning, and food is avoided for at least 30 minutes to allow adequate drug absorption.

Oral and injectable formulations of semaglutide are similarly effective in reducing blood glucose (with low risk of hypoglycaemia) and body weight, as considered in detail in Chapter 36. In clinical trials, oral semaglutide has similar beneficial cardio-renal effects, safety profile, and therapeutic applications to injectable semaglutide.

α -Glucosidase inhibitors

Studies conducted in the late 1970s noted that inhibitors of intestinal α -glucosidase enzymes could retard the final steps of carbohydrate digestion, with a consequent delay in the absorption of sugars. By the early 1980s, it was demonstrated that this approach could reduce postprandial hyperglycaemia in diabetes [84]. Acarbose, the first α -glucosidase inhibitor, was introduced in the early 1990s. Subsequently, two further agents, miglitol and voglibose, were introduced in some countries (Figure 35.16). In people who consume meals containing complex carbohydrate, α -glucosidase inhibitors can effectively reduce post-prandial glucose excursions. These agents also have a good safety record, but their application has been limited by gastrointestinal side effects and modest efficacy.

Mode of action

α -Glucosidase inhibitors competitively inhibit the activity of α -glucosidase enzymes in the brush border of enterocytes lining the intestinal villi (Figure 35.17). They bind to the enzymes with high affinity, preventing the enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays completion of carbohydrate digestion and can defer the process distally along the intestinal tract, leading to a delay in glucose absorption [84,85]. Different α -glucosidase inhibitors have different affinities for the various α -glucosidase enzymes. This gives slightly different activity profiles (e.g. acarbose has greatest affinity for glycoamylase > sucrase > maltase > dextrinases, whereas miglitol is a stronger inhibitor of sucrase).

It is emphasized that α -glucosidase inhibitors can only be effective if the person is consuming complex digestible carbohydrate. These agents do not significantly affect the absorption of glucose *per se*. By moving glucose absorption more distally along the intestinal tract, α -glucosidase inhibitors may alter the release of

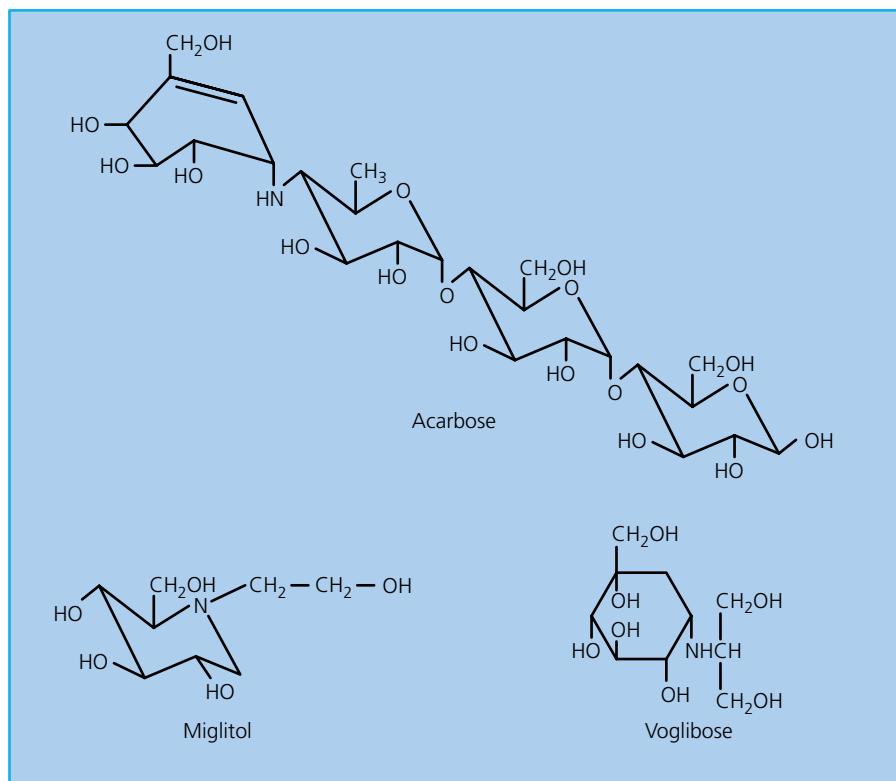


Figure 35.16 Chemical structures of the α -glucosidase inhibitors acarbose, miglitol, and voglibose.

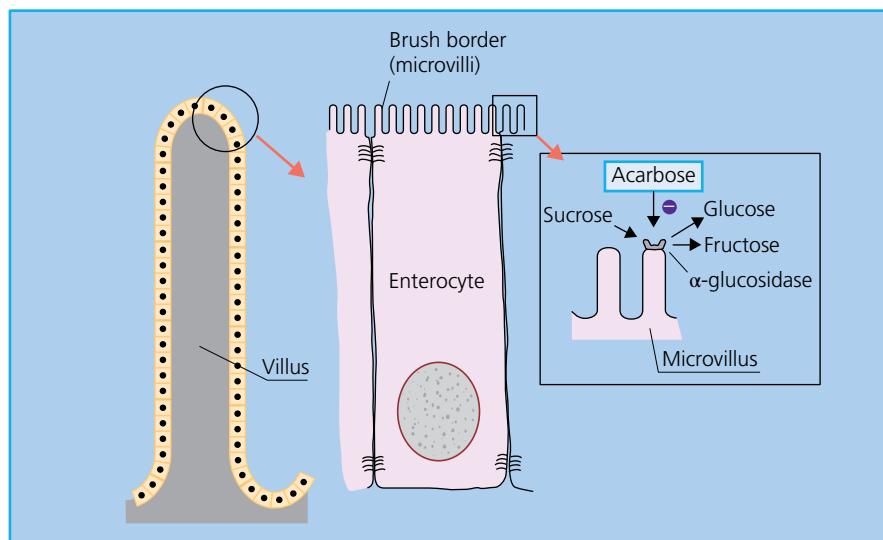


Figure 35.17 Mode of action of α -glucosidase inhibitors. α -Glucosidase inhibitors competitively inhibit the activity of α -glucosidase enzymes in the brush border of enterocytes lining the intestinal villi, preventing these enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays carbohydrate digestion.

glucose-dependent incretin hormones such as GIP and GLP-1, which affect nutrient-induced insulin secretion. Hence release of GIP, which occurs mainly from the jejunal mucosa, may be reduced by α -glucosidase inhibitors, whereas secretion of GLP-1 (mostly from the ileal mucosa) is increased. α -Glucosidase inhibitors probably reduce post-prandial insulin concentrations through the attenuated rise in post-prandial glucose levels [84, 85].

Pharmacokinetics

Acarbose is degraded by amylases in the small intestine and by intestinal bacteria; <2% of the unchanged drug is absorbed along

with some of the intestinal degradation products. Absorbed material is mostly eliminated in the urine within 24 hours [84]. Miglitol is almost completely absorbed and eliminated unchanged in the urine.

Indications and contraindications

α -Glucosidase inhibitors can be used as monotherapy, usually for people with type 2 diabetes with post-prandial hyperglycaemia but only slightly raised fasting glycaemia; however, they are more commonly used as an add-on to other therapies, again to target post-prandial hyperglycaemia [84, 85]. α -Glucosidase inhibitors can also

be used to extend the post-prandial period to reduce inter-prandial glycaemic troughs or hypoglycaemia in individuals receiving a sulfonylurea and/or insulin. Acarbose prevents the progression of IGT to type 2 diabetes [86], although this is not a licensed use.

When starting an α -glucosidase inhibitor, advice should be given that a diet containing complex digestible carbohydrate is important. α -Glucosidase inhibitors should be taken with meals, starting with a low dose (e.g. 50 mg/day acarbose) and slowly uptitrating over several weeks. Monitoring of post-prandial glycaemia is often helpful. Hypoglycaemia is unlikely when used as monotherapy, but gastrointestinal symptoms commonly limit initial tolerability and dose titration. Symptoms tend to be reduced by slow titration and usually subside with time, possibly reflecting some adaptation of the intestinal tract, but tolerability is poor.

α -Glucosidase inhibitors are contraindicated for people with a history of chronic intestinal disease, and as high dosages of acarbose can occasionally increase liver enzyme concentrations, it is recommended to measure transaminase concentrations periodically in those receiving a maximum dosage (200 mg acarbose three times daily). Raised liver enzymes should remit as the dosage is reduced, otherwise alternative causes of hepatic dysfunction should be considered.

Efficacy

Because α -glucosidase inhibitors target post-prandial glucose excursions during meals that contain complex carbohydrate, their effectiveness is entirely dependent on following an appropriate diet. As monotherapy, these agents can reduce peak post-prandial glucose concentrations by 1–4 mmol/l. The incremental area under the post-prandial plasma glucose curve can be more than halved in some individuals, and there is usually some extended duration of effect to modestly lower basal glycaemia up to ~1 mmol/l. The decrease in HbA_{1c} can be 0.5–1.0% (6–11 mmol/mol), provided that a high dose of the drug is tolerated and an appropriate diet is maintained [84, 85].

Although overall reductions in HbA_{1c} are usually modest, α -glucosidase inhibitors offer several useful features: they do not cause weight gain or frank hypoglycaemia and they may reduce inter-prandial episodes of hypoglycaemia. When combined with other anti-diabetes agents, α -glucosidase inhibitors can reduce post-prandial hyperinsulinaemia, and they often lower plasma triglyceride concentrations. An α -glucosidase inhibitor can produce minor alterations to the intestinal absorption of other oral glucose-lowering agents when used in combination therapy, but α -glucosidase inhibitors usually provide additive efficacy gains when used in combination with any other class of glucose-lowering agent [84, 85]. Despite the link between post-prandial hyperglycaemia and cardiovascular risk, a five-year study in people with coronary heart disease and IGT found no effect of acarbose on a composite of major adverse cardiovascular events (cardiovascular death, non-fatal MI or stroke, unstable angina, or hospitalization for heart failure) [87].

Adverse effects

Gastrointestinal side effects represent the main problem with α -glucosidase inhibitors. For example, in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, 31% of acarbose-treated participants compared with 19% on placebo discontinued treatment early [88]. If the dosage is too high (relative to the amount of complex carbohydrate in the meal), undigested oligosaccharides pass into the large bowel. These are fermented, causing flatulence, abdominal discomfort, and sometimes diarrhoea, but usually ameliorating with slower titration and time. Hypoglycaemia is uncommon and there are no clinically significant

drug interactions, although use in conjunction with agents affecting gut motility or cholestyramine is not recommended.

Bromocriptine

The dopamine D₂ receptor agonist bromocriptine (Figure 35.18), which has long been used to treat pituitary tumours and Parkinson disease (albeit in a different formulation), has an indication for use in the treatment of type 2 diabetes in some countries [89, 90].

Mode of action

Studies in animals have noted that the interruption of dopaminergic pathways in the hypothalamus is associated with the development of insulin resistance, and this can be reversed by localized dopamine infusion. Studies in individuals with type 2 diabetes suggest that a low dose of a rapid-acting formulation of bromocriptine administered early in the morning soon after waking can temporarily boost hypothalamic dopamine. This appears to rebalance several features of the circadian periodicity of glucose homeostasis by reducing sympathetic tone and enhancing the neural suppression of hepatic glucose production. Additionally, there is a reduction of adipose tissue lipolysis and an improvement in peripheral glucose disposal without elevation of plasma insulin, indicating improved peripheral insulin sensitivity [89, 90].

Pharmacokinetics

The low-dose quick-release formulation of bromocriptine used for blood glucose lowering is rapidly absorbed (t_{max} by 1 hour), highly protein bound, rapidly removed by the liver (mostly metabolized by CYP3A4), and eliminated via the bile; the half-life is ~6 hours. Prolactin levels are reduced consistent with increased dopaminergic activity.

Indications and contraindications

Based on considerable experience with the use of bromocriptine for other purposes, use to treat type 2 diabetes requires caution if individuals are prone to low blood pressure, various psychotic disorders, or somnolence, and exclusion of those who experience migraine or take dopaminergic antagonists. Potential interactions with other medications that influence or may be influenced by changes in CYP3A4 should be appreciated, and evidence regarding use during pregnancy is limited.

Efficacy

In clinical trials, participants with type 2 diabetes receiving a low dose (0.8–4.8 mg) of quickly acting bromocriptine early in the morning showed HbA_{1c} reductions of ~0.5–0.7% (5–8 mmol/mol) when it

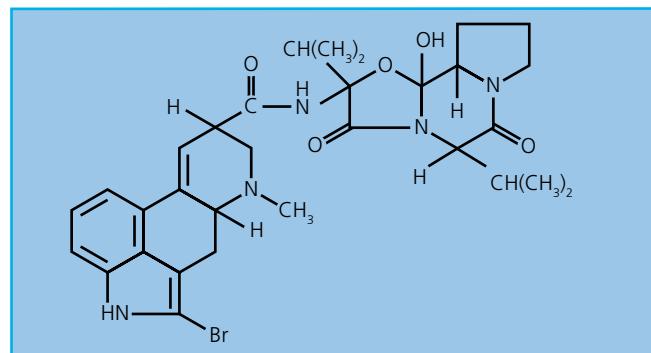


Figure 35.18 Chemical structure of bromocriptine.

was taken as monotherapy or in combination with other oral glucose-lowering agents. Fasting and post-prandial glucose, fatty acid, and triglyceride concentrations were reduced, insulin was not raised, risk of hypoglycaemia was low, and there was no weight gain [89,90].

Adverse effects

Although high doses of bromocriptine carry some long-term risk for pulmonary and pericardial fibrosis, hypotension, and aggravation of psychotic disorders, these were not seen with low doses during clinical trials for type 2 diabetes.

Colesevelam

In addition to its use as a bile acid sequestrant, colesevelam (a polyallylamine derivative) also has an indication for glucose lowering in some countries.

Mode of action

The glucose-lowering mechanism of colesevelam is not clear. By interrupting the enterohepatic circulation of bile acids, colesevelam appears to reduce the availability of bile acids to activate the bile acid receptor-1 (TGR5) and the farnesoid X receptor (FXR), which results in increased hepatic glucose metabolism [91]. A further possibility is that the bile acids are carried more distally along the intestine owing to their entrapment by colesevelam. This could bring more bile acids into contact with TGR5 receptors on L cells, which could enhance the secretion of GLP-1.

Pharmacokinetics

Up to three 625 mg tablets of colesevelam can be taken with each of two main meals daily; the colesevelam is not absorbed.

Indications and contraindications

Colesevelam requires caution if any intestinal disorders, especially obstruction, are known or suspected. Colesevelam can alter the absorption of other oral medications, including oral glucose-lowering therapies, and dose adjustments may be required.

Efficacy

Clinical trials with colesevelam in type 2 diabetes have noted modest reductions of HbA_{1c} of ~0.5% (5 mmol/mol) when used as an add-on to metformin, sulfonylurea, or insulin. There is no effect on body weight, low risk of hypoglycaemia, and, consistent with its use in the treatment of hypercholesterolemia, there is usually a reduction in LDL cholesterol [91].

Adverse effects

Colesevelam may increase circulating triglycerides and cause abdominal symptoms, especially constipation.

Anti-obesity therapies

Obesity, especially excess visceral adiposity, predisposes to diabetes, increases insulin resistance, complicates glycaemic management, and substantially increases the risk of vascular disease [92]. The blood glucose-lowering efficacy of lifestyle measures to reduce adiposity in individuals with type 2 diabetes and obesity is well appreciated, although it is often difficult to achieve and maintain significant weight loss in these people [93]. Several studies have

noted the reductions in blood glucose that accompany the use of pharmacological anti-obesity therapies in type 2 diabetes. Whether this is entirely explained by greater weight loss and improved diet is unclear, because some anti-obesity therapies may have some modest independent glucose-lowering effects [94].

In conjunction with a mildly hypocaloric and reduced-fat diet, the intestinal lipase inhibitor orlistat (120 mg three times daily with meals) can reduce dietary fat absorption by up to 30%. In individuals with type 2 diabetes and overweight or obesity, this typically reduces weight by an extra 2–3 kg, and additional reductions in HbA_{1c} of 0.28–1.1% (3–12 mmol/mol) have been reported [94].

Other anti-obesity agents, notably a phentermine-topiramate combination (Qsymia[®], Vivus, Campbell, CA, USA), and a buproprion–naltrexone combination (Contrave[®], Currax Pharmaceuticals, Brentwood, TN, USA), have been shown in clinical trials to improve glycaemic indices in people with type 2 diabetes in association with weight loss [94]. However, these anti-obesity therapies are not approved in many regions; carry their own contraindications, cautions, and side effects; and may interfere with the absorption or actions of other therapies, including glucose-lowering agents. The use of high doses of some GLP-1 receptor agonists to address obesity as well as type 2 diabetes is considered in Chapters 36 and 38.

Fixed-dose combinations

As early, individualized, and intensified interventional approaches to manage hyperglycaemia in type 2 diabetes have gained acceptance, the use of combinations of two or more oral agents with different mechanisms of action has become commonplace [3,4]. Indeed, some guidelines suggest that individuals presenting with moderate to severe hyperglycaemia may be considered for initial pharmacotherapy with a combination of glucose-lowering agents [4]. To facilitate combination therapy, several fixed-dose, single-tablet dual combinations are available (Table 35.14). These are designed to provide bioequivalence and thereby similar efficacy, although minor adjustments to the formulation may also allow some extra blood glucose-lowering efficacy.

Fixed-dose dual combinations can offer convenience, reduce the *pill burden*, and simplify administration regimens, and they may increase medication taking compared with equivalent combinations of separate tablets. Lower doses of two different types of agents rather than a high dose of one agent may also provide a way to achieve efficacy while circumventing adverse effects [95]. Although single tablets could reduce titration flexibility, most of the commonly used dosage combinations have been accommodated. A recent study has demonstrated rapid and sustained improvements in glucose levels with initial triple therapy [96], and fixed-dose triple combination tablets (e.g. metformin/linagliptin/empagliflozin and metformin/saxagliptin/dapagliflozin) are now becoming available [97]. It is reiterated that dose-related side effects of any combination therapy necessitate the same cautions and contraindications as apply to each active component.

Conclusions

A minimalistic archetypal algorithm to treat hyperglycaemia in type 2 diabetes is shown in Figure 35.19. This illustrates the typical sequence of pharmacological interventions advocated in most

Table 35.14 Fixed-dose single-tablet dual combinations of glucose-lowering agents.

Tablet ^a	Components	Strengths (mg)
Glucovance	Metformin + glibenclamide	250:1.25; 500:2.5; 500:5
Metaglip	Metformin + glipizide	250:2.5; 500:2.5; 500:5
Avandamet	Metformin + rosiglitazone	500:1; 500:4; 500:2; 1000:2; 1000:4
Competact (Actoplus Met)	Metformin + pioglitazone	500:15; 850:15
Eucreas	Metformin + vildagliptin	850:50; 1000:50
Janumet	Metformin + sitagliptin	500:50; 1000:50;
Prandimet	Metformin + repaglinide	500:1; 500:2
Kombiglyze	Metformin + saxagliptin	500:5; 1000:2.5; 1000:5
Jentadueto	Metformin + linagliptin	500:2.5; 850:2.5; 1000:2.5
Kazano (Vipdomet)	Metformin + alogliptin	500:12.5; 1000:12.5
Avaglim (Avandaryl)	Rosiglitazone + glimepiride	4:1; 4:2; 4:4; 8:2; 8:4
Tandemact (Duetact)	Pioglitazone + glimepiride	30:2, 30:4, 45:4
Xigduo	Metformin + dapagliflozin	850:5; 1000:5
Vokanomet	Metformin + canagliflozin	1000:50
Incresync	Pioglitazone + alogliptin	30:12.5
Glyxambi	Empagliflozin + linagliptin	10:5; 25:5
Synjardy	Metformin + empagliflozin	850:5; 850:12.5; 1000:5; 1000:12.5
Segluramet	Metformin + ertugliflozin	500/2.5; 500/7.5; 1000/2.5; 1000/7.5

^a The availability of tablets and component strengths differ between countries.

Names vary between Europe and the USA. Alternative names are given in parentheses.

current guidelines. Guidelines should be interpreted with flexibility, however, to ensure that the care plan, treatment targets, and selection of therapies are individualized to suit the circumstances of the patient. The value of lifestyle intervention as initial and ongoing therapy in conjunction with pharmacological agents should not be underestimated. In view of the progressive natural history of type 2 diabetes, the introduction of drug therapy, the need for periodic uptitration of dosage, and the use of combination therapy can be expected for most people with type 2 diabetes.

A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes suggests that the preferred first-line glucose-lowering agent is usually metformin. If adequate glycaemic levels are not achieved or maintained, the addition of a second pharmacological agent should take particular account of a high level of risk or existence of cardiovascular and/or renal disease irrespective of the extent of hyperglycaemia [3]. Addition of a GLP-1 receptor agonist is favoured if atherosclerotic cardiovascular disease predominates, whereas addition of an SGLT-2 inhibitor is favoured if heart failure or chronic kidney disease predominates. All available glucose-lowering agents could be considered as second-line pharmacotherapy for individuals at lesser risk of cardiovascular or renal complications, taking account of the need to avoid hypoglycaemia, control body weight, and respect affordability.

The latest consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology also gives emphasis to the importance of weight management and addressing key cardiovascular risk factors (blood pressure and lipids) while avoiding hypoglycaemia [4]. Metformin remains the

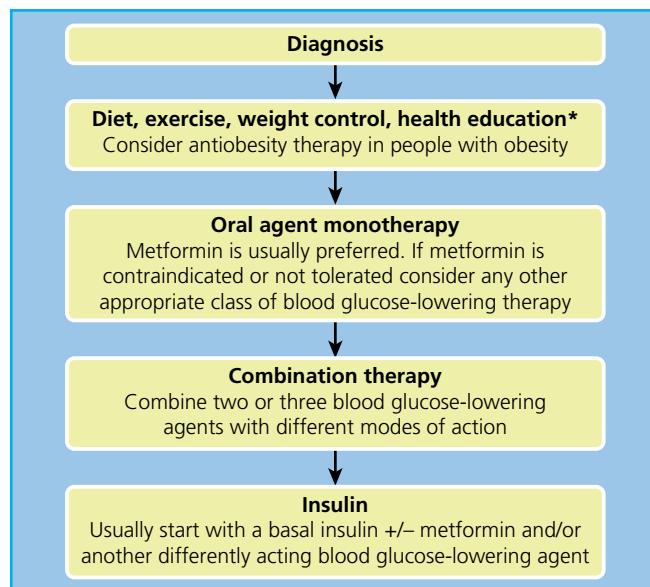


Figure 35.19 Archetypal algorithm used in the treatment of hyperglycaemia in type 2 diabetes (except for those presenting with severe hyperglycaemia who may require immediate insulin therapy). Start with lifestyle measures (diet and exercise). If the individualized glycaemic target is not achieved quickly using lifestyle measures, then add pharmacological therapy without delay. The selected monotherapy is uptitrated to achieve the desired glycaemic effect. If an uptitration step does not add benefit or is not tolerated, go back a step. When the desired glycaemic effect is not achieved or adequate titration is not tolerated, move promptly to the addition of a second agent with a different mode of action and uptitrate. If the desired glycaemic control is not achieved or maintained, consider triple therapy or introduce insulin while maintaining one or two of the existing therapies where appropriate. Respect drug cautions and contraindications at all times, monitor as required, and try to select glycaemic targets that are realistic, safely achievable, and avoid hypoglycaemia. Various guidelines (e.g. see [3, 4]) offer more detail with suggested glycaemic targets and suggested sequence orders for the introduction of the pharmacotherapies. *Lifestyle advice is reinforced throughout.

preferred first-line glucose-lowering agent, but this consensus defines HbA_{1c} levels at which dual and triple combination therapy should be considered, whether newly diagnosed or not. Thus, two differently acting glucose-lowering agents are suggested for people with HbA_{1c} ≥ 7.5% (59 mmol/mol) and triple therapy if HbA_{1c} > 9% (75 mmol/mol), or insulin if significantly symptomatic.

A range of differently acting oral agents is available: metformin and thiazolidinediones counter insulin resistance, but in different ways; sulfonylureas, meglitinides, and DPP-4 inhibitors increase insulin secretion, but with differences of time course and mechanism; SGLT-2 inhibitors increase renal glucose elimination; and α-glucosidase inhibitors slow carbohydrate digestion. Additionally, GLP-1 receptor agonists increase insulin secretion and reduce glucagon. When adequate glycaemic levels are not achieved or not maintained, it is important to proceed to the next therapeutic stage without delay to avoid periods of excessive hyperglycaemia. Insulin should be considered when other therapies do not provide adequate glycaemic levels or are unsuitable. Integrated management to address cardiovascular risk and comorbid conditions is essential. Glucose monitoring, making therapeutic adjustments for efficacy, safety, avoidance of hypoglycaemia, and contraindications, requires constant vigilance and forms an integral part of the treatment process. Early, effective, and sustained glycaemic management is essential to minimize the risk of complications later in life.

36

Non-insulin Parenteral Therapies

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Key points

- Obtaining sufficient systemic exposure of peptide-based drugs following oral administration is challenging owing to the acidic environment, the presence of proteolytic enzymes in the stomach, and the limited permeability of peptides through the gastrointestinal epithelium.
- Several available non-insulin parenteral therapies used for the treatment of type 2 diabetes are based on the gut-derived hormone glucagon-like peptide 1 (GLP-1).
- GLP-1 is a glucose-lowering (via insulinotropic and glucagonostatic effects) and satiety-promoting hormone secreted from enteroendocrine L cells found in the intestinal epithelium.
- GLP-1 receptor agonists (GLP-1RAs) form part of the treatment algorithms and guidelines for type 2 diabetes.
- GLP-1RAs target a broad spectrum of the pathophysiology of type 2 diabetes, improving glycaemic levels and reducing hunger, food intake, and body weight.
- Differences in the structure, pharmacokinetics, and size of the different GLP-1RAs determine their individual effects on glycated haemoglobin (HbA_{1c}), body weight, dosing frequency (convenience), and tolerability (adverse effects).
- Adverse effects of GLP-1RAs typically affect the gastrointestinal tract (mainly nausea, vomiting, and/or diarrhoea) in a dose-dependent manner and diminish over time.
- Large-scale cardiovascular outcome trials have shown beneficial effects of continuous-acting GLP-1RA treatment added to standard of care, including a reduced risk of major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, and cardiovascular-related death).
- One available non-insulin parenteral therapy based on the pancreatic β -cell hormone amylin is available as adjunct treatment of insulin-treated type 1 diabetes and type 2 diabetes.
- Amylin is co-secreted with insulin from β cells and reduces gastric emptying, appetite, and post-prandial glucagon secretion.
- Amylin analogues have clinical benefits on HbA_{1c} and body weight in diabetes.
- Non-insulin parenteral therapies based on single-molecule dual- or triple-receptor agonists acting via the GLP-1 receptor, the glucose-dependent insulinotropic polypeptide (GIP) receptor, the amylin receptor, and/or the glucagon receptor are currently being evaluated for the treatment of type 2 diabetes.

During recent decades, the globally increasing prevalence of obesity and associated type 2 diabetes has promoted extensive research with the aim of clarifying the physiological and pharmacological role of pancreas- and gut-derived peptide hormones in the regulation of glucose homeostasis and feeding behaviour. Exploitation of these peptide hormones for the treatment of diabetes has primarily relied on the development of stable peptide-based drugs (suitable for subcutaneous injection, i.e. parenteral therapies) mimicking and potentiating the effects of the endogenous peptide hormones.

the GLP-1 receptor (GLP-1R), has increased treatment options and helped clinicians tailor individualized treatments for people with type 2 diabetes. GLP-1-based treatment modalities (i.e. the small-molecule dipeptidyl peptidase 4 [DPP-4] inhibitors reducing the enzymatic inactivation and degradation of endogenous GLP-1 and the exogenous peptide-based GLP-1R agonists [GLP-1RAs]) have been welcomed by healthcare professionals and people with diabetes. In particular, the GLP-1RA drug class is a pivotal part of the international type 2 diabetes treatment algorithms and guidelines, because of its glucose-dependent glucose-lowering action (active only when plasma glucose levels are high with a consequent low risk of hypoglycaemia), body weight-reducing effect, and cardiovascular protective effects [1–3]. The GLP-1RA drug class represents one of the most thoroughly investigated and monitored in terms of safety and efficacy owing to the increased requirements of regulatory agencies (particularly the US Food and Drug Administration [FDA] and European Medicines Agency [EMA]) for extensive safety data on new anti-diabetes drugs coinciding with final development of these drugs. A few GLP-1RAs have also been

Glucagon-like peptide 1, the GLP-1 receptor, and GLP-1 receptor agonists

The successful development of glucose-lowering drugs based on the physiological effects of the gut incretin hormone glucagon-like peptide 1 (GLP-1), a peptide hormone released from enteroendocrine L cells in response to nutrient ingestion and acting through

approved for the treatment of overweight and obesity and currently several studies are evaluating the applicability of GLP-1RA treatment in other metabolic disease states and related conditions.

In the first part of the chapter, a historical overview of the investigations leading to the discovery of the gut incretin hormone GLP-1 and its potential as a glucose-lowering drug is presented. The physiology of native GLP-1 is outlined, followed by the pharmacology, safety, and efficacy of the individual GLP-1RAs currently available for the treatment of type 2 diabetes. We also include the recently developed, first orally available GLP-1RA, oral semaglutide (Rybelsus[®], Novo Nordisk, Bagsværd, Denmark). Finally, perspectives for GLP-1RA treatment within other disease areas and their potential position in future treatment algorithms are highlighted.

Historical overview

The introduction of GLP-1-based treatment modalities at the beginning of the third millennium was the result of a century of investigations. In 1906, extracts of mucosa from porcine small intestine were tested by Moore et al. as a treatment for diabetes in the hope that, ‘the pancreas secretion might be stimulated by the substance of the nature of a hormone yielded by the duodenal mucosa membrane’ [4]. In 1928, Zunz and LaBarre described a hypoglycaemic effect following injection of extracts from small intestinal mucosa and, using cross-circulation experiments, showed that the effect was mediated through the pancreas [5]. Four years later, LaBarre named the unidentified substance thought to exert this effect *incretin* in order to dissociate it from secretin (which stimulates exocrine pancreatic secretion), discovered by Bayliss and Starling at the beginning of the twentieth century [6]. Then, in 1964, McIntyre et al. and Elrick et al. demonstrated that orally administered glucose evokes a greater insulin response than intravenously administered glucose, and both groups hypothesized that gut-derived factors could have potentiating effects on insulin secretion after oral glucose ingestion [7, 8]. A few years later, in 1967, this finding was confirmed by Perley and Kipnis, who administered oral glucose and, on a separate day, copied the oral glucose curve with an isoglycaemic intravenous glucose infusion in individuals of normal weight and with obesity with diabetes, and in healthy individuals without diabetes [9]. They concluded that the insulin response to isoglycaemic intravenous glucose administration only

amounted to 30–40% of that seen after oral administration of glucose; they had come across the *incretin effect*, the phenomenon of oral glucose eliciting a higher insulin response than intravenous glucose at identical plasma glucose profiles. However, at that time the insulinotropic substances eliciting this effect were unknown.

In 1970, gastric inhibitory polypeptide, secreted from small intestinal enteroendocrine K cells in response to ingestion of nutrients, was discovered [10] and, eventually, this 42 amino acid polypeptide was shown to be insulinotropic at elevated glucose concentrations and was renamed glucose-dependent insulinotropic polypeptide (GIP) [11]. Later, experimental and clinical studies suggested that the gut produces more than a single insulinotropic hormone of importance for glucose homeostasis [12]. In 1983, the gene encoding the human pancreatic hormone, glucagon, was cloned, and the structure of its precursor, proglucagon, was surprisingly shown to include the sequence of two glucagon-like peptides including GLP-1 (Figure 36.1) in addition to glucagon itself [13]. The gene was found to be expressed in both pancreatic α cells and enteroendocrine L cells in the small intestine [14]. The primary transcripts and translational products of the gene in the two types of cells are identical, but the post-translational processing differs in the two tissues (Figure 36.2) [14–16]. In the pancreas, proglucagon is cleaved by prohormone convertase 2 to glucagon, glicentin-related pancreatic peptide (GRPP), and a major proglucagon fragment. Apart from glucagon, these fragments seem to be biologically inactive. In contrast, in the intestinal L cells, proglucagon is processed by prohormone convertase 1/3 to GLP-1, glucagon-like peptide 2 (GLP-2), and glicentin. The 30 amino acid peptide GLP-1 is secreted in response to nutrient ingestion and is strongly insulinotropic, an incretin hormone [17, 18]. GLP-2 is also secreted in response to nutrient ingestion and is a key regulator of small intestinal growth; GLP-2 receptor agonists have been developed for the treatment of short bowel syndrome [19, 20]. The bioactive forms of GLP-1, amidated and glycine-extended GLP-1, respectively, are designated GLP-1(7–36) amide and GLP-1(7–37) (Figure 36.1).

Many hormones have been suspected to contribute to the incretin effect, but today there is ample evidence to suggest that the incretin effect is mainly conveyed by the two incretin hormones, GIP and GLP-1. In 1983, Nauck et al. showed that the incretin effect is reduced in people with type 2 diabetes [21]. The

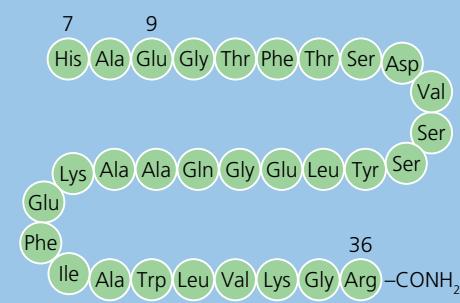


Figure 36.1 Native human glucagon-like peptide 1 (GLP-1) circulates as GLP-1(7–36) amide (illustrated here) or glycine-extended GLP-1(7–37). The enzyme dipeptidyl peptidase 4 (DPP-4) inactivates the hormone by cleaving off the two N-terminal amino acids (His and Ala).

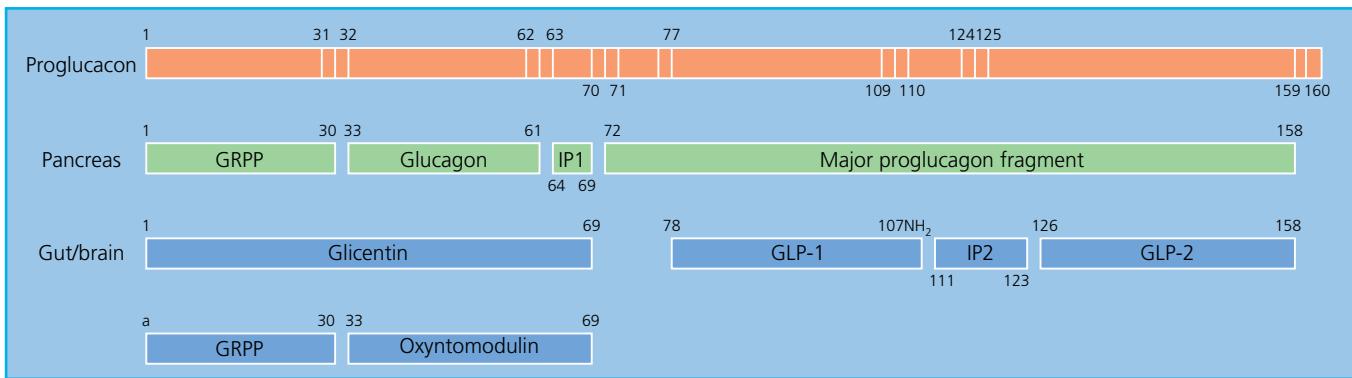


Figure 36.2 Proglucagon processing in human pancreatic α cells (predominantly by prohormone convertase 2) and in enteroendocrine L cells in the small intestine (predominantly by prohormone convertase 1/3). In proglucagon-producing neurons in the nucleus tractus solitarii (brain), proglucagon is most likely predominantly processed by prohormone convertase 1/3 as in the gut. GLP, glucagon-like peptide; GRPP, glicentin-related pancreatic peptide; IP, intervening peptide.

precise mechanisms behind this pathophysiological characteristic remain somewhat controversial. In the 2000s, publications reported reduced secretion of GLP-1 in individuals with type 2 diabetes [22, 23], but recent meta-analyses suggest that the secretion of GLP-1 among people with type 2 diabetes is generally normal [24, 25]. In contrast to the severely reduced insulinotropic effect of GIP in type 2 diabetes [26], the insulinotropic effect of GLP-1 is sustained in these individuals, albeit with reduced potency. Furthermore, GLP-1 retains its glucagonostatic effect in individuals with type 2 diabetes [27, 28].

The reduced incretin effect in type 2 diabetes, the early reports on reduced post-prandial GLP-1 responses, and the preserved glucose-dependent insulinotropic and glucagonostatic effects of GLP-1 constituted important incentives to pursue GLP-1 as a target for the treatment of type 2 diabetes. The other incretin hormone, GIP, was initially not pursued as a glucose-lowering drug owing to its severely diminished insulinotropic effect in type 2 diabetes combined with reports suggesting glucagonotropic effects of GIP. Other studies suggested that GIP may act as a fat storage hormone promoting lipogenesis, adipokine secretion, and weight gain. Nevertheless, as GIP, like GLP-1, is a substrate of DPP-4, it may contribute to the glucose-lowering effect of DPP-4 inhibitors, and dual or even triple hormonal receptor agonists involving GIP receptor stimulation are currently in clinical development for the treatment of type 2 diabetes and other metabolic disorders, such as obesity and non-alcoholic fatty liver disease. The dual GIP/GLP-1 receptor agonist tirzepatide developed for once-weekly subcutaneous injection exerts considerable reductions in glycated haemoglobin (HbA_{1c}) and body weight in individuals with type 2 diabetes and overweight or obesity in its Phase III clinical programme [29].

GLP-1 physiology and anti-diabetes effects

Proglucagon distribution, GLP-1 release, and metabolism

The glucagon gene is expressed in pancreatic α cells as well as in the enteroendocrine L cells and a subset of central nervous system neurons in the nucleus tractus solitarii. The processing of proglucagon into *pancreatic* glucagon or *intestinal* GLP-1 (and GLP-2) depends on tissue-specific prohormone convertases (Figure 36.2). In the pancreas, prohormone convertase 2 represents the predominant

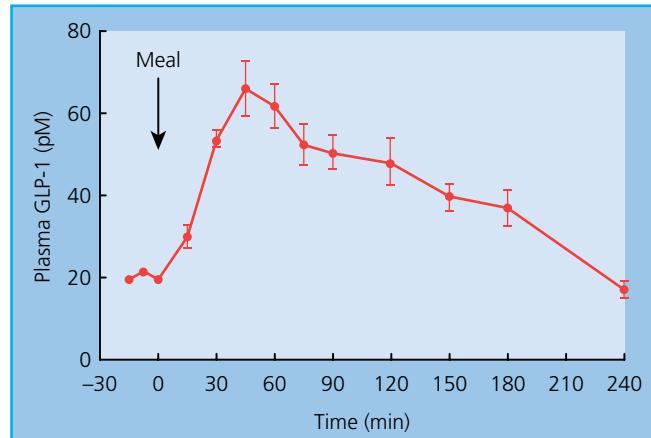


Figure 36.3 Mean post-prandial plasma concentrations (\pm standard error of the mean) of glucagon-like peptide 1 (GLP-1) in healthy individuals. Source: Based on Sonne et al. 2014 [31].

prohormone convertase and, therefore, glucagon production is favoured. Conversely, in the gut, prohormone convertase 1/3 is abundant and processing of proglucagon predominantly yields the hormones GLP-1 and GLP-2 (and oxyntomodulin) (Figure 36.2). Nevertheless, the distribution of the two prohormone convertases may not be as stringent and their enzymatic specificities may not be as high as previously considered and, thus, small amounts of GLP-1 and GLP-2 may be formed in the pancreas, and similarly, gut-derived glucagon secretion may also occur [30].

The most robust physiological stimulus for GLP-1 secretion is meal ingestion. Within 5–15 minutes of eating, plasma GLP-1 concentrations start to rise, and peak levels are typically reached after 45–60 minutes (Figure 36.3). Fat, carbohydrates, and protein all stimulate GLP-1 secretion. The interaction of nutrients with luminal microvilli of the L cell apical parts results in GLP-1 secretion from the baso-lateral parts into the intestinal bloodstream. In this process, associations between glucose absorption and metabolism within the L cell and GLP-1 secretion have been observed. Furthermore, L cells express several G protein-coupled receptors, which can be activated by short- and long-chain fatty acids, bile acids, and possibly other factors that thereby stimulate GLP-1 secretion. In addition, paracrine (e.g. via somatostatin and GIP) and neurohormonal mechanisms (via vagus and sympathetic

neural activation) have been suggested to contribute to post-prandial GLP-1 secretion.

After secretion, GLP-1 is degraded by the enzyme DPP-4. This enzyme is widely expressed and is highly active in the liver, the intestinal and renal brush border membranes, and the lungs. It is also found on capillary surfaces and in a soluble form in plasma. DPP-4 cleaves off the two N-terminal amino acids of peptides with a penultimate proline or alanine residue, and this completely abolishes the insulinotropic activity of GLP-1. Thus, after secretion of GLP-1, the active hormone is rapidly degraded to an inactive metabolite in the circulation, resulting in a clearance, which exceeds cardiac output, and an apparent half-life of 1–1.5 min. The truncated metabolite is eliminated more slowly through the kidneys and endogenous protease activity, with a half-life of 4–5 min.

GLP-1 receptor distribution and physiological effects of GLP-1

The GLP-1R is found within the pancreas, lung, adipose tissue, kidney, heart, vascular smooth muscle, peripheral nervous system, and several specific nuclei in the central nervous system (CNS) [32, 33]. The exact effect of receptor activation in several of these tissues remains to be established, and here emphasis will be put on receptor activation that relates to the clinical effects observed with GLP-1RA treatment.

Effects on pancreatic insulin and glucagon secretion

Specific receptors for GLP-1 are found in the pancreatic β -cell plasma membrane. The receptor belongs to the glucagon subfamily of G protein-coupled receptors. Following binding and subsequent activation of the receptor, several intracellular pathways are initiated [32, 33], which ultimately results in intracellular accumulation of cyclic adenosine monophosphate, closure of ATP-sensitive K^+ channels, elevation of cytosolic Ca^{2+} concentrations, and mobilization and exocytosis of insulin-containing granules. Importantly, GLP-1R activation in β cells leads only to insulin secretion when glucose concentrations are elevated above 4–5 mmol/l [34]. Thus, GLP-1 can be perceived to act as a β -cell sensitizer potentiating glucose-induced insulin secretion. In addition to its glucose-dependent insulinotropic effect, GLP-1 enhances all steps of insulin biosynthesis and insulin gene transcription. Furthermore, GLP-1 is involved in β -cell growth and differentiation and may protect cells from apoptosis [32, 33]. However, the role of these cell cycle regulatory mechanisms in relation to human physiology and pathophysiology and GLP-1RA treatment remains to be established.

In pancreatic cells, GLP-1 exerts glucagon-suppressive effects. As for its insulinotropic effect, this glucagonostatic effect is glucose dependent and is likewise only active when plasma glucose levels are elevated above 4–5 mmol/l [28]. The mechanisms by which GLP-1 reduces α -cell secretion of glucagon remain incompletely understood. Thus, it is controversial whether GLP-1-induced glucagon suppression is mediated via GLP-1Rs on pancreatic α cells (which have been shown to exist in small amounts in some studies, whereas other studies have not detected them) or whether indirect mechanisms (e.g. via glucagon-suppressive effects of β -cell secretory products and/or somatostatin from pancreatic δ cells) are at play; or perhaps most likely a combination of these effects.

Effects on the gastrointestinal tract

GLP-1 reduces gastrointestinal motility and intermittent GLP-1R activation has a pronounced effect on gastric emptying of both liquid and solid meals [35]. This phenomenon has been referred to

as the *ileal brake*; that is, GLP-1 secreted from enteroendocrine cells in the distal small intestine slows further delivery of nutrients to the small intestines from the stomach [36]. GLP-1-induced deceleration of gastric emptying translates into reduced post-prandial plasma glucose excursions [37]. By contrast, prolonged GLP-1R activation leads to tachyphylaxis of this effect [38], which most likely explains the sustained effect of short-acting GLP-1RAs on post-prandial plasma glucose excursions and the lesser effects seen with long-acting GLP-1RAs [39].

Effects on appetite and food intake

GLP-1Rs are found in both the peripheral nervous system and CNS, with GLP-1R-positive neurons in the hypothalamus and the brainstem. The pathways controlling modulation of food intake by GLP-1 are not fully understood, however activation of GLP-1Rs in the brain, specifically the circumventricular organs, is believed to be responsible for the reduced appetite and food intake observed after GLP-1 administration [33]. Nevertheless, modulation of food intake by GLP-1 may also involve vagal afferent neurons. The GLP-1 effect on food intake has been demonstrated in clinical studies, where infusion of GLP-1 in lean individuals and those with obesity with and without diabetes causes dose-dependent reductions in *ad libitum* food intake and increases satiety [40]. However, as GLP-1R knockout mice are not obese, GLP-1R activation is not likely to be a prerequisite for body weight regulation in normal physiology [41]. Nevertheless, GLP-1R activation and its related effects on appetite and food intake constitute an important part of the body weight-lowering effect of pharmaceutical GLP-1RAs [42].

Effects on the cardiovascular system

The effect of GLP-1 on the cardiovascular system has attracted much attention and is amplified by the beneficial effect of GLP-1RAs on cardiovascular disease progression in clinical studies. The GLP-1R is expressed in both the heart atria and ventricles as well as the sinoatrial node [33]. Since most studies have applied supra-physiological GLP-1 doses, the physiological role of the GLP-1R in the heart remains unclear [43]. However, mice lacking the GLP-1R exhibit impaired left ventricular contractility and diastolic function, and also impaired responses to exogenous epinephrine, indicating a role for GLP-1 in cardiac structure and function [44]. Infusion of GLP-1 and GLP-RAs induces an increase in heart rate, which is mediated through both the autonomic nervous system as well as GLP-1R located at the sinoatrial node [45]. Furthermore, some studies have shown that GLP-1 protects the ischaemic and reperfused myocardium in rats [46], improves the ejection fraction in individuals treated with angioplasty after acute myocardial infarction [47], and improves left ventricular function and systemic haemodynamics in dogs with induced dilated cardiomyopathy [48]. GLP-1 reduces the post-prandial rise in triglycerides and lowers free fatty acid concentrations in healthy individuals [49], and improves endothelial dysfunction in individuals with type 2 diabetes and coronary heart disease [50]. Lastly, GLP-1 may exert a beneficial effect on the cardiovascular system through decreased inflammation and oxidative stress [51].

Effects on renal function

GLP-1 increases natriuresis through inhibition of the Na^+/H^+ exchanger in the proximal tubules, which may in part explain why GLP-1RAs have subtle antihypertensive effects [52, 53]. Additionally, GLP-1RA reduces glomerular hyperfiltration and albuminuria in individuals with type 2 diabetes [54]. The exact

localization of the GLP-1R in the kidney remains controversial; however, current evidence suggests that it is expressed in preglomerular afferent arterioles, whereas its presence in tubular and juxtaglomerular cells is uncertain [33]. Whether the natriuretic effect of GLP-1 is exerted directly through renal GLP1-Rs, modulation of the atrial natriuretic peptide or the renin–angiotensin system, or a neural pathway remains unclear.

Neuroprotective effects

Finally, GLP-1 has been associated with improved learning in rats and has also displayed neuroprotective effects, but again human studies have not established GLP-1 as a neuroprotective hormone so far or provided convincing evidence for significant effects of GLP-1R agonism on neurodegenerative diseases [55].

Most of what is known about GLP-1's pleiotropic physiological effects stems from studies of pancreatic islet function, particularly β -cell function. It is well acknowledged that GLP-1-induced insulinotropic and glucagonostatic effects represent the main mediators of the normalization of fasting plasma glucose and diurnal plasma glucose excursions and also improved glycaemic levels observed in studies utilizing native GLP-1 in people with type 2 diabetes [56–59]. Such studies have been of great importance to the development of GLP-1RAs.

GLP-1 receptor agonists for the treatment of diabetes

In 2005, the GLP-1RAs were introduced into clinical practice, and since 2009 they have been included in the joint position statements on the treatment of type 2 diabetes by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA). Recently GLP-1RAs have been

recommended as the first injectable therapy before insulin [60]. The GLP-1RAs, which exert the pleiotropic effects of the native gut hormone GLP-1, target a broad spectrum of the multifaceted pathophysiology of type 2 diabetes, and improve glucose homeostasis with a low risk of hypoglycaemia combined with body weight loss [61, 62]. Furthermore, they reduce cardiovascular events [63]. The introduction of the GLP-1RAs has generated substantial clinical interest and they are increasingly prescribed by clinicians worldwide. Until recently, all GLP-1RAs were administered by subcutaneous injection; however, one GLP-1RA, semaglutide, is now available as an oral formulation, which may facilitate use of this class earlier in the treatment cascade owing to wider acceptance from the individual with type 2 diabetes and healthcare professionals [64].

As several GLP-1RAs have emerged, it has become apparent that there are clinically relevant differences between them, making the therapeutic field challenging to navigate. Currently, seven GLP-1RAs are approved for treating people with type 2 diabetes (Table 36.1) [61, 62]. The challenge in developing a GLP-1RA is that native GLP-1 is rapidly degraded by the enzyme DPP-4, resulting in a short half-life (1–2 min) [65]. To overcome this, GLP-1RAs resistant to degradation by DPP-4 have been developed using two different strategies. The first strategy is based on the naturally occurring polypeptide exendin-4, which was originally isolated from the saliva of the lizard *Heloderma suspectum*. Exendin-4 is DPP-4 resistant, but activates the GLP-1R with equal efficacy to native GLP-1. The other strategy is based on the structure of native GLP-1, with a few amino acid alterations that protect the molecule from being degraded by DPP-4. The main difference between the GLP-1RAs resides in the pharmacokinetic profiles that largely divide them into short-acting and long-acting GLP-1RAs (Table 36.1). The differences in similarity to native GLP-1, pharmacokinetics, and molecular size of the GLP-1R agonists are important, as the efficacy and tolerability seem to depend on these differences.

Table 36.1 Pharmacokinetic properties of approved GLP-1RAs.

GLP-1 RAs		Approval year		Reference amino acid	Pharmacokinetics (single-dose administration)				Antibody development (% of individuals)
Compound	Category	FDA	EMA		Time to peak	Half-life	Elimination		
Exenatide twice daily	Short acting	2005	2006	Exendin-4 (53% homology with native GLP-1)	2.1–2.2 h	2.4 h	Mainly renal	35	
Lixisenatide	Short acting	2016	2013	Exendin-4 (53% homology with native GLP-1)	~2 h	3 h	Mainly renal	56–70	
Liraglutide	Long acting	2010	2009	GLP-1 (97% homology with native GLP-1)	11.0–13.8 h	13 h	Peptide hydrolysis, renal (6%) and faecal (5%)	8.6	
Exenatide once weekly	Long acting	2012	2011	Exendin-4 (53% homology with native GLP-1)	NA	2.4 h	Mainly renal	57	
Dulaglutide	Long acting	2014	2014	GLP-1 (~90% homology with native GLP-1)	48 h	4.7 d	Peptidases and renal	1.6	
Semaglutide	Long acting	2017	2019	GLP-1 (94% homology to native GLP-1)	24 h	7 d	Peptidases and renal	0.01–3.50	
Oral semaglutide	Long acting	2019	2020	GLP-1 (94% homology to native GLP-1)	<1–4 h	7 d	Peptidases and renal	0.5	

EMA, European Medicines Agency; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide 1; GLP-1RA, glucagon-like peptide 1 receptor agonist.

Source: Adapted from Andreassen et al. 2021 [62].

Short-acting GLP-1RAs

The short-acting GLP-1RAs are readily absorbed after subcutaneous injection and are resistant to degradation by DPP-4, but are still subject to renal elimination, which confers a plasma half-life of ~2–4 h [66,67]. They are administered twice daily (exenatide) or once daily (lixisenatide), which results in relatively large fluctuations in plasma concentrations during the day, and intermittent activation of GLP-1Rs.

Exenatide twice daily

Exenatide was introduced in 2005 (Byetta[®], AstraZeneca, Cambridge, UK) and is a synthetic version of exendin-4, which shares only 53% amino acid sequence homology with human GLP-1 [68,69]. Exenatide is primarily cleared in the kidneys by glomerular filtration [67], and the half-life after subcutaneous injection is ~2.4 h, with detectable plasma concentrations up to 10 h after injection [68]. Exenatide is recommended for twice-daily administration starting at 5 µg twice daily, which may be increased to 10 µg twice daily after one month if well tolerated. To obtain the maximum effect, exenatide should be injected within 60 minutes before the two main meals. The clinical effects of exenatide twice daily were investigated in the AC2993 diabetes Management for Improving Glucose Outcome (AMIGO) trials [69–71]. These trials showed significant reductions in HbA_{1c} versus placebo, and a modest reduction in fasting plasma glucose versus placebo. Post-prandial plasma glucose excursions are blunted in the exenatide-treated participants versus placebo, presumably driven primarily by a substantial deceleration in gastric emptying. Importantly, the effect on post-prandial plasma glucose was only evident during meals with concomitant drug administration; that is, not during lunch where no drug was administered [72]. The average weight loss amounted to 1–4 kg in the exenatide-treated groups versus comparators [73]. The main side effects of exenatide are mild to moderate nausea, diarrhoea, and vomiting [74]. The risk of hypoglycaemia is low with exenatide unless combined with sulphonylurea and insulin.

Lixisenatide once daily

Lixisenatide was approved in 2013 in Europe (Lyxumia[®], Sanofi, Paris, France) and in the USA in 2016 (Adlyxin[®], Sanofi, Bridgewater, NJ, USA) [75]. As with exenatide, lixisenatide is based on exendin-4, but with a deletion of a proline and an addition of six lysine amino acids at the C-terminus [76]. Clinical trials have demonstrated efficacy and tolerability with a once-daily dose of 20 µg, as evaluated in the clinical trial programme GetGoal [67,77,78]. These trials showed that lixisenatide lowered HbA_{1c} and resulted in moderate reductions of fasting plasma glucose versus placebo. Lixisenatide showed effects on post-prandial plasma glucose during a standardized meal test versus placebo, but only when the drug was administered immediately before food ingestion [74]. A dose-dependent decrease in body weight was seen with the 20 µg once-daily lixisenatide, but in some studies the weight reductions were not superior to placebo [79,80]. The most common side effects of lixisenatide treatment are of gastrointestinal origin (nausea and diarrhoea), consistent with other GLP-1RAs. A head-to-head trial of lixisenatide versus exenatide twice daily reported non-inferiority of lixisenatide regarding HbA_{1c} reduction, slightly better tolerability with nausea, diarrhoea, and vomiting, and fewer episodes of symptomatic hypoglycaemia with lixisenatide. However, lixisenatide treatment was inferior regarding weight loss [77].

Continuous-acting GLP-1RA

Several continuous-acting GLP-RA peptides are available. Different modifications have been applied to prolong the receptor activation. These modifications include:

- Incorporation of the GLP-RA in injectable depot-forming microspheres (exenatide once weekly).
- Attachment of a fatty acid side-chain, which allows reversible binding to albumin (liraglutide and semaglutide).
- Fusion with the Fc fragment of immunoglobulin G (dulaglutide, efglantide).

The longer half-lives of these compounds allow administration with longer intervals, while at the same time reducing fluctuations of plasma peptide levels, resulting in continuous activation of GLP-1Rs [61,62]. Recently, oral semaglutide reached the market, a combination of semaglutide and an absorption enhancer, which protects semaglutide of degradation and facilitates the absorption of semaglutide across the gastric mucosa [81].

Exenatide once weekly

Exenatide was developed as an extended-release formulation approved in Europe in 2011 and in the USA at the beginning of 2012 (Bydureon[®], AstraZeneca, Cambridge, UK) [82]. Exenatide once weekly contains exendin-4 encased in microspheres made of biodegradable polymer [83]. The pharmacokinetic profile depends almost solely on the absorption, and over time the biologically active exenatide given as a weekly injection is derived from multiple previous injections undergoing different phases of microsphere dissolution. The extended-release formulation of exenatide once weekly was examined in the phase III clinical trial program Diabetes therapy utilization: researching changes in HbA_{1c} weight and other factors through intervention with exenatide once weekly (DURATION) [84–89]. In two head-to-head studies, it was demonstrated that once-weekly (2 mg) exenatide was superior with regard to glucose lowering to the twice-daily (10 µg) formulation of exenatide, but with similar reductions in body weight [86,88]. Both formulations of exenatide were generally well tolerated; the most frequent adverse event, nausea, was less common with the once-weekly than the twice-daily compound [87]. Once-weekly exenatide 2 mg was also compared in a head-to-head trial with once-daily (1.8 mg) liraglutide [87], with greater reductions in HbA_{1c} and weight loss in the liraglutide-treated group, but once-weekly exenatide was better tolerated [87].

Liraglutide once daily

Liraglutide was approved for clinical use in Europe in 2009 and in the USA in 2010 (Victoza[®], Novo Nordisk) [90]. The structure of liraglutide is based on native GLP-1 with an Arg34Lys substitution and the addition of a 16-carbon fatty acid chain at Lys26, leaving liraglutide with a 97% homology with native GLP-1 (Table 36.1). The effects of liraglutide in doses uptitrated to 1.8 mg daily have been investigated in the phase III clinical trial programme Liraglutide Effect and Action in Diabetes (LEAD) [91–97]. Liraglutide significantly lowered HbA_{1c}, fasting plasma glucose, and weight compared with the placebo-treated group. Liraglutide also reduced post-prandial plasma glucose excursions compared with placebo; this effect was, however, primarily mediated by a decrease in pre-prandial (e.g. fasting) glucose values, which is consistent with the observation that liraglutide has small to moderate effects on gastric emptying [97]. The LEAD studies reported significant reductions in systolic blood pressure of up to 6 mmHg, but also a small increase in heart rate of 2–4 beats per minute in the

liraglutide-treated group [95,97]. The most frequently reported adverse events were gastrointestinal (nausea; mild and less persistent compared with treatment with exenatide twice daily) [98]. Compared with exenatide twice daily, liraglutide demonstrated greater reduction in fasting plasma glucose, but weight reductions were equal between the two groups [98]. In a head-to-head trial liraglutide reduced both fasting plasma glucose reductions, HbA_{1c}, and weight more than lixisenatide [99]. Another head-to-head trial with once-daily (1.8 mg) liraglutide demonstrated superiority compared with once-weekly (1.5 mg) dulaglutide with respect to body weight reduction [100].

Dulaglutide once weekly

Dulaglutide (Trulicity[®], Eli Lilly and Company, Indianapolis, IN, USA) was approved in 2014 by the FDA and 2015 by the EMA [101]. It comprises two GLP-1 moieties covalently linked to a human immunoglobulin G (IgG) 4-Fc heavy chain, which acts as an inert plasma carrier. Dulaglutide, used as a 1.5 mg once-weekly dose, has been examined in the phase III clinical trial programme Assessment of weekly administration of LY2189265 in diabetes (AWARD), and has also been compared head to head with exenatide twice daily, sitagliptin, and liraglutide [102–104]. Clinical trials showed dose-dependent reductions of HbA_{1c}, fasting plasma glucose, and weight reductions. Safety data indicate a low incidence of hypoglycaemia and the most frequently reported adverse events were gastrointestinal, primarily nausea, which seemed to reduce over time. Dulaglutide 1.5 mg once weekly showed non-inferiority to liraglutide 1.8 mg once daily for HbA_{1c} reduction after 26 weeks, but a greater weight loss was seen in the liraglutide-treated group [100]. As with other GLP-1RA, the most common adverse events are mild to moderate and transient nausea and diarrhoea. Recently, escalation of dulaglutide from 1.5 mg to 3.0 mg or 4.5 mg demonstrated clinically relevant, dose-related reductions in HbA_{1c} and body weight with similar safety profiles, and all three doses are now available for the treatment of type 2 diabetes [105].

Semaglutide once weekly (injection)

Semaglutide once weekly (Ozempic[®], Novo Nordisk [106]) was approved in 2018 by the FDA and EMA as a subcutaneously administered GLP-1RA that is structurally closely related to liraglutide, but with the attachment of a C-18 fatty acid chain (instead of the C-16 fatty acid chain in liraglutide) for improved albumin binding. There is also an alanine to α-aminoisobutyric acid substitution at position 8, which decreases degradation by DDP-4. The efficacy and safety of semaglutide in doses up titrated to 1 mg once weekly were investigated in the phase III clinical trial programme Semaglutide unabated sustainability in treatment of type 2 diabetes (SUSTAIN). Results from the trials support the superiority of semaglutide for reduction of HbA_{1c} and weight loss versus placebo as well as active comparators, including sitagliptin, canagliflozin, exenatide once weekly, dulaglutide, liraglutide, and insulin glargine [107–113]. Interestingly, exposure-response analyses showed a clear relationship reflecting plasma levels of semaglutide obtained after subcutaneous semaglutide and subsequent reductions in HbA_{1c} and body weight [114]. Consistent with these findings, the proportions of people reporting nausea or vomiting with semaglutide subcutaneously were also related to the plasma concentration [114]. The prevalence of gastrointestinal adverse events with once-weekly semaglutide and dulaglutide was similar at a full dose.

Semaglutide once daily (oral)

Oral semaglutide (Rybelsus [115]) was approved in 2019 by the FDA and in 2020 by the EMA. Oral semaglutide is a combination of semaglutide and the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), which protects semaglutide from degradation in the stomach and facilitates the absorption of semaglutide across the gastric mucosa [64,81]. The efficacy and safety of daily oral semaglutide (3, 7, and 14 mg) were investigated in the phase III clinical trial programme Peptide innovation for early diabetes treatment (PIONEER), which included 10 multinational studies [116–122]. Individuals recruited for this programme were people with type 2 diabetes from across a broad range of disease durations and background therapies, and were representative of many individuals typically encountered in clinical practice. Oral semaglutide 14 mg was superior in reducing HbA_{1c} versus empagliflozin (25 mg) when used as second-line treatment in individuals not reaching their target on metformin [117], and superiority was also seen versus sitagliptin (100 mg) [118]. Oral semaglutide (up titrated to 14 mg) was non-inferior to subcutaneous liraglutide (1.8 mg once daily) in decreasing HbA_{1c} [119]. Body weight reductions were similar for oral semaglutide compared with empagliflozin [117], but with greater reductions than sitagliptin [118] and liraglutide [119]. These observations suggest that oral semaglutide may provide some weight management benefits versus other commonly prescribed subcutaneous GLP-1RAs. Overall, oral semaglutide is well tolerated, with a safety profile consistent with the GLP-1RA drug class. The risk of hypoglycaemia was low, and the most common adverse events were gastrointestinal, with nausea and diarrhoea generally being the most frequently reported manifestations [64]. Currently higher doses (up to 50 mg) of oral semaglutide are being investigation for the treatment of type 2 diabetes and obesity [123–126].

Albiglutide once weekly

Albiglutide was a once-weekly GLP-1RA for subcutaneous administration approved in 2014 in both the USA (Tanzeum[®], GlaxoSmithKline, Durham, NC, USA) and Europe (Eperzan[®], GlaxoSmithKline, Brentford, UK), but in 2018 it was withdrawn from the market for commercial reasons.

Efpeglenatide once weekly

Efpeglenatide is a once-weekly exendin-4-based subcutaneously administrated GLP-1RA under development. The modified exendin-4 has been conjugated with an IgG4 Fc fragment to avoid DPP-4 degeneration and renal clearance [127,128]. Efpeglenatide has not yet been approved by the FDA.

Cardiovascular outcome trials with GLP-1RA in diabetes

The cardiovascular safety of all approved GLP-1RAs has been investigated in large-scale cardiovascular outcome trials, except for the short-acting exenatide twice daily, which was approved before cardiovascular outcome trials were mandated by the FDA and EMA (Table 36.2). The cardiovascular outcome trials are international, multicentre, double-blinded, randomized trials, which have compared the cardiovascular effect of GLP-1RAs with placebo when added to standard therapy. All trials have applied the same composite primary endpoint of major adverse cardiovascular events comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, except for the Evaluation of Lixisenatide in Acute Coronary

Table 36.2 Overview of currently published cardiovascular outcome trials including baseline characteristics and outcomes.

Cardiovascular outcome trials of GLP-1RAs									
Trial drug	Trial name	Year of completion	Number of individuals	Median follow-up (years)	Age (years)	HbA _{1c} (%)	CVD	Exposure to trial drug	MACE (HR [95% CI])
Lixisenatide	ELIXA	Feb 2015	6068	2.1	60	7.7	100%	91%	1.02 (0.89–1.17)
Liraglutide	LEADER	Dec 2015	9340	3.8	64	8.7	81.3%	84%	0.89 (0.78–0.97)
Semaglutide	SUSTAIN 6	Mar 2016	3297	2.1	65	8.7	83.0%	87%	0.74 (0.58–0.95)
Exenatide once weekly	EXSCEL	May 2017	14752	3.2	62	8.1	73.1%	76%	0.91 (0.83–1.00)
Albiglutide	HARMONY Outcomes	Nov 2017	9463	1.6	64	8.7	100%	87%	0.78 (0.68–0.90)
Dulaglutide	REWIND	Aug 2018	9901	5.4	66	7.3	31.5%	82%	0.88 (0.79–0.99)
Semaglutide (oral)	PIONEER-6	Sep 2018	3183	1.3	66	8.2	84.7%	75%	0.79 (0.57–1.11)
Efpeglenatide	AMPLITUDE-O	Dec 2020	4076	1.8	65	8.9	89.6%	89%	0.73 (0.58–0.92)

CI, confidence interval; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular event.

Syndrome (ELIXA) trial, in which the primary composite endpoint also included hospitalization for unstable angina [61–63].

The ELIXA trial, which investigated the cardiovascular safety of lixisenatide, was the first cardiovascular outcome trial to provide data for a GLP-1RA and the only cardiovascular outcome trial to provide data for a short-acting GLP-1RA [129]. The trial included individuals with type 2 diabetes and recent acute coronary syndrome, and showed that lixisenatide was non-inferior to placebo in reducing the primary composite endpoint. Hence, the available data are currently not supporting any beneficial cardiovascular effect of short-acting GLP-1RAs.

Several continuous-acting GLP-1RAs have proved to reduce major adverse cardiovascular events. The first cardiovascular outcome trials to provide data for continuous-acting GLP1-RAs were the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the SUSTAIN 6 trial, which investigated the cardiovascular safety of liraglutide and semaglutide, respectively [130, 131]. These trials included individuals with type 2 diabetes and established cardiovascular disease or high risk of cardiovascular disease. Both liraglutide and semaglutide proved superior to placebo in reducing major adverse cardiovascular events, thereby being the first GLP-1RAs with a proven effect on the prevention of cardiovascular events.

The next cardiovascular outcome trial to present data on the cardiovascular safety of a GLP-1RA was the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, which also was the largest of the cardiovascular outcome trials with >14 000 participants [132]. The trial was designed to have 70% individuals with pre-existing cardiovascular disease and 30% without cardiovascular disease. In this trial, exenatide once weekly was non-inferior to placebo, but superiority was not proved. The participants in EXSCEL were younger and had a lower HbA_{1c}, a lower prevalence of cardiovascular disease, and a lower time on active treatment during the trial than previous cardiovascular outcome trials, which may partly explain the inability of exenatide once weekly to obtain superiority. Both dulaglutide and albiglutide subsequently were shown to reduce major adverse cardiovascular events in their respective cardiovascular outcome trials [133, 134]. In the

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial, dulaglutide reduced major adverse cardiovascular events in a population with a markedly lower level of established cardiovascular disease at baseline when compared to any of the other cardiovascular outcome trials, which predominantly included individuals with established cardiovascular disease [133]. This finding supports a role for dulaglutide and potentially the other continuous-acting GLP-1RAs in the primary prevention of cardiovascular disease in type 2 diabetes.

The PIONEER-6 trial investigating the cardiovascular safety of oral semaglutide included the smallest population and had the shortest follow-up time of the completed cardiovascular outcome trials [135]. Oral semaglutide demonstrated non-inferiority, but not superiority, compared with placebo. The estimated hazard ratio of major adverse cardiovascular events was roughly like that of subcutaneous semaglutide, but with a markedly wider confidence interval, and hence the study was likely underpowered to detect any significant effect. Whether oral semaglutide has a beneficial cardiovascular effect remains to be explored in the ongoing Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL) trial [136]. The last of the cardiovascular outcome trials to be completed was the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial, which investigated the cardiovascular safety of efpeglenatide and included individuals with type 2 diabetes and established cardiovascular disease or current kidney disease plus a least one cardiovascular risk factor [128]. This was the first trial to demonstrate a significant reduction in major adverse cardiovascular events for an exendin-4-based GLP-1RA.

Whereas the currently conducted cardiovascular outcome trials support a class effect for continuous-acting GLP-1RAs on the risk of cardiovascular disease, the trials have revealed an inconsistent effect on the individual major adverse cardiovascular event components. However, in a meta-analysis of the currently published cardiovascular outcome trials including >60 000 individuals, a significant effect on each of the components (cardiovascular death, fatal or non-fatal myocardial infarction, and fatal or non-fatal stroke) was found [63]. The meta-analysis also found that treatment with a GLP-1RA reduced the risk of hospitalization for heart failure.

It is important to recognize that the populations in the cardiovascular outcome trials are different and results from the different trials cannot be directly compared. The prevalence of established cardiovascular disease varied from 32% to 100%, which affected the incidence of major adverse cardiovascular events and thereby the number needed to treat. However, in a meta-analysis, the number needed to treat to prevent one incident major adverse cardiovascular event over a weighted average median follow-up period of three years was 65 individuals [63].

In addition to investigating the effect of GLP-1RAs on cardiovascular disease, most cardiovascular outcome trials have included renal secondary endpoints. Treatment with GLP-1RA reduced a broad composite renal outcome comprising development of macroalbuminuria, doubling of serum creatinine, or at least 40% decline in estimated glomerular filtration rate (eGFR), kidney replacement therapy, or death due to kidney disease [137]. However, this effect was mainly driven by a decrease in macroalbuminuria, and whether GLP-1RAs reduce worsening in kidney function and delay progression to dialysis is still to be determined. Nevertheless, in a sensitivity analysis excluding data from the ELIXA trial, which stands out as the only cardiovascular outcome trial investigating a short-acting GLP-1RA, treatment with GLP-1RAs led to a significant reduction of 18% in worsening of kidney function, defined as either doubling of serum creatinine or $\geq 40\%$ decline in eGFR [63].

Safety Issues

The safety of GLP-1RAs has been extensively studied in pre-clinical studies, the large clinical trial programmes, as well as the cardiovascular outcome trials. The most common adverse events observed in clinical trials of GLP-1RAs involve the gastrointestinal system and are mainly nausea, vomiting, and diarrhoea. These events are dose dependent and diminish over time. Differences exist in the reported occurrence of these gastrointestinal effects between each GLP-1RA. Other identified potential safety issues include hypoglycaemia, pancreatic adverse events, thyroid neoplasms, immunogenicity issues, and interactions with other medicinal products [68, 75, 82, 90, 101, 106, 115].

Hypoglycaemia

GLP-1RAs generally confer a low risk of severe hypoglycaemia, as the clinical insulin-stimulatory effects are only present at plasma glucose levels >4 mmol/l (72 mg/dl) [138]. In monotherapy or combination with other anti-diabetes agents that have a low risk of hypoglycaemia (e.g. metformin), the GLP-1RAs uncommonly cause hypoglycaemia [68, 75, 82, 90, 101, 106, 115]. In trials in which the GLP-1RAs were combined with a hypoglycaemic agent, such as a sulfonylurea or insulin, the incidence of non-severe hypoglycaemia was significantly higher (up to one-third of participants), depending on trial duration, study population, and the dose of insulin and/or sulfonylurea. When a GLP-1RA has been combined with insulin treatment in clinical trials, symptomatic hypoglycaemic events have been reported in ~25% of individuals, and slightly more with short-acting than continuous-acting GLP-1RAs [139].

Pancreatic adverse events

Since the introduction of GLP-1-based therapy, pancreatic adverse effects, in particular pancreatitis and pancreatic cancer, have been a major concern. The concern for pancreatic safety was spurred by

post-marketing reports of pancreatitis during GLP-1RA treatment. According to an analysis based on the FDA adverse event reporting database for the years 2005–2009 [140], pancreatitis was reported as an adverse event more than six times as frequently for individuals administered exenatide compared with other (non-GLP-1-based) therapies for type 2 diabetes. This may have been a so-called Weber effect, which constitutes a peak in adverse event reporting at the end of the second year after regulatory approval of a drug followed by a continuous decline thereafter [141]. In 2013–2014, the EMA and FDA undertook an extensive appraisal of the existing pre-clinical and clinical safety data together with the observational evidence. They concluded that data were too inconsistent to establish a certain connection between GLP-1RA administration and pancreatic adverse effects, but owing to the uncertainty of the estimates, a causal role could not be completely excluded [142]. A major issue in relation to the spontaneous reports of pancreatic adverse events is the fact that people with type 2 diabetes generally have an up to four times higher risk of pancreatitis than those without diabetes [143]. In contrast to early increases in spontaneously reported events, acute pancreatitis and pancreatic cancer events have been extremely rare in the randomized clinical trials with the GLP-1RAs [144]. Data from cardiovascular outcome trials with adjudicated pancreatic events showed that the incidence of pancreatitis was similar (~0.3%) in GLP-1RA- and placebo-treated individuals with type 2 diabetes [130, 144, 145]. It is important for the interpretation that individuals with a high risk of pancreatitis (e.g. previous pancreatitis) were excluded from participating in most of these trials. Reassuringly, a recent meta-analysis of 22 population-based observational studies did not identify an association with GLP-1RA use and any pancreatic pathology [146]. Nonetheless, acute pancreatitis is still listed as an adverse event for all GLP-1RAs [68, 75, 82, 90, 101, 106, 115]. So far there are no data to suggest differences in adverse pancreatic effects between the GLP-1RAs (e.g. between short- and continuous-acting agents [147]). Individuals started on treatment with any of the GLP-1RAs should be informed of the potential risk and characteristic symptoms of acute pancreatitis; and caution is advised when prescribing GLP-1RAs to those with a risk of or a history of pancreatitis [68, 75, 82, 90, 101, 106, 115].

Thyroid adverse events

The pre-clinical development programme of several GLP-1RAs exposed significant increases in medullary thyroid carcinoma (thyroid C-cell neoplasm) in rodents [68, 75, 82, 90, 101, 106, 115]. The fact that these C-cell neoplasms were not detected in monkeys [148] suggests important species differences. Accordingly, in comparison with rodent thyroid glands, C cells are much less abundant in human thyroid tissue and, equally importantly, GLP-1Rs are present in much lower amounts per C cell [148]. Thyroid events and medullary thyroid carcinoma were closely monitored in the clinical trial programmes of all GLP-1RAs, including their cardiovascular outcome studies and in post-marketing surveillance. The collective evidence does not suggest that GLP-1RA treatment causes a higher risk of thyroid cancers in humans [144, 146, 149].

Immunogenicity issues

The GLP-1RAs are large molecules that can raise an immune response. This is evidenced by measurable levels of antibodies directed against epitopes on the GLP-1RA in some individuals. Generally, the exendin-4-based GLP-1RAs (exenatide, lixisenatide, and efpeglenatide) raise more antibodies (~25–74% of treated

individuals) than the GLP-1RAs with higher peptide sequence homology to native human GLP-1 (liraglutide, semaglutide, albiglutide, and dulaglutide), where antibodies can be detected in 1–9% of those treated. There is conflicting evidence on the clinical relevance of these antibodies [150–152]. However, the presence of high levels of neutralizing antibodies may limit the clinical effects of at least some of the GLP-1RAs (as is evident with exenatide, where high levels are present in 1–6% of individuals, associated with a lower clinical efficacy [151, 153]). Hypersensitivity reactions and local injection-site reactions are inconsistently reported in the trials, but may also depend on immunogenicity. Injection-site reactions include local nodule formation, redness, or itching that occurs in 0–22% of individuals treated with a GLP-1RA for up to a year. Interestingly, injection-site reactions are more frequent in individuals who develop antibodies [82]. However, other excipients in the drug formulation (e.g. the prolonged-release delivery systems in the GLP-1RA for once-weekly administration or fatty acid side-chains to the GLP-1-moecity) may also be important factors in the development of injection-site reactions. Thus, exenatide once weekly caused much more injection site pruritus than exenatide twice daily (18% vs 1%) [88] and injection-site reactions occurred in more individuals given albiglutide than in those given liraglutide (13% vs 5%) [154].

Interactions with other medical products

None of the GLP-1RAs interacts with the hepatic metabolism of other medicinal products; specific interactions with acetaminophen, digoxin, oral contraceptives, lisinopril, metformin, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and warfarin have been studied in clinical trials [68, 75, 82, 90, 101, 106, 115]. However, all the GLP-1RAs delay gastric emptying with acute dosing, and therefore have the potential to prolong the absorption of concomitantly administered oral medicinal products. Importantly, the effect on gastric emptying diminishes with time for the continuous-acting GLP-1RAs owing to rapid tachyphylaxis, already evident from the first day of treatment [38]. Therefore, the interaction through delayed gastric emptying is mainly of clinical relevance with the short-acting GLP-1RAs and in a situation with concomitant administration of medicinal products with a narrow therapeutic-toxic ratio that require careful clinical or biochemical monitoring. The interaction can be alleviated by administration of the other medicinal product one hour before or four hours after the administration of the short-acting GLP-1RA [68, 75].

Amylin and amylin analogues

Historical overview

Amyloid deposits were discovered a century ago and are described as a pathological feature of people with diabetes and those with insulinomas. In 1987, amylin was isolated from amyloid deposits and there was speculation on whether it had important endocrine effects [155, 156]. Amylin is stored and secreted with insulin from the β cells [157] and type 1 diabetes is considered an amylin-deficient state owing to β -cell destruction, and the hormones exhibiting complementary roles in the regulation of plasma glucose [158]. The physiological actions of amylin involve inhibition of appetite and gastric emptying, and may also involve suppression of glucagon

secretion in relation to meal intake [158]. The development of amylin analogues focuses on the clinically beneficial effects on glycaemic levels, especially post-prandially, and body weight in the treatment of diabetes.

Amylin physiology

Amylin release, metabolism, regulation of secretion and receptor

Amylin and insulin are stored together in secretory granules and are co-released from the pancreatic β cells [159]. The release of amylin is stimulated by nutrient ingestion and gut-derived incretin hormones (GLP-1 and GIP) and through neural signalling. Amylin is released during meals and together with insulin in a corresponding high-frequency pulsatile pattern, but at a 1:100 ratio [159]. Deviation from this secretion pattern has been observed in several conditions, including diabetes and obesity, but the mechanisms of the altered amylin secretion pattern and its potential implications are unknown [160]. In contrast to insulin, which is eliminated primarily in the liver, amylin is eliminated mainly through renal metabolism [158]. Amylin acts on a composite receptor with two parts. The *core* part comprises a calcitonin receptor, which is a transmembrane class B G protein-coupled receptor [161, 162]. Two splice variants of the calcitonin receptor (a and b) exist, and they are complexed with one of three receptor activity-modifying proteins (RAMP1, RAMP2, and RAMP3), creating diverse amylin receptors (AMY1, AMY2, and AMY3) [163]. Amylin appears to bind with high affinity to six different emerging receptors [162].

Amylin's effect on gastric emptying and central effects on appetite and food intake

Amylin and GLP-1 share overlapping physiological properties. Both peptide hormones slow nutrient delivery to the small intestine by decelerating gastric emptying, suppress post-prandial glucagon secretion, and reduce appetite, albeit through seemingly different pathways [164]. Dose-response studies performed in rats investigating the influence on gastric emptying exerted by several different subcutaneously injected gastrointestinal hormones (amylin, cholecystokinin octapeptide [CCK-8], GIP, GLP-1, glucagon, and pancreatic peptide) showed that amylin was the most potent inhibitor of these [165]. Correspondingly, subcutaneous injection of a selective amylin receptor antagonist in rats revealed an acceleration of gastric emptying [166, 167]. Importantly, the ability of amylin to inhibit gastric emptying is overridden by the occurrence of hypoglycaemia [168]. Whether amylin's decelerating effect on gastric emptying contributes to its anorectic effects remain uncertain. Nevertheless, exogenous amylin reduces meal size and, furthermore, peripherally or centrally infused amylin receptor antagonist produces an opposite effect, suggesting that amylin is a physiological regulator of food intake [169].

Amylin exerts its anorectic actions via direct effects on the CNS [164, 169, 170]. c-Fos expression (a marker of neuronal activity) is induced by amylin in target neurons in different brain regions involved with metabolic regulation [171]. The area postrema located in the hindbrain is the primary and most important site of amylin action. This assumption is based on studies of rodents undergoing area postrema ablation, which demonstrated a complete abrogation of amylin's anorexigenic effects [172, 173]. After area postrema activation, the amylin signal is conveyed to the

forebrain via distinct relay stations and to regions of hypothalamus known to be involved in feeding behaviour. Within the lateral hypothalamic area, amylin diminishes the expression of orexigenic neuropeptides such as orexin and melanin-concentrating hormone [160,171,173]. The area postrema is favourably located as a target of central hormone action owing to the permeable blood-brain barrier in this region. Other brain sites suggested to be important contributors to amylin's anorexic effects include the subfornical organ, the nucleus accumbens, and the dorsal raphe of the brain-stem [172,173]. Amylin's anorectic effect relies on both satiety-promoting effects and attenuation in feeding reward neurocircuits [174]. Whether amylin also exerts peripheral actions has been investigated in muscle, liver, and adipose tissue of mice and adipose tissue of humans [175,176], and physiological effects were clearly evident with stimulation of distinct signalling pathways after application of amylin. However, the presence of amylin receptors in these peripheral tissues remains uncertain.

Amylin analogues for the treatment of diabetes

The discovery of amylin's glucose and body weight-lowering effects makes it attractive for therapeutic purposes. However, the instability and propensity to self-aggregate complicated the clinical development of drugs based on native sequence human amylin [157]. The problem was solved by substituting a few amino acids in the rat sequence of amylin with proline residues [164]. This enhanced the solubility and markedly reduced amyloid fibril formation of the bioactive peptide [177]. The actions and pharmacokinetic and pharmacodynamic properties of a synthetic amylin analogue, pramlintide, are very similar to those of native amylin [157]. Numerous clinical trials tested the efficacy and safety of pramlintide ahead of its approval by the FDA in 2005. Currently, this sole available amylin analogue is marketed in the USA as Symlin® (Amylin Pharmaceuticals, San Diego, CA, USA). The drug is approved for adjunct treatment of type 1 diabetes and type 2 diabetes, when optimal glucose levels are not achieved with insulin administration alone or combined with other glucose-lowering drugs [178]. Pramlintide is administered in conjunction with meal-time insulin therapy [177]. The plasma elimination half-life is ~48 min when injected subcutaneously in the thigh or the abdomen. The drug is primarily eliminated by the kidneys, like native amylin [179]. The most common adverse events related to pramlintide treatment are of gastrointestinal origin, including decreased appetite, vomiting, and stomach pain, with mild-to-moderate nausea being most frequent. However, these effects are generally transient and can be minimized by slow uptitration. No clear correlation between gastrointestinal symptoms and therapy-induced weight loss has been found [180]. Although pramlintide is well tolerated overall, it is associated with an increased risk of insulin-induced severe hypoglycaemia, particularly in people with type 1 diabetes [181].

Clinical studies investigating the acute and short-term effects of pramlintide have demonstrated reductions in post-prandial glucose excursions and 24 h glucose profile [182]. These glycaemic improvements were observed in acute studies and with continued dosing for 2–4 weeks and are likely due to decreased gastric emptying. Whether amylin-induced attenuation of post-prandial glucagon release contributes remains uncertain. Several larger long-term trials with pramlintide have also been conducted. Hollander et al. investigated HbA_{1c} and weight management with adjuvant pramlintide therapy in 656 individuals with type

2 diabetes with HbA_{1c} ≥8% (64 mmol/mol) who were requiring insulin treatment either alone or combined with oral anti-diabetes medications at baseline [158]. Participants were randomized to receive pramlintide at different doses or placebo for 52 weeks. Treatment with pramlintide twice daily led to a reduction from baseline in HbA_{1c} of −0.62% (7 mmol/mol) at week 52 (vs −0.25% [3 mmol/mol] with placebo). Body weight change at week 52 from baseline was sustained in individuals receiving 120 µg twice daily (−1.4 kg) versus 90 µg twice daily (−0.5 kg) or placebo (+0.7 kg) [158]. The 1155 participants with type 2 diabetes and body mass index >25 kg/m², who received pramlintide 120 µg twice daily in the study, were included in a pooled *post hoc* analysis with corresponding participants from another large-scale trial [154,183]. Significant reductions in both HbA_{1c} (−0.43%; 5 mmol/mol) and body weight (−2.0 kg) from baseline to week 26 (compared with placebo) were found with adjunctive pramlintide therapy. These data indicate that pramlintide added to insulin therapy yields further reductions in HbA_{1c} and a concomitant weight loss in individuals with type 2 diabetes.

Perspectives for non-insulin parenteral therapies

Evidence from large-scale trials focusing on cardiovascular safety has established GLP-1RA as a cornerstone in type 2 diabetes treatment. In contrast to older anti-diabetes agents, several GLP-1RAs confer substantial body weight loss and prevent cardiovascular morbidity and death within few years of initiating therapy in type 2 diabetes. Based on these extraordinary results, the future use of the GLP-1RAs is likely to expand. Two GLP-1RAs (liraglutide and semaglutide) have been approved in higher doses for the treatment of obesity and new avenues for type 2 diabetes-associated conditions are also being specifically investigated. Thus, trials are ongoing in type 2 diabetes-associated chronic kidney disease [184], eye disease [185], and heart failure with preserved ejection fraction [186], but also type 1 diabetes [187] and non-alcoholic fatty liver disease and non-alcoholic steatohepatitis [188]. In addition, potential effects on neurological diseases such as Alzheimer disease [189], Parkinson disease [190], and depression [191] are also possible and are currently being investigated.

When treating complicated metabolic diseases, such type 2 diabetes, intervening with more than one regulatory pathway is often desirable due to additive effects. Along these lines, several dual and/or triple receptor agonists, where activation of the GLP-1R is combined with activity at other peptide hormone receptors, are in clinical development. The combined agonism of GLP-1R and the GIP, glucagon, or amylin receptors is particularly promising and several unimolecular multiagonist treatment compounds simultaneously activating two or more of these receptors, besides the GLP-1R, are in late clinical development for the treatment of type 2 diabetes, obesity, and/or non-alcoholic steatohepatitis [192,193]. Major caveats for the success of these compounds include the unclear translation to clinical efficacy and safety in humans, and an aggravated risk of untoward immunological reactions and unforeseen off-target effects, which have to compare favourably to the well-established clinical efficacy and safety of optimally dosed GLP-1RAs.

37

How to Use Type 2 Diabetes Treatments in Clinical Practice

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Key points

- Numerous pharmacological options for the management of type 2 diabetes are available.
- The choice of appropriate anti-diabetes therapy is guided by the presence of clinically important comorbidities and underlying cardiovascular risk.
- Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are the treatment of choice in people with heart failure or chronic kidney disease.
- Specific SGLT-2 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs) are prioritized in people with established or at high risk of developing atherosclerotic cardiovascular disease.
- In those with low absolute cardiovascular risk, therapeutic decisions should consider the efficacy and safety profile of potential agents and avoid increased treatment burden.
- In the presence of obesity, GLP-1RAs or SGLT-2 inhibitors are preferred.

- In those with non-alcoholic steatohepatitis (NASH), pioglitazone and some GLP-1RAs are recommended.
- For treatment of hyperglycaemia, metformin remains the initial choice in most people, including those with newly diagnosed type 2 diabetes, due to the extensive experience with its use, overall efficacy and safety profile, and affordability.
- Additional important considerations affect real-life therapeutic decisions and the likelihood that people will take their medication as prescribed, including the values and preferences of the informed individual, tolerability issues, practical matters, and drug availability and affordability.
- Clinicians should continually update their knowledge of the pharmacological management of type 2 diabetes and avoid clinical inertia by regularly reassessing the overall clinical profile of those they treat.

In recent years, pharmacotherapy for type 2 diabetes has departed from focusing solely on the management of hyperglycaemia to mitigation of cardiovascular risk [1–3]. The changing landscape in the management of type 2 diabetes was largely imposed by findings from cardiovascular outcomes trials, which suggest a beneficial effect on hard clinical endpoints for certain classes of anti-diabetes agents, namely sodium–glucose cotransporter 2 inhibitors (SGLT-2) and glucagon-like peptide 1 receptor agonists (GLP-1RAs). In this context, clinicians should consider indicators of high risk of, or established, atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure when choosing the optimal treatment. In this chapter, we review the main glucose-lowering drug classes in terms of their benefits and harms, and their current place in the management of type 2 diabetes.

to follow (Chapters 35 and 36; Table 37.1). Medications approved for the treatment of type 2 diabetes fall into the following main categories:

- Insulin-sensitizing agents, which include biguanides represented solely by metformin, as well as thiazolidinediones represented by pioglitazone; the use of rosiglitazone has practically ceased due to concerns about an increased risk of myocardial infarction [4].
- Insulin secretagogues (sulfonylureas, meglitinides).
- Incretin mimetics (dipeptidyl-peptidase 4 [DPP-4] inhibitors, GLP-1RAs, dual glucose-dependent insulinotropic polypeptide [GIP] and GLP-1RAs).
- Agents that induce glycosuria (SGLT-2 inhibitors).
- Agents that block intestinal absorption of carbohydrates (α -glucosidase inhibitors).
- Insulin.

There are also other medications with glucose-lowering properties (e.g. bile acid sequestrants, dopamine-2 agonists, and amylin mimetics) that are either licensed for the treatment of type 2 diabetes only in specific regions or whose use in clinical practice is very limited.

Therapeutic options

The number of diabetes drugs has expanded substantially over the preceding years and evidence from cardiorenal outcomes trials is rapidly accruing at a pace that practising clinicians might find hard

Table 37.1 Characteristics of agents used for the treatment of type 2 diabetes in the USA or Europe.

Class	Medications	Primary physiological action(s)	Main advantages	Main disadvantages
Biguanides	Metformin	↓ Hepatic glucose production ↑ Glucose uptake in peripheral tissues	Extensive experience No hypoglycaemia Weight neutral (potential for modest loss) ? Reduction in CV events or all-cause mortality Low cost	Gastrointestinal adverse events Vitamin B ₁₂ deficiency Contraindicated with eGFR <30 ml/min/1.73 m ² Lactic acidosis (rare)
Sulfonylureas	Glibenclamide (or glyburide) Glidiazide Glipizide Glimepiride	↑ Insulin secretion	Extensive experience ↓ Microvascular complications Low cost	Hypoglycaemia ↑ Weight Dose adjustment/avoidance in CKD ? Cardiovascular safety 'Pancreatic exhaustion'
Meglitinides (or glinides)	Nateglinide Repaglinide	↑ Insulin secretion	↓ Post-prandial glucose excursions Dosing flexibility Relatively safe in advanced CKD	Hypoglycaemia ↑ Weight ? Cardiovascular safety
Thiazolidinediones (or glitazones)	Pioglitazone	↑ Insulin sensitivity	No hypoglycaemia ↓ Cardiovascular events ↓ Liver steatosis	↑ Weight ↑ Fractures Oedema/heart failure Bladder cancer
DPP-4 inhibitors (or gliptins)	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion	No hypoglycaemia Weight neutral Well tolerated	Modest glycaemic efficacy Skin reactions ↑ Hospitalizations for heart failure (saxagliptin) Dose adjustment in CKD (except for linagliptin) ? Pancreatitis, pancreatic neoplasms ? Arthralgia
GLP-1 receptor agonists	Dulaglutide Exenatide Exenatide LAR Liraglutide Lixisenatide Subcutaneous semaglutide Oral semaglutide	Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion Delay gastric emptying ↑ Satiety	No hypoglycaemia ↓ Weight ↓ Post-prandial glucose excursions ↓ CV events Prevent progression of albuminuria ↓ Liver steatosis ↓ Mortality	Injectable (except oral semaglutide), local site reactions, require training Gastrointestinal adverse events ? Pancreatitis, pancreatic neoplasms Gallbladder disease ? Medullary carcinoma ↑ Heart rate High cost
GIP/GLP-1 receptor agonists	Tirzepatide	Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion Delay gastric emptying ↑ Satiety Improve lipid homeostasis ↑ Insulin sensitivity	No hypoglycaemia ↓ Weight	Injectable Gastrointestinal adverse events High cost Currently in development
SGLT-2 inhibitors (or gliflozins)	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Insulin independent inhibition of glucose reabsorption in the proximal convoluted tubule → glucosuria	No hypoglycaemia ↓ Weight ↓ Blood pressure ↓ CV events in high-risk individuals ↓ Hospitalizations for heart failure Prevent progression of CKD ↓ Mortality	Genitourinary tract infections Volume depletion (dizziness, orthostatic hypotension, syncope) esp. in older people, CKD, or those on diuretics Dose adjustment in CKD (see labels of individual agents for renal dose considerations) Lower glycaemic efficacy at low eGFR ↑ Risk for amputation (canagliflozin) ↑ Risk for fracture (canagliflozin) Euglycaemic ketoacidosis (rare) High cost

(continued)

Table 37.1 (Continued)

Class	Medications	Primary physiological action(s)	Main advantages	Main disadvantages
Insulins	<ul style="list-style-type: none"> Basal <ul style="list-style-type: none"> • Human NPH • Detemir • Degludec (U-100 and U-200) • Glargin (U-100, U-300, and biosimilars) Prandial <ul style="list-style-type: none"> • Human regular • Aspart (including faster acting) • Glulisine • Lispro (U-100, U-200, and ultra-rapid) Premixed 	<ul style="list-style-type: none"> ↑ Glucose disposal ↓ Hepatic glucose production 	<ul style="list-style-type: none"> Nearly universal response Theoretically unlimited efficacy ↓ Microvascular complications 	<ul style="list-style-type: none"> Hypoglycaemia ↑ Weight Injectable, require training Frequent self-monitoring and dose adjustment High cost (insulin analogues) Treatment burden may lead to reluctance to take insulin

CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl-peptidase 4; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; LAR, long-acting release; NPH, neutral protamine Hagedorn; SGLT-2, sodium–glucose cotransporter 2.

Metformin

Metformin is an oral biguanide that first received marketing approval in Europe in 1957 and the USA in 1994; it has the advantage of targeting insulin resistance, which is considered an early feature of type 2 diabetes. It acts mainly by suppressing gluconeogenesis in the liver, thereby reducing hepatic glucose production. Moreover, it leads to increased peripheral glucose uptake mainly in skeletal muscles, possibly by enhancing the binding of insulin to its receptors. It appears to be ineffective in tissues that are insensitive to insulin such as the brain [5]. Several other physiological effects have also been described, such as decreased fatty acid oxidation and increased intestinal glucose use, potentially mediated by release of intestinal GLP-1. About 90% of the drug is eliminated in the urine.

The maximal daily dose of metformin is 3000 mg in Europe or 2550 mg in the USA and the drug is usually administered in 2–3 divided doses that are taken with meals. To improve gastric tolerance the drug should be introduced at a dose of 500 or 850 mg twice daily, which should be adjusted slowly in biweekly intervals. Given the rising rates of obesity and the associated prevalent cases of type 2 diabetes among younger individuals, use of metformin is now allowed in children from 10 years of age, but the maximum recommended dose for the paediatric population is 2000 mg. Extended-release formulations for once-daily dosing and fixed-dose combinations with other oral anti-diabetes agents are available.

Metformin is contraindicated in severe renal impairment with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m². In Europe, the daily dose of metformin should not exceed 2000 mg for those with stage 3A chronic kidney disease (eGFR 45–59 ml/min/1.73 m²), whereas for individuals with stage 3B chronic kidney disease (eGFR 30–44 ml/min/1.73 m²) the maximal daily metformin dose is 1000 mg. In the USA, initiation of metformin is not recommended with an eGFR between 30 and 45 ml/min/1.73 m². Annual monitoring of serum creatinine is required and people with moderate renal impairment should be educated to withhold metformin during acute illness or if the administration of iodinated contrast media is planned.

Experience with metformin is extensive and no major safety concerns have arisen to date. Metformin does not increase the risk of hypoglycaemia and can have a small effect to reduce body weight [6]. Because of its favourable efficacy, safety profile, and low cost, it is generally considered as first-line therapy for most people with type 2 diabetes unless contraindicated or not tolerated. Intensive treatment with metformin was also associated with a lower incidence of all-cause mortality compared to diet in people with overweight and newly diagnosed type 2 diabetes in a substudy of the UK Prospective Diabetes Study (UKPDS) [7,8]. However, in another substudy that was also performed within the UKPDS, addition of metformin to sulfonylurea resulted in increased mortality compared with sulfonylurea alone [7]. No firm explanation could be given for this controversial finding, and based on later follow-up data it was attributed to chance [9]. A meta-analysis incorporating data from both UKPDS substudies and additional smaller randomized controlled trials found a neutral effect of metformin on all-cause mortality [10]. Consistently, metformin had no effect on major cardiovascular events over a 21-year median follow-up of participants in the Diabetes Prevention Program (DPP) and Diabetes Prevention Program Outcomes Study (DPPOS) [11].

Metformin is commonly associated with gastrointestinal side effects including metallic taste, bloating, abdominal discomfort, and soft bowel movements or diarrhoea. These symptoms may improve over time and can be mitigated by gradual dose titration. The most concerning safety issue is metformin-associated lactic acidosis. This extremely uncommon but potentially life-threatening condition usually develops in the setting of critical illness that predisposes to hypoperfusion or hypoxaemia, including renal insufficiency, liver disease, and shock, or as a result of drug overdose. Finally, metformin reduces vitamin B₁₂ absorption in the small intestine, which might present as peripheral neuropathy, although the drug rarely causes megaloblastic anaemia. Clinicians might offer periodic monitoring of serum vitamin B₁₂ concentrations, especially for high-risk people such as those on a vegan diet or after bariatric surgery [12].

Sulfonylureas

Sulfonylureas are the oldest class of oral anti-diabetes compounds. They bind to sulfonylurea receptors in pancreatic β cells and stimulate insulin release by inhibiting adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cell membrane, which in turn results in calcium influx and consequent exocytosis of insulin. Because they constantly stimulate insulin secretion, sulfonylureas are very effective in terms of glycated haemoglobin (HbA_{1c}) lowering, especially at early stages of the disease in people with residual β -cell function. Nevertheless, sulfonylureas are associated with a lack of a durable effect on glucose lowering, which is related to the declining insulin-producing capacity of β cells, a phenomenon known as *pancreatic exhaustion*. First-generation agents are no longer used in clinical practice and have been replaced by second-generation sulfonylureas including glipizide (also available as a modified-release formulation), gliclazide (also known as glyburide), and glimepiride (also classified as a third-generation sulfonylurea), which have a prolonged duration of action and more convenient dosing scheme [13].

Hypoglycaemia is a major limitation of this class, because sulfonylureas increase insulin release irrespective of blood glucose concentrations. Hypoglycaemia might be prolonged and require hospitalization. It is more likely to occur after exercise or in the fasting state. Because sulfonylurea metabolites are renally excreted, the risk of hypoglycaemia is higher in people with chronic kidney disease. Hence, the drugs should be initiated at the lower end of the approved dose range and carefully titrated, especially in older individuals or those with chronic kidney disease.

Sulfonylureas should also be given with caution or avoided in people in whom severe hypoglycaemia can be fatal, such as those with coronary artery disease. Concomitant use of sulfonylureas with intensified insulin regimens should generally be avoided. People should be educated regarding the recognition and management of hypoglycaemia. Weight gain is another undesirable effect of sulfonylureas and is attributed to the anabolic effects of insulin. On the other hand, the drugs are relatively inexpensive and remain a reasonable choice when cost is the primary consideration in treatment decisions [3].

Evaluation of cardiovascular safety for newly approved anti-diabetes agents has become a regulatory requirement since 2008 [14], but large-scale cardiovascular outcomes trials have not been mandated for older agents, including metformin and sulfonylureas. Observational studies and randomized controlled trials comparing second-generation sulfonylureas against various anti-diabetes agents suggest the possibility of an increased risk for cardiovascular events relative to metformin, which might be secondary to potential cardioprotection with metformin [15]. However, dedicated cardiovascular outcomes trials comparing mostly glimepiride either with pioglitazone or the DPP-4 inhibitor linagliptin did not identify a detrimental effect [16, 17].

Meglitinides

Meglitinides (or glinides) including nateglinide and repaglinide are secretagogues that have a similar mechanism of action to sulfonylureas, although they act via different pancreatic β -cell receptors. They have a rapid onset but short duration of action, thereby controlling post-prandial glucose excursions. These agents need frequent dosing and might be considered in people with erratic meal schedules. Meglitinides have a similar risk for weight gain as sulfonylureas, but possibly a lower risk for hypoglycaemia. Repaglinide is principally metabolized by the liver and can be used

safely in people with mild to moderate renal impairment, although meglitinides should be titrated slowly based on blood glucose levels to minimize the risk of hypoglycaemia [18].

Pioglitazone

Pioglitazone belongs to the thiazolidinediones class, also known as glitazones, which act by activating peroxisome proliferator-activated receptors (PPAR), especially PPAR- γ [19]. These nuclear receptors are expressed predominantly in adipocytes and skeletal muscles and regulate the transcription of specific genes involved in glucose and lipid metabolism. As a result of PPAR- γ activation, cells become more dependent on the oxidation of glucose to yield energy for cellular processes. Pioglitazone has a delayed onset of action, but provides durable reduction in HbA_{1c} and could offer an advantage in certain clinical settings, such as individuals with severe insulin resistance or non-alcoholic steatohepatitis (NASH) [20]. It does not cause hypoglycaemia, but is associated with weight gain as well as fluid retention due to increased sodium reabsorption in the collecting tubules, especially if used concomitantly with insulin [20]. Consequently, the drug may precipitate or worsen heart failure. In addition, pioglitazone use has been linked to an increased risk of bladder cancer and fractures [21, 22]. Finally, pioglitazone may decrease the incidence of cardiovascular events [23–25].

α -Glucosidase inhibitors

α -Glucosidase inhibitors (acarbose, miglitol, voglibose) inhibit the absorption of carbohydrates from the small intestine. They modestly decrease HbA_{1c} [26], but can be useful for reducing post-prandial hyperglycaemia [27]. Since α -glucosidase inhibitors prevent the degradation of complex carbohydrates into glucose, some carbohydrates will remain in the intestine and be delivered to the colon, causing gastrointestinal side effects such as flatulence and diarrhoea. As such, α -glucosidase inhibitors are contraindicated in individuals who have chronic intestinal diseases and in those who have conditions that may deteriorate as a result of increased gas formation in the intestine [27]. Moreover, hypoglycaemia in people treated with these agents can only be effectively improved with the ingestion of glucose. Acarbose is the most commonly used drug of this class, and also the most widely studied. In particular, in the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose significantly increased reversion of impaired glucose tolerance (IGT) to normal glucose tolerance and was associated with a 49% relative risk reduction in the development of cardiovascular events [28, 29]. The Acarbose Cardiovascular Evaluation (ACE) trial, however, which randomized 6522 people with coronary heart disease and IGT to acarbose or placebo and had a follow-up of a median of five years, showed no reduction in the risk of major cardiovascular events with acarbose, although progression to diabetes was reduced [30].

Dipeptidyl-peptidase 4 inhibitors

DPP-4 inhibitors, also referred to as gliptins, are a class of oral anti-diabetes agents that target the enzyme DPP-4, which deactivates endogenous incretins including GIP and GLP-1. Incretins are gut-derived hormones that stimulate glucose-dependent insulin release from the pancreatic islets while suppressing glucagon secretion, and are responsible for the incretin effect, defined as an enhanced insulin secretion following oral glucose administration compared with an isoglycaemic intravenous challenge [31]. In people with type 2 diabetes the incretin effect is substantially reduced or even lost.

DPP-4 inhibitors have a modest effect on lowering blood glucose and a neutral effect on body weight, but carry a minimal risk for hypoglycaemia in the absence of therapies that may otherwise cause hypoglycaemia [6, 32]. They can be used as add-on therapy to metformin or as monotherapy in people with type 2 diabetes for whom metformin is not well tolerated or is contraindicated. Licensed DPP-4 inhibitors across Europe and the USA include alogliptin, linagliptin, saxagliptin, and sitagliptin. Vildagliptin is licensed in Europe but has not received marketing authorization by the US Food and Drug Administration (FDA). The dose of DPP-4 inhibitors should be adjusted based on renal function, with the exception of linagliptin, which is primarily eliminated via the enterohepatic system and can therefore be used in people with end-stage kidney disease.

DPP-4 inhibitors were historically the first anti-diabetes agents evaluated in the context of dedicated cardiovascular outcomes imposed by drug regulators [14]. These trials recruited people at high cardiovascular risk and showed that DPP-4 inhibitors do not increase the risk for major cardiovascular events, including non-fatal myocardial infarction, stroke, and cardiovascular death [33–37]. Nevertheless, an increased risk of hospitalization from worsening heart failure was observed following treatment with saxagliptin.

DPP-4 inhibitors are generally well tolerated. An increased risk of pancreatic adverse events including acute pancreatitis and pancreatic cancer was initially postulated among people treated with incretin mimetics, based primarily on data from post-marketing surveillance systems and animal studies, which suggested higher rates of pancreatic intraepithelial neoplasia with incretin therapies. However, these safety signals have been subsequently alleviated [38]. A potential association of DPP-4 inhibitors with respiratory and urinary tract infections has also been reported. The association of DPP-4 inhibitors with infections has been largely refuted, although it remains questionable whether cases of nasopharyngitis are more common with sitagliptin [39]. Other adverse effects with DPP-4 inhibitors include elevated liver enzymes, skin lesions, inflammatory bowel disease, and joint pain [40]. The favourable safety profile of DPP-4 inhibitors taken together with their modest effect on glycaemia suggests that these agents might be an attractive treatment option for frail individuals in whom intensive glycaemic management and ensuing harms should be avoided.

Glucagon-like peptide 1 receptor agonists

GLP-1 is an incretin produced by the enteroendocrine L cells that enhances peripheral insulin action, slows gastric emptying, and inhibits glucagon secretion. Endogenous GLP-1 has a short half-life and is rapidly deactivated by DPP-4. As such, pharmaceutical efforts have led to the development of synthetic, degradation-resistant GLP-1RAs with favourable pharmacokinetic properties. The first licensed GLP-1RA was exenatide, a synthetic exendin-4 that was discovered in lizard saliva [31]. Licensed GLP-1RAs also include liraglutide and lixisenatide, which are administered once daily by subcutaneous injection, as well as dulaglutide, exenatide extended release, and semaglutide, which are administered once weekly. An oral formulation of semaglutide administered once daily has also received marketing authorization.

GLP-1RAs are effective in improving glycaemic levels, although intraclass variations are noted. Subcutaneous semaglutide is probably the most potent agent in terms of HbA_{1c} lowering, whereas shorter-acting agents such as lixisenatide exhibit less pronounced glycaemic benefits [26]. Because the effects of GLP-1RAs on insulin

secretion are glucose dependent, while the counter-regulatory release of glucagon in response to low blood glucose is fully preserved, the risk of hypoglycaemia is minimal. However, dose adjustments of other anti-diabetes medications known to cause hypoglycaemia, such as insulin, sulfonylureas, or meglitinides, might be necessary on initiation of GLP-1RAs. Weight loss is a further advantage of therapy with GLP-1RAs. Besides slowing gastric emptying, thereby inducing nausea and vomiting as side effects, it has been proposed that GLP-1RAs promote satiety by directly acting on appetite centres in the hypothalamus. Of note is that liraglutide 3.0 mg daily and semaglutide 2.4 mg once weekly have received marketing authorization for weight management as an adjunct to a reduced-calorie diet and increased physical activity for adults with obesity (body mass index [BMI] $\geq 30 \text{ kg/m}^2$) or overweight (BMI $\geq 27 \text{ kg/m}^2$) with at least one comorbidity irrespective of the presence of type 2 diabetes.

Cardiovascular outcomes trials have shown that dulaglutide, liraglutide, and subcutaneous semaglutide reduce the composite cardiovascular endpoint of non-fatal myocardial infarction, stroke, and cardiovascular death [41–43]. Oral semaglutide reduced cardiovascular death [44], whereas exenatide extended release and lixisenatide had a neutral effect on cardiovascular endpoints [45, 46]. Moreover, dulaglutide and subcutaneous semaglutide decreased incidence of stroke, while extended-release exenatide, liraglutide, and oral semaglutide reduced all-cause mortality [26]. The cardiovascular benefits of GLP-1RAs cannot be attributed to improved glycaemic levels alone and might be related to effects on other important risk factors such as body weight, blood pressure, and cholesterol profile [6]. Emerging evidence suggests that these drugs might independently attenuate the progression of atherosclerosis. Based on the aforementioned findings, GLP-1RAs are now recommended in people with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors [1]. This recommendation is not contingent on HbA_{1c}, in recognition of the glucose-independent cardiovascular benefits of these agents [1, 2]. These recommendations are also reflected in the revised labelling of dulaglutide, liraglutide, and subcutaneous semaglutide, for which the indication has been expanded beyond glycaemic management to include the reduction of major cardiovascular events.

GLP-1RAs are generally effective and safe in people with declining kidney function. Dulaglutide, liraglutide, and semaglutide can be used without dose adjustments, even in severe renal impairment for which treatment options beyond insulin therapy are limited. Based on data from cardiovascular outcomes trials, GLP-1RAs ameliorate the progression of albuminuria, although no long-term benefit was observed with respect to decline in eGFR [47].

The main side effects of therapy with GLP-1RAs are nausea and to some extent vomiting and diarrhoea, which are related to slowing of gastric emptying. These symptoms are dose dependent and usually wane during the course of treatment. Slow dose escalation to minimize these side effects is suggested. GLP-1RAs should be avoided in people with gastroparesis. Local site reactions appear more common with GLP-1RAs compared with insulin injections. Similar to DPP-4 inhibitors, early concerns about an increased risk of acute pancreatitis or pancreatic cancer have largely abated [38]. Animal studies have also suggested a potential association of certain GLP-1RAs with thyroid C-cell neoplasms and as a precaution these agents should be avoided in people with a history of medullary cancer or multiple endocrine neoplasia 2. GLP-1RAs could possibly increase risk for gallbladder adverse events including acute cholecystitis [42], although it remains unclear whether these side effects are caused by

rapid weight loss or other underlying mechanisms. Finally, an increased incidence of diabetic retinopathy complications was observed with subcutaneous semaglutide, but it is unclear whether this effect was mediated by a rapid decline of HbA_{1c} [43]. Therefore, frequent retinal screening to detect progression of retinopathy might be prudent for individuals treated with semaglutide.

Sodium–glucose cotransporter 2 inhibitors

SGLT-2 is expressed in the proximal convoluted tubule and is responsible for the reabsorption of ~90% of the filtered glucose load. SGLT-2 inhibitors, also called gliflozins, are a recent addition to the therapeutic armamentarium for type 2 diabetes. They lead to increased urinary glucose excretion, thereby lowering plasma glucose levels. Because of this insulin-independent mode of action, SGLT-2 inhibitors do not increase the risk of hypoglycaemia. Nevertheless, the glycaemic efficacy of SGLT-2 inhibitors is relatively modest and limited by any decline in renal function. Other benefits include weight loss and modest blood pressure reduction as a result of osmotic diuresis [48]. Currently, four SGLT-2 inhibitors have been approved by regulatory authorities in Europe and the USA, namely canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

The SGLT-2 inhibitor cardiovascular outcomes trials have changed the landscape in the management of type 2 diabetes [49–52]. Empagliflozin and canagliflozin reduced major cardiovascular events, whereas empagliflozin also showed a benefit for all-cause mortality. The cardiovascular benefits of SGLT-2 inhibitors generally occur early in the course of treatment and are probably multidimensional in nature. The underlying mechanisms could involve glycaemic levels, weight loss, blood pressure reduction, lowering of uric acid levels, or changes in arterial stiffness. All SGLT-2 inhibitors consistently lowered hospitalizations for heart failure, an observation that can partly be explained by natriuresis. Risk reduction of worsening heart failure is a class effect that has been corroborated in people who received empagliflozin or dapagliflozin even in the absence of type 2 diabetes [53–55]. As such, dapagliflozin and empagliflozin are now indicated for chronic heart failure.

SGLT-2 inhibitors also reduce the risk of end-stage kidney disease [56–58]. The FDA has updated the indications for most SGLT-2 inhibitors to reflect cardiorenal protection. The drugs stabilize kidney function and alleviate the progression of albuminuria, possibly through activation of tubuloglomerular feedback, which leads to a reduction of intraglomerular pressure and prevents hyperfiltration. Initiation of SGLT-2 inhibitors is associated with a temporary decrease in eGFR, which stabilizes over time, a pattern that is also observed with renin–angiotensin system blockade. Assessment of renal function is recommended before initiation of SGLT-2 inhibitors and periodically thereafter (at least yearly). Dose adjustments are necessary for canagliflozin and empagliflozin in people with moderate renal impairment (eGFR <60 ml/min/1.73 m²).

The most common adverse effects of therapy with SGLT-2 inhibitors are genital mycotic infections, which are related to glucosuria and include mainly cases of balanoposthitis in men and vulvovaginal candidiasis in women. They are generally of mild to moderate intensity, respond well to standard therapy, and do not tend to reoccur. Urinary tract infections are less common and reports of pyelonephritis, urosepsis, or Fournier's gangrene are extremely rare. A numerical imbalance of bladder cancer cases was also noted in the clinical development programme of dapagliflozin, but early detection after short exposure and potential detection bias due to frequent urinalysis point against causality. Volume depletion-related adverse events including dizziness, orthostatic hypotension,

and syncope may also be precipitated by SGLT-2 inhibitors in older individuals, people with renal impairment, and in cases of concomitant therapy with thiazides or loop diuretics. The risk of acute kidney injury does not appear to be increased. Thrombosis due to haemoconcentration is another theoretical concern. The incidence of fractures was higher among those taking canagliflozin, but was likely related to falls resulting from volume depletion. For canagliflozin an increased risk of amputations was also reported and, as such, consideration may be given to stopping treatment in people who develop events that may precede amputation, such as lower-extremity skin ulcer, infection, osteomyelitis, or gangrene [26, 48]. Finally, people treated with SGLT-2 inhibitors might be prone to the development of diabetic euglycaemic ketoacidosis in the setting of intercurrent illness [59]. In these individuals the absence of marked hyperglycaemia might delay the recognition and treatment of this rare complication. People should be advised to withhold treatment with SGLT-2 inhibitors during acute illness or in the perioperative period, and the drugs should be avoided in people predisposed to diabetic ketoacidosis (e.g. pancreatic insufficiency or alcohol abuse).

Dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonists

Combined GLP-1 and GIP receptor activation has also been examined as a promising therapeutic option, based on the rationale that the two incretins can have synergistic and complementary actions [60]. Tirzepatide is the first dual GIP and GLP-1 receptor agonist that has received marketing approval by the FDA for the treatment of type 2 diabetes. It has greater affinity to the GIP, rather than GLP-1, receptor and is administered subcutaneously once weekly. Meta-analysis has shown that tirzepatide is more efficacious in lowering HbA_{1c} than once-weekly GLP-1RAs (semaglutide and dulaglutide) and basal insulin analogues [61]. Treatment with tirzepatide also induced greater body weight reduction compared with GLP-1RAs, but was associated with an increased incidence of gastrointestinal adverse events, mostly nausea [61]. Limited cardiovascular data, derived mostly from one trial, suggest that tirzepatide does not increase the risk of major cardiovascular events [62].

Insulin

Due to the progressive nature of the disease, many people with type 2 diabetes will eventually require insulin therapy. Insulin might also be the sole therapeutic option for certain populations such as people with advanced kidney disease or cirrhosis. Insulin has theoretically unlimited efficacy with respect to HbA_{1c} lowering that is constrained only by the development of hypoglycaemia. However, insulin therapy is associated with weight gain and requires considerable self-management skills and adequate support, because of the need for more frequent blood glucose monitoring and dose adjustment. People should also receive training in the recognition and management of hypoglycaemic episodes.

Human insulin has largely been replaced by insulin analogues, which are produced by modifications to the amino acid sequence of insulin that alter its pharmacokinetic properties (Chapter 31). The following formulations of insulin are available in the USA or Europe:

- Human insulins:
 - Short-acting regular insulin.
 - Concentrated regular insulin U-500.
 - Intermediate acting neutral protamine Hagedorn (NPH), also called isophane insulin.
 - Premixed combinations of these.

- Basal insulin analogues:
 - Insulin glargine U-100 and biosimilars.
 - Insulin detemir.
 - Ultra-long-acting insulin degludec.
 - Concentrated forms of insulin glargine U-300 and insulin degludec U-200.
- Prandial insulin analogues:
 - Short- and rapid-acting insulins aspart, glulisine, and lispro.
 - Faster-acting insulin aspart.
 - Ultra-rapid lispro.
- Premixed basal/prandial regimens.

Basal insulin is meant to cover the basic metabolic requirements, whereas prandial insulin regulates mealtime glucose excursions. People with type 2 diabetes progressing to insulin therapy usually start with once-daily bedtime administration of basal insulin, although NPH and insulin detemir may also be dosed twice daily. The starting dose of basal insulin is 10 units or 0.1–0.2 units/kg and titration is based on fasting glucose levels. The differences in glycaemic efficacy among basal insulin analogues are likely minimal and of limited clinical significance. Newer agents including insulin degludec and glargin U300 have longer duration of action and lower rates of nocturnal hypoglycaemia, whereas insulin detemir might have a more favourable profile with respect to weight gain [63]. Concentrated preparations such as degludec U-200 and glargin U-300 allow injection of a reduced volume and might be more convenient for people with higher requirements because of insulin resistance. Basal insulin analogues are considerably more costly than NPH, although cheaper biosimilars have become available. Finally, data from cardiovascular safety trials are reassuring for insulin glargin and degludec [64,65].

Once basal insulin dose has exceeded 0.5 units/kg or if the fasting glucose target is met but the desired HbA_{1c} target has not been achieved, insulin therapy should be intensified by adding doses of prandial to basal insulin. A starting dose of 4 units or 0.1 units/kg of prandial insulin (or 10% of the amount of basal insulin) is initially administered at the largest meal of the day. Dose can be gradually increased by 1–2 units or 10–15% to meet post-prandial glucose targets. If the HbA_{1c} is still above target, this basal-plus scheme can then be advanced to a basal-bolus regimen with the stepwise addition of mealtime insulin injections. During this process decreasing doses of basal insulin might be required to avoid hypoglycaemia. Regular human insulin should be administered ~30 minutes before start of the meal to match post-prandial glucose excursions. The rapid-acting insulin analogues aspart, glulisine, and lispro have an onset of action within 15 minutes of injection and quicker return to baseline concentrations. Finally, the newly approved faster-acting insulin aspart and ultra-rapid lispro have accelerated absorption and even earlier onset of action, but also earlier offset of exposure. In this regard, they resemble more closely physiological mealtime insulin secretion and could therefore offer better post-prandial glucose regulation while minimizing the risk of post-prandial hypoglycaemia [66].

Alternatively, for individuals using basal insulin for whom prandial coverage is required, the regimen can be converted to two doses of premixed basal/prandial insulin by splitting the total insulin dose. Premixed regimens might be more practical for people with frailty for whom tight glycaemic levels are not desirable, whereas basal-bolus regimens allow greater flexibility for people with irregular eating habits [3].

Clinicians and people with diabetes sometimes are reluctant to start insulin, which may delay timely intensification of therapy

(therapeutic inertia). People with diabetes might find it difficult to accept insulin therapy because of fear of injections, life restrictions, or risk of hypoglycaemia. Moreover, starting insulin therapy could be felt as a personal failure in the management of the disease. Healthcare providers should address these misconceptions during the clinical encounter and avoid using insulin therapy as a threat to motivate people [67]. Notably, modern, prefilled pen devices have appreciably simplified insulin administration.

Rationale for treatment selection

Glycaemic management

Management of hyperglycaemia has traditionally guided the initiation and escalation of glucose-lowering therapy in people with type 2 diabetes. Indeed, landmark trials have corroborated the beneficial effects of tight glycaemic levels, mainly for the reduction of microvascular complications. In contrast, the impact of intensive glucose lowering on incident macrovascular events is less certain [8,68,69]. Measurement of HbA_{1c} remains the primary tool for assessment of glycaemia. The test reflects average glucose levels over ~3 months and is strongly predictive of diabetes-related complications. Observational studies suggest that each 1% (11 mmol/mol) reduction in HbA_{1c} is associated with risk reductions of 37% for microvascular complications, 14% for myocardial infarction, and 21% for diabetes-related mortality [70]. Nevertheless, as HbA_{1c} decreases, a U-shaped relationship with all-cause mortality and cardiac events is observed [71], especially in older individuals and people with frailty or established cardiovascular disease, for whom hypoglycaemia is a limiting factor for intensifying treatment. The HbA_{1c} target for most people with type 2 diabetes is <7% (53 mmol/mol), but it may be lower for well-motivated individuals, while higher HbA_{1c} goals such as <8% (64 mmol/mol) might be more appropriate for people with limited life expectancy [72]. If prevention of hypoglycaemia is a therapeutic priority, the use of sulfonylureas or insulin is discouraged. The vast majority of studies for medications for type 2 diabetes have utilized HbA_{1c} as the primary outcome measure for glycaemic efficacy. Anti-diabetes drugs have variable glucose-lowering effects, with insulin regimens and specific GLP-1RAs producing the greatest HbA_{1c} reduction [26]. The newly approved dual GIP/GLP-1 receptor agonist tirzepatide offers an even more pronounced HbA_{1c} reduction, as high as 2% (22 mmol/mol) [61].

The standard approach to glycaemic management has been to initiate metformin monotherapy followed by the stepwise addition of anti-diabetes agents until the individualized HbA_{1c} target is reached. The Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes (VERIFY) trial showed that upfront combination therapy with metformin plus a DPP-4 inhibitor improves the durability of the glycaemic effect compared with sequential addition of anti-diabetes drugs [73]. Combination therapy can target multiple physiological derangements simultaneously and could also decrease medication burden and improve medication taking. GLP-1RAs are considered first-line injectable therapy in type 2 diabetes and should be prioritized over basal insulin, because they have comparable glycaemic efficacy, induce weight loss, and confer a low risk of hypoglycaemia [74]. For people with catabolic symptoms including weight loss, hypertriglyceridaemia, and ketosis or severe hyperglycaemia (i.e. HbA_{1c}>10% [86 mmol/mol] or blood glucose levels ≥300 mg/dl [16.7 mmol/l]), introduction of insulin should be considered. After resolution of glucose

toxicity, the therapeutic regimen may be simplified [1]. Fixed ratio combinations of GLP-1RAs with basal insulin allowing co-administration through a single injection are also commercially available. These co-formulations provide further improvements in glycaemia while balancing out weight gain and risk of hypoglycaemia [75].

The HbA_{1c} test has limitations, as it does not capture hypoglycaemic episodes or glucose variability and results might be unreliable under circumstances that alter red blood cell turnover (anaemia, haemoglobinopathies, or end-stage renal disease with erythropoietin therapy). In these situations, capillary glucose measurements may supplement treatment decisions. Beyond people receiving insulin therapy for whom frequent measurements are required for dose titration, self-monitoring of blood glucose has limited clinical value in terms of glycaemic management and is associated with higher treatment cost without evidently improving quality of life [76]. In recent years, continuous glucose monitoring (CGM) has been fully incorporated into the management of type 1 diabetes, although evidence supporting its use in type 2 diabetes remains limited. Time in range (TIR) and the glucose management indicator (GMI) derived from CGM are useful metrics of glucose levels that correlate well with HbA_{1c}. The ambulatory glucose profile (AGP), which includes time below and above target range, can be used to develop a more personalized treatment plan, especially for people receiving insulin therapy [77]. Remote access to CGM data will also potentially transform healthcare encounters. In the near future, it is expected that more trials in type 2 diabetes will evaluate the effect of anti-diabetes agents on TIR instead of HbA_{1c} as the primary glycaemic endpoint.

Management for prevention of complications

Evidence from cardiovascular outcomes trials

In the past, regulatory bodies approved new medications for diabetes solely on the basis of their glucose-lowering potential, even though it was recognized that regulation of hyperglycaemia is a surrogate for reducing the microvascular, and to a lesser extent the macrovascular, complications of diabetes. Evidence on the potential benefit of glucose-lowering drugs on specific cardiovascular outcomes first became available for metformin in a substudy of the UKPDS; UKPDS 34 was a randomized controlled trial that assessed whether intensive treatment with metformin reduced the risk of diabetes-related complications compared to conventional treatment policy (diet alone) in 753 individuals with overweight and newly diagnosed type 2 diabetes [7]. After a median follow-up of 10.7 years, participants allocated to metformin had risk reductions of 32% for any diabetes-related endpoint (a composite of mortality and vascular outcomes) and 36% for all-cause mortality [7].

Following a similar rationale to that of the UKPDS, and also based on trial data suggesting a beneficial effect of thiazolidinediones on multiple cardiovascular risk factors, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) studies evaluated the cardiovascular effects of pioglitazone and rosiglitazone, respectively [23, 78]. The PROactive study (5238 participants) found that, over an average period of 34.5 months, pioglitazone reduced the composite of all-cause mortality, or myocardial infarction, or stroke versus placebo (hazard ratio [HR] 0.84; 95% confidence interval [CI] 0.72 to 0.98). However, the effect of pioglitazone on the primary outcome (composite of all-cause mortality, non-fatal myocardial

infarction including silent myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle) was not significant [23]. The RECORD trial (4447 participants) found that rosiglitazone in combination with metformin or sulfonylurea was non-inferior to metformin and sulfonylurea dual therapy in terms of the composite outcome of cardiovascular death, myocardial infarction, or stroke (three-component major adverse cardiovascular events, MACE) [78]. Notably, in both trials thiazolidinediones considerably increased the risk of heart failure compared to control.

In 2008 the FDA, and later the European Medicines Agency, required that a dedicated cardiovascular outcomes trial be conducted as a prerequisite for the regulatory approval of new anti-diabetes drugs [14]. This change in policy was probably influenced by an earlier FDA decision to reject the approval of muraglitazar following the publication of a relevant meta-analysis of cardiovascular outcomes [79], but was mainly triggered by the findings of a meta-analysis for rosiglitazone [4]. This meta-analysis suggested that rosiglitazone, which was widely used in the USA and Europe at that time, increased the risk of myocardial infarction compared to placebo and other anti-diabetes regimens [4]. Subsequently, several cardiovascular outcomes trials have been completed, mainly for DPP-4 inhibitors, GLP-1RAs, and SGLT-2 inhibitors.

To achieve feasible and adequate power, cardiovascular outcomes trials typically have assessed the composite endpoint of MACE as primary outcome and have recruited people with type 2 diabetes and increased cardiovascular risk, defined as history of atherosclerotic disease or presence of multiple cardiovascular risk factors. The main findings of cardiovascular outcomes trials in type 2 diabetes for anti-diabetes drugs approved in the USA or Europe are presented in Table 37.2. In summary, trials of DPP-4 inhibitors have demonstrated a neutral effect on cardiovascular outcomes. Similarly, in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, insulin glargine had a neutral effect on cardiovascular outcomes [64], while in the Trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events (DEVOTE), insulin degludec was non-inferior to insulin glargine with respect to major cardiovascular events [65]. Notable favourable effects on MACE and mortality outcomes were evident in cardiovascular outcomes trials of specific GLP-1RAs and SGLT-2 inhibitors. Moreover, both drug classes have demonstrated benefits in kidney outcomes, while SGLT-2 inhibitors also improved heart failure endpoints. Consequently, the effect of specific SGLT-2 inhibitors on these outcomes has also been assessed in dedicated trials focusing on people with chronic kidney disease or heart failure irrespective of history of diabetes. As such, current guidance in the pharmacological management of type 2 diabetes advocates that choice of therapeutic options should be primarily based on atherosclerotic cardiovascular risk profile and presence of chronic kidney disease, heart failure, or obesity-related morbidities [1, 80].

Among cardiovascular outcomes trials with GLP-1RAs, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was the first to be reported. Over a median follow-up of 24 months, ELIXA compared once-daily lixisenatide (at a maximum daily dose of 20 µg) with placebo in 6068 people with type 2 diabetes and a recent (within 180 days) acute coronary event [46]. Lixisenatide was non-inferior, but not superior, to placebo for the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina (four-component MACE), with an HR of 1.02 (95% CI 0.89 to 1.17) [46].

Table 37.2 Findings from major cardiovascular outcome trials for pharmaceutical agents approved for the treatment of type 2 diabetes in Europe or the USA.

Anti-diabetes agent	Trial ^a	Major adverse cardiovascular events ^b	Hospitalization for heart failure	All-cause mortality
Pioglitazone	PROACTIVE [23]	0.82 (0.70 to 0.97)	1.41 (1.10 to 1.80)	0.96 (0.78 to 1.18)
	TOSCA.IT [16]	0.96 (0.74 to 1.26)	1.57 (0.76 to 3.24)	1.08 (0.71 to 1.65)
DPP-4 inhibitors				
Alogliptin	EXAMINE [33, 34]	0.96 (≤ 1.16) ^c	1.07 (0.79 to 1.46)	0.88 (0.71 to 1.09)
Linagliptin	CARMELINA [35]	1.02 (0.89 to 1.17)	0.90 (0.74 to 1.08)	0.98 (0.84 to 1.13)
	CAROLINA [17]	0.98 (0.84 to 1.14)	1.00 (0.84 to 1.20)	0.91 (0.78 to 1.06)
Saxagliptin	SAVOR-TIMI 53 [36]	1.00 (0.89 to 1.12)	1.27 (1.07 to 1.51)	1.11 (0.96 to 1.27)
Sitagliptin	TECOS [37]	0.99 (0.89 to 1.10)	1.00 (0.83 to 1.20)	1.01 (0.90 to 1.14)
GLP-1 receptor agonists				
Dulaglutide	REWIND [41]	0.88 (0.79 to 0.99)	0.93 (0.77 to 1.12)	0.90 (0.90 to 1.01)
Exenatide LAR	EXSCEL [45]	0.91 (0.89 to 1.00)	0.94 (0.78 to 1.13)	0.86 (0.77 to 0.97)
Lixisenatide	ELIXA [46]	1.02 (0.89 to 1.17)	0.96 (0.75 to 1.23)	0.94 (0.78 to 1.13)
Liraglutide	LEADER [42]	0.87 (0.78 to 0.97)	0.87 (0.73 to 1.05)	0.85 (0.74 to 0.97)
Subcutaneous semaglutide	SUSTAIN-6 [43]	0.74 (0.58 to 0.95)	1.11 (0.77 to 1.61)	1.05 (0.74 to 1.50)
Oral semaglutide	PIONEER 6 [44]	0.79 (0.57 to 1.11)	0.86 (0.48 to 1.55)	0.51 (0.31 to 0.84)
SGLT-2 inhibitors				
Canagliflozin	CANVAS PROGRAM [49]	0.86 (0.75 to 0.97)	0.67 (0.52 to 0.87)	0.87 (0.74 to 1.01)
Dapagliflozin	DECLARE-TIMI 58 [51]	0.93 (0.84 to 1.03)	0.73 (0.61 to 0.88)	0.93 (0.82 to 1.04)
Empagliflozin	EMPA-REG OUTCOME [52]	0.86 (0.74 to 0.99)	0.65 (0.50 to 0.85)	0.68 (0.57 to 0.82)
Ertugliflozin	VERTIS CV [50]	0.97 (0.85 to 1.11)	0.70 (0.54 to 0.90)	0.93 (0.80 to 1.08)
Basal insulin analogues				
Degludec	DEVOTE [65]	0.91 (0.78 to 1.06)	0.88 (0.72 to 1.08)	0.91 (0.76 to 1.11)
Glargine U-100	ORIGIN [64]	1.02 (0.94 to 1.11)	0.90 (0.77 to 1.05)	0.98 (0.90 to 1.08)

Results are expressed as hazard ratios and 95% confidence intervals. Green indicates a favourable effect, yellow indicates a neutral effect, and red indicates a detrimental effect. DPP-4, dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide 1; LAR, long-acting release; SGLT-2, sodium-glucose cotransporter 2.

^a Comparisons against placebo except for the TOSCA-IT trial, in which pioglitazone was compared with sulfonylureas; the CAROLINA trial, in which linagliptin was compared with glimepiride; and the DEVOTE trial, in which insulin degludec was compared with glargine U-100.

^b Composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (including also urgent coronary revascularization in the TOSCA-IT trial for pioglitazone and hospitalization for unstable angina in the ELIXA trial for lixisenatide).

^c Upper boundary of the one-side repeated confidence interval.

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9340 participants with type 2 diabetes were randomized to either once-daily 1.8 mg (or the maximum tolerated dose) liraglutide or placebo in addition to their standard care and were followed over a median of 3.8 years [42]. All participants were at increased cardiovascular risk, defined as either an age of more than 50 years with a history of a cardiovascular condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease, or heart failure) or an age of more than 60 years with at least one cardiovascular risk factor (including microalbuminuria, hypertension, left ventricular dysfunction, or an ankle-brachial index of less than 0.9). Most participants (81.3%) had established cardiovascular disease, chronic kidney disease of stage 3 or higher, or both. Treatment with liraglutide reduced the incidence of the primary outcome of first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (three-component MACE) with an HR of 0.87 (95% CI

0.78 to 0.97). This effect was mainly driven by a reduction in cardiovascular mortality (HR 0.78; 95% CI 0.66 to 0.93), whereas the effects on non-fatal myocardial infarction and on non-fatal stroke did not significantly differ between liraglutide and placebo. Treatment with liraglutide also reduced the incidence of all-cause mortality (HR 0.85; 95% CI 0.74 to 0.97) and of the composite kidney outcome (HR 0.78; 95% CI 0.67 to 0.92), the latter being primarily driven by the effect on new-onset macroalbuminuria [42, 81].

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) assessed the cardiovascular effects of once-weekly exenatide versus placebo in 14 752 people with type 2 diabetes over a median of 3.2 years [45]. As per the trial design, ~70% of enrolled participants had a previous cardiovascular event prior to randomization, defined as a history of major clinical manifestation of coronary artery disease, ischaemic cerebrovascular disease, or atherosclerotic peripheral artery disease. The primary outcome of three-component MACE occurred in fewer participants in the exenatide arm

compared with the placebo arm, yielding a marginally non-significant HR of 0.91 (95% CI 0.83 to 1.00). Incidence of all-cause mortality was lower in the exenatide arm (HR 0.86; 95% CI 0.77 to 0.97); however, this effect was not deemed significant on the basis of the hierarchical testing plan that was implemented [45].

The cardiovascular profile of once-weekly subcutaneous semaglutide was evaluated in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), in which 3297 participants were randomized in a 1:1:1:1 ratio to semaglutide 0.5 mg, or 1 mg, or two volume-matched placebo arms [43]. The eligibility criteria regarding participants' cardiovascular risk profile at baseline were identical to those in the LEADER trial [42], and the percentage of enrolled individuals with established vascular disease (83%) was also similar to the LEADER trial. SUSTAIN-6 was not event driven but had a predefined 104-week treatment period. Both doses of semaglutide were superior to placebo in reducing the three-component MACE (HR 0.74; 95% CI 0.58 to 0.95) and the outcome of new or worsening nephropathy comprising macroalbuminuria, doubling of serum creatinine, or the need for renal-replacement therapy (HR 0.64; 95% CI 0.46 to 0.88). However, diabetic retinopathy complications were more frequent with semaglutide in comparison to placebo (HR 1.76; 95% CI 1.11 to 2.78) [43].

The once-daily oral formulation of semaglutide was assessed in the Peptide Innovation for Early Diabetes Treatment (PIONEER 6) trial [44]. Although it was event driven, PIONEER 6 was designed to assess the non-inferiority, and not the superiority, of oral semaglutide versus placebo. It followed 3183 participants over a median of 15.9 months, 2695 (84.7%) of whom had established cardiovascular disease or chronic kidney disease, while the remainder had cardiovascular risk factors only. The primary outcome of MACE occurred in 3.8% of participants receiving semaglutide (at a target daily dose of 14 mg) and in 4.8% of participants allocated to placebo, thus confirming the non-inferiority of oral semaglutide compared with placebo. Treatment with oral semaglutide was also associated with reduced all-cause mortality (HR 0.51; 95% CI 0.31 to 0.84) and cardiovascular mortality (HR 0.49; 95% CI 0.27 to 0.92); however, the trial was neither designed nor adequately powered to assess the superiority of semaglutide over placebo on any of these outcomes [44].

The effect of once-weekly dulaglutide on cardiovascular endpoints was assessed in the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial [41]. As opposed to the other cardiovascular outcomes trials with GLP-1RAs, only 31.5% of the 9091 participants in the REWIND trial had previous cardiovascular disease. The remainder were either older than 60 years with at least two risk factors (tobacco use, dyslipidaemia, hypertension, or obesity) or older than 55 years with myocardial ischaemia, coronary, carotid, or lower-extremity stenosis exceeding 50%, left ventricular hypertrophy, eGFR <60 ml/min/1.73 m², or albuminuria. During a median follow-up of 5.4 years, MACE occurred in fewer participants assigned to dulaglutide than those assigned to placebo (HR 0.88; 95% CI 0.79 to 0.99). In terms of individual MACE components, dulaglutide versus placebo significantly reduced non-fatal stroke (HR 0.76; 95% CI 0.61 to 0.95), but not non-fatal myocardial infarction or cardiovascular death [41]. Moreover, dulaglutide was superior to placebo in reducing a composite kidney outcome comprising the development of macroalbuminuria, a sustained 30% or greater decline in eGFR, or renal replacement therapy (HR 0.85; 95% CI 0.77 to 0.93) [41]. As was

also the case with the LEADER trial, this effect was mainly driven by the favourable effect on new-onset macroalbuminuria.

Once-weekly albiglutide was compared with placebo in the Harmony Outcomes trial, which included 9463 people with type 2 diabetes and established coronary, cardiovascular, or peripheral artery disease [82]. During a median follow-up of 1.6 years, albiglutide was superior to placebo in reducing MACE (HR 0.78; 95% CI 0.68 to 0.90). Interestingly, albiglutide was the only GLP-1RA that achieved statistical significance versus placebo in terms of reducing the incidence of myocardial infarction (HR 0.75; 95% CI 0.61 to 0.90) [82]. Albiglutide has been withdrawn from the market by the manufacturer in both the USA and Europe for economic reasons.

More recently, the cardiovascular and renal effects of once-weekly efpeglenatide were assessed in the Effect of efpeglenatide on cardiovascular outcomes (AMPLITUDE-O) trial [83]. Of the 4076 participants, ~90% had a history of coronary artery disease, stroke, or peripheral artery disease, while the remaining participants had kidney disease and at least one cardiovascular risk factor. Over a median follow-up of 1.81 years, compared to placebo, efpeglenatide (at a maintenance dose of 4 mg or 6 mg per week) reduced MACE (HR 0.73; 95% CI 0.58 to 0.92) and the composite kidney outcome of macroalbuminuria plus a decrease in kidney function (HR 0.68; 95% CI 0.57 to 0.79). An interesting finding of a subgroup analysis in AMPLITUDE-O was that the beneficial cardiovascular effects of efpeglenatide did not seem to be affected by the concomitant use of an SGLT-2 inhibitor (15% of trial participants) [83]. Efpeglenatide is not available for clinical use.

The dual GIP/GLP-1 receptor agonist tirzepatide was not associated with an increased incidence of MACE with insulin glargine in the Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4) trial over one year of treatment [84]. However, SURPASS-4 was not designed to assess cardiovascular outcomes; the ongoing SURPASS-CVOT trial (NCT04255433) is expected to elucidate the cardiovascular profile of tirzepatide.

A meta-analysis synthesizing data from eight cardiovascular outcomes trials found that GLP-1RAs as a drug class reduced MACE by 14% (HR 0.86; 95% CI 0.80 to 0.93) in comparison to placebo, corresponding to a number needed to treat (NNT) of 65 (95% CI 45 to 130) for a period of three years [85]. Across trials, the point estimate of each individual trial, albeit not always statistically significant, was consistently in favour of the GLP-1RA arm, except for lixisenatide in the ELIXA trial. It has been speculated that this may be partly attributed to the shorter half-life of lixisenatide (2–3 h) than other GLP-1RAs, suggesting that exposure to lixisenatide in ELIXA might have been lower than optimal in view of its once-daily dosing [85]. When ELIXA was excluded from the meta-analysis, heterogeneity was reduced, leading to the certainty of evidence regarding the overall effect of GLP-1RAs on MACE to be classified as high [85] according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria [86]. In terms of individual MACE components, meta-analysis results suggested that GLP-1RAs, compared with placebo, significantly reduced the risk of cardiovascular mortality, myocardial infarction, and stroke by 13%, 10%, and 17%, respectively. All-cause mortality was also reduced with GLP-1RAs, with an HR of 0.88 (95% CI 0.82 to 0.94) corresponding to an NNT of 114 (95% CI 76 to 228) for a period of three years. Treatment with a GLP-1RA was associated with an 11% lower risk of hospitalization for heart failure and a 21% lower risk of a broad composite kidney outcome [85]. These findings have been corroborated in an additional

meta-analysis [87]; however, their clinical interpretation should take into consideration that, across GLP-1RA trials, details about heart failure were often incomplete and not standardized, while the effect on the composite kidney outcome was primarily driven by the reduction in the macroalbuminuria component (HR 0.74; 95% CI 0.67 to 0.82) [87].

One question of particular clinical relevance is whether the overall cardiovascular benefits of GLP-1RAs are equally applicable both to people with established atherosclerotic disease and to people with cardiovascular risk factors only. In this regard, the majority of participants in individual cardiovascular outcomes trials had established cardiovascular disease (ranging between 70% and 100%), the only exception being the REWIND trial, in which ~70% of participants had a combination of cardiovascular risk factors but not established vascular disease. An earlier meta-analysis of five trials suggested that the overall beneficial effect of GLP-1RAs on MACE was evident solely in individuals with a history of cardiovascular disease, based on the statistically significant value of the test for interaction between subgroups (P for interaction) [88]. However, subsequent meta-analyses incorporating data from all eight trials found no significant interaction between the two subgroups of people with and without established cardiovascular disease in terms of the overall effect estimate on MACE, even though the subgroup estimate was greater in those with known cardiovascular disease [85,89]. Nevertheless, the credibility and clinical interpretation of these meta-analyses of subgroups should not be based solely on the value of a statistical test for interaction between subgroups, but additional aspects should also be taken into consideration [90].

Among cardiovascular outcomes trials with SGLT-2 inhibitors, the Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG OUTCOME) was the first to be reported. EMPA-REG OUTCOME assessed the effects of empagliflozin (at a dose of either 10 mg or 25 mg) on cardiovascular events versus placebo in 7020 adults with type 2 diabetes and established cardiovascular disease (history of myocardial infarction, stroke, single- or multi-vessel coronary artery disease, or occlusive peripheral artery disease) [52]. Over a median follow-up of 3.1 years, participants who received empagliflozin had a lower rate of the primary outcome of three-component MACE (HR 0.86; 95% CI 0.74 to 0.99), cardiovascular mortality (HR 0.62; 95% CI 0.49 to 0.77), and all-cause mortality (HR 0.68; 95% CI 0.57 to 0.82). Treatment with empagliflozin also reduced hospitalization for heart failure by 35% and the composite kidney outcome of incident or worsening nephropathy by 39% [52,56]. This beneficial effect was evident in each individual component of the composite kidney outcome, comprising macroalbuminuria, doubling of serum creatinine, and initiation of renal-replacement therapy [56].

The cardiovascular effects of canagliflozin (100 mg or 300 mg) were examined in 10 142 people with type 2 diabetes in the CANVAS Program, which integrated data from the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R) [49]. CANVAS was designed with the aim of meeting the 2008 FDA cardiovascular safety (non-inferiority) requirements, and as such was insufficient to enable a test of a positive cardiovascular effect (superiority) of canagliflozin over placebo [49]. On this ground, CANVAS-R was undertaken with a similar design to CANVAS to jointly achieve statistical power to detect plausible favourable effects of canagliflozin on cardiovascular and kidney outcomes [91]. Participants' eligibility criteria were identical in both trials, with ~65% of the CANVAS Program population having

a history of cardiovascular disease, and the remaining being 50 years or older with two or more cardiovascular risk factors. During a median follow-up of 126 weeks in the overall CANVAS Program, MACE occurred in fewer participants assigned to canagliflozin than those assigned to placebo, with an HR of 0.86 (95% CI 0.75 to 0.97). In addition, fewer participants in the canagliflozin group were hospitalized for heart failure (HR 0.67; 95% CI 0.52 to 0.87) and had the composite kidney outcome of sustained reduction in eGFR, need for renal-replacement therapy, or renal death (HR 0.60; 95% CI 0.47 to 0.77) [49].

In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, 17 160 people with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease were randomized to either dapagliflozin 10 mg or placebo and were followed for a median of 4.2 years [51]. A notable characteristic differentiating DECLARE-TIMI 58 from other cardiovascular outcomes trials with SGLT-2 inhibitors was that this trial included more than 10 000 individuals (~60% of the trial population) without evident cardiovascular disease but with multiple risk factors. MACE was originally the sole primary outcome, but the study protocol was amended to include the composite of cardiovascular death or hospitalization of heart failure as a second primary outcome. The rate of MACE was similar between dapagliflozin and placebo (HR 0.93; 95% CI 0.84 to 1.03), while dapagliflozin was superior to placebo in reducing the composite of cardiovascular death or hospitalization for heart failure (HR 0.83; 95% CI 0.73 to 0.95). The latter finding, however, was due to the lower rate of hospitalization for heart failure in the dapagliflozin group (HR 0.73; 95% CI 0.61 to 0.88) and not due to an effect on cardiovascular mortality. Dapagliflozin significantly reduced by 24% the incidence of the composite kidney outcome of more than 40% reduction in eGFR, new end-stage renal disease, or death from renal or cardiovascular causes [51].

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) examined the cardiovascular effects of ertugliflozin (5 mg or 15 mg) compared to placebo in 8246 people with type 2 diabetes and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral artery systems [50]. During a median follow-up of 3.0 years, ertugliflozin was non-inferior, but not superior, to placebo in terms of MACE (HR 0.97; 95% CI 0.85 to 1.11), its individual components, and the composite kidney outcome of death from renal causes, renal replacement therapy, or doubling of serum creatinine. Consistent with other SGLT-2 inhibitors, ertugliflozin reduced the incidence of hospitalization for heart failure versus placebo with an HR of 0.70 (95% CI 0.54 to 0.90) [50].

Based on the results of individual cardiovascular outcomes trials, all four SGLT-2 inhibitors consistently reduced hospitalization for heart failure, all SGLT-2 inhibitors except ertugliflozin improved kidney outcomes, while empagliflozin and canagliflozin had a beneficial effect on MACE. These findings were synthesized in a meta-analysis that produced pooled estimates for all SGLT-2 inhibitors as a drug class and explored the heterogeneity of outcomes assessed by individual SGLT-2 inhibitors in the overall class [92]. Results of this meta-analysis showed that the predominant beneficial effect of SGLT-2 inhibitors was the reduction in hospitalization for heart failure compared to placebo, with an HR of 0.68 (95% CI 0.61 to 0.76). This estimate was highly consistent with no evidence of statistical heterogeneity across the class, given that a significant effect in favour of the SGLT-2 inhibitor arm was achieved in each individual trial. An overall beneficial effect of SGLT-2 inhibitors

was also shown on MACE (HR 0.90; 95% CI 0.85 to 0.95) and on cardiovascular mortality (HR 0.85; 95% CI 0.78 to 0.93); however, a significant degree of heterogeneity was observed in the analyses for both outcomes, especially cardiovascular mortality, reflecting possible differences between individual SGLT-2 inhibitors in terms of their effects on atherosclerotic events [92]. Some degree of heterogeneity was also present in the analysis for the composite kidney endpoint (HR 0.62; 95% CI 0.56 to 0.70), most likely due to VERTIS-CV trial, as ertugliflozin was the only SGLT-2 inhibitor without a demonstrated benefit on kidney outcomes. Another potential source of heterogeneity could be the fact that there were differences in the components of the composite kidney outcome across trials [92]. In this regard, a meta-analysis focusing on the renal effects of SGLT-2 inhibitors used more consistent definitions across trials with canagliflozin, dapagliflozin, and empagliflozin for clinically important kidney outcomes [93]; based on this meta-analysis, the three SGLT-2 inhibitors improved all kidney outcomes with no evidence of heterogeneity between trials [93].

As for GLP-1RAs, it is clinically relevant to establish whether the observed effects of SGLT-2 inhibitors in people with type 2 diabetes and increased cardiovascular risk are consistent regardless of history of established atherosclerotic disease. Meta-analyses of cardiovascular outcomes trials that assessed the effects of SGLT-2 inhibitors in two subgroups according to the presence of established atherosclerotic cardiovascular disease did not find evidence of a modification effect regarding the overall beneficial effect of SGLT-2 inhibitors versus placebo on MACE, cardiovascular mortality, hospitalization for heart failure, and a composite kidney outcome [92]. However, data for the subgroup of participants without atherosclerotic disease (individuals with multiple risk factors only) were available only for dapagliflozin and canagliflozin [92].

Although long-term head-to-head trials comparing GLP-1RAs with SGLT-2 inhibitors are lacking, indirect comparisons from network meta-analyses found that both classes confer comparable benefits on all-cause mortality, cardiovascular mortality, and MACE [26, 94, 95]. Moreover, GLP-1RAs might be more effective in preventing stroke, whereas SGLT-2 inhibitors reduce hospitalizations for heart failure [26, 94, 95]. Some intraclass differences between agents might also exist, but it is unclear whether these comparative estimates are clinically meaningful [26]. A complementary source of comparative effectiveness evidence is large registry-based cohort studies utilizing real-world data of new users of GLP-1RAs or SGLT-2 inhibitors. In particular, five cohort studies have corroborated the superiority of SGLT-2 inhibitors over GLP-1RAs in reducing heart failure hospitalizations [96–100], whereas two of these studies also found that SGLT-2 inhibitors were more effective in reducing a composite cardiovascular endpoint [96, 97]. Interestingly, emerging data suggest that, due to their different mechanisms of action, both drug classes may be considered as combination therapy to enhance their favourable effect on metabolic variables and possibly to provide complementary cardiovascular benefits [1, 101, 102].

Evidence from kidney outcomes trials

Secondary and exploratory analyses of type 2 diabetes cardiovascular outcomes trials suggested that SGLT-2 inhibitors can improve kidney outcomes; however, none of these trials was designed to assess kidney outcomes specifically in people with chronic kidney disease [49–52]. In this regard, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

(CREDENCE) trial was the first large-scale randomized trial to assess the effects of canagliflozin on kidney outcomes in people with type 2 diabetes and albuminuric chronic kidney disease, the latter defined as an eGFR of 30 to <90 ml/min/1.73 m² and a urinary albumin-to-creatinine ratio of >300 [57]. The 4401 participants were randomized to either canagliflozin 100 mg or placebo, and were followed over a median period of 2.6 years. Stable treatment (for at least four weeks before randomization) with an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker was a prerequisite for all eligible participants. The primary composite outcome of end-stage kidney disease, or doubling of serum creatinine level, or death from renal or cardiovascular causes occurred in significantly fewer participants receiving canagliflozin with an HR of 0.70 (95% CI 0.59 to 0.82). Additionally, treatment with canagliflozin reduced the risk for MACE by 20% and for the composite of cardiovascular death or hospitalization for heart failure by 31% [57].

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial was based on the same rationale, aiming to assess the kidney and cardiovascular effects of dapagliflozin in a dedicated chronic kidney disease population [58]. However, in contrast to CREDENCE, the primary hypothesis in DAPA-CKD was that the kidney effects of dapagliflozin occur in people with chronic kidney disease irrespective of the presence of type 2 diabetes. As such, DAPA-CKD included a considerable number of participants without type 2 diabetes at baseline (~32.5% of the 4304 participants). Moreover, in its eligibility criteria, DAPA-CKD used lower thresholds than CREDENCE both for eGFR (25–75 ml/min/1.73 m²) and for albuminuria (urinary albumin-to-creatinine ratio of >200) [58]. The primary composite kidney outcome was reduced by 39% (HR 0.61; 95% CI 0.51 to 0.72) in the dapagliflozin arm. Treatment with dapagliflozin was also associated with a lower incidence of all-cause mortality (HR 0.69; 95% CI 0.53 to 0.88) and of the composite of cardiovascular mortality or hospitalization for heart failure (HR 0.71; 95% CI 0.55 to 0.92) [58]. Subgroup analyses of DAPA-CKD indicated that these effects were consistent regardless of presence of type 2 diabetes [103].

Both CREDENCE and DAPA-CKD required the presence of macroalbuminuria for inclusion in addition to reduced eGFR. In contrast, the Effect of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk (SCORED) trial evaluated the dual SGLT-2 and SGLT-1 inhibitor sotagliflozin in people with type 2 diabetes and chronic kidney disease, regardless of the degree of albuminuria [104]. The original two primary outcomes in SCORED were MACE and the composite of cardiovascular mortality or hospitalization for heart failure; however, due to the trial's early cessation and the subsequent fewer than planned accrued number of events, the primary outcome was changed to the total number of cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure. During a median follow-up of 16 months, the primary outcome occurred in fewer people in the sotagliflozin arm, compared with placebo (HR 0.74; 95% CI 0.63 to 0.88) [104]. Sotagliflozin has not received marketing approval for type 2 diabetes.

Empagliflozin in patients with chronic kidney disease (EMPA-KIDNEY) is an event-driven randomized trial evaluating the effect of empagliflozin 10 mg against placebo on the primary outcome of kidney disease progression or cardiovascular death in people with chronic kidney disease [105]. Between May 2019 and April 2021,

6609 participants were randomized, of whom 44% had type 2 diabetes and 27% had a history of cardiovascular disease. Trial results are anticipated in the near future [105].

A meta-analysis has synthesized cardiovascular outcomes trials and kidney outcomes trials of SGLT-2 inhibitors, using data only for people who had both type 2 diabetes and chronic kidney disease across all trials [106]. In this population, SGLT-2 inhibitors, compared to placebo, reduced MACE by 17%, hospitalization for heart failure by 38%, and a kidney composite outcome by 34%. Individual MACE components and all-cause mortality were also significantly reduced with SGLT-2 inhibitors. In addition, beneficial effects of SGLT-2 inhibitors on MACE, hospitalization for heart failure, and kidney outcomes were evident even in the subgroup of participants with an eGFR of <45 ml/min/1.73 m² [106].

With regard to GLP-1RAs, no dedicated kidney outcomes trial is currently available. However, cardiovascular outcomes trials with GLP-1RAs have included people with an eGFR as low as 15 ml/min/1.73 m² [85]. A meta-analysis of eight cardiovascular outcomes trials found that the overall beneficial effect of GLP-1RAs on MACE (HR 0.85; 95% CI 0.78 to 0.93) was consistent between those with an eGFR of ≤60 ml/min/1.73 m² and the subgroup with an eGFR of >60 ml/min/1.73 m², as suggested by the non-significant value of the statistical test for subgroup differences [85]. More definitive evidence about the kidney and cardiovascular effects of GLP-1RAs in people with chronic kidney disease are expected on completion of the FLOW trial (NCT03819153), which is evaluating whether subcutaneous semaglutide can slow the progression of chronic kidney disease in people with type 2 diabetes and renal impairment [107].

Evidence from heart failure trials

People with type 2 diabetes have an increased risk of developing heart failure, which further increases morbidity, mortality, and occurrence of other adverse outcomes (Chapter 50). Therefore, careful consideration should be paid when choosing among pharmacological treatment options in those individuals with type 2 diabetes with established or high risk for developing heart failure. Pioglitazone should be avoided because it has been associated with an increased risk of heart failure [108]. Cardiovascular outcomes trials suggest that DPP-4 inhibitors have a neutral effect on heart failure outcomes, except for saxagliptin, which was associated with a higher rate of hospitalization for heart failure versus placebo (3.5% vs 2.8%) in the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial [36]. Caution is therefore warranted if saxagliptin is used in people with a history of heart failure. Meta-analyses of cardiovascular outcomes trials have found a modest effect of GLP-1RAs in reducing hospitalization for heart failure that was marginally significant [85,89]. Although it is unclear whether this finding is clinically meaningful, it deserves to be further examined. The effect of the GIP/GLP-1 receptor agonist tirzepatide on heart failure endpoints in people with heart failure with preserved ejection fraction and obesity is being evaluated in the Study of tirzepatide in participants with heart failure with preserved ejection fraction and obesity (SUMMIT) trial (NCT04847557). A considerable beneficial effect on heart failure outcomes, in particular hospitalization for heart failure, has been shown consistently in all cardiovascular outcomes trials with SGLT-2 inhibitors. As a result, agents from this drug class have subsequently been evaluated in large-scale trials that focused on people with heart failure and assessed heart failure outcomes as their primary endpoint.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial was the first dedicated heart failure trial with an SGLT-2 inhibitor. DAPA-HF randomized a total of 4744 participants with New York Heart Association (NYHA) class II, III, or IV heart failure and reduced ejection fraction (≤40%) to either dapagliflozin or placebo [55]. Over a median duration of 18.2 months, the primary composite outcome of worsening of heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death occurred in fewer participants receiving dapagliflozin (HR 0.74; 95% CI 0.65 to 0.85). This beneficial effect was also evident in the subgroup of participants who had type 2 diabetes (42% of the trial population). Treatment with dapagliflozin significantly improved the individual components of the primary outcome and all-cause mortality [55]. The Empagliflozin outcome trial in people with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) used the same key eligibility criteria (heart failure with reduced ejection fraction) and the same primary outcome as DAPA-HF [54]. During a median follow-up of 16 months, empagliflozin 10 mg reduced the risk of the primary outcome by 25% versus placebo, an effect that was consistent in the subgroup of participants with diabetes (~50% of the 3730 participants) [54]. A meta-analysis pooling data from both trials concluded that dapagliflozin and empagliflozin consistently reduced the composite of hospitalization for heart failure and cardiovascular death by ~25% in people with heart failure and reduced ejection fraction, regardless of the presence or absence of type 2 diabetes [109].

In the Empagliflozin outcome trial in patients with chronic heart failure and a preserved ejection fraction (EMPEROR-Preserved), empagliflozin was assessed in individuals with heart failure with preserved ejection fraction (>40%) [53]. The 5988 participants, 49% of whom had diabetes, were randomized to either empagliflozin 10 mg or placebo and were followed over a median of 26.2 months. The primary composite outcome of cardiovascular death or hospitalization for heart failure occurred in fewer participants assigned to empagliflozin compared with placebo (HR 0.79; 95% CI 0.69 to 0.90), an effect that was mainly related to a lower risk of hospitalization for heart failure (HR 0.73; 95% CI 0.61 to 0.88). In a subgroup analysis, these findings appeared consistent regardless of the presence of diabetes [53]. Individuals with heart failure with preserved ejection fraction are also the focus of the Dapagliflozin Evaluation to improve the Lives of patients with pReserved ejection fraction heart failure (DELIVER) trial, a randomized trial examining whether dapagliflozin is superior to placebo in reducing the composite of worsening heart failure or cardiovascular death [110]. Recruitment in DELIVER was completed in January 2021 with 6263 participants and an anticipated median follow-up of 27 months [110].

The Effect of sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure (SOLOIST-WHF) trial compared the dual SGLT-2 and SGLT-1 inhibitor sotagliflozin with placebo over a median of 9.0 months in 1222 people with heart failure with either reduced or preserved ejection fraction [111]. All participants had type 2 diabetes and were recently hospitalized for worsening heart failure. The rate of the primary outcome of the total number of cardiovascular deaths, hospitalizations, and urgent visits for heart failure (first and subsequent events) was significantly lower in the sotagliflozin group than in the placebo group (HR 0.67; 95% CI 0.52 to 0.85) and this benefit was consistent in the two prespecified subgroups of participants with an ejection fraction <50% and ≥50%. SOLOIST-WHF was originally designed to assess

the primary outcome of cardiovascular death or hospitalization for heart failure in ~4000 participants; however, its primary endpoint was changed because, similar to the SCORED trial, the trial ended early due to lack of funding [111].

Apart from these heart failure trials, additional evidence supporting the beneficial effects of SGLT-2 inhibitors in people with heart failure comes from subgroup analyses of the original cardiovascular outcomes trials that recruited people with type 2 diabetes and increased cardiovascular risk. In particular, a meta-analysis synthesized data from EMPAREG-OUTCOME, CANVAS Program, DECLARE-TIMI 58, and VERTIS CV and compared the cardiovascular effects of SGLT-2 inhibitors between the two subgroups of people with and without heart failure within the overall populations of all four trials [92]. The findings showed that SGLT-2 inhibitors reduce the composite of cardiovascular death or hospitalization for heart failure in both subgroups [92]. Based on the overall evidence both from cardiovascular outcomes trials and from heart failure trials, the SGLT-2 inhibitor class consistently confers clinically important benefits in heart failure endpoints in people who have either type 2 diabetes, or heart failure, or both.

Management of obesity and associated comorbidities

The obesity epidemic is paralleled not only by the increasing prevalence of type 2 diabetes, but also by other cardiometabolic adverse effects, including high blood pressure, elevated cholesterol and triglyceride levels, liver steatosis and fibrosis, obstructive sleep apnoea, and most importantly cardiovascular disease. Promoting weight loss through increased physical activity and energy restriction plays a key role in the management of type 2 diabetes, but behavioural changes are hard to implement. Sulfonylureas, pioglitazone, as well as basal insulin are associated with weight gain, while metformin and DPP-4 inhibitors have a neutral effect on body weight. By contrast, GLP-1RAs induce weight loss by slowing gastric emptying and by promoting satiety, while treatment with SGLT-2 inhibitors leads to urinary excretion of excess calories due to glucosuria. Use of agents from these two classes, in particular GLP-1RAs, results in sustainable weight reduction and, as such, people with type 2 diabetes for whom weight loss or maintenance is a therapeutic priority should be treated preferably with a GLP-1RA or an SGLT-2 inhibitor [1,6]. Certain GLP-1RAs including liraglutide and subcutaneous semaglutide have received marketing authorization at higher doses for chronic weight management irrespective of the presence of type 2 diabetes. Based on a network meta-analysis assessing pharmacological therapies for obesity, high-dose semaglutide is likely the most effective agent, achieving body weight reductions that could be as high as 10% [112]. In addition, currently available data from randomized controlled trials suggest that in people with type 2 diabetes the dual GIP/GLP-1 receptor agonist tirzepatide has an impressive weight-lowering potential, superior to that of subcutaneous semaglutide [61]. The effect of tirzepatide as an anti-obesity medication is being investigated in the ongoing Study of tirzepatide in participants with obesity or overweight (SURMOUNT) clinical trial programme.

People with type 2 diabetes who have overweight or obesity often have comorbid NASH, which currently represents the most common liver disorder in Western countries and has become the leading indication for liver transplantation in the USA. Insulin resistance is a shared characteristic of type 2 diabetes and obesity and is considered as a key pathogenic driver of NASH. Despite the

growing prevalence of the condition, management is largely based on lifestyle modification and treatment of individual components of the metabolic syndrome, due to lack of licensed disease-specific interventions that could prevent progression of hepatic steatosis to liver fibrosis and cirrhosis [113]. Nevertheless, emerging evidence suggests that certain anti-diabetes drugs including pioglitazone, GLP-1RAs, and to a lesser extent SGLT-2 inhibitors might have a favourable effect on NASH. Based on liver biopsy studies, pioglitazone was associated with reductions in hepatic steatosis and lobular inflammation, but not with improvement in fibrosis score [114]. Treatment with liraglutide and semaglutide resulted in histological resolution of NASH and halted progression of fibrosis [115,116]. Studies utilizing mostly magnetic resonance-based techniques for assessment of liver fat content have also suggested potential benefits for dulaglutide as well as several SGLT-2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin [117,118]. On the basis of this evidence, the American Association of Clinical Endocrinology advocates the use of pioglitazone or GLP-1RAs for people with type 2 diabetes and biopsy-proven NASH [113]. Both drug classes should be considered when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and non-invasive tests, while GLP-1RAs, pioglitazone, or SGLT2 inhibitors can probably be considered to offer cardiometabolic benefit in people with type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) [113].

For people with type 2 diabetes and morbid obesity, bariatric surgery is a highly effective alternative for weight loss compared with lifestyle and medical interventions that confers superior glycaemic and other metabolic management, mitigates cardiovascular risk, and may even provide survival benefits. Metabolic surgery often reduces the number of anti-diabetes medications needed to restore euglycaemia and can induce remission of diabetes and clearance of NASH. The procedure is generally safe when performed in high-volume centres with experience in gastrointestinal surgery. Bariatric surgery is therefore recommended to treat type 2 diabetes in screened surgical candidates with $BMI \geq 40 \text{ kg/m}^2$, as well as in people with $BMI 35\text{--}40 \text{ kg/m}^2$ who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with non-surgical methods. Bariatric surgery could also be considered in people with type 2 diabetes with $BMI 30\text{--}34 \text{ kg/m}^2$ [119].

Precision medicine-based approach

An alternative approach for choosing among anti-diabetes medications is in line with the concept of precision medicine and suggests that people with type 2 diabetes can be clustered into five distinct subgroups according to various clinical variables, such as age at onset of diabetes, HbA_{1c} , BMI, or measures of insulin resistance [120]. These subgroups have been reproduced in large-scale populations and have been associated with different risks of developing diabetes-related complications and responses to specific treatments. Based on this rationale, certain drugs can be more efficacious for specific clinical phenotypes of type 2 diabetes. In particular, it has been suggested that insulin and insulin secretagogues are likely the therapy of choice for the clusters of severe autoimmune diabetes (SAID) and severe insulin-deficient diabetes (SIDD), insulin sensitizers for people with severe insulin-resistant diabetes (SIRD), and metformin for mild obesity-related diabetes (MOD) [120]. A recent study aiming to validate these novel subtypes in the DEVOTE, LEADER, and SUSTAIN-6 cardiovascular outcomes trials found that the highest risk for cardiovascular events

was evident in participants with high HbA_{1c} and low BMI who most closely resembled the SIDD cluster [121]. Nevertheless, this suggested classification system of diabetes should not be considered final at present, as it is still evolving and requires further refinements to achieve better predictive power [120].

Therapeutic decision making in the clinical setting

Currently, choice of appropriate anti-diabetes therapy is primarily guided by the presence of clinically important comorbidities and underlying cardiovascular risk. For people with type 2 diabetes and chronic kidney disease, SGLT-2 inhibitors are most likely better suited due to their kidney and cardiovascular protection, whereas a long-acting GLP-1RA is recommended for individuals who cannot use an SGLT-2 inhibitor [122]. SGLT-2 inhibitors should also be prioritized in people with type 2 diabetes and heart failure [1, 80, 123]. Specific GLP-1RAs and SGLT-2 inhibitors are recommended for people with type 2 diabetes and with established atherosclerotic disease or with multiple cardiovascular risk factors [1, 2, 80]. The level of certainty in this recommendation is probably higher for the former subgroup, because some cardiovascular outcomes trials have focused exclusively on people with established cardiovascular disease, while in trials that recruited both subgroup populations fewer events were recorded for participants with multiple risk factors only. Although the definition used for multiple risk factors was not identical among these trials, in most cases it comprised a combination of at least three risk factors such as dyslipidaemia, obesity, smoking, age, or hypertension. The cardiovascular benefits of GLP-1RAs and SGLT-2 inhibitors appear to be independent of their glucose-lowering effect and of prior metformin use [124–126]; it is therefore reasonable to treat people who have type 2 diabetes and any of the cardiovascular comorbidities mentioned with these agents irrespective of baseline HbA_{1c} or metformin therapy [2].

It is unclear, however, whether the favourable cardiovascular effects of GLP-1RAs or SGLT-2 inhibitors are applicable to people with type 2 diabetes who have fewer than three risk factors. In this regard, a network meta-analysis of 298 randomized controlled trials found no clinically meaningful differences between anti-diabetes medications for mortality and vascular outcomes in people at low cardiovascular risk [26]. Another network meta-analysis estimated absolute effects of treatment with GLP-1RAs and SGLT-2 inhibitors on cardiovascular and kidney outcomes for different categories of baseline cardiovascular risk. In particular, relative effect estimates from pooled trial data, which were largely driven by cardiovascular outcomes trials, were combined with baseline risk estimates derived from epidemiological data [95]. The estimated absolute treatment effects were very low for people with few or no cardiovascular risk factors, leading to a weak recommendation regarding the use of either a GLP-1RA or an SGLT-2 inhibitor in this population [95, 127]. This underlines not only the importance of prudent use of finite resources, but also the need to consider and avoid increased treatment burden and potential side effects that might be associated with the use of agents for cardiorenal protection in people with very low absolute cardiovascular risk. As such, key drivers for therapeutic decisions in people with low underlying risk are management of glycaemia, body weight, or

associated morbidities such as NASH. Metformin remains the agent of choice for treatment of hyperglycaemia in most cases, including newly diagnosed type 2 diabetes, due to the extensive experience with its use, overall efficacy and safety profile, and affordability [1, 80]. In the presence of obesity or NASH, specific medications are preferable, such as GLP-1RAs or SGLT-2 inhibitors for the former, and pioglitazone and some GLP-1RAs for the latter condition.

Additional important considerations can affect real-life therapeutic decisions and people's willingness to follow these decisions. For example, treatments with increased hypoglycaemic risk, such as sulfonylureas or intensive insulin regimens, should be avoided in individuals in whom hypoglycaemia can be life threatening. Moreover, agent- or class-specific adverse events, such as gastrointestinal adverse events with metformin or with GLP-1RAs, can limit the use of these medications in some people. Pharmacological treatment of older people with diabetes and frailty should also be given special attention; in particular, despite the cardiovascular benefits of GLP-1RAs or SGLT-2 inhibitors even in older populations [128], treatment with these agents is often not feasible due to practical concerns (e.g. need for subcutaneous administration of GLP-1RAs), susceptibility to dangerous side effects (e.g. falls due to volume depletion caused by SGLT-2 inhibitors), or drug availability and affordability issues. With respect to the latter, diabetes and the associated costs of managing the disease and its complications affect ethnic minorities and low-income populations disproportionately. Beyond novel therapies, increased emphasis on social determinants of health is even more necessary to tackle disparities and ensure humane and affordable care for all people with type 2 diabetes [129].

It is equally important that clinical decisions attend to the values and preferences of the informed individual with type 2 diabetes. This person-centred approach means that it is not the clinician who should exclusively make therapeutic decisions: it is an ethical imperative that the affected individual participates as an equal partner in decision making. Personal values and preferences may include experience of former and current related illnesses, other relevant life experiences, health habits, goals and expectations, social or family support, or personal beliefs about medical interventions. Depending on these factors, people may have polarized perceptions, ranging from no specific views to concrete predispositions, on how to proceed with their treatment. Research has suggested that considerable variation can also exist between the preferences of physicians and those of people with type 2 diabetes when it comes to weighting the merits and drawbacks of available medications [130]. Moreover, people's actions may also deviate from the preferences and views they themselves had previously expressed during the clinical consultation with their physician.

Keeping these in mind and given the complex and chronic nature of type 2 diabetes, as well as the constantly evolving diabetes research informing guidelines formulation, clinicians should not only continually update their knowledge on the pharmacological management of the disease, but also regularly reassess the overall health profile, relevant comorbidities, and personal perceptions of those they treat. By doing so, meaningful deliberations between caregivers and individuals affected by type 2 diabetes can be achieved, leading to well-informed decisions with minimal treatment burden that motivate both parties to mutually collaborate in a holistic management plan.

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Weight Management and Metabolic Surgery

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Key points

- Weight loss in its own right is increasingly being recognized as an important therapeutic target for people with obesity and type 2 diabetes, which can be achieved using several different modalities. The key to the success of any treatment is weight loss that is maintained.
- Lifestyle modification including caloric restriction can produce clinically significant weight loss; however, sustaining this long term is challenging. Evidence to demonstrate a resultant improvement in cardiovascular risk factors or mortality is limited.
- Evidence from more than 13 randomized controlled trials has consistently demonstrated that, irrespective of the procedure performed, bariatric surgery is more effective than medical therapy for the treatment of obesity and type 2 diabetes.
- The recent development of a number of medications producing clinically significant weight loss may present new treatment options to a wider demographic of people than surgery.

Weight loss in itself and weight management in people with type 2 diabetes allow for the alteration of the primary disease process, obesity. In those with impaired glucose tolerance or early diabetes it may prevent disease progression or induce remission, whereas for those with established disease it may improve glycaemic levels while reducing treatment burden. Additionally, for those with complications of type 2 diabetes, such as macrovascular complications, sustained weight loss may actually prevent progression or reversal of established complications, including diabetic kidney disease [1]. Like any intervention, the individual benefit of weight loss to those with type 2 diabetes will vary and may be of most value in those primarily with insulin resistance, while those with β -cell dysfunction will likely benefit to a lesser degree.

In addition to improving glycaemic levels, the treatment of hypertension and dyslipidaemia, in their own right, is critical in reducing the risk of cardiovascular death. It is also recognized that weight-based therapeutic goals have a place in the management of individuals with obesity and type 2 diabetes. Weight reduction not only presents the opportunity to modify the underlying disease process, but has further metabolic benefits, including a reduction in the systemic inflammatory response, and improved blood pressure, dyslipidaemia, and quality of life. Although there are many therapeutic interventions available to aid weight loss, it is important to recognize that sustained long-term weight loss is critical to improving clinically relevant outcomes. The heterogeneous nature of both type 2 diabetes and obesity means there will be a degree of inter-individual variation in response to any single treatment. The availability of different treatment modalities presents the opportunity to implement an individualized approach to weight management as well as the potential to combine treatments, which may act by complementary but distinct mechanisms.

Diet, lifestyle, and psychological support

Owing in part to the perceived simplicity and relatively low cost, diet and lifestyle interventions have long been favoured as a means of promoting weight loss in individuals with obesity and type 2 diabetes, with the aim of reducing glycaemic levels, inflammatory markers, as well as cardiovascular risk factors. Although several studies have demonstrated that weight loss through diet or exercise-based interventions resulted in improved glycaemic levels and cardiovascular risk factors, including lipids and blood pressure, questions remained regarding the impact of these interventions on the risk of cardiovascular morbidity and mortality [2–4]. The Look AHEAD (Action for Health in Diabetes) trial demonstrated that an intensive lifestyle modification programme achieved clinically significant weight loss with a concomitant improvement in glycated haemoglobin (HbA_{1c}) and cardiovascular risk factors aside from low-density lipoproteins (LDL). In spite of this, the trial was stopped early on the basis of futility, as it did not result in a reduction in the primary endpoint of decreased rates of cardiovascular events [5]. A *post hoc* analysis of the results, however, showed a relationship between the magnitude of weight loss and improved cardiovascular risk. In individuals who lost >10% of their body weight in the first year, there was a 21% reduction in the risk of fatal and non-fatal cardiovascular events [6].

More recently, the implementation of a very low-calorie diet (VLCD) or total meal replacement has garnered increasing attention, in part due to the results of the Diabetes Remission Clinical Trial (DiRECT). The primary care-led intervention comprised a strict 12–20-week period of 800 kcal/d weight loss phase, during which the individuals had only formula diet, followed by food

reintroduction and structured support for weight loss maintenance. Of the individuals in the intervention arm, 46% and 36% were in remission from type 2 diabetes after one and two years, respectively, with sustained weight loss being linked to the maintenance of remission [7]. Although this study demonstrated promising results with regard to diabetes remission following significant weight loss, it also highlighted the critical issue surrounding dietary or lifestyle interventions as a means of treating type 2 diabetes, namely the sustainability of the intervention and resultant ability to maintain weight loss. At one year, nearly 25% of the participants demonstrated a 15 kg weight loss, which fell to just 11% after two years, which in part likely represents a proportion of individuals who were no longer able to follow the diet as prescribed.

With all dietary or lifestyle interventions, the aim of inducing weight loss through a caloric deficit remains valid and in most cases is effective in the short term in producing volitional weight loss. However, they are unsustainable for many individuals in the long term, with subsequent weight regain. Critically, VLCD and total meal replacement, in particular, do not address the underlying disease process of obesity and may only exacerbate hunger, which reduces the likelihood of long-term weight loss maintenance. In spite of this, dietary interventions may be effective in a small subgroup of individuals and may have a role for those who have not previously been on supervised weight loss programmes, as they are a low-risk intervention. Clinicians should be mindful that the majority of individuals will require treatment intensification with the addition of alternative modalities to produce clinically relevant and sustained weight loss.

Prior to undergoing bariatric surgery, people with obesity are typically advised to engage in a supervised weight loss programme; however, the duration and exact structure are variable. Preoperative weight loss is positively correlated in some studies with increased postoperative weight loss, fewer complications, as well as a reduction in liver volume, which facilitates surgical access [8,9]. Dietary changes are required in the postoperative period and generally involve modifying eating patterns to include regular, small meals, high in protein, while following supplementation guidelines, which vary according to the type of surgery. In the postoperative period there is no evidence to support that participation in a supervised exercise programme alone results in significant additional weight loss or preservation of lean mass [10,11]. In spite of this, studies have demonstrated that engagement with a regular exercise programme following bariatric surgery can increase cardiorespiratory fitness, strength, and physical function and people undergoing surgery are generally advised to engage in regular physical activity [11–13].

Psychological support is a central element in the multidisciplinary management of people with obesity, particularly those undergoing bariatric surgery in both the preoperative and postoperative periods. As such, bariatric surgery should only be provided in units where psychological support is available [14]. People with obesity are more likely to suffer from psychological issues including anxiety, depression, poor self-image, prior trauma, and disordered eating, which all have implications for quality of life [15,16]. The identification of maladaptive eating behaviours preoperatively, including binge eating and emotional eating, is important as they are unlikely to be improved following surgery and are associated with poorer weight loss outcomes [17].

The British Obesity Metabolic Surgery Society guidelines have broken the psychological support pathway into a pre- and postoperative stepped model involving three levels: online support, group workshops, and individualized support delivered by a trained

psychologist [18]. During the preoperative period, the role of psychological support is not to screen out those who are unsuitable for surgery, but rather to identify potential barriers to weight loss or success with bariatric surgery and implement support where possible. Psychological support is critical to helping those undergoing surgery to identify the means of setting realistic expectations, as well as strategies for how they will adapt and manage the challenges in the postoperative period [18]. Some people with previously well-managed mental health issues may experience a period of destabilization, including those with substance misuse disorders.

Pharmacotherapy

The ideal anti-obesity pharmacotherapy is theoretically one that is more effective than dietary or lifestyle intervention, while being less invasive and potentially available to a wider demographic than bariatric surgery. Until recently no such agent existed, with many of the previously available drugs being either ineffective, dangerous, or both. Widespread media coverage of serious side effects linked to the use of now recalled medications such as sibutramine and phentermine/fenfluramine has contributed to a general reluctance from both clinicians and individuals with obesity to consider their use. In recent years, there has been remarkable progress made in the development of novel agents, which show excellent tolerability and safety while promoting clinically significant weight loss. These may further broaden the availability of therapeutic options for those with obesity and type 2 diabetes. Broadly speaking, these novel agents can be divided into two main subclasses: anti-obesity medications that are specifically targeting weight loss; and diabetes medications that are primarily licensed for treating hyperglycaemia but also promote weight loss.

Anti-obesity medications

Orlistat is a gastric and pancreatic lipase inhibitor, which works primarily by reducing the absorption of dietary fat. Randomized controlled trials (RCTs) have shown that orlistat can result in a 5–10% weight loss associated with an improvement in glycaemic levels and cardiovascular risk factors [19,20]. It is associated with gastrointestinal symptoms, particularly diarrhoea, and is often poorly tolerated, largely limiting its long-term use.

More recently developed anti-obesity medications largely act centrally to produce appetite suppression, which may in part be responsible for the decreased incidence of gastrointestinal side effects and greater tolerability. The combination of naltrexone and bupropion acts in a synergistic manner, with bupropion activating proopiomelanocortin (POMC) receptor neurons in the arcuate nucleus to decrease appetite and naltrexone further enhancing this effect. The COR-II trial demonstrated its efficacy in promoting weight loss in individuals with obesity, with nearly one-third of participants achieving >10% weight loss after 56 weeks of treatment [21].

Another combined anti-obesity medication, phentermine and topiramate, produces appetite suppression and also alters energy balance, resulting in weight loss and concomitant improvements in glycaemic levels. The CONQUER study demonstrated that in those with type 2 diabetes, there was a mean weight loss of 9.4% after a 56-week period of treatment associated with 37% of the individuals achieving an HbA_{1c}<6.5% (48 mmol/mol) despite a reduced need for diabetes medications [22].

Coming from the same drug class as fenfluramine, which has been withdrawn, lorcaserin is a selective 5-HT_{2c} agonist that produces appetite suppression through activation of POMC neurons. In the Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) 52-week placebo-controlled trial, lorcaserin produced a >5% weight reduction from baseline in 44.7% of people with type 2 diabetes [23]. A reduction in HbA_{1c} was also seen, with 52% of participants achieving a level of <7% (53 mmol/mol) at one year. Lorcaserin use is not associated with the valvular defects seen with fenfluramine, which were thought to be secondary to increased mitotic activity mediated via its effect on 5-HT_{2B} receptors [24]. The market approval for lorcaserin, however, was withdrawn because of an increased occurrence of cancer during a safety clinical trial.

Although none of these drugs in themselves directly mediates changes in glycaemic levels, the weight loss they produce may modify the underlying disease process of type 2 diabetes and improve glucose metabolism.

Anti-diabetes medications

Several medications that were initially licensed to treat type 2 diabetes induce significant weight loss and there is increasing interest in how indications for their use can be expanded (Table 38.1). Mimicking some of the neurohormonal changes induced by bariatric surgery, glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide, liraglutide, and dulaglutide, produce not only improved glycaemic levels, but clinically significant reductions in body weight and cardiovascular risk factors, including blood pressure and lipids. These medications act in a glucose-dependent manner to stimulate insulin secretion while inhibiting glucagon production and therefore have a low risk of hypoglycaemia [25]. They also act to modulate hunger within the gastrointestinal tract by slowing gastric emptying as well as centrally, promoting satiety

by activating receptors in the arcuate nucleus of the hypothalamus. Clinical trials involving both liraglutide and semaglutide have demonstrated that 33% and 13% of the individuals achieve 10% weight loss, respectively [26, 27]. Critically, in people with type 2 diabetes, the use of GLP-1 receptor agonists reduces the risk of fatal and non-fatal cardiovascular events.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors act by decreasing the renal reabsorption of glucose, which not only improves glycaemia but results in clinically significant weight loss through an obligate calorie loss in the urine. A pooled analysis of outcomes of phase three trials comparing canagliflozin to placebo demonstrated that 25% of the individuals had >5% weight loss [28]. There were also weight-dependent improvements in HbA_{1c} and systolic blood pressure, with weight loss accounting for 15% and 42% of changes in each, respectively. The use of both canagliflozin, dapagliflozin, and empagliflozin reduces fatal and non-fatal cardiac events, with the EMPA-REG OUTCOME trial demonstrating a 38% relative risk reduction in fatal cardiovascular events with empagliflozin compared to placebo in people with type 2 diabetes [29, 30].

When considering the use of weight loss pharmacotherapy, there remain questions regarding timing and indications for initiation and stopping. Anti-obesity medications remain an underutilized treatment modality for individuals with obesity and type 2 diabetes, in part because of perceptions regarding efficacy and safety. These concerns are not reflective of the currently available medications and diabetes drugs that promote weight loss are increasingly being used.

Anti-obesity medications may be useful in the pre- and postoperative periods for individuals undergoing bariatric surgery [31]. It is well recognized that a proportion of people will experience weight gain or a plateau of weight loss following bariatric surgery for a variety of reasons, and in these circumstances the addition of

Table 38.1 Drugs used to manage obesity.

Drug name	Dosing	Mechanism of action	Expected weight loss	Common side effects
Semaglutide	2.4 mg weekly via SC injection	GLP-1 analogue ↑ Glucose sensitivity, satiety ↓ Gluconeogenesis, gastric emptying	-15.8% mean body weight change >10% weight loss in 70% of recipients	Nausea Diarrhoea
Liraglutide	3 mg OD via SC injection	GLP-1 analogue ↑ Glucose sensitivity, satiety ↓ Gluconeogenesis, gastric emptying	-6.4% mean body weight change >10% weight loss in 26% of recipients	Nausea Diarrhoea
Orlistat	120 mg TDS	Lipase inhibitor ↓ Absorption of dietary fat	-5% to 10% mean weight loss >5% weight loss in 52% of recipients	Diarrhoea Steatorrhoea
Naltrexone/bupropion	16 mg naltrexone /180 mg bupropion BD	Naltrexone: μ opioid receptor antagonist Bupropion: norepinephrine and dopamine reuptake inhibitor	-6.4% mean weight loss >10% weight loss in 28% of recipients	Nausea Headache Constipation
Phentermine/topiramate	7.5 mg phentermine/46 mg topiramate or 15/92 mg	Phentermine: centrally acting sympathomimetic Topiramate: anti-convulsant ↓ Appetite via hypothalamus	-10.9% weight loss from baseline >10% weight loss in 48% of recipients on high dose	Paraesthesia Dizziness Dry mouth Insomnia Constipation

BD, twice daily; GLP-1, glucagon-like peptide-1; OD, daily; SC, subcutaneous; TDS, thrice daily.

pharmacotherapy may be beneficial. The GRAVITAS study demonstrated the benefits of combining liraglutide with Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) for individuals with persistent or recurrent type 2 diabetes. Over the 26-week study period, 46% of the individuals in the liraglutide group lost >5% of their baseline body weight compared to 9% in the placebo group. Weight loss was also accompanied by improved HbA_{1c}, with 42% of the individuals in the treatment group reaching an HbA_{1c} < 6.5% (48 mmol/mol) compared to 13% in the control group [32]. Although evidence for the use of pharmacotherapy in the postoperative period is limited to a relatively small number of studies, one study reported a greater response to the initiation of medications in those with a weight loss plateau rather than those who had regained weight [33].

Treatment cessation guidance is clearer for most newly approved anti-obesity medications in Europe and the USA. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have provided *stopping rules* to identify individuals who are likely to be *responders* to any specific treatment [34]. Although there is some variability between different drugs, it is generally advisable that individuals should not continue to take anti-obesity medications if they have lost <5% weight after 12 weeks at the full treatment dose. These guidelines are derived from studies that reported that early weight loss following initiation of a dietary or pharmacological intervention is strongly predictive of long-term outcomes [35, 36].

Bariatric surgery

The initial development of bariatric surgery originally stemmed from the observation that individuals undergoing surgical resection for upper gastrointestinal cancers frequently experienced profound and often problematic weight loss. This prompted the recognition that these same procedures could be used for individuals with obesity, making weight loss the primary indication rather than an unintended side effect of surgery. Critically, bariatric surgery not only provided clinically significant weight loss for individuals with obesity, but resulted in sustained weight loss in the long term.

Types of bariatric surgery

Since the early adoption of bariatric procedures, there have been dramatic developments not only from a technical standpoint in developing safer and highly effective procedures and approaches, but also from a mechanistic view, gaining a better understanding of the weight loss-dependent and independent physiological changes evoked by bariatric surgery and their long-term impact on obesity and related complications. Worldwide, more than 99.1% of primary bariatric procedures are now performed laparoscopically according to the latest IFSO Global Registry Report [37]. Refinement of techniques and the development of bariatric surgery are seen as a specialist area of practice, with morbidity and mortality rates now on a par with laparoscopic cholecystectomy and hysterectomy [38]. Although there is a growing body of level 1 evidence to support the efficacy of bariatric surgery in producing sustained long-term weight loss and resolution of comorbidity, no RCTs have demonstrated the superiority of one procedure over another; however, there are ongoing trials that may provide some clarity on this matter. Determining

which procedure to perform should take into account individual comorbidities, the presence of obesity-related metabolic complications, potential short- and long-term risks of procedure-related complications, as well as the surgeon's experience.

Sleeve gastrectomy

Although a relatively new procedure, sleeve gastrectomy now accounts for 50% of all bariatric surgery, becoming the most commonly performed bariatric procedure worldwide [39]. Sleeve gastrectomy was originally one component of the two-stage duodenal switch procedure; however, once the substantial weight loss achieved was recognized, it was developed as a standalone procedure. The increased popularity of sleeve gastrectomy has been attributed in part to the perception that it is faster and less technically challenging to perform than traditional procedures, such as RYGB, while producing similar weight loss and resolution of comorbidity. Sleeve gastrectomy is associated with a significant reduction in ghrelin as a result of resection of the gastric fundus, along with post-prandial increases in GLP-1 and peptide tyrosine-tyrosine (PYY), which play important roles in appetite modulation and glucose homeostasis [39]. Sleeve gastrectomy may be associated with the development of new-onset or worsening of pre-existing reflux, which should be discussed preoperatively [40]. There is also concern regarding the development of Barrett's metaplasia as a result, and endoscopic surveillance in the postoperative period is now recommended one year postoperatively and every two to three years thereafter [41].

Adjustable gastric banding

There has been a dramatic reduction in the use of adjustable gastric banding, accounting for only 3.3% of all bariatric procedures in the 2021 IFSO Global Registry Report [37]. The fall in popularity is largely attributable to the view that it leads to a lesser degree of weight loss and resolution of obesity comorbidity compared to other widely available procedures, while being associated with a relatively high reintervention rate. Nevertheless, it can produce weight loss of ~20%, which is nearly equivalent to other bariatric procedures, although this requires close follow-up that may not be achievable in most healthcare settings [42, 43]. It is a relatively low-risk and reversible procedure and may still be considered in certain scenarios. Adjustable gastric banding may contribute to weight loss by promoting satiety during periods of fasting, likely mediated by vagal afferents [44].

Roux-en-Y gastric bypass

RYGB is a procedure that provides reliable weight loss and amelioration of obesity-related complications, particularly type 2 diabetes, with several RCTs supporting its use. It has decreased in popularity in recent years, in part due to its relative technical difficulty compared to sleeve gastrectomy, requiring the formation of two anastomoses. The mechanisms by which RYGB acts have been extensively investigated; it produces similar neurohormonal changes to sleeve gastrectomy, although perhaps with a more exaggerated response, with an increase in postprandial GLP-1 and PYY [45]. These changes have important effects on modifying the gut-brain axis controlling hunger, appetite, and satiety as well as mediating changes in bile acid metabolism [46]. In contrast to sleeve gastrectomy, which may produce worsening of reflux symptoms, RYGB is a treatment for people with obesity and reflux in its own right, and thus may be a more appropriate choice than sleeve gastrectomy in this specific context [47].

One anastomosis gastric bypass

One anastomosis gastric bypass (OAGB) has emerged as a simplified version of RYGB, involving the formation of a small gastric pouch and the anastomosis of a loop of jejunum to the stomach, forming a gastro-jejunostomy. Similar to RYGB, this procedure results in the bypass of the proximal small bowel; however, it does not require the formation of a second jejuno-jejunal anastomosis. An RCT with two-year follow-up demonstrated that it resulted in weight loss and resolution of type 2 diabetes that was non-inferior to RYGB [48]. In comparison to RYGB, there was a higher rate of nutritional complications as well as steatorrhoea. Concerns have also been raised about the worsening of gastro-oesophageal reflux following OAGB in those with preoperative symptoms of reflux, as well as the development of *de novo* gastro-oesophageal reflux in people with a prior diagnosis of hiatus hernia [49]. Evidence to support its use is limited as it is a relatively new procedure, and longer-term studies are needed to determine if weight loss and metabolic improvements are sustained in the long term.

Biliopancreatic diversion and duodenal switch

Although biliopancreatic diversion and duodenal switch is recognized as the procedure that produces the greatest degree of weight loss and long-term remission of type 2 diabetes, it is infrequently performed. Following biliopancreatic diversion and duodenal switch, people may lose >70% excess weight, and a 10-year follow-up study has demonstrated a diabetes remission rate of 50% compared with 25% following RYGB [50, 51]. In spite of these rather impressive outcomes, this procedure accounts for only a small fraction of all procedures due in part to the technical challenge, but also as a result of the increased risk of both short- and long-term complications. In comparison to all other bariatric procedures, biliopancreatic diversion and duodenal switch has the highest associated 30-day mortality and one-year complication rate, which are attributable to pulmonary embolism and anastomotic leak, respectively [52]. Much of the weight loss following biliopancreatic diversion and duodenal switch is secondary to the relatively long segment of small bowel bypassed and very short (80–100 cm) common channel; however, this is also responsible for many of the long-term complications of the procedure related to nutrient deficiencies. People need to have lifelong nutrient supplementation and close follow-up monitoring, but even despite this they may remain deficient. A proportion will be refractory to treatment and up to 10% require reoperation to correct the ongoing micronutrient deficiency [53, 54]. Iron, vitamin B₁ and B₁₂, folate, and fat-soluble vitamin levels are particularly problematic. The importance of close follow-up should not be underestimated, as nutrient deficiency may lead to irreversible complications, including Wernicke's encephalopathy and neuropathy.

Efficacy of bariatric surgery

There is a strong evidence base supporting the efficacy of bariatric surgery. The Swedish Obese Subjects (SOS) study, a prospective cohort study, has demonstrated the remarkable durability of weight loss in individuals undergoing bariatric procedures. Over a follow-up period of 20 years, people undergoing bariatric surgery maintained a mean change in body weight of -18%, which showed only a minor increase from the lowest point of -23% at two years post-operatively [55, 56]. When comparing the two most commonly performed procedures, sleeve gastrectomy and RYGB, RCTs have shown that although there was greater weight loss and change in body mass index (BMI) following RYGB, the difference was not

statistically different [57, 58]. Looking beyond weight loss, in comparison to matched individuals with obesity receiving usual care, there was a reduction in all-cause mortality, including that from cardiovascular events as well as certain forms of cancer [56].

Early perceptions of bariatric surgery as a procedure limited to weight loss alone have shifted as mechanistic studies have demonstrated that bariatric surgery has multisystem effects. The ability to reliably induce and maintain weight loss has provided a model to gain greater insight into and understanding of the impact of weight loss on obesity-related diseases, particularly type 2 diabetes. Through weight loss-dependent and -independent pathways, bariatric surgery results in the modification of several pathological processes driving the development of obesity, as well as reducing the risk of obesity-related complications. The rapid, metabolic changes induced by bariatric surgery are in part mediated by neurohormonal changes that result in rapid improvements in glycaemia in people with type 2 diabetes that are independent of weight loss. The findings from these mechanistic studies have been supported by more than 13 RCTs, which have consistently demonstrated the positive effects on glucose levels following bariatric surgery, irrespective of the procedure performed compared to medical treatment for type 2 diabetes and prior to the onset of weight loss [42, 51, 59–69]. As such, the second Diabetes Surgery Summit (DSS-II) developed guidelines that saw bariatric surgery as a key element in the treatment for type 2 diabetes in individuals with obesity. These recommendations have been endorsed by international governing bodies including the American Diabetes Association and the International Diabetes Federation as a central part of their management algorithms [70, 71].

The adoption of a diabetes-focused model of care with metabolic surgery saw treatment targets being largely driven by improved glycaemic levels, with weight loss viewed as a secondary goal of treatment of lesser consequence. This view ignores the role of obesity in the underlying pathophysiology of type 2 diabetes, and studies have shown that bariatric surgery can modify several pathways contributing to the development of obesity. The modification of the gut–brain axis following bariatric surgery, altering the release of several critical gastrointestinal hormones implicated in the regulation of appetite and satiety, has been highlighted as of particular importance in mediating long-term weight loss maintenance by decreasing the symptoms of hunger associated with obesity. GLP-1 and PYY are both secreted primarily by L cells in the terminal ileum, and increased levels in the postoperative period have been implicated in the sustained weight loss produced following sleeve gastrectomy and RYGB [72]. Increased secretion of GLP-1 in the postoperative period is directly linked to the rapid improvements in glucose metabolism, but it also plays a role in appetite regulation. This effect is enhanced by PYY, a hypothalamic regulator of satiety that mediates decreased gastric acid secretion and delayed gastric emptying, both of which counteract some of the orexigenic effects mediated by falling leptin levels following bariatric surgery [73]. The alterations in gut hormones may also be potentiated by the anatomical bypass of the proximal small bowel, resulting in elevated plasma bile acids. Following RYGB, terminal ileal L cells are stimulated by the passage of undiluted bile acids, which produces a subsequent further increase in postprandial GLP-1 levels, contributing to increased satiety and weight loss maintenance in the postoperative period [46].

The improved glycaemic levels following bariatric surgery are related to both weight-independent mechanisms, such as alterations in neurohormonal signalling, and weight-dependent mechanisms. Although changes in the early postoperative period allowing rapid

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In-Hospital Treatment and Surgery in People with Diabetes

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Key points

- The number of people with diabetes in hospital continues to increase.
- Hyperglycaemia (particularly in those people not known to have diabetes prior to hospital admission or those experiencing stress hyperglycaemia) and hypoglycaemia are associated with increased levels of harm, defined using whatever measure is chosen.
- Levels of knowledge about diabetes among healthcare staff remain inadequate and levels of satisfaction about inpatient diabetes care remain low.
- The role and early involvement of a diabetes inpatient specialist team are stressed as an important factor in the education of people with diabetes and staff.
- Several national and international guidelines are now available to help teams manage this increasingly complex cohort of patients, and aim to achieve suitable glycaemic levels that avoid symptomatic hyperglycaemia or debilitating hypoglycaemia.
- The lack of robust data means that the target glucose concentrations for hospitalized individuals with diabetes have yet to be clearly determined.

Known diabetes in hospital

The prevalence of diabetes in the general population of Western Europe is approximately 6–7%, and is expected to rise significantly over the next 20–30 years [1]. The prevalence of diabetes in other parts of the world is much higher; in North America and the Caribbean it is reported to be between 10.5% and 11.1% overall, with some counties of the USA having a prevalence of 33% [1,2]. Having diabetes more than doubles the risk of being hospitalized for any given condition [3], which is reflected in the high prevalence of diabetes in hospitals. Data from the 2019 UK National Diabetes Inpatient Audit (NaDIA) showed that the prevalence of people with diabetes in hospital ranged from 8.3% to 31%, with a mean of 18.1% [4]. People with diabetes have a longer length of hospital stay and higher mortality rates than those without the condition [5]. This translates to greater costs; in the UK in 2010, it was estimated that diabetes accounted for over 10% of the entire budget of the National Health Service (NHS), with the excess costs of people with diabetes in hospital equating to between £573 million and £686 million per annum [6]. In the USA, data suggest that in 2017, 25% of the health budget was spent on diabetes, equating to \$327 billion, a rise of 25% (after adjusting for inflation) from 2012 [7,8].

Undiagnosed diabetes and stress hyperglycaemia in hospital

Aside from those with known diabetes prior to hospital admission, many people with hyperglycaemia are admitted without a prior diagnosis of diabetes. These include those with previously unknown diabetes but who continue to have hyperglycaemia after discharge. However, some people may develop transient hyperglycaemia during their inpatient stay that normalizes after discharge, so-called *stress hyperglycaemia* [9, 10]. The glucose values that represent stress hyperglycaemia vary, with some suggesting a fasting glucose level of $\geq 7.0 \text{ mmol/l}$ (126 mg/dl) or a random blood glucose level of $> 11.1 \text{ mmol/l}$ (200 mg/dl) [10], while the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) more recently defined it as any glucose level $> 7.8 \text{ mmol/l}$ (140 mg/dl) in an individual without a prior diagnosis of diabetes [3, 11]. Taken together, the number of people in hospital with either diabetes or transient hyperglycaemia is significant, with a prevalence of between 32% and 38% on general wards [12, 13] and between 28% and 80% of those with critical illness or undergoing cardiac surgery [13–17].

Pathophysiology of hyperglycaemia in acute illness

In fasting healthy individuals, glucose levels are usually maintained between 3.9 and 5.6 mmol/l (70 and 100 mg/dl). Glucose concentrations are finely controlled to match endogenous glucose production from the liver (with approximately 20% of the total coming from the kidneys) and glucose utilization by peripheral tissues [18–21]. The glucose concentrations are controlled by the balance of insulin and the counter-regulatory hormones, glucagon, catecholamines, growth hormone, and cortisol. At relatively low concentrations, insulin is a potent inhibitor of lipolysis, free fatty acid oxidation, and ketogenesis. As insulin concentrations increase, it lowers glucose concentrations, first by inhibiting hepatic gluconeogenesis and glycogenolysis, and then increasing peripheral glucose uptake and promoting glycogen synthesis. At even higher concentrations, insulin prevents protein breakdown and finally, at the highest concentrations, insulin acts to promote skeletal muscle formation [22,23].

Hyperglycaemia develops as a result of an imbalance between the glucose-lowering effect of insulin and the glucose-raising counter-regulatory response. Hyperglycaemia occurs as a result of (i) increased gluconeogenesis; (ii) accelerated glycogenolysis; and (iii) impaired glucose uptake and utilization in peripheral tissues [24]. The first two of these constitute the major contribution to hyperglycaemia. Skeletal muscle breakdown leads to an increased delivery of gluconeogenic precursors in the form of amino acids. Fat breakdown leads to an increased quantity of free fatty acids delivered to the liver. These effects may be exacerbated by prolonged starvation or during the fasting needed in the perioperative period [25]. In people without diabetes, a compensatory increase in insulin secretion helps to mediate against these catabolic effects. Without the glucose-lowering effects of insulin, the activity of gluconeogenic enzymes, in particular phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase, is increased [20,26]. During times of illness or stress, the increased concentrations of counter-regulatory hormones alter carbohydrate metabolism by inducing insulin resistance, increasing hepatic glucose production, and reducing peripheral glucose utilization [9,10]. A major consequence of severe hyperglycaemia is an osmotic diuresis that, if not countered, leads to dehydration and electrolyte disturbances, due to urinary loss of sodium, potassium, magnesium, and phosphate. The resulting increased plasma osmolality leads to a pro-coagulant state. In addition, hyperglycaemia results in raised concentrations of inflammatory cytokines and markers of oxidative stress such as tumour necrosis factor α , interleukin (IL)-6, IL-1 β , IL-8, and C-reactive protein [27–30]. These pro-inflammatory cytokines are associated with the development of insulin resistance by interfering with intracellular pathways downstream of the insulin receptor [27,29,31–34]. Furthermore, inflammatory cytokine concentrations fall when the glucose returns to normal [29].

There are other causes of hyperglycaemia that may be more specifically related to hospital admission [35]. These include co-administered medications such as enteral or parenteral nutrition, vasopressors, or corticosteroids. Almost 13% of all people in hospital were receiving corticosteroids, of whom 13% had a prior diagnosis of diabetes [36]. However, despite corticosteroid use being a cause of hyperglycaemia, which is associated with harm, only 20.8% of those on corticosteroids were having glucose monitoring [36]. In a recent study of people admitted with inflammatory

bowel disease and treated with steroids, 60% had a recorded episode of hyperglycaemia, including 57% who did not have a diagnosis of diabetes [37]. This issue is likely to become of greater concern with the evidence that corticosteroid use, in particular dexamethasone, reduces mortality in those admitted with moderate SARS-CoV-2 infection treated with oxygen therapy [38–42]. People with diabetes are at increased risk of being hospitalized with SARS-CoV-2 and their outcomes are worse than those without hyperglycaemia or diabetes [43–46]. Guidelines from the Joint British Diabetes Societies (JBDS) Inpatient Care Group in the UK and Diabetes UK are available to help tackle the management of hyperglycaemia and diabetes for those with or without Covid-19 infection [47,48].

Evidence of harm from in-hospital hyperglycaemia and effect of glucose lowering

Prior to the publication of large, randomized controlled trials in the 1990s, it had been well recognized that suboptimal diabetes management in ambulatory people with either type 1 diabetes or type 2 diabetes was associated with worse outcomes. The Diabetes Control and Complications Trial [49] and UK Prospective Diabetes Study [50] showed that interventions to improve glycaemic levels maintained over many years were associated with improved outcomes. In the world of hospitalized individuals with diabetes, there is compelling evidence that high blood glucose concentrations are associated with higher in-hospital morbidity and mortality, prolonged length of stay, unfavourable post-discharge outcomes, and significant excess healthcare costs in medical and surgical specialties [2,12,51–54]. Umpierrez et al. showed that individuals with new-onset hyperglycaemia had a striking 18-fold increase in in-hospital mortality, whereas people with known diabetes had a 2.7-fold increase in in-hospital mortality, compared with people with normoglycaemia [12]. In 2004, a joint position statement from the American College of Endocrinology (ACE) and the AACE on hospitalized individuals with diabetes and metabolic management concluded that hyperglycaemia in hospitalized individuals is a common, serious, and costly healthcare problem. There was a strong recommendation for early detection of hyperglycaemia and an aggressive management approach to improve outcomes [3]. In the UK, the JBDS has produced a series of guidelines on managing various aspects of diabetes care during hospital admission, which also recommend aggressive glucose management [48].

Hyperglycaemia, measured by glucose or glycated haemoglobin (HbA_{1c}), in the perioperative period is associated with poor outcomes in several surgical specialties, most often in those not previously known to have diabetes [53–59]. These poor outcomes include longer length of hospital stay and time in the intensive care unit (ICU), development of urinary tract and surgical site infections, and mortality. The reasons for these adverse outcomes are multifactorial, but include failure to identify those with diabetes and/or hyperglycaemia [60]; multiple comorbidities, including microvascular and macrovascular complications [61–67]; complex polypharmacy and insulin prescribing errors [68]; increased perioperative and post-operative infections [54,69,70]; associated hypoglycaemia and hyperglycaemia [54]; lack of or inadequate institutional guidelines for management of diabetes and/or hyperglycaemia during the admission [54,71]; and inadequate knowledge of diabetes and hyperglycaemia management among staff delivering care [72–74].

Having a diagnosis of diabetes prior to surgery is associated with a lowering of risk despite the hyperglycaemia [53, 54, 75], implying that the knowledge of diabetes is protective. It may be that people with diabetes have more attention paid to them, and thus have more contact with nursing and medical staff, which may mean that postoperative problems are picked up sooner [75]. What remains to be determined is whether it is the hyperglycaemia *per se* that causes the increased harm, or whether the high glucose is a marker for underlying disease severity.

While it is well established that perioperative hyperglycaemia is associated with harm, the association between high preoperative HbA_{1c} and outcomes is uncertain [76] because of a lack of high-quality prospective observational studies examining the relationship between HbA_{1c} and postoperative morbidity and mortality. The risks appear to increase when preoperative HbA_{1c} is >64 mmol/mol (8%), leading the UK JBDS guidelines to recommend a preoperative level of <69 mmol/mol (8.5%) [55].

There are increasing data, particularly from surgical specialties, to suggest that achieving optimal glycaemic levels during hospitalization is associated with improved outcomes [77, 78]. It was therefore surprising to see that the UK National Institute for Health and Care Excellence (NICE) suggest that there was little evidence to show that tight glucose management improves postsurgical outcomes in people with type 2 diabetes, or those not known to have diabetes, and that 'tight blood glucose control is not necessary for people in these two groups', although this likely represents the high level of evidence required by NICE to make solid recommendations [79]. For people with type 1 diabetes in the hospital, NICE recommends aiming for a blood glucose target of between 5.0 and 8.0 mmol/l [80]. Glycaemic targets are discussed in more detail in the next section.

Glycaemic targets for individuals with diabetes in hospital

The threshold for diagnosing hyperglycaemia during admission to hospital has been suggested as a random glucose >7.8 mmol/l (140 mg/dl) [11, 81]. In addition, it has been recognised that hypoglycaemia (*i.e.* blood glucose <4.0 mmol/l; 72 mg/dl) is associated with increased morbidity and mortality [82–84]. Hypoglycaemia is usually related to pre-existing comorbidities and the severity of intercurrent illness, rather than to medication use [85]. To reduce the impact of hypoglycaemia, there is a general consensus that glucose concentrations should not be allowed to fall below this threshold, although there are arguments that even 4.0 mmol/l is too low [86]. However, until recently the lack of robust data showing that aggressive glucose lowering reduces the excess morbidity and mortality associated with hyperglycaemia has meant that it has been difficult to reach an agreed consensus on what the target glucose concentrations should be in people with diabetes. Different targets have been suggested for different categories of inpatients, for instance those in the ICU compared with those on a general ward, or those due to undergo surgery.

Intensive care unit

A significant amount of work has been undertaken to establish the optimal glycaemic levels that are associated with the lowest morbidity and mortality since the first study published in 2001 on individuals in the surgical ICU in Belgium [17]. That study compared outcomes in over 1500 inpatients randomized to a group

given *usual care* – that is, glucose concentrations maintained between 10.0 and 11.1 mmol/l (180–200 mg/dl) – or treated with *intensive insulin therapy*, with glucose concentrations maintained between 4.4 and 6.1 mmol/l (80–110 mg/dl) and intravenous insulin given using an infusion pump. The mean glucose concentration in the usual care group was 8.5 mmol/l (153 mg/dl) and the mean concentration in the intensively treated arm was 5.7 mmol/l (103 mg/dl). Those randomized to the intensive insulin group did significantly better in all outcomes [17]. In particular, their mortality was reduced by 34%, but other outcome measures were also significantly improved, including less bacteraemia, less antibiotic use, shorter length of time on a ventilator, and fewer days in the ICU [17]. The authors then repeated the study in a medical ICU, with a mean glucose concentration in the intensively treated arm of 6.2 mmol/l (111 mg/dl), and showed that intensive insulin therapy was associated with a reduction in overall morbidity and a reduction in mortality if the stay on the ICU was over three days [83]. As a result of these two seminal studies, it had been suggested that the target for this cohort of inpatients should be between 4.4 and 6.1 mmol/l (80 and 110 mg/dl). However, subsequent attempts to reproduce these findings proved inconclusive, with most similar studies being unable to achieve similar reductions in morbidity or mortality [87–91]. Some of these subsequent studies were stopped early because of the significantly increased risk of harm due to the high frequency of severe hypoglycaemia [88–90].

In view of these and other findings, different recommendations have been published. A joint statement from the ADA and the AACE in 2014 recommended specific glycaemic targets in the ICU. They advocated for insulin initiation when glucose concentrations are persistently greater than 10.0 mmol/l (180 mg/dl), aiming for a glucose concentration between 7.8 and 10.0 mmol/l (140 and 180 mg/dl) [92]. They also suggested that in those centres with more experience in glucose management, a lower target of 6.1–7.8 mmol/l (110–140 mg/dl) may be appropriate provided that there is no increase in the incidence of severe hypoglycaemia [92]. By contrast, the Society of Critical Care Medicine in the USA recommends that glucose-lowering therapy is initiated once glucose levels rise above 8.3 mmol/l (150 mg/dl), and glucose concentrations should not be allowed to rise above 10.0 mmol/l (180 mg/dl) or drop below 3.9 mmol/l (70 mg/dl) [93]. Others have suggested that glycaemic targets vary according to a known or unknown diagnosis of diabetes [94], while there have been concerns that tight glycaemic management in critically ill individuals may do more harm than good [95].

A review of the literature on glucose levels in the ICU showed that there remained a wide variation in recommended targets, as well as methods to achieve them [96]. Of more concern, however, was a Chinese study reporting that many physicians did not know that hypoglycaemia in the people under their care was associated with harm, showing that more education was needed [97]. In summary, the issue of glycaemic targets in the ICU has yet to be resolved.

General wards

Studies from a variety of specialties show that hyperglycaemia in people in hospital is associated with negative outcomes [52, 98–101]; however, there is a paucity of good-quality data to inform the ideal targets for blood glucose in general wards. Until relatively recently, there were few data showing that optimizing glycaemic levels reduces the excess morbidity and mortality seen in hospital. Data are now emerging from surgical settings to show that achieving a glucose concentration of <8.3 mmol/l (150 mg/dl) is associated with

a lower risk of developing surgical site infection [78]. In the UK, the JBDS has published a series of consensus-based guidelines on several aspects of care for this increasingly large cohort [48]. It advocates that the target glucose concentration should be between 6.0 and 10.0 mmol/l (108 and 180 mg/dl), with a concentration of 4.0–12.0 mmol/l (72–216 mg/dl) being acceptable for medical patients and for conscious surgical patients, although the lower target of 4.0 mmol/l has recently been challenged [86]. The levels advocated by the JBDS are at slight variance with the USA, where the guidelines suggest targets for fasting glucose concentrations of <7.8 mmol/l (140 mg/dl) and a random glucose target of <10.0 mmol/l (180 mg/dl) [81]. Targets for those who are at the end of life are more relaxed (Chapter 73), aiming at avoiding symptomatic hypoglycaemia or hyperglycaemia, with concentrations of 6.0–15.0 mmol/l (108–270 mg/dl) being advocated in the UK [102] and similar but slightly lower levels in the USA [11].

Current recommended standards of hospital care for people with diabetes

Data from the USA in 2017 indicated that 38.7% of hospital bed days, accounting for an estimated 62.9 million days, were either attributable to or incurred by people with diabetes [7]. In the UK in 2019 people with diabetes occupied between 8.3% and 31% (mean 18.1%) of hospital beds [4]. Previous work from NaDIA and elsewhere has shown that the majority of people with diabetes were admitted for reasons other than diabetes, with ~90% admitted as an emergency [2, 103]. In addition, one in four people admitted with heart failure, heart attack, or stroke has diabetes [2].

Professional organizations from different countries publish recommended standards of hospital care. The International Diabetes Federation (IDF), an umbrella organization of more than 200 national diabetes associations in over 160 countries, offers a broad perspective on care relating to people with type 1 diabetes and type 2 diabetes during hospitalization, but acknowledges that not all countries have the infrastructure or resources to offer the same care standard for all. It therefore offers three care categories – recommended care, limited care, and comprehensive care – to which member organizations can benchmark [104, 105]:

- *Recommended care.* This is evidence-based care that is cost-effective in most nations with a well-developed service base, and with healthcare funding systems consuming a significant part of national wealth. Recommended care should be available to all people with diabetes and the aim of any healthcare system should be to achieve this level of care. However, as there are considerable variations in resources throughout the world, other levels of care are described that acknowledge low- and high-resource situations.
- *Limited care.* This is the lowest level of care that anyone with diabetes should receive, as standard medical resources and fully trained health professionals are often unavailable in poorly funded healthcare systems. However, even with limited and cost-effective resources, this level of care aims to achieve a high proportion of what can be achieved by recommended care. Only low-cost or high cost-effectiveness interventions are included at this level.
- *Comprehensive care.* This level of care includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving the best possible outcomes. However, the evidence base supporting the use of some of these expensive or new technologies is relatively weak.

Similar themes emerge when reviewing these documents relating to care, including the following:

- A diabetes diagnosis should be clearly identified in the hospital medical case records.
- All people with diabetes admitted to hospital should have their blood glucose level and HbA_{1c} measured, with results available to all members of the healthcare team.
- There should be an emphasis on insulin safety, particularly when using intravenous insulin infusion.
- Recommended blood glucose targets for people with diabetes in hospital should be stated, thereby reducing the risk of hypoglycaemia and hyperglycaemia.
- Discharge planning should be implemented on admission to hospital.
- Systems and policies should be in place that recognize the specific needs of people with diabetes in hospital.
- Each hospital should identify a clinical lead for inpatient care for people with diabetes.
- All people with diabetes should have access to a specialist inpatient multidisciplinary diabetes team.
- Staff caring for people with diabetes should be appropriately trained and competent in the management of inpatient diabetes.
- Diabetes self-management should be integrated into usual ward care.

Because of the ageing population, there are specific needs that also need to be considered. These are dealt with in more detail elsewhere [104, 106] (Chapter 72).

Minimizing length of stay

Reducing excess hospital length of stay is one of the principal aims of good care. Prolonged length of stay may occur for a multiplicity of reasons, but is often because of diabetes mismanagement secondary to inadequate staff knowledge and lack of education [72–74]. Insulin errors are associated with a longer hospital stay, and although it is recognized that certified diabetes educators (CDEs) and diabetes specialist nurses (DSNs) are effective in reducing length of stay, the majority of people with diabetes do not come into contact with these healthcare professionals during admission [107, 108]. The IDF and the ADA, as well as the JBDS in the UK, are among many organizations that have put discharge planning as a priority at the time of admission and not as an afterthought just prior to discharge [81, 109, 110]. Intervention by the diabetes inpatient team reduces the incidence of hypoglycaemia, reduces length of stay, and prevents 30-day readmission [111]. One systematic review and meta-analysis showed that reducing hypoglycaemia rates reduced length of stay by over four days [112].

Discharge planning defines the agreed management plan for that episode of care, including assessment and prompt referral to the specialist team if necessary, and can aid in anticipating and therefore preventing problems. When possible, this planning should be done in collaboration with the person with diabetes.

Patient safety

The issues surrounding inpatient safety focus predominantly on insulin and diabetes management errors, as well as the risks of infection or debilitation associated with extended length of hospital stay. Globally, insulin is one of the five highest-risk medications [113]. One-third of all hospital medical errors that cause death within 48 hours of the error involve insulin administration. Insulin medication errors can occur at any stage in the process of prescribing, preparing, and delivering the medication [114]. Errors

involving insulin infusion have been highlighted particularly in the last few years [103, 115]. In the UK, the 2019 NaDIA showed that 37.2% of those in hospital with type 1 diabetes and 40.3% of those with type 2 diabetes experienced an insulin-related drug error [4].

The UK National Patient Safety Agency reviews all medication errors, including those relating to insulin. In 2010, it published a six-year audit of reported insulin errors described as moderate and severe; 3881 reports were received and these included inpatient deaths [114]. It is well recognized that insulin errors occur because of the medication's complexity and its narrow therapeutic window. Initiatives to improve insulin prescribing and reduce these risks [116] include the introduction of electronic prescribing, while specialist diabetes pharmacists have been associated with lower error rates [117].

The use of sodium–glucose co transporter 2 (SGLT-2) inhibitors is beneficial for those with heart failure, and delays the progression of renal disease [118–124]. However, they increase the risk of dehydration, worsening renal function, and genital yeast infections. There is also a low but significant risk of developing euglycaemic or hyperglycaemic diabetic ketoacidosis (DKA). Although there are few data to support routine use of SGLT-2 inhibitors in the acute setting, if a person is already taking them prescribers should remain cautious, with a low threshold for temporarily discontinuing them [125].

Diabetes self-management

When not in hospital, people with diabetes are accustomed to managing their own condition. Traditionally, people with diabetes are disempowered in the management of their diabetes as soon as they are admitted, and for many this disempowerment is a negative experience [109, 126, 127]. The IDF has promoted the need for individuals to be enabled to self-manage their own condition [109]. Self-management includes the whole process of adjusting insulin treatment in response to self-measured glucose values [128]. The USA and UK have also set national standards defining the principles of self-management of diabetes, but there is general acceptance that there is no best practice education programme that meets the needs of all people with diabetes [129, 130].

Although this is an institutional decision, in principle individuals with diabetes in hospital should be given the opportunity to decide whether they wish to self-manage their condition during their admission, provided that they are well enough to do so. The key principle of self-management is that the person with diabetes has primary responsibility for making the decision about whether they should self-manage their own diabetes. Individuals suitable for self-management in hospital must be competent adults with a stable level of consciousness who successfully manage their diabetes at home. In addition, while in hospital it is advised that these people have the physical skills appropriate to self-administer insulin, be accustomed to performing glucose monitoring, and have adequate oral intake. In the event that self-care is deemed unsafe or impossible (e.g. critically ill, post-surgery, or unwillingness to self-manage), there must be a governance arrangement to assess their competency and, if necessary, supersede the individual's right to self-care. Hospitals should have a person-centred policy for diabetes self-management. Encouraging and supporting individuals to take as much responsibility for their diabetes management as they wish, and their clinical status allows, are likely to enhance the experience during a hospital stay [128, 131]. Part of this involves institutions providing written information for staff and patients to explain the responsibilities of self-management. For elective surgical patients, this written information may be provided at the time of

the pre-assessment clinic. In addition, for elective admissions, a care plan should be agreed at that time to establish whether the person with diabetes wishes to self-manage and the circumstances in which this may not be possible [128].

At the time of admission, the responsible nurse and the person with diabetes should again agree on the circumstances in which the individual with diabetes should or should not self-manage. Ideally, an agreement form should be signed by both the person with diabetes and the responsible nurse. People with diabetes should be able to monitor their glucose with their own glucose monitoring equipment, but results should be made available to hospital staff. For hospitals that utilize centrally uploaded glucose monitors, it is useful to maintain some monitoring on hospital equipment to allow system safety netting to continue. In addition, the technique for glucose testing and insulin administration should also be assessed. Once the person with diabetes has administered their own insulin, the dose self-administered should be recorded on the prescription chart, or an entry made on an electronic prescription by a member of staff.

To allow people with diabetes to keep and administer their own insulin, facilities should be available for safe storage of insulin and disposal of sharps in the ward environment. In addition, the institution should ensure that the timing and content of meals are suitable for people with diabetes; this is a common cause of unhappiness and dissatisfaction among those with diabetes [132].

It is important that clinical circumstances be regularly assessed during the admission to ensure that the individual's ability to self-manage has not been compromised by their clinical condition. If there are doubts or disagreements between the person with diabetes and the staff as to whether they can self-manage, then the diabetes specialist team may need to be involved.

Patient satisfaction

The experience of people with diabetes in hospital is important and plays a crucial role when developing local and national guidelines, but there is little in the worldwide literature evaluating experience during hospitalization. The UK has, however, gathered a large amount of information on patient satisfaction through two sources.

The Diabetes Inpatient Satisfaction Study was a cross-sectional study carried out in the UK measuring diabetes treatment satisfaction and its relationship to diabetes care in hospital by the validated Diabetes Treatment Satisfaction Questionnaire for Inpatients in over 1300 people with insulin-treated diabetes [132, 133]. Satisfaction with the general diabetes treatment was high, but there were high levels of extreme dissatisfaction with meal choices and quality, and lack of similarity of hospital meals to normal domestic choices: 23% would never or rarely have made similar meal choices at home.

Hyperglycaemia or hypoglycaemia was reported for much of the hospital stay (20% and 7%, respectively) and 26% reported at least one severe hypoglycaemic episode. More frequent hyperglycaemia or hypoglycaemia was associated with significantly poorer overall satisfaction scores and negative well-being scores and lower satisfaction with the timing of medication in relation to meals. Factors that were significantly associated with the highest levels of satisfaction were the amount of time spent with a diabetes inpatient specialist nurse (DISN) and insulin self-administration [132].

Satisfaction questionnaires were an integral part of NaDIA, which has run over several years [4]. The 2019 audit showed a wide variation in satisfaction scores between institutions, but a consistent finding was that the patient experience had worsened since

2011 in terms of meal choice, meal timing, and the individuals' perception of the knowledge of diabetes among the staff caring for them [4].

The role of the diabetes specialist team

The person with diabetes remains at the heart of the specialist team. Diabetes specialist inpatient teams are multidisciplinary and should include a consultant in diabetes with a specialist interest in inpatient care, who often is seen as the lead, working closely with DISNs or CDEs, diabetes dieticians, pharmacists, and specialist podiatrists. Extended foot team members should include orthopaedic and vascular surgeons, microbiologists, tissue viability nurses, and interventional radiologists. When necessary, rehabilitation teams should also be available. The specialist team should work together by individually contributing their specialist skills to provide a holistic approach to patient care. The success of such teamwork requires a culture that invests in excellent communication between the person with diabetes, diabetes specialists, and non-specialist teams to activate timely intervention to prevent glycaemic deterioration during the hospital stay.

Involvement of the specialist diabetes team, and in particular DISNs and CDEs, significantly reduces length of stay and insulin errors and improves the patient experience, while reducing readmissions [6, 107, 135–136].

A CDE is a health professional in North America who possesses comprehensive knowledge of and experience in diabetes management. Unlike the DISN in the UK, the role is not exclusive to nursing, but CDEs must have a relevant health-related degree and undergo extensive training. Both CDEs and DISNs educate and support people affected by diabetes to understand and manage the condition and promote self-management to achieve individualized behavioural and treatment goals that optimize health outcomes. Working in close partnership with people in the community, such as social workers, case managers, and home care coordinators, they are able to facilitate a smooth care pathway from hospital to home at discharge. The DSNs, who work exclusively in diabetes care, and the CDEs are also integral to providing ongoing staff training and may also be prescribers [107]. Aside from clinical care, they are frequently involved in medical and nursing education. Despite these numerous attributes, the 2019 NaDIA showed that almost one-fifth of UK hospitals do not have a DISN, while the number of hospitals offering inpatient dietetic or podiatry support is even worse [4].

Staff education

One of the key roles for the diabetes inpatient team is to educate ward-based non-specialist healthcare professionals and others, including paramedical, nursing, and medical students. Ward staff may have little or no protected time for education and training other than mandatory training defined by the employing organization. Despite the large numbers of people with diabetes in hospital, often the only mandatory training in diabetes is in blood glucose monitoring. People with diabetes, who may have a high level of knowledge about their condition, are therefore frequently managed by nursing and medical staff who only have a rudimentary knowledge and training in diabetes care [72–74, 137]. Hence it is the senior physicians who have the responsibility for educating junior medical staff, while the CDE and DISN teams are often best placed to offer education to ward-based staff because they can use the opportunity when reviewing patients to provide education to other non-specialist staff. Utilizing multiple professional groups, including medical, nursing, and pharmacy staff, to provide consistent safety messages to all professions will help to maximize the impact of education in a hospital setting.

Because so many people in hospital have diabetes, it is almost impossible for specialist team members to see every person on a regular basis. In the UK, specialist teams therefore have drawn up a priority list of those who should be referred for assessment (Figure 39.1); this can be adapted based on local need. Ward-based and specialist nursing staff in the UK have to undergo a revalidation process that includes ascertaining the views of the person with diabetes and demonstrating competency [137, 138].

Management of in-hospital hyperglycaemia

The ADA has stated that it is incumbent on organizations to ensure that diabetes is appropriately managed in hospital [81]. This sentiment is similar to one echoed by the now decommissioned NHS Institute for Innovation and Improvement in the UK, which said that it is as unacceptable for hospitals not to have a glycaemic management policy as it is for them not to have an infection control policy.

People with diabetes occupy a significant proportion of hospital beds, with one in six in the UK and about one in four in the USA [4, 7]. This does not include those who develop raised

Always refer	Consider referral	Not necessary
<ul style="list-style-type: none"> • Acute coronary syndrome • DKA/HHS • Severe/repeat hypos • New type 1 diabetes • IVII – outside target limits • Persistent hyperglycaemia • Use of U500/Humulin R • Pregnancy • Enteral nutrition • Sepsis • Patient request • Pump patients • Adolescents • Ulcerated feet 	<ul style="list-style-type: none"> • New type 2 diabetes – symptomatic • Unable to self-manage • Impaired consciousness • Vomiting • Educational needs • NBM for more than 24 h • Stress hyperglycaemia • Steroid therapy • End-of-life management • Pre-surgery admission • Glucose concentration >12 mmol/L 	<ul style="list-style-type: none"> • New type 2 diabetes - no symptoms • Minor hypoglycaemia • Transient hyperglycaemia • Simple education needs • Routine dietetic advice • Well-controlled diabetes • Good self-management skills • Routine diabetes care

Figure 39.1 Prioritization of those who should be seen by a specialist diabetes inpatient team. DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycaemic syndrome; IVII, intravenous insulin infusion; NBM, nil by mouth. Source: Adapted from ThinkGlucose.

Table 39.2 Transition from intravenous to subcutaneous insulin.

Insulin	Optimal glucose levels, i.e. HbA _{1c} <59 mmol/mol (7.5%)	Suboptimal glucose levels	Monitoring blood glucose for all individuals
Basal insulin	<p>Restart usual dose of insulin when it is due (usually with either breakfast or evening meal). Do not stop VRIII until at least 30–60 min after insulin has been given and patient has eaten</p> <p>If it is necessary to stop VRIII but the basal insulin is not due for several hours, give half the usual dose of basal insulin. This will provide background insulin until the usual dose can be recommenced</p>	In addition, discuss with local diabetes inpatient team. Insulin regimen may need adjusting	CBG should be checked 1 h after discontinuing VRIII and at least 4-hourly for the next 24 h, to ensure that there is no rebound hyper- or hypoglycaemia
Once- or twice-daily mixed insulin	<p>Restart usual dose of insulin together with a meal (either breakfast or evening meal). Do not stop VRIII until at least 30–60 min after insulin has been given and the individual has eaten</p> <p>If it is necessary to stop VRIII at lunchtime, give half the usual breakfast dose of mixed insulin. This will provide essential background insulin until the usual dose can be recommenced</p>		
Multiple daily insulin injections (MDI or basal bolus)	<p>Restart usual diabetes treatment together with a meal</p> <p>Basal insulin will usually have been continued. Restart bolus dose of insulin together with the next meal. Do not stop VRIII until at least 30–60 min after bolus insulin has been given and the individual has eaten</p> <p>If basal insulin has been stopped, background insulin must be restarted prior to stopping VRIII. Ideally, continue VRIII until basal insulin is given and a meal is due, and stop at least 30–60 min after basal and bolus insulin is restarted</p> <p>If it is necessary to stop VRIII, but basal insulin is not due for several hours, give half the usual daily dose of basal insulin, along with a meal and bolus insulin. This will provide essential background insulin until the usual dose can be recommenced</p>		
Insulin pump (CSII)	<p>Restart usual basal rate via CSII</p> <p>Do not stop VRIII until at least 30 min after insulin has been recommenced via CSII</p> <p>Give bolus insulin according to patient's usual regime. It is not typically necessary to wait until a mealtime to switch back to CSII therapy</p> <p>Avoid restarting CSII at bedtime</p>		

CBG, capillary blood glucose; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; VRIII, variable-rate intravenous insulin infusion.
Source: Modified from George et al. 2015 [167].

Box 39.2 Converting from Intravenous to Subcutaneous Insulin

Step 1

Calculate the total daily dose (TDD) using either of two methods: weight based, or using the dose delivered for the last sixhours using a variable-rate intravenous insulin infusion (VRIII).

In frail, older individuals, those with renal failure (chronic kidney disease stage 4 or 5) or severe hepatic failure, or those with newly diagnosed type 1 diabetes:

$$\text{TDD} = 0.3 \times \text{body weight in kg}$$

All other adults:

$$\text{TDD} = 0.5 \times \text{body weight in kg}$$

Ideally, 24hours of data should be utilized to make the calculation, but if this is not available then all available data on hourly

insulin requirements should be used. For example, if six hours of data are available, then the calculation is as follows:

Total dose of insulin administered in the last 6 hours of the VRIII / 6 = average hourly dose Average hourly dose × 20 (not 24, to reduce risk of hypoglycaemia) = estimated TDD

Step 2

Use the TDD to convert the individual to either a premixed twice-daily insulin regimen or a multiple basal bolus dose regimen.

For a basal bolus regimen, 50% of the TDD is usually given as basal insulin, and the remainder as rapid-acting insulin, divided equally between breakfast, lunch, and evening meal.

For a twice-daily, premixed insulin regimen, individuals usually need 60% of the TDD at breakfast and the remaining 40% with the evening meal.

Source: Modified from George et al. 2015 [167].

thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists – are unlikely to result in hypoglycaemia owing to their modes of action, unless co-prescribed with insulin or sulfonylureas. Hypoglycaemia should be excluded in any person with diabetes who is acutely unwell, drowsy, unconscious, unable to cooperate, or presenting with aggressive behaviour or seizures. In-hospital hypoglycaemia is defined as a blood glucose level ≤ 3.9 mmol/l (70 mg/dl) [81]. Hypoglycaemia in hospital is widespread and coupled with insufficient knowledge of how to detect and manage it [82, 142].

Frequency of hypoglycaemia in hospital

Hypoglycaemia is given as the primary cause of hospital admission in about 5% of all people admitted with type 1 diabetes, and 1.5% of those with type 2 diabetes [178]. The 2019 UK NaDIA showed that 16.5% of people with diabetes in hospital experienced one or more hypoglycaemic episodes with a blood glucose less than 3.0–4.0 mmol/l (54–72 mg/dl), with 6.8% experiencing one or more hypoglycaemic episodes below than 3.0 mmol/l (54 mg/dl), and 1.4% requiring rescue treatment with intravenous glucose or intramuscular glucagon [4].

Farrokhi et al. reported a prevalence of severe hypoglycaemia ranging from 5% to 32% in those treated with insulin [179]. The highest proportion of episodes took place overnight (34.3%), between 9 p.m. and 9 a.m., when snack availability was likely to have been lowest; these observations have been confirmed elsewhere [180]. People treated with sulfonylureas were more likely to experience hypoglycaemia than those using insulin (75.3% vs 59.3%) [103, 180, 181].

The tight glycaemic levels achieved in ICUs led to much higher reported rates of hypoglycaemia, with the incidence of blood glucose ≤ 2.2 mmol/l (40 mg/dl) ranging from 5% to 18.7% [83, 87, 89, 182].

Causes of in-hospital hypoglycaemia

Common causes of hypoglycaemia are listed in Table 39.3. One of the most serious and common causes of hypoglycaemia is insulin prescription errors, including misreading poorly written prescriptions, such as when U is used for units (e.g. 4 U becoming 40 units), or confusing the insulin name with the dose (e.g. Humalog Mix25 becoming Humalog 25 units). The advent of electronic prescribing may be responsible for the small reductions in prescribing errors

reported by NaDIA [103]. Risk factors for hypoglycaemia include older age (>70 years), cognitive impairment, nephropathy, insulin or sulfonylurea treatment, being of Black, Asian or minority ethnic groups, raised C-reactive protein, being admitted as an emergency, and having low sodium or albumin concentrations [181, 184, 185].

Mortality and length of stay associated with in-hospital hypoglycaemia

Lake et al. published a systematic review and meta-analysis on the effects of hypoglycaemia during a hospital admission [112]. They found that experiencing a blood glucose of <4.0 mmol/l (72 mg/dl) led to an increased length of stay of 4.1 days (95% confidence interval [CI] 2.36 to 5.79) compared to those who did not. In addition, the relative risk (RR) of mortality was double (RR 2.09; 95% CI 1.64 to 2.67) [112]. Those experiencing an episode of hypoglycaemia had a 66% increased risk of death within one year, compared to those with no hypoglycaemia [186].

Management of in-hospital hypoglycaemia

People experiencing hypoglycaemia require prompt treatment with quick-acting carbohydrate to return their blood glucose levels to the normal range. The quick-acting carbohydrate should be followed by giving long-acting carbohydrate, either as a snack or as part of a planned meal. When it is safe to do so, a blood glucose measurement should be taken to confirm hypoglycaemia (especially if there is any suspicion that the person may be currently under the influence of alcohol or non-prescription drugs). If measurement is difficult (e.g. during a seizure), then treatment should not be delayed.

Adults who have suboptimal glycaemic levels may start to experience symptoms of hypoglycaemia at blood glucose levels >4.0 mmol/l (72 mg/dl), but the thresholds for cognitive dysfunction are unaffected; therefore, the only reason for treatment is symptomatic relief. Hence adults who are experiencing hypoglycaemia symptoms but have a blood glucose level >4.0 mmol/l (72 mg/dl) should be treated with a small carbohydrate snack only, such as a medium banana, a slice of bread, or a normal meal if due. All adults with a blood glucose level <4.0 mmol/l (72 mg/dl) with or without symptoms of hypoglycaemia should be treated as shown in Figure 39.2.

When rescue treatment is required, intramuscular glucagon should only be given once. It should not be given to those with a

Table 39.3 Potential causes of in-hospital hypoglycaemia.

Medical issues	Carbohydrate intake issues
<ul style="list-style-type: none">• Inappropriate use of stat or PRN rapid/short-acting insulin• Acute discontinuation of long-term steroid therapy• Recovery from acute illness/stress• Mobilization after illness• Major amputation of a limb• Incorrect type of insulin or oral hypoglycaemic therapy prescribed and administered• Inappropriately timed insulin or oral hypoglycaemic therapy in relation to meal or enteral feed• Change of insulin injection site• Intravenous insulin infusion with or without glucose infusion• Inadequate mixing of intermediate-acting or mixed insulins• Regular insulin doses or oral hypoglycaemia therapy being given in hospital when these are not routinely taken at home	<ul style="list-style-type: none">• Missed or delayed meals• Less carbohydrate than normal• Change of timing of the biggest meal of the day (i.e. main meal at midday rather than evening)• Lack of access to usual between-meal or before-bed snacks• Prolonged starvation time, e.g. nil by mouth• Vomiting• Reduced appetite• Reduced carbohydrate intake

PRN, as required.

Source: Modified from Stanisstreet et al. 2020 [183].



Figure 39.2 Algorithm for the treatment of hypoglycaemia in adults with diabetes in hospital. Hypoglycaemia is defined as a blood glucose level of <4.0 mmol/l (72 mg/dl). If the patient is symptomatic but the blood glucose is >4.0 mmol/l (72 mg/dl), then a small carbohydrate snack should be given for symptom relief. ABC, airway, breathing, circulation; CDE, certified diabetes educator; DSN, diabetes specialist nurse; NBM, nil by mouth. Source: Joint British Diabetes Societies for Inpatient Care 2022 [183].

history of known liver disease, or those with depleted glycogen reserves (e.g. alcohol excess), because it will likely be considerably less effective. A new formulation of intranasal glucagon has recently become available that has a similar efficacy to the intramuscular formulation [187]. When intravenous glucose is required 10% glucose is preferred, because retreatment rates were the same as those for 50% glucose, with lower risk of extravasation injury and lower likelihood of resultant high blood glucose concentrations [183, 188].

Evidence for treatment options

There is limited evidence regarding the quantity of quick-acting carbohydrate required to treat an episode of hypoglycaemia successfully. The initial quantities chosen were the result of expert consensus subsequently backed up by glucose clamp studies [189, 190]. Subsequent work has shown that ~20 g of rapid-acting carbohydrate is often sufficient, with less than 10 g likely to be inadequate [191, 192]. Chocolate- and sucrose-containing foods should be avoided, because the high fat content in chocolate slows gastric emptying, thus delaying absorption, and sucrose needs to be cleaved by intestinal disaccharidases prior to absorption [193, 194]. Fresh fruit juice or glucose-containing tablets or gel remain the most frequently used treatment for hypoglycaemia and are an essential component of Hypoboxes, which are commercially available [183, 190, 195]. The suggested contents of a Hypobox can be found in Box 39.3.

All hypoglycaemic events should be documented in the clinical records. The underlying cause of hypoglycaemia should be investigated and risk of recurrence reduced where possible. Regular capillary blood glucose monitoring should be continued for 24–48 hours. The person with diabetes should be told to continue this at home if they are to be discharged. Hypoglycaemia education should be given or a referral made to the DISN/CDE.

Box 39.3 Suggested Contents of a Hypobox

- A copy of the locally agreed hypoglycaemia algorithm (laminated and attached to the inside of the lid)
- 2 × 200 ml cartons of fruit juice
- 2 packets of glucose tablets
- 1 mini-pack of biscuits (source of long-acting carbohydrate)
- 3 tubes (one box) of glucose gel
- 20% glucose intravenous solution (100 ml vial)
- 1 × 18G intravenous cannula
- 1 × 16G intravenous cannula
- 1 × 10 ml sterile syringe
- 3 × 10 ml 0.9% sodium chloride solution ampoules for flush
- 1 × 21G sterile needle
- Chlorhexidine spray/alcohol wipes
- 1 dressing cover for the intravenous cannula
- 10% glucose for intravenous infusion (500 ml bag)
- Audit form
- Instructions on where to send the audit form and replenish supplies
- 1 glucagon pack: to be kept in the nearest drug refrigerator or labelled with a reduced expiry date of 18 months if it is stored at room temperature

Source: Modified from JBDS 2020 [183].

Surgery in people with diabetes

Perioperative and postoperative hyperglycaemia is associated with short- and long-term harm, which has been reported in many settings, including general surgery [53, 54], cardiac surgery [196], vascular surgery [197, 198], neurosurgery [199], orthopaedic surgery [200, 201], colorectal surgery [202], trauma [203], breast surgery [204], liver transplantation [205], hepatobiliary and pancreatic surgery [206], cholecystectomy [207], burns [58], and foot and ankle surgery [208]. These harms include surgical site infection [59], length of time in hospital, acute kidney injury, myocardial infarction, time spent in an ICU or on a ventilator, and death. The perioperative mortality rate is up to 50% higher than in people without diabetes [54]. In addition, people with diabetes are less likely to be offered day-case surgery, are more likely to have emergency surgery, have longer lengths of stay following admission, and have a higher rate of 28-day readmission following surgery [209]. Thus, there is an imperative to optimize glycaemic levels prior to surgery and around the time of the operation. However, for elective surgery this optimization would require a great deal of coordination between all the teams and individuals involved in the care of the person with diabetes. In the UK, the National Confidential Enquiry into Patient Outcome and Death conducted a study into perioperative care and showed that there were several parts of the patient journey that could be improved [61]. Its recommendations are listed in Table 39.4.

Currently, there is a lack of good communication between primary care and surgeons when referring for elective surgery [60, 61]. This is important, because individuals who have been identified as having diabetes prior to surgery have a significantly lower risk of poor outcomes, regardless of their glycaemic levels [53]. This may be because of the improved communication between staff. Furthermore, if an individual is treated with an intravenous insulin infusion, it is likely that they will have more frequent contact with nursing staff, if only to have a capillary glucose measurement taken. Indeed, pooled data from a large number of Veterans Affairs (VA) hospitals in the USA suggested that people known to have diabetes were more likely to have their glucose checked postoperatively (with higher preoperative HbA_{1c} being associated with a higher number of tests) [75]. In addition, those with higher postoperative glucose concentrations were more likely to go onto insulin [75]. Hence if complications do occur, they may be picked up at an earlier stage.

In the UK, the JBDS guideline for the perioperative management of adults with diabetes recommends that the glucose targets for patients undergoing surgery are to keep levels between 6.0 and 10.0 mmol/l (108 and 180 mg/dl), with an acceptable range of 4.0–12.0 mmol/l (72–216 mg/dl) in the awake surgical patient [55]. In those who are asleep, or unable to communicate, the risk of developing hypoglycaemia increases at the lower limit, hence the range is recommended to be 6.0–12.0 mmol/l (108–216 mg/dl) [86, 210]. The USA and other countries do not yet have similar guidelines, although given the recent evidence that a perioperative HbA_{1c} level of >8.0% (64 mmol/mol) is associated with greater harm, organizations may begin to address this in the future [140, 211].

Due to the greatly increased risk of postoperative complications associated with hyperglycaemia, it may be necessary for units to adopt a policy to measure a capillary glucose level in at-risk individuals at the preoperative assessment clinic or at the time of acute admission, to ensure that those with undiagnosed hyperglycaemia,

Table 39.4 List of recommendations around peri-operative diabetes care made by the UK National Confidential Enquiry into Patient Outcome and Death in its report on perioperative diabetes care.

1. Write and implement a national joint standard and policy for the multidisciplinary management of patients with diabetes who require surgery.
2. Appoint a clinical lead for perioperative diabetes care in hospitals where surgical services are provided.
3. Use a standardized referral process for elective surgery to ensure appropriate assessment and optimization of diabetes.
4. Ensure that patients with diabetes undergoing surgery are closely monitored and their glucose levels managed accordingly.
5. Ensure a safe handover of patients with diabetes from theatre recovery to ward, which should be documented in the case notes.
6. Develop a preoperative assessment clinic policy and standards for the management of patients with diabetes. These should be developed by the lead anaesthetist and the clinical lead for perioperative diabetes management.
7. Ensure that patients with diabetes attending a preoperative assessment clinic prior to elective surgery have (i) access to the diabetes multidisciplinary team; and (ii) written instructions regarding their diabetes management plan prior to surgery.
8. A clinical lead for day surgery should be in place in all hospitals providing day surgery services.
9. Cancellation of elective surgery in patients with diabetes should be avoided, particularly for known clinical reasons.
10. Develop and implement referral criteria for surgical inpatients with diabetes to members of the diabetes multidisciplinary team members as required.
11. Record and monitor the time at which a patient begins fasting (for surgery or clinical reasons).
12. Prioritize patients with diabetes on the operating list to avoid prolonged starvation.
13. Provide patients with diabetes with education and information about their diabetes management at discharge from hospital as part of the discharge planning process.

Source: Modified from National Confidential Enquiry into Patient Outcome and Death 2018 [61].

either diabetes or stress hyperglycaemia, can be identified early and appropriately treated promptly.

Potential mechanisms of beneficial effects of glucose lowering in surgical settings

Although the data to show that lowering blood glucose is beneficial in surgical patients are only emerging now, it is well recognized that insulin has several beneficial effects on the inflammatory cascade that are independent of its metabolism-regulating effect. These effects include reducing the degree of oxidative stress by its action on free radical production and clearance [213], and also beneficial effects on reducing pro-inflammatory cytokine levels in addition to improving white cell and endothelial function [213–215]. These effects may be in part responsible for the reduction in surgical site infections and reduced mortality seen when optimal glucose concentrations are maintained [78, 216]. What constitutes *optimal glycaemic management*, however, varies between studies [216].

The role of primary care in supporting diabetes care before elective surgery

The patient journey for elective surgery usually starts with a primary care assessment and referral to the surgeons [55]. A study of 1919 referrals made to all surgical specialties across 11 hospitals across one week in the East of England showed that communication between primary and secondary care at the time of referral for a

surgical opinion is poor [60]. There were 8.8% of referrals for people with diabetes (compared to the 6.5% prevalence of diabetes in the general population). Of those taking a glucose-lowering agent, 22% had diabetes mentioned as a comorbidity in the letter. Only 7.7% of those with diabetes had a recent HbA_{1c} documented, and 11.8% had the medication listed [60]. While a meta-analysis suggested that there was no relationship between HbA_{1c} and outcomes in surgical patients [217], studies have shown that improving glycaemic management reduces the risk of developing surgical site infections [78].

In the absence of randomized controlled trials, the current guidelines are pragmatic because it is well recognized that high-risk surgical patients are often older and have multiple coexisting medical conditions. Attempts to lower glycaemic levels aggressively may be associated with harm in the form of hypoglycaemia. However, HbA_{1c} levels >64 mmol/mol (8%) are associated with poor outcomes [211] and the UK National Guidelines suggest that HbA_{1c} should be <69 mmol/mol (8.5%) [55]. Hence it is incumbent on the primary care provider to optimise glycaemic levels prior to referral, if possible, or after referral is made, to reduce the risk of the procedure being cancelled or postponed owing to hyperglycaemia and the risk of harm postoperatively. The information provided by the primary care team should help the surgeon when individuals are seen in the surgical outpatient clinic.

Preoperative assessment

If the decision is made to operate, then the surgeon should communicate the presence of diabetes to the preoperative assessment team, the anaesthetists, and the operating list planners, so that the patient may be placed early on a theatre list to minimize starvation time and subsequent metabolic disturbance. This would also increase the likelihood that they could be same-day admissions. In addition, the provision should be made for postoperative admission to critical care, if this is indicated, especially with people who are at high risk and with suboptimal glycaemic levels.

The opportunity to optimize preoperative glycaemic levels should be taken, either by referring back to the primary healthcare team responsible for their diabetes or using a DSN or CDE as necessary [209]. The management of other comorbidities should also be optimized. There should be good lines of communication between the pre-assessment team and the surgical team, such that the patient is aware when they are due to come in, where they are due to go, and what time their surgery is. They should also have explicit written instructions on how to manage their diabetes medication. These are shown in Tables 39.5 and 39.6.

Many people with diabetes in the UK have been inappropriately denied day-case surgery [6]. This means that these individuals are unnecessarily admitted to hospital for an overnight hospital stay, adding to the cost burden, in the belief that being in hospital will lead to glycaemic optimization. However, the reality is likely to be that the person is admitted to a ward the evening prior to surgery, when there are fewer nursing staff available, treated with a VR III, and looked after by one of the most junior members of the medical team, who may have inadequate levels of knowledge of diabetes management [72–74]. More recently, initiatives have been put into place in many institutions to improve perioperative care [218, 219].

Hospital admission

During the hospital admission, it is important that the individualized care plan is communicated to all staff involved in the care of the person with diabetes and that all efforts are made to minimize the metabolic consequences of starvation and surgical stress. Work

Table 39.5 Guidelines for perioperative adjustment of insulin.

	Insulins	Day prior to admission	Morning surgery	Afternoon surgery
Long-acting insulin	Once-daily long-acting (morning) (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Doses should remain unchanged	Dose will need to be reduced by 20% and blood glucose should be checked on admission	Dose will need to be reduced by 20% and blood glucose should be checked on admission
	Once-daily long-acting (lunchtime) (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Dose will need to be reduced by 20%	Restart insulin at normal dose when eating and drinking	Restart insulin at normal dose when eating and drinking
	Once-daily long-acting (evening) (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Dose will need to be reduced by 20%	No dose adjustment necessary	No dose adjustment necessary
	Twice-daily long-acting (e.g. Hypurin®, Bovine Lente, Lantus®, Levemir®, Tresiba®, Insulatard®, Humulin I®, Insuman Basal®, Abasaglar®, Toujeo®, Semglee®, Xultophy®)	Morning dose will need to stay the same Evening dose will need to be reduced by 20%	Morning dose will need to be reduced by 20% and blood glucose should be checked on admission Evening dose will remain unchanged	Morning dose will need to be reduced by 20% and blood glucose should be checked on admission Evening dose will remain unchanged
Premixed insulin	Twice-daily premixed (e.g. Novomix 30®, Humulin M3®, Humalog Mix 25®, Humalog Mix 50®, Insuman Comb 15®, Insuman Comb 25®, Insuman Comb 50®, Hypurin Porcine 30/70 Mix®)	Morning and evening doses should remain unchanged	Halve usual morning dose. Blood glucose should be checked on admission Resume normal insulin with evening meal	Halve usual morning dose. Blood glucose should be checked on admission Resume normal insulin with evening meal
	Three times per day premixed (e.g. Novomix 30®, Humulin M3®, Humalog Mix 25®, Humalog Mix 50®, Insuman Comb 15®, Insuman Comb 25®, Insuman Comb 50®, Hypurin Porcine 30/70 Mix®)	Doses should remain unchanged	Halve usual morning dose. Blood glucose will be checked on admission Omit lunchtime dose Resume normal insulin with evening meal	Halve usual morning dose. Blood glucose should be checked on admission Omit lunchtime dose Resume normal insulin with evening meal
Mixture of short- and intermediate-acting insulin	Twice-daily (two different types of insulin) combined by the patient into one injection	Morning and evening doses should remain unchanged	Calculate the total dose of both morning insulins and give half of this total dose as intermediate-acting insulin only, in the morning	Calculate the total dose of both morning insulins and give half of this total dose as intermediate-acting insulin only, in the morning
	Short-acting (e.g. Insuman Rapid®, Humalog®, Actrapid®, Hypurin® Bovine Neutral, Hypurin® Porcine Neutral, NovoRapid®, Humulin S®, Apidra®, Fiasp®, Lyumjev®)		Blood glucose should be checked on admission	Blood glucose should be checked on admission
	AND intermediate-acting (e.g. Hypurin® Bovine Isophane, Hypurin® Porcine Isophane, Insulatard®, Humulin I®, Insuman Basal®)		Resume normal insulin with evening meal	Resume normal insulin with evening meal
Short-acting insulin	Short-acting insulin with meals (2–4 doses a day) (e.g. Insuman Rapid®, Humalog®, Actrapid®, Hypurin® Bovine Neutral, Hypurin® Porcine Neutral, NovoRapid®, Humulin S®, Apidra®, Fiasp®, Lyumjev®)	Doses should remain unchanged	Omit morning dose if no breakfast is eaten Blood glucose should be checked on admission Omit lunchtime dose if not eating and drinking normally Resume normal insulin with evening meal	Take usual morning insulin dose with breakfast Omit lunchtime dose if not eating Blood glucose should be checked on admission Resume normal insulin with evening meal

Resume taking normal insulin the morning after surgery (procedure). However, blood glucose may be higher than usual for a day or so.

If a variable-rate intravenous insulin infusion is used, then the dose of long-acting insulin should be reduced by 20%. Short-acting, intermediate, and pre-mixed insulins should be discontinued. Normal insulin doses should be recommenced when that person is eating and drinking normally.

At the preoperative assessment clinic, all individuals should have emergency treatment for hypoglycaemia written on their drug chart, i.e. 40% glucose gel, and 20% glucose rapid-acting insulin should also be prescribed.

If the patient requires an ongoing variable-rate intravenous insulin infusion, then the long-acting background insulin should be continued but at 80% of the usual dose. Normal insulin doses should be recommenced when the person is eating and drinking normally.

Table 39.6 Guidelines for perioperative adjustment of non-insulin medication.

Diabetes medication	Day prior to admission	Timing of surgery		
		Morning surgery	Afternoon surgery	If a VRIII is being used
Acarbose	Take as normal	Omit morning dose if not eating	Give morning dose if eating	Stop if VRIII running, do not restart until eating and drinking normally
Meglitinide (repaglinide or nateglinide)	Take as normal	Omit morning dose if not eating	Give morning dose if eating	VRIII running, do not restart until eating and drinking normally
Metformin (eGFR >60 ml/min/1.73 m ² and procedure not requiring use of contrast media, or major liver surgery ^a)	Take as normal	If taken once or twice a day – take as normal If taken three times per day, omit lunchtime dose	If taken once or twice a day – take as normal If taken three times per day, do not take lunchtime dose	VRIII running, do not restart until eating and drinking normally
Sulfonylurea (e.g. glibenclamide, gliclazide, glipizide, glimepiride)	Take as normal	Omit on morning of surgery If taken twice daily, take evening dose	Do not take on day of surgery	VRIII running, do not restart until eating and drinking normally
Pioglitazone	Take as normal	Take as normal	Take as normal	VRIII running, do not restart until eating and drinking normally
DPP-4 inhibitor (e.g. sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin)	Take as normal	Take as normal	Take as normal	VRIII running, do not restart until eating and drinking normally
GLP-1 receptor agonist (e.g. exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide)	Take as normal	Take as normal	Take as normal	Take as normal
SGLT-2 inhibitor ^b (e.g. dapagliflozin, canagliflozin, empagliflozin, ertugliflozin)	Take as normal	Do not take on day of surgery	Do not take on day of surgery	Omit until eating and drinking normally
Sotagliflozin (an SGLT-1/2 inhibitor)				

The person with diabetes should resume taking their normal tablets the morning after surgery if they are eating and drinking normally.
Warn the person with diabetes that their blood glucose control may be erratic for a few days after the procedure.
In the case of major liver surgery (i.e. removal of three or more liver segments), then metformin should be stopped 48 h prior to surgery.

DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; NBM, nil by mouth; SGLT-2, sodium–glucose co transporter 2; VRIII, variable-rate intravenous insulin infusion.

^a If contrast medium is to be used and eGFR <60 ml/min/1.73 m², metformin should be omitted on the day of the procedure and for the following 48 h.

^b If there is likely to be a period of reduction in oral intake prior to a procedure – e.g. colonoscopy – then the drug should be omitted starting on the day of the reduced intake. This may mean omitting the drug the day prior to the procedure, as well as the day of the procedure. US and other guidelines recommend stopping SGLT2 inhibitors 72 hours prior to a planned procedure.

Source: Modified from Dhatariya et al. 2015 [55].

has shown that adequate staff education can be difficult to achieve [220–222]. At the same time, optimal glycaemic levels should be achieved using the standard of care for that institution, such as a basal bolus insulin regimen [154, 173]. The principles of the enhanced recovery after surgery programme should be put into place. However, the role of preoperative carbohydrate loading in people with diabetes remains controversial [223]. When the starvation time is short – that is, less than one missed meal – there is no need for a VRIII; however, if the starvation period is likely to be longer, then one should be *in situ* and the use of long-acting insulin should be continued to prevent rebound hyperglycaemia when the intravenous insulin regimen is stopped [177]. During the entire admission, pressure areas, including heels and feet, should be regularly inspected.

In the operating theatre and recovery

While the person with diabetes is in theatre and in recovery, glucose and electrolyte concentrations should be monitored and normoglycaemia should be maintained [225]. The use of

multimodal analgesia with an appropriate antiemetic to permit an early return to a normal diet and the usual diabetes regimen is paramount, although the use of dexamethasone in this situation remains a matter for debate [225].

Postoperative period

Several factors influence glycaemic levels in the postoperative period, including a variation in nutritional intake, the discontinuation of the usual blood glucose-lowering medication, the decrease in physical activity, the increase in stress hormones, and the presence of infection or pain. It is therefore important that glycaemic levels are maintained in addition to fluid and electrolyte balance and that pain and postoperative nausea and vomiting are controlled.

Hospital discharge

In the preoperative stage and prior to hospital discharge, it is important to identify factors that may delay discharge from hospital and to make the necessary arrangements to allow the person to go back to their usual place of care once medically fit. The person

should be made aware that the metabolic and endocrine effects of surgery may last for several days because of ongoing changes in the amount that they eat, their activity levels, and the levels of stress hormones. The person should be advised that their blood glucose management may need to change for some time postoperatively and that more frequent monitoring may be required. The diabetes specialist team or usual provider of diabetes care should be involved in this discussion.

Emergency surgery

For those requiring emergency surgery where preoperative glycaemic optimization is not possible, the use of a VR III is likely to be necessary, trying to maintain a blood glucose level between 6.0 and 10.0 mmol/l (108 and 180 mg/dl). This should be continued until the person is eating and drinking normally. Some individuals who are not known to have diabetes may develop transient hyperglycaemia (so-called stress hyperglycaemia) [9, 10]. These individuals should be treated just as aggressively as people known to have diabetes, because their risk of postoperative complications is far higher than in those who were previously known to have diabetes [53, 54, 226].

Continuous subcutaneous insulin infusions (pumps)

The use of an insulin pump depends on the length of surgery and the length of starvation. If the length of starvation is short – that is, less than one missed meal – the pump therapy can usually be continued and the person should remain on their basal rate until they are eating and drinking normally [227]. Regular blood glucose testing is necessary. If, however, the starvation period is likely to be prolonged, then the pump should be discontinued and a VR III started. If there is a period of post- or perioperative hypotension, or significant use of inotropes, then peripheral skin perfusion may be compromised, thus reducing the absorption of insulin given subcutaneously and possibly necessitating treatment with a VR III, especially if the person is unable to self-manage. If the insulin pump has been discontinued and replaced with a VR III, the insulin pump should be restarted once the person is eating and drinking normally and the VR III should be discontinued 30 minutes after the first mealtime bolus.

There remains some uncertainty about the use of continuous subcutaneous insulin infusion (CSII) during an operation. The use of a diathermy in close proximity to the pump may interfere with its function, so the pump should be placed as far away as possible. Pump manufacturers suggest avoiding pumps when a diathermy is being used, but strategies have been developed to try to use them safely [228, 229].

Glucocorticoid use

Prior to the Covid-19 pandemic and the evidence that glucocorticoid use reduces morbidity and mortality in the infected population [38–42], the prevalence of steroid use in hospitals was estimated to be approximately 13% [36]. The use of steroid treatment in people with pre-existing diabetes is likely to result in worsening glucose levels, which is termed steroid-induced hyperglycaemia. This rise warrants temporary additional, and more active, glycaemic management. A rise in glucose level may occur in

people without a known diagnosis of diabetes, and this is termed steroid-induced diabetes. It may or may not resolve when the steroids are withdrawn. Short courses of steroids resulting in minimal periods of hyperglycaemia may not warrant intervention, although higher-dose steroids, for longer periods, may result in significant symptomatic hyperglycaemia with the potential for acute complications [230]. Hence addressing the hyperglycaemia may reduce these risks.

Steroid therapy: impact on blood glucose

Steroids may be administered by various regimens and at variable doses. A single daily dose of steroid (e.g. prednisolone/prednisone) in the morning is the commonest mode of administration. In susceptible individuals, this will often result in a rise in blood glucose by late morning that continues through to the evening. Overnight, the blood glucose generally falls back to baseline levels by the next morning. Therefore, treatment should be tailored to treating the hyperglycaemia, while avoiding nocturnal and early-morning hypoglycaemia.

Multiple daily doses of steroid, be it intravenous hydrocortisone or oral dexamethasone, can cause a hyperglycaemic effect throughout the 24-hour period. A twice-daily premixed or basal bolus regimen may be needed if oral medication or once-daily insulin proves insufficient to treat the hyperglycaemia. Close attention should be paid to blood glucose monitoring and early intervention may be necessary.

Glucose levels in most individuals can be predicted to rise ~4–8 hours following the administration of oral steroids, and sooner following the administration of intravenous steroids. Again, capillary blood glucose monitoring is paramount to guide appropriate therapeutic interventions. Conversely, glucose levels may improve to pre-steroid levels 24 hours after intravenous steroids have been discontinued. If oral steroids are weaned over several weeks, the glucose levels may decline in a dose-dependent fashion, but this may not occur, particularly in those with previously undiagnosed diabetes.

Monitoring

At the commencement of steroid therapy, or for those already on a supraphysiological dose of corticosteroid, capillary blood glucose testing should be initiated twice daily, prior to breakfast and perhaps most appropriately prior to the evening meal, when the hyperglycaemic effect of a morning dose of steroid is likely to be greatest.

Medication options for people taking steroid therapy

Non-insulin therapies

Given their mode of action, a short-acting sulfonylurea taken once daily may best manage the glucose excursion associated with a once-daily oral steroid. The dose of sulfonylurea may be maximally titrated in the morning to reduce the risk of hypoglycaemia. Intuitively, pioglitazone may seem an appropriate choice to manage steroid-induced hyperglycaemia; however, the evidence base for its use is weak [231]. There are currently no data to support the use of GLP-1 receptor agonists or DPP-4 inhibitors; however, their mode of action may suggest that they would be beneficial in this circumstance. A study examining the effect of dapagliflozin in steroid-induced hyperglycaemia showed no benefit [232].

Insulin therapies

Morning administration of intermediate-acting basal human insulin may closely fit the glucose excursion induced by a single morning dose of oral steroid. Basal insulin analogues may be appropriate if hyperglycaemia is present for more prolonged periods. However, care should be taken to identify and protect against hypoglycaemia overnight and in the early morning if long-acting insulin analogues are used in this context. In those taking multiple steroid doses per day, a basal bolus regimen may be considered to be the best option.

Hospital discharge

When an individual is discharged from hospital on steroid therapy, a clear strategy for the management of hyperglycaemia or potential hyperglycaemia, and the titration of therapy to address the hyperglycaemia, should be communicated to the community diabetes team (if available) and primary care team. Individuals commenced on steroids in hospital and discharged after a short stay with the intention of continuing high-dose steroids should receive standard education regarding diabetes, encompassing the risks associated with hyper- and hypoglycaemia, such as dysglycaemia-related symptoms on which to seek advice.

If steroids are discontinued prior to discharge, and hyperglycaemia persists, then capillary blood glucose (CBG) testing should be continued on discharge until normoglycaemia returns or until a definitive test for diabetes is undertaken (HbA_{1c} , fasting glucose, or oral glucose tolerance test). If steroid treatment is ceased in hospital and CBG tests are in the normal range, then post-discharge testing is not recommended. A definitive test for diabetes should still be undertaken at least six weeks after steroid cessation.

Steroid treatment in end-of-life care

People with diabetes at the end stages of life have a unique set of clinical needs (Chapter 73). Steroid therapy is frequently used in palliative care for symptom control, usually as dexamethasone or prednisolone/prednisone. The hyperglycaemia associated with once-daily steroid therapy can often be managed by morning administration of a long-acting sulfonylurea, or morning intermediate-acting basal human insulin. However, if steroids are taken twice daily, it is probable that an alternative approach will be needed. Twice-daily short-acting sulfonylurea or isophane insulin can be effective, but there is a risk of early-morning hypoglycaemia. If hypoglycaemia is a concern, a once-daily long-acting insulin analogue given in the morning may be a safer, less complex regimen, especially for those new to insulin.

Short-term courses (<3 days) of steroids may only require closer CBG testing, but longer courses will require a review of glucose-lowering therapy and may result in a switch from oral agents to insulin. In the latter situation, an intermediate-acting basal human insulin given once daily could be considered. In those without a diagnosis of diabetes prior to the commencement of steroids, CBG testing and patient and carer education should be undertaken.

Hospital readmission

Readmission for those with diabetes is common, with hypoglycaemia and hyperglycaemia during acute hospital admission being risk factors [51]. Work has been done to identify what interventions are

available to minimize the risk of readmission, which include the provision of specialist diabetes teams, whole-system embracement of recognition of the need to improve diabetes during hospitalization with a hospital-wide approach, continuous quality improvement programmes, and good communications between secondary and primary care on discharge [233].

Foot care

In the UK, the diabetic foot remains the commonest cause for a diabetes-specific acute hospital admission [103], and it was estimated that in 2014–2015 ~£1 in every £110 spent by the NHS in England was on diabetes-related foot disease [234], much of this on in-hospital care (Chapter 53). A multidisciplinary foot team, including a specialist podiatrist, diabetologist, vascular and orthopaedic surgeon, interventional radiologist, tissue viability nurse, microbiologist, DSN/CDE, and orthoptist, leads to better outcomes [235–237]. Specialist diabetes podiatrists provide the best value when considering admission avoidance, reducing length of hospital stay, and lowering amputation rates [238, 239].

The general principles for foot care in people with diabetes should apply to all admissions, not just those with active foot disease. These measures include taking a specific foot history and an inspection of the feet, looking for evidence of neuropathy, ischaemia, ulceration, inflammation, and/or infection, deformity, or Charcot neuroarthropathy. It is important to take the shoes, socks, and any dressings off the feet to inspect any underlying wounds, ensuring that pressure areas are healthy. The feet should be inspected daily during the hospital stay and any new problems should be managed in conjunction with the specialist diabetes foot multidisciplinary team.

Conclusions

People with diabetes are twice as likely to be admitted to hospital and stay twice as long as those without diabetes. They have worse outcomes and a poorer experience than those without diabetes. Given the large numbers of people with diabetes in hospital, and the considerable excess costs associated with their care, diabetes inpatient care is now being taken more seriously. However, although there is a wealth of evidence that specialist inpatient diabetes teams reduce length of stay, reduce errors in prescribing, and improve the patient experience and clinical outcomes, many institutions still lack teams specializing in inpatient diabetes.

There are numerous national and international guidelines that should make the inpatient care of people with diabetes easier to achieve. Much work remains to be done to provide more evidence to substantiate the consensus opinions within the guidelines, but as more evidence accrues showing which interventions work, the excess morbidity and mortality seen in this cohort of patients should reduce to equal those of individuals without diabetes. Until more evidence is available, it remains incumbent on those delivering the care to ensure that an attitude of nihilism is avoided – *the absence of evidence does not mean the absence of effect*. All attempts should be made to achieve suitable glycaemic levels, while avoiding symptomatic hyperglycaemia or debilitating hypoglycaemia.

40 Hypoglycaemia in Diabetes

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Key points

- Iatrogenic hypoglycaemia is a key limiting factor in the glycaemic management of diabetes. It occurs during treatment with a sulfonylurea, a glinide, or insulin.
- The key physiological defences against falling plasma glucose concentrations are decrements in insulin and increments in glucagon and epinephrine. The behavioural defence is carbohydrate ingestion prompted by symptoms that are the result of both sympathetic neural activation and neuroglycopenia.
- Hypoglycaemia in diabetes is the result of therapeutic hyperinsulinaemia. As glucose levels fall, increments in glucagon are lost because of β -cell failure in type 1 diabetes and advanced type 2 diabetes. In that setting, attenuated increments in epinephrine cause the syndrome of defective glucose counter-regulation.
- Attenuated increments in sympathetic neural activity largely bring about the syndrome of impaired awareness of hypoglycaemia. The failure to recognize impending hypoglycaemia is largely because the glucose threshold for sympathoadrenal activation falls below that for cognitive impairment.
- The main causes of defective glucose counter-regulation and impaired awareness of hypoglycaemia in diabetes include duration of diabetes, residual β -cell reserve, repeated episodes of hypoglycaemia, antecedent exercise, or sleep.
- Impaired awareness of hypoglycaemia and reduced sympathoadrenal activation are in part reversible in many individuals with diabetes. This may result from as little as 2–3 weeks' scrupulous avoidance of hypoglycaemia. Running high glucose levels does not provide additional benefit and is unnecessary.
- The risk factors for hypoglycaemia are related to this pathophysiology and include both relative and absolute therapeutic insulin excess, complete endogenous insulin deficiency, a history of severe hypoglycaemia, impaired awareness of hypoglycaemia, antecedent exercise, sleep, alcohol, and medication.
- This pathophysiology explains why the incidence of iatrogenic hypoglycaemia increases over time in type 2 diabetes, approaching that in type 1 diabetes. Most episodes of hypoglycaemia occur in people with type 2 diabetes, reflecting the larger numbers affected by type 2 diabetes globally.
- Minimizing the risk of iatrogenic hypoglycaemia requires acknowledging the problem, educating and empowering people with diabetes to effectively self-manage while applying the principles of flexible intensive insulin therapy, and addressing the risk factors. This includes agreeing individualized glucose targets, taking into account age, life expectancy, comorbidities, and the wishes of the person with their diabetes.
- Advances in diabetes technology including insulin analogues, continuous glucose monitoring, insulin pumps, and hybrid closed-loop systems have considerable potential to reduce hypoglycaemic risk. They appear more effective when combined with education that teaches effective self-management.
- Some individuals continue to experience recurrent severe hypoglycaemia despite structured education and the use of technology. Specifically designed psycho-educational approaches may offer a useful additional option.
- Maintenance of individualized glycaemic targets that can be accomplished safely in a given individual at a given stage of their diabetes journey is in the person's best interest. Concerns about hypoglycaemia should not be an excuse for suboptimal glycaemic management.

Overview of the clinical problem

Iatrogenic hypoglycaemia is one of the main limiting factors in the glycaemic management of diabetes [1]. It causes negative biological, psychological, and social consequences in most people with type 1 diabetes and in many with advanced type 2 diabetes. Indeed, as well as provoking substantial morbidity, hypoglycaemia is sometimes fatal. Episodes of hypoglycaemia compromise physiological and behavioural defences against subsequent falling plasma glucose

concentrations and thus induce a vicious cycle of recurrent hypoglycaemia. By preventing attainment of relative euglycaemia, hypoglycaemia deprives people with diabetes of the proven benefits of keeping close to target glucose levels.

Hypoglycaemia in diabetes is fundamentally iatrogenic, and essentially a side effect of pharmacokinetically imperfect treatments with an insulin secretagogue (e.g. a sulfonylurea or a glinide) or with exogenous insulin causing hyperinsulinaemia. This is often combined with a mismatch in the amount of carbohydrates consumed or in special situations, for example during physical exercise,

following excessive alcohol, or in groups that are particularly vulnerable, such as during pregnancy, at the extremes of age, in people with impaired awareness of hypoglycaemia, and those with comorbidities such as hepatic or renal impairment. Thus, hypoglycaemia is typically the net result of relative or absolute therapeutic insulin excess and compromised physiological and behavioural defences against falling plasma glucose [1].

In this chapter, we first explore physiological homeostatic mechanisms that prevent hypoglycaemia through glucose counter-regulation, before discussing specific acquired defects of glucose counter-regulation in diabetes, which provides an insight into risk factors for hypoglycaemia. We then discuss the size of the clinical problem followed by the biological impact of hypoglycaemia, with a specific focus on both neurological and cardiovascular consequences. Finally, we discuss hypoglycaemia in children and adolescents, including how hypoglycaemia can be approached in clinical practice, prior to providing an overall perspective on where additional research is required to address current and future needs of people with diabetes.

Hypoglycaemia and the brain

The brain relies on glucose as an obligate oxidative fuel under physiological conditions and, despite the average brain only constituting ~2% of total body weight, cerebral function accounts for 20% of whole-body glucose utilization [1–4]. The brain is almost entirely dependent on a continuous supply of glucose from the circulation for normal function. This is because it cannot synthesize glucose, utilize physiological concentrations of circulating non-glucose fuels such as amino acids, ketones, and lactate effectively, or store more than a few minutes' supply as glycogen [1, 5]. This requires the plasma glucose concentration to be maintained within a tight homeostatic range to allow facilitated diffusion of sufficient glucose via glucose transporters (GLUT) across the blood–brain barrier (GLUT1) and into neurones (GLUT3) to maintain critical cerebral function. Hypoglycaemia of sufficient depth causes functional brain failure through disruption in adenosine triphosphate (ATP) and creatine phosphate metabolism, two key substrates for brain function [3, 6]. Perturbations in cerebral function are initially reversible; however, with severe prolonged hypoglycaemia there is complete depletion of ATP and creatine phosphate, which can cause permanent cerebral damage and even death [3, 6]. This explains both the vulnerability of individuals to hypoglycaemia and the array of defences that have evolved as a stress response to maintain near-normal plasma glucose concentrations.

Responses to hypoglycaemia

Falling plasma glucose concentrations cause a sequence of responses in individuals without diabetes termed *counter-regulatory responses* (opposing the regulatory effects of insulin) (Figure 40.1) [1, 7–11]. The first physiological response, which occurs as plasma glucose concentrations decline, is a decrease in insulin secretion followed by release of glucagon and epinephrine, which increase endogenous glucose concentrations by stimulating gluconeogenesis and glycogenolysis (Figure 40.2). Lower plasma glucose levels cause a more intense sympathoadrenal (sympathetic neural and adrenomedullary) response that reduces peripheral glucose utilization and inhibits insulin secretion, in addition to triggering symptoms that prompt a behavioural response and ingestion of food. Raised cortisol and growth hormone concentrations stimulate gluconeogenesis and reduce peripheral glucose utilization, but since subsequent increases in blood glucose lag in time, these responses are less

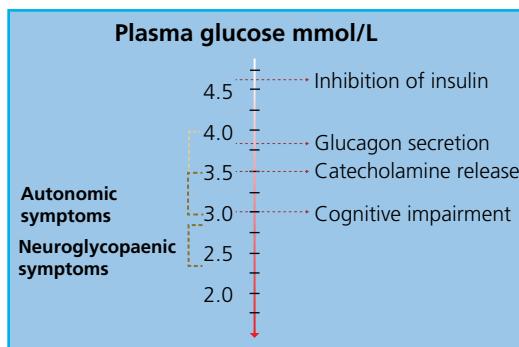


Figure 40.1 Hierarchical counter-regulatory responses to hypoglycaemia.

Source: Created by A. Iqbal in Biorender.com.

relevant in acute counter-regulation of hypoglycaemia [13]. Even lower plasma glucose concentrations cause functional brain failure, which is on a clinical continuum ranging from deficits in executive function to coma and even death [3].

Clinical manifestations of hypoglycaemia

The symptoms and signs of hypoglycaemia are not specific [10, 14]. Thus, in clinical practice it can be helpful to evaluate hypoglycaemia using Whipple's triad:

- Symptoms, signs, or both, consistent with hypoglycaemia.
- A low, reliably measured plasma glucose concentration.
- Resolution of those symptoms and signs after the plasma glucose is raised.

Symptoms of hypoglycaemia can be broadly categorized into neuroglycopenic and neurogenic symptoms. Neuroglycopenic symptoms occur as a result of impaired cerebral function and include cognitive impairment, loss of concentration, confusion, behavioural changes, and psychomotor abnormalities and, at lower plasma glucose concentrations, seizures and coma [1, 3, 10, 14]. Neurogenic symptoms occur in response to activation of both the sympathetic (palpitations, tremulousness, and arousal/anxiety) and parasympathetic (sweating, hunger, and paraesthesia) components of the autonomic nervous system in response to hypoglycaemia [10, 14]. Central mechanisms may also be involved in some of the latter symptoms, such as hunger that prompts a behavioural response to consume food [15]. Awareness of hypoglycaemia is at least in part the result of the perception of neurogenic symptoms [10], which are more prominent at the diagnosis of diabetes, but with time neuroglycopenic symptoms become more prominent.

Signs of hypoglycaemia include pallor and diaphoresis, the result of adrenergic cutaneous vasoconstriction and cholinergic activation of sweat glands, respectively [1]. Neuroglycopenic manifestations are often observable and those affected may complain of confusion or loss of concentration.

Counter-regulation during hypoglycaemia

Given the near-total dependence of the brain on a normal and stable systemic glucose concentration and the serious consequences of hypoglycaemia on cerebral function, a tight systemic glucose balance is maintained under physiological conditions. Bidirectional fluxes in plasma glucose that could result in hypoglycaemia or hyperglycaemia are prevented. This is achieved through homeostatic regulation of endogenous glucose production, principally in the liver but also in the kidneys, and this is balanced with peripheral glucose utilization by skeletal muscle [1, 6]. Insulin plays a key role in regulating endogenous glucose production and peripheral

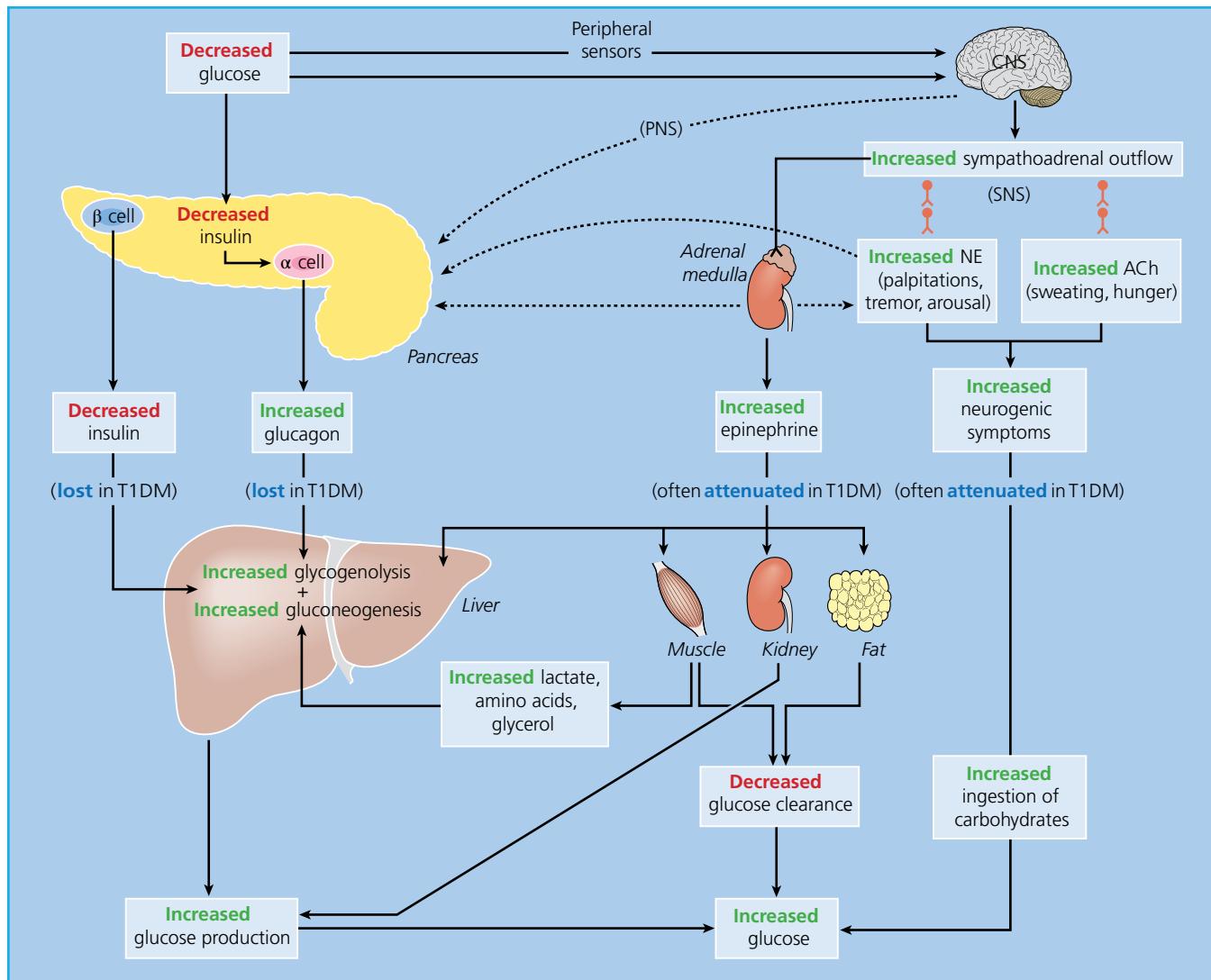


Figure 40.2 Physiological and behavioural defences against hypoglycaemia in humans. ACh, acetylcholine; α cell, pancreatic islet α cell; β cell, pancreatic islet β cell; NE, norepinephrine; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; T1DM, type 1 diabetes. Source: Cryer 2006 [12]. Reproduced with permission from the American Society for Clinical Investigation.

glucose utilization in non-neuronal tissues, although other neurotransmitters, metabolic substrates, and hormones are involved (Figures 40.1 and 40.2) [6, 16].

The processes of counter-regulation that correct hypoglycaemia involve an array of hormones. Seminal contributions from experimental medicine studies from the mid-1970s to the early 1990s have established an order of relative importance within counter-regulatory hormonal responses that can be conceptualized as lines of defence against hypoglycaemia [17–20]. The first physiological defence against hypoglycaemia is a decrease in pancreatic islet β -cell insulin secretion. This occurs as plasma glucose concentrations decline below 4.7 mmol/l (85 mg/dl) (Figure 40.1) and favours increased hepatic and renal glucose production, with virtual cessation of glucose utilization by insulin-sensitive tissues such as muscle (Figure 40.2). The second physiological defence is an increase in pancreatic islet α -cell glucagon secretion. This occurs as plasma glucose concentrations fall just below 3.9 mmol/l (70 mg/dl) (Figure 40.1) and stimulates glucose release through glycogenesis and glycogenolysis (Figure 40.2). Under physiological conditions, pancreatic α cells are under tonic

inhibition of intra-islet insulin [17]. During hypoglycaemic conditions, a decrease in intra-islet insulin among other β -cell secretory products, including the neurotransmitter γ -aminobutyric acid and zinc [1, 21–23], signals increased glucagon secretion. Further, a secondary putative mechanism that results in increased glucagon production is through activation of both the sympathetic and parasympathetic branches of the autonomic nervous system [1, 24]. As blood glucose concentrations fall further and just below the physiological range, the third physiological defence of epinephrine secretion from the adrenal medulla comes into play. This stimulates glucose release through gluconeogenesis and glycogenolysis, largely via β_2 -adrenergic stimulation, as well as reducing peripheral glucose utilization by inhibiting insulin secretion via α_2 -adrenergic receptors (Figure 40.2) [1, 6, 25]. Adrenomedullary epinephrine secretion becomes critical when glucagon is deficient. There is also a norepinephrine response to hypoglycaemia, which is largely secreted from the adrenal medulla but compared to epinephrine appears to play a less prominent role in glucose counter-regulation [14]. Additional hormones released when blood glucose levels fall between

3.6–3.9 mmol/l (65–70 mg/dl) are growth hormone and cortisol [8,9]. Collectively, these hormones induce gluconeogenesis, lipolysis, and ketogenesis over several hours and are thus less relevant to acute counter-regulation [26]. They may have an important role in initiating longer-term adaptive responses to hypoglycaemia [27].

These complex homeostatic mechanisms are chiefly controlled by the central nervous system (CNS) [6]. The evidence supporting this is primarily derived from animal studies, where direct glucose infusion into the brain to maintain euglycaemia was studied with parallel induction of peripheral hypoglycaemia [28]. In these experiments in rats, peripheral hypoglycaemia did not result in activation of glucagon and catecholamine counter-regulation. This and other studies led to the hypothesis that the ventromedial hypothalamic nucleus in the brain is a key glucose sensor for hypoglycaemia counter-regulation [28]; however, the ventromedial hypothalamic nucleus is likely to be one part of a larger glucose-sensing network in the brain [6]. Glucose-sensing neurones are highly specialized cells that employ changes in ambient glucose levels to alter their action potential, thus transducing a metabolic signal into neuronal activity [29]. Glucokinase and ATP-sensitive K⁺ channels appear to be primarily involved in glucose sensing and subsequent counter-regulation [29,30]. There may also be important species differences between rodents and humans.

If these physiological defences fail to abort an episode of developing hypoglycaemia, lower plasma glucose concentrations cause a more intense sympathoadrenal response that causes neurogenic symptoms and is primarily driven by sympathetic neural activation as opposed to adrenomedullary discharge (Figure 40.2) [14]. These symptoms cause awareness of hypoglycaemia that prompts the behavioural defence of carbohydrate ingestion. Physiological responses act in concert to prevent hypoglycaemia in healthy people without diabetes, but are typically compromised in people with type 1 diabetes and those with advanced (i.e. absolutely endogenous insulin-deficient) type 2 diabetes (Figure 40.2) [1].

Pathophysiology of glucose counter-regulation in diabetes

Insulin excess

Absolute or relative therapeutic hyperinsulinaemia is a key factor in producing iatrogenic hypoglycaemia [1]. Whether any given episode of therapeutic hyperinsulinaemia results in clinically significant hypoglycaemia in people with diabetes, however, is also determined by the integrity of hormonal and behavioural mechanisms that ordinarily constitute the counter-regulatory defence. Counter-regulatory deficiencies in diabetes are not a binary 'present or absent' phenomenon, but exist on a continuum that is influenced by several factors. Since some of these impairments appear to be functional, this implies they may be reversible (Figure 40.2; Table 40.1) [27,32,33].

Defective glucose counter-regulation

Insulin

Individuals with fully developed (minimal residual β -cell function) type 1 diabetes and advanced insulin-treated type 2 diabetes are unable to self-regulate endogenous insulin secretion in response to falling plasma glucose concentrations (Table 40.1) [34]. This compromises the first counter-regulatory defence against hypoglycaemia,

Table 40.1 Responses to falling plasma glucose concentrations in humans.

Plasma glucose	Individuals	Plasma		
		Insulin	Glucagon	Epinephrine
↓	No-diabetes	↓	↑	↑
↓	Type 1 diabetes ^a	No ↓	No ↑	Attenuated ↑
↓	Early type 2 diabetes	↓	↑	↑
↓	Late type 2 diabetes ^a	No ↓	No ↑	Attenuated ↑

^a These alterations account for the appearance of defective glucose counter-regulation and impaired awareness of hypoglycaemia in people with type 1 diabetes and late type 2 diabetes.

Source: Reproduced by permission from Cryer 2008 [31].

as therapeutic delivery of insulin or sulfonylureas and related medication results in unregulated hyperinsulinaemia [21]. Hyperinsulinaemia promotes glucose lowering through peripheral glucose uptake in the liver, skeletal muscle, and adipose tissue in addition to suppressing gluconeogenesis and inhibiting lipolysis, which generates alternate fuels [27]. In addition, insulin inhibits pancreatic α -cell glucagon release, partly through direct local action in the pancreas [35] but also through central modulation in the ventromedial hypothalamic nucleus [36].

Glucagon

In the absence of the ability to switch off endogenous insulin in response to falling glucose concentrations, people with diabetes have to rely on glucagon secretion, which is the second line of physiological defence against hypoglycaemia. Glucagon plays a primary role in opposing the glucose-lowering effects of insulin during hypoglycaemia, accounting for ~40% of glucose recovery [37]. However, impaired glucagon responses to hypoglycaemia are apparent as early as within the first year of diagnosis in type 1 diabetes [38] and are significantly diminished in most people within five years after diagnosis (Table 40.1) [39]. Glucagon and other counter-regulatory responses to hypoglycaemia are less extensively studied in type 2 diabetes, but limited evidence suggests that in type 2 diabetes glucagon responses are initially either elevated or modestly reduced (Table 40.1) [40–43], but become gradually impaired [33,44–46].

An interesting phenomenon observed in clinical practice is that some individuals with type 2 diabetes, especially those with suboptimal metabolic management and thus relatively high ambient plasma glucose concentrations, report symptoms suggestive of counter-regulation occurring at normal glucose values. Furthermore, experimental data suggest that the threshold for activation of counter-regulatory responses to hypoglycaemia may be reset to normal glucose values in some individuals with type 2 diabetes [41]. Loss of a glucagon response results in significantly reduced glycogenolysis and gluconeogenesis and increases the risk of severe hypoglycaemic episodes [27,47]. Mechanisms that lead to loss of α -cell glucagon release in diabetes are not fully understood. Several mechanistic studies have been performed in animals, which may not directly apply to the human condition due to species differences in pancreatic physiology. It appears, however, that the α -cell defect, at least in those with type 1 diabetes, is specific to hypoglycaemia, as α -cell stimulation with amino acids such as arginine results in an intact glucagon response [17]. The α -cell glucagon

release appears to be impaired on account of a functional as opposed to a structural defect, raising the theoretical possibility of interventions that may re-enable glucagon secretion in response to a hypoglycaemic stimulus.

One plausible explanation for the loss of glucagon response to hypoglycaemia in type 1 diabetes and advanced type 2 diabetes is β -cell failure, as described in the *intra-islet* hypothesis [21, 33]. As intra-islet insulin, among other β -cell secretory products, regulates α -cell glucagon secretion in response to hypoglycaemia [17], with progressive β -cell failure either through T-cell-mediated autoimmune destruction in type 1 diabetes or gradual β -cell loss with advancing type 2 diabetes, the absence of intra-islet insulin signalling results in a loss of the glucagon response to hypoglycaemia [48]. Heller et al. were the first to explore the *intra-islet* hypothesis in humans and contrasted this with animal data [49]. They studied glucagon responses in healthy volunteers who underwent two hypoglycaemic clamps, one with intravenous tolbutamide infusion to stimulate high portal insulin concentrations, and compared this with a standard intravenous insulin infusion clamp with an equivalent hypoglycaemic nadir. They showed a reduced glucagon response to tolbutamide-induced hypoglycaemia where portal insulin concentrations were high, suggesting that intra-islet insulin signalling contributes to regulation of glucagon release during hypoglycaemia in humans [49].

Other early experimental data that support the *intra-islet* hypothesis were a demonstration of impaired glucagon secretion during hypoglycaemia, closely mirroring a decline in C-peptide levels (a marker of endogenous β -cell function) in people with insulin-treated diabetes [50]. In a more recent study, when people with insulin-treated type 2 diabetes were compared with those on

oral hypoglycaemic agents only, there was no difference in the peak glucagon response during a hypoglycaemic clamp [51]. However, this was almost certainly because even insulin-treated participants had relatively preserved β -cell function (mean C-peptide 1000 pmol/l). A similarly designed study examined glucagon responses to experimental hypoglycaemia in people with type 2 diabetes treated with oral hypoglycaemic agents and compared people treated with insulin and lower mean basal C-peptide values (mean C-peptide insulin-treated group 364 pmol/l vs mean C-peptide oral hypoglycaemic group 1026 pmol/l) [33]. Here, mean glucagon responses following 60 minutes of experimental hypoglycaemia were significantly higher in the oral hypoglycaemic group compared to the insulin-treated group. Further, recent observational studies in both type 1 diabetes and insulin-treated type 2 diabetes suggest that the incidence of continuous glucose monitoring (CGM)-recorded hypoglycaemia is significantly lower in those with preserved C-peptide levels, inferring an intact glucagon response and lending credence to the *intra-islet* hypothesis [52, 53].

Catecholamines

With both the first and second physiological defences against hypoglycaemia being lost, people with diabetes have to rely on the catecholamine (principally epinephrine) response to hypoglycaemia—the third line of defence. Notably, when the glucagon response is poor, hepatic glucose production during hypoglycaemia and exercise is significantly modulated by catecholamines, highlighting the critical nature of this *fail safe* [27, 54, 55]. However, in those with type 1 diabetes and advanced type 2 diabetes, the epinephrine response to hypoglycaemia is progressively attenuated (Figure 40.3; Table 40.1) [1, 32, 33, 39]. An attenuated adrenomedullary epinephrine response

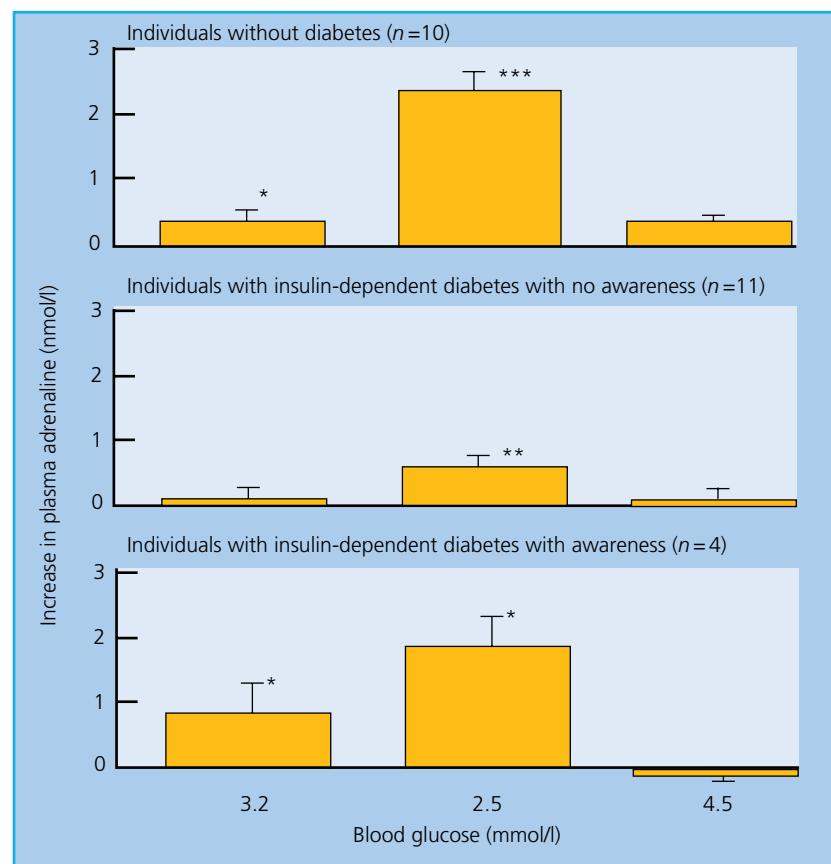


Figure 40.3 Mean (\pm standard error [SE]) plasma epinephrine concentrations during stepped hyperinsulinaemic hypoglycaemic glucose clamps in 10 individuals without diabetes and 15 individuals with insulin-dependent diabetes ($n = 4$ with intact awareness of hypoglycaemia and $n = 11$ with reduced awareness of hypoglycaemia symptoms). Source: Heller et al. 1987 [56]. Reproduced with permission from The Lancet.

together with an absent glucagon response is associated with a 25-fold [47] or greater [57] increase in the risk of severe hypoglycaemia in type 1 diabetes. In addition, a diminished adrenal epinephrine response is a marker for an attenuated autonomic response to hypoglycaemia, including a sympathetic neural response (Table 40.1), which is primarily responsible for reduced neurogenic symptoms [14] and the clinical syndrome of impaired awareness of hypoglycaemia. The adrenal glands are regulated by the autonomic nervous system [27]. The impaired catecholamine response to hypoglycaemia in individuals with type 1 diabetes and advanced type 2 diabetes arises mainly through an altered sympathetic drive, with a gradual shifting of the glycaemic threshold for activation to lower glucose values [58]. There is no structural defect in the secretory apparatus within the adrenal medulla, however, given that a catecholamine response to alternate stimuli such as exercise remains intact [55, 58].

Overall, the pathophysiology of glucose counter-regulation is similar in type 1 diabetes and advanced (i.e. absolutely endogenous insulin deficiency) type 2 diabetes, albeit with different time courses (Table 40.1) [1, 32, 33]. The pathogenesis of an episode of iatrogenic hypoglycaemia involves therapeutic hyperinsulinaemia, resulting in falling plasma glucose concentrations and loss of the appropriate reduction in insulin and compensatory secretion of glucagon. Each episode of hypoglycaemia, in turn, reduces the sympathoadrenal responses to subsequent hypoglycaemia. Because β -cell failure, which causes loss of both insulin and glucagon responses [1, 32, 33], occurs rapidly in type 1 diabetes but more insidiously in type 2 diabetes, the syndromes of defective glucose counter-regulation and impaired awareness of hypoglycaemia develop early in type 1 diabetes but later in type 2 diabetes. This temporal pattern of compromised glycaemic defences explains why iatrogenic hypoglycaemia becomes progressively more frequent as individuals approach the insulin-deficient end of the spectrum of type 2 diabetes.

Impaired awareness of hypoglycaemia

Important work by Heller and Cryer in the early 1990s showed that in healthy volunteers, a single episode of hypoglycaemia is sufficient to attenuate sympathoadrenal (and glucagon) responses to subsequent hypoglycaemia [20]. This phenomenon, subsequently replicated in those with type 1 diabetes (Figures 40.4 and 40.5) [32, 59] and type 2 diabetes [60], reduces an individual's ability to perceive the onset of hypoglycaemia symptoms [60]. Hypoglycaemia of greater depth [61], longer duration [62], and higher frequency [63, 64] results in a greater attenuation of counter-regulatory responses to subsequent hypoglycaemia [27]. It is unclear, however, if the progressive impairment in sympathoadrenal responses that occurs in diabetes of increasing duration is entirely due to repeated hypoglycaemia [34]. Clinical experience indicates that many individuals with longstanding insulin-treated diabetes have a diminished ability to perceive the symptoms of acute hypoglycaemia. No holistic definition for the clinical syndrome of impaired hypoglycaemia awareness exists, but it is recognized that absolute unawareness is rare and thus the term *hypoglycaemia unawareness* has been replaced with *impaired awareness of hypoglycaemia* [34].

Scales developed by Gold [65] and Clarke [66] are two tools used in routine clinical practice to identify impaired awareness of hypoglycaemia in type 1 diabetes, but they have limitations. Recent studies have used a Gold score of ≥ 4 to define impaired awareness of hypoglycaemia [67, 68]; however, there is significant variation in how impaired awareness of hypoglycaemia is defined in older studies, making it challenging to draw meaningful comparisons between

populations, especially where duration of treatment with insulin differs. Where there is broad consistency in definitions of impaired awareness of hypoglycaemia, the reported prevalence is $\sim 25\%$ in type 1 diabetes, rising to $\sim 50\%$ after 25 years or more of treatment [69–71]. In type 2 diabetes, the prevalence of impaired awareness of hypoglycaemia is $\sim 8\text{--}10\%$ [72, 73], with the prevalence being higher in insulin-treated type 2 diabetes [72]. This is intuitive, as the duration of insulin treatment is a key predictor of rates of severe hypoglycaemia, with higher rates reported in both type 1 diabetes and type 2 diabetes with longer treatment duration [74]. Interestingly, when individuals with type 1 diabetes and type 2 diabetes were matched for duration of treatment with insulin in one study [75], hypoglycaemia rates were comparable. This has important implications for healthcare resources around the world, since the global prevalence of type 2 diabetes is far higher, comprising 90% of all cases of diabetes [76]. Improved access to insulin together with longer life expectancies will mean that hypoglycaemia will continue to remain a significant clinical challenge [77].

Although impaired awareness of hypoglycaemia is largely the result of reduced release of the neurotransmitters norepinephrine and acetylcholine [1, 14], there is decreased β -adrenergic sensitivity, specifically reduced cardiac chronotropic sensitivity to isoproterenol, in affected individuals [78, 79]. However, vascular sensitivity to β_2 -adrenergic agonism was not found to be reduced in people with impaired awareness [80]; reduced sensitivity to β -adrenergic signalling of neurogenic symptoms remains to be demonstrated in those with impaired awareness of hypoglycaemia, and it would be necessary to postulate decreased cholinergic sensitivity to explain reduced cholinergic symptoms such as sweating.

Mechanisms of counter-regulatory failure and impaired awareness

Epidemiological and mechanistic studies have shown that duration of type 1 diabetes and insulin treatment in type 2 diabetes are key contributors to deficient counter-regulation and impaired awareness of hypoglycaemia. Repeated episodes of hypoglycaemia are also fundamental to these pathological syndromes that make insulin-treated individuals so susceptible to the limitations of therapeutic insulin and other therapies.

Following the seminal studies conducted in the early 1990s, further studies showed that an episode of antecedent hypoglycaemia can attenuate counter-regulatory responses to further hypoglycaemia up to one week later [81]. Brief twice-weekly episodes of mild hypoglycaemia have a similar effect [82]. Furthermore, prior exercise [83–85] and sleep [86–88] cause diminished counter-regulation to subsequent hypoglycaemia. Prolonged effects of antecedent hypoglycaemia on diminished counter-regulation to subsequent hypoglycaemia appear to explain why tight glycaemic management with intensive insulin therapy can lead to a resetting of the glycaemic threshold at which counter-regulatory mechanisms are activated [34, 59, 89]. Thus, stimuli such as prior hypoglycaemia, sleep, and exercise can plausibly contribute to transient impaired awareness of hypoglycaemia by attenuating the sympathoadrenal and resultant neurogenic symptom responses to subsequent hypoglycaemia.

It remains unclear how these factors lead to chronic impaired awareness. Nonetheless, recurrent episodes of hypoglycaemia of sufficient depth and duration progressively blunt and impair normal counter-regulatory responses to hypoglycaemia, predisposing people with diabetes to a vicious cycle of ever more frequent hypoglycaemia episodes with a falling glycaemic threshold to activate counter-regulation (Figure 40.6) [34, 90]. Cryer has termed

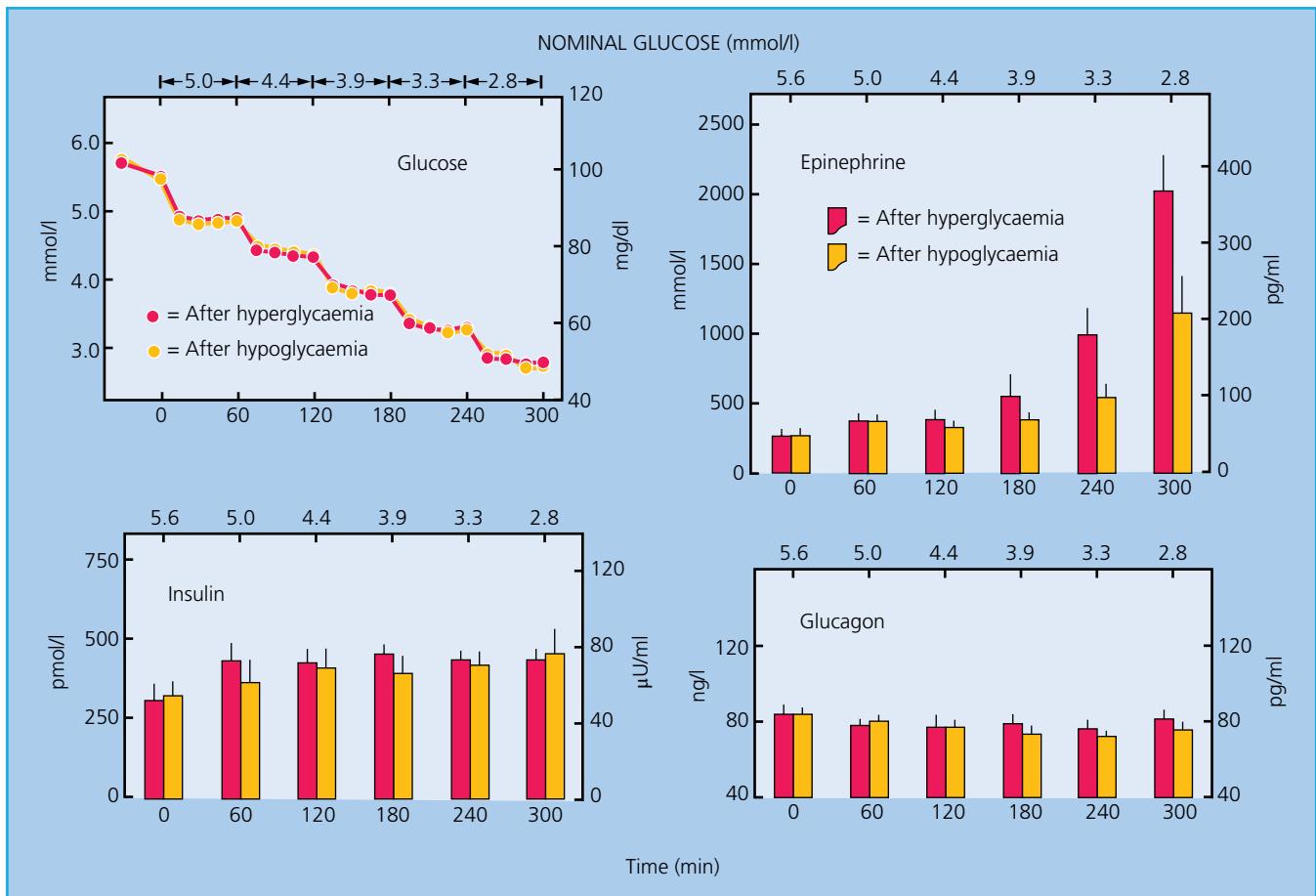


Figure 40.4 Mean (\pm standard error [SE]) plasma glucose, insulin, epinephrine, and glucagon concentrations during hyperinsulinaemic stepped hypoglycaemic clamps in people with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycaemia (red circles and columns) and on mornings following afternoon hypoglycaemia (yellow circles and columns). Source: Dagogo-Jack et al. 1993 [32]. Reproduced with permission from the American Society for Clinical Investigation.

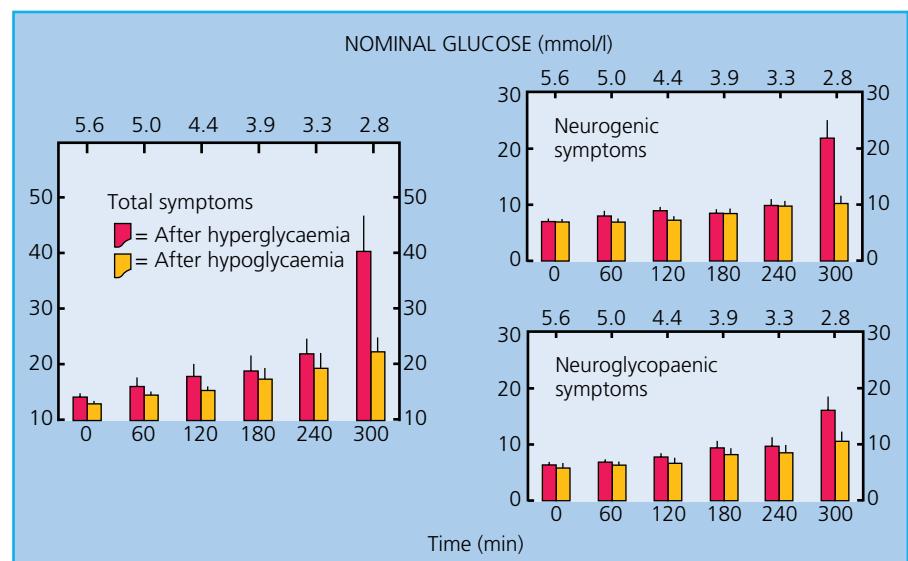


Figure 40.5 Mean (\pm standard error [SE]) total, neurogenic, and neuroglycopaenic symptom scores during hyperinsulinaemic stepped hypoglycaemic clamps in people with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycaemia (red columns) and on mornings following afternoon hypoglycaemia (yellow columns). Source: Dagogo-Jack et al. 1993 [32]. Reproduced with permission from the American Society for Clinical Investigation.

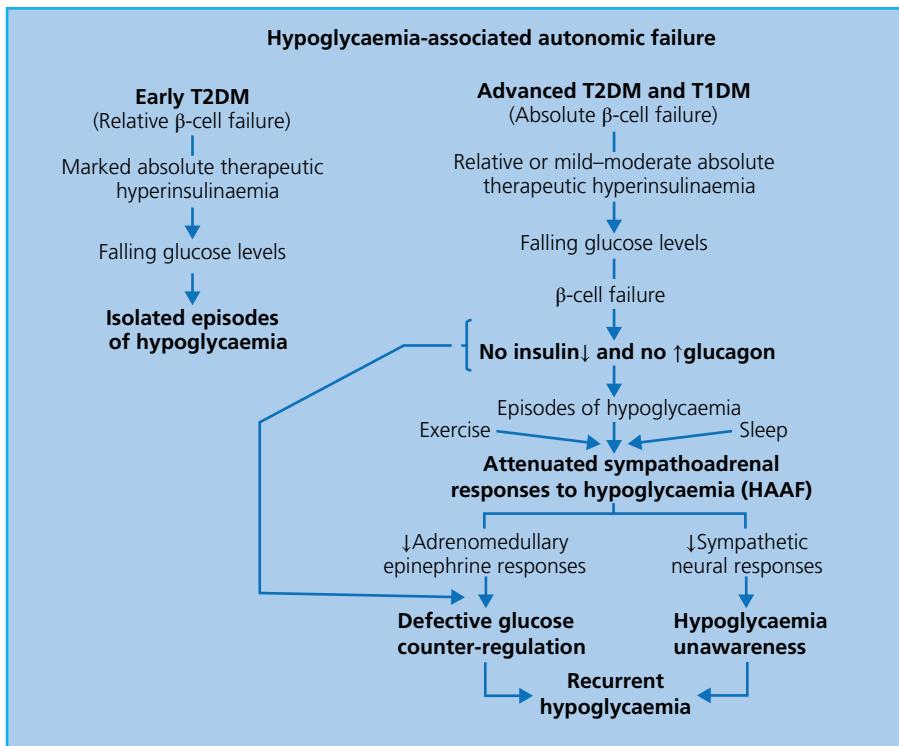


Figure 40.6 Hypoglycaemia-associated counter-regulatory impairment in the pathogenesis of iatrogenic hypoglycaemia in diabetes. HAAF, hypoglycaemia-associated autonomic failure; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

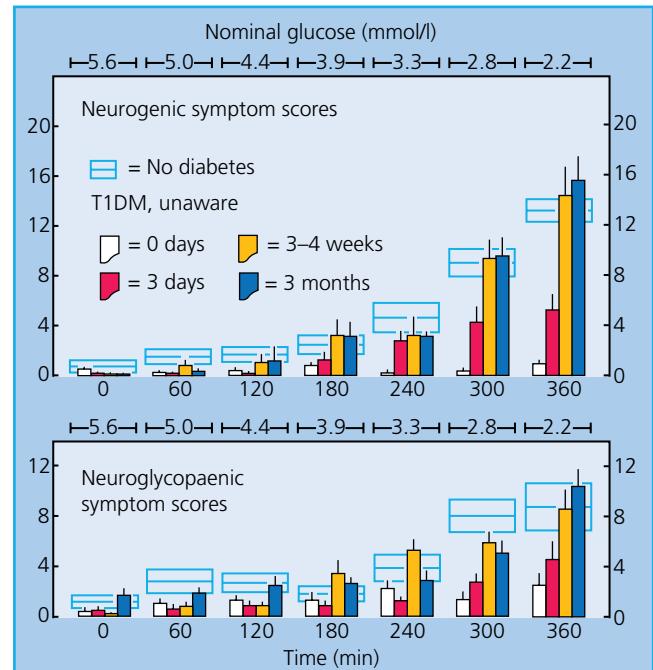


Figure 40.7 Mean (\pm standard error [SE]) neurogenic and neuroglycopenic symptom scores during hyperinsulinaemic stepped hypoglycaemic clamps in individuals without diabetes (open rectangles) and in people with type 1 diabetes (T1DM; columns) at baseline (0 days), after three days of inpatient strict avoidance of hypoglycaemia, and after three to four weeks and three months of outpatient scrupulous avoidance of hypoglycaemia. Source: Dagogo-Jack et al. 1994 [94]. Reproduced with permission from the American Diabetes Association.

this phenomenon *hypoglycaemia-associated autonomic failure* in diabetes [91]. This is a dynamic functional disorder that is distinct from classic diabetic autonomic neuropathy [1,34], a common neuropathic complication of diabetes. While there is no failure of the autonomic system in hypoglycaemia-associated autonomic failure, an attenuated sympathoadrenal response to a given level of hypoglycaemia, a key feature of hypoglycaemia-associated autonomic failure, is common to diabetic autonomic neuropathy [92,93]. However, since structural autonomic neuropathy is generally only observed in individuals with a long duration of diabetes, it is difficult to assess the additional contribution of autonomic neuropathy to counter-regulatory failure. A more accurate term would be hypoglycaemia-associated counter-regulatory impairment, to distinguish it from impairment secondary to other factors such as treatment duration, exercise, and sleep; nevertheless, the term hypoglycaemia-associated autonomic failure is now used widely.

The clinical impact of hypoglycaemia-associated counter-regulatory impairment is well established in type 1 diabetes [32,82,94–98]. Recent antecedent hypoglycaemia, even asymptomatic nocturnal hypoglycaemia, reduces epinephrine, symptomatic, and cognitive responses to a given level of subsequent hypoglycaemia [98], reduces detection of hypoglycaemia in the clinical setting [82], and reduces defence against hyperinsulinaemia [32] in type 1 diabetes. Perhaps the most compelling evidence to support the concept of hypoglycaemia as a cause of counter-regulatory impairment is the finding, initially by three independent research teams [94–98], that as little as 2–3 weeks of scrupulous avoidance of hypoglycaemia reverses impaired awareness of hypoglycaemia (Figure 40.7) and improves the attenuated epinephrine component of defective glucose counter-regulation in most affected individuals.

People with advanced type 2 diabetes are also at risk for acquired counter-regulatory impairment [33]. Glucagon responses to hypoglycaemia are lost [33], as they are in type 1 diabetes. Furthermore, the glycaemic thresholds for sympathoadrenal and symptomatic (among other) responses to hypoglycaemia are shifted to lower plasma glucose concentrations by recent antecedent hypoglycaemia [33], as they are in type 1 diabetes.

There are three recognized causes of counter-regulatory failure, each of which leads to attenuated sympathoadrenal and symptomatic (among other) responses to a given level of hypoglycaemia [1]. Antecedent hypoglycaemia related counter-regulatory failure [20, 32, 33] led the concept. Exercise-related counter-regulatory failure [84–86] is exemplified by late post-exercise hypoglycaemia, which typically occurs 6–15 hours after strenuous exercise and is often nocturnal [99, 100]. Sleep-related counter-regulatory failure [87–89] is the result of further attenuation of the sympathoadrenal response to hypoglycaemia during sleep. Sleeping individuals are therefore much less likely to be awakened by hypoglycaemia than individuals without diabetes [87, 89]. There may well be additional, as yet unrecognized, functional, and therefore potentially reversible, causes of hypoglycaemia-associated counter-regulatory impairment [1]. In addition, there may be a structural component [1].

The mechanisms of counter-regulatory impaired awareness are summarized in Figure 40.8 [1]. Loss of the insulin and glucagon responses to falling plasma glucose concentrations caused by therapeutic hyperinsulinaemia is the result of β -cell failure in type 1 diabetes and advanced type 2 diabetes.

In the setting of absent insulin and glucagon responses to falling plasma glucose concentrations, attenuated sympathoadrenal responses cause both defective glucose counter-regulation and impaired awareness of hypoglycaemia. The underlying mechanism responsible for the attenuated sympathoadrenal response is poorly understood, but it is plausible that it is at the level of the brain (or the afferent or efferent components of the sympathoadrenal system) (Figure 40.8). The proposed mechanisms include the systemic

mediator, brain fuel transport, and brain metabolism hypotheses, all of which have been previously reviewed [21, 101, 102].

Much of the research into the pathogenesis of counter-regulatory failure has focused on the hypothalamus, the central integrator of the sympathoadrenal responses to hypoglycaemia [102]. While the primary alteration could reside in the hypothalamus, the changes in hypothalamic function could be secondary to those in other brain regions. For example, measurements of regional cerebral blood flow with $[^{15}\text{O}]$ water and positron emission tomography (PET) [103] indicate that hypoglycaemia activates widespread but interconnected brain regions, including the medial prefrontal cortex, the lateral orbitofrontal cortex, the thalamus, the globus pallidus, and the periaqueductal grey region. These studies also show that recent antecedent hypoglycaemia both reduces the sympathoadrenal and symptomatic responses and causes a greater increase in synaptic activity in the dorsal midline thalamus during subsequent hypoglycaemia [11]. Hence there may be a cerebral network that results in thalamic inhibition of hypothalamic activity in hypoglycaemia-associated counter-regulatory impairment (Figure 40.8) [11]. That suggestion is generically consistent with the findings of various patterns of ^{18}F -deoxyglucose uptake in people with type 1 diabetes with and without impaired awareness of hypoglycaemia [104].

More recently, Choudhary et al. have investigated brain responses to hypoglycaemia in type 1 diabetes with and without impaired awareness of hypoglycaemia [105]. Using three-dimensional pseudo-continuous arterial spin labelling (3DpCASL) magnetic resonance imaging (MRI), they demonstrated changes in cerebral blood flow in response to hypoglycaemia in brain regions involved in arousal, decision making, and reward in those with impaired awareness of hypoglycaemia. They hypothesized that changes in these neural pathways may disrupt these individuals' ability to recognize and effectively manage hypoglycaemia [105]. They extended this work by restoring awareness of hypoglycaemia in those with type 1 diabetes through enrolment on a structured education programme (Dose Adjustment for Normal Eating), specialist support, and sensor-augmented pump therapy [106]. Cerebral blood flow responses during hypoglycaemia

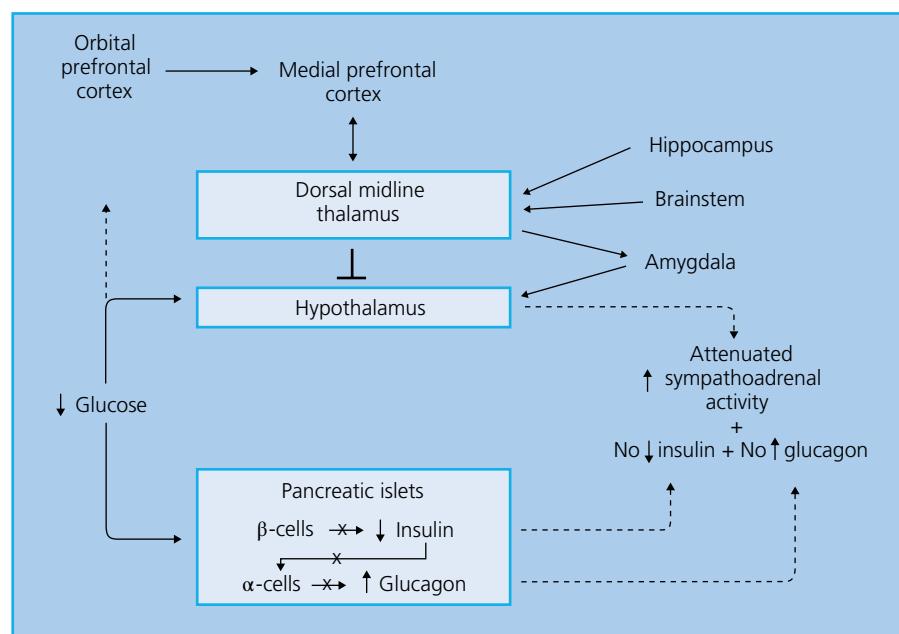


Figure 40.8 Pancreatic islet, hypothalamic, and cerebral network mechanisms of hypoglycaemia-associated autonomic failure (HAAF) in diabetes. Source: Cryer 2008 [1]. Reproduced with permission from the American Diabetes Association.

were studied pre- and post-intervention using 3DpCASL MRI. Interestingly, following restoration of hypoglycaemia awareness, increased blood flow was seen in neural pathways involved in self-awareness and decision making (anterior cingulate cortex), suggesting reversibility in brain responses lost in impaired awareness of hypoglycaemia [106]. However, brain regions involved in arousal and emotional processing (fronto-thalamic networks) were less responsive to restoration of hypoglycaemia awareness [106]. This may partly explain why some individuals with impaired awareness of hypoglycaemia never fully achieve restoration of awareness with use of structured education and diabetes technology [106].

Experimental limitations in studying the mechanisms contributing to hypoglycaemia in diabetes

It remains unclear how duration of diabetes and antecedent hypoglycaemia, the two key contributors to impaired awareness and counter-regulatory failure, interact mechanistically in causing the syndromes that underly the vulnerability of those with insulin-treated diabetes to hypoglycaemia. Most experimental work has focused on antecedent hypoglycaemia, as it is more easily reproduced in the laboratory whether in clinical experimental models or in animal studies. Since impaired awareness is increasingly observed as the duration of diabetes increases, it may reflect structural changes within the brain that prevent the reversal of sympathoadrenal failure to hypoglycaemia by avoiding further episodes. Reversal studies have shown restoration of awareness, at least in part without any improvement in rises in counter-regulatory hormones, particularly epinephrine, suggesting that sympathoadrenal responses to hypoglycaemia are still impaired [94–98].

Conversely, there are those with a long duration of diabetes who show full awareness of hypoglycaemia and still develop sweating and tremor. Have they largely avoided hypoglycaemia throughout their lives by running higher glucose levels or do they possess or have they acquired other protective mechanisms that protect against hypoglycaemia? For example, those who retain some endogenous insulin secretion in type 1 diabetes continue to exhibit a hypoglycaemic response to glucagon [107].

Another limitation in studying mechanisms of counter-regulatory failure and impaired awareness is an inability to clearly define the clinical phenotype. Some cases of impaired awareness may be almost entirely due to repeated episodes of hypoglycaemia and largely reversible (this is often seen in children), whereas others may be due to a gradual decline in hypoglycaemic warnings as their diabetes progresses due to different mechanisms that are irreversible.

These limitations may help to understand why, over 30 years after the clinical studies that described repeated hypoglycaemia as an important cause of counter-regulatory failure, we still rely on avoidance of hypoglycaemia as a treatment for impaired awareness and have not yet developed any effective pharmacological therapies that can treat or prevent it.

Risk factors for hypoglycaemia in diabetes

The risk factors for hypoglycaemia in diabetes follow directly from the pathophysiology of glucose counter-regulation. They are based on the principle that iatrogenic hypoglycaemia is typically the result

of an interplay between relative or absolute therapeutic insulin excess and compromised physiological and behavioural defences against falling plasma glucose concentrations in type 1 diabetes and advanced type 2 diabetes [1, 108].

Absolute or relative insulin excess

The conventional risk factors for hypoglycaemia in diabetes are based on the premise that absolute or relative therapeutic insulin excess is the sole determinant of risk (Table 40.2) [1, 108]. Absolute therapeutic insulin excess occurs when insulin secretagogue or insulin doses are excessive, ill-timed, or of the wrong type, or when insulin clearance or metabolism is reduced, as in renal or hepatic failure. Relative therapeutic insulin excess occurs under a variety of conditions. It occurs when exogenous glucose delivery is decreased (for example, following missed or low-carbohydrate meals and during the overnight fast), when glucose utilization is increased (for example, during and shortly after exercise), when endogenous glucose production is decreased (for example, following alcohol ingestion), and when sensitivity to insulin is increased (for example, after weight loss or improved glycaemic levels and during the night). People with diabetes, their caregivers, and physicians have to work together in identifying and addressing these risk factors when the problem of iatrogenic hypoglycaemia is recognized. Overall, however, these factors likely explain only a minority of episodes of hypoglycaemia [109].

Compromised defences against hypoglycaemia

The risk factors indicative of impaired counter-regulatory responses and impaired awareness (Table 40.2) [50, 108, 110–115] include absolute endogenous insulin deficiency [50, 108, 110, 111, 113, 114]; a history of severe iatrogenic hypoglycaemia, impaired awareness of hypoglycaemia, or both; recent antecedent hypoglycaemia, prior exercise, or sleep [108, 110, 111, 115]; and intensive glycaemic therapy (i.e. lower glycated haemoglobin [HbA_{1c}], lower glycaemic targets, or both) [108, 110–115]. The degree of endogenous insulin deficiency (i.e. β -cell failure) determines the extent to which insulin levels will not decrease and glucagon levels will not increase as plasma glucose concentrations fall in response to therapeutic hyperinsulinaemia. A history of severe hypoglycaemia indicates, and that of impaired awareness of hypoglycaemia implies, a long duration of diabetes, recent antecedent hypoglycaemia, or both. The latter causes attenuated sympathoadrenal and symptomatic responses to

Table 40.2 Risk factors for hypoglycaemia in diabetes.

Relative or absolute insulin excess

- 1.** Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
- 2.** Exogenous glucose delivery is decreased (e.g. following missed meals and during the overnight fast)
- 3.** Glucose utilization is increased (e.g. during and shortly after exercise)
- 4.** Endogenous glucose production is decreased (e.g. following alcohol ingestion)
- 5.** Sensitivity to insulin is increased (e.g. in the middle of the night and following weight loss or improved glycaemic levels)
- 6.** Insulin clearance or metabolism is decreased (e.g. with renal or liver failure)

Hypoglycaemia-associated counter-regulatory impairment

- 1.** Absolute endogenous insulin deficiency
- 2.** A history of severe hypoglycaemia, impaired awareness of hypoglycaemia, or both, and also recent antecedent hypoglycaemia, prior exercise, and sleep
- 3.** Intensive glycaemic therapy (lower glycated haemoglobin [HbA_{1c}], lower glycaemic goals)

subsequent hypoglycaemia. Studies of intensive glycaemic therapy with a control group treated to a higher HbA_{1c} level consistently report higher rates of hypoglycaemia in the group treated to lower HbA_{1c} levels in type 1 diabetes [116–118] and type 2 diabetes [113, 119, 120]. The challenge in clinical practice is to allow people with diabetes to derive the benefits of intensive glycaemic management while minimizing the risk and consequences of hypoglycaemia.

Magnitude of the clinical problem of hypoglycaemia in diabetes

Diabetes is an increasingly common disease and iatrogenic hypoglycaemia affects most of those with type 1 diabetes and people with type 2 diabetes treated with insulin or secretagogues [1, 5]. Indeed, because maintenance of euglycaemia is needed over a lifetime of diabetes, the barrier of hypoglycaemia ultimately affects most people with diabetes [1, 5].

Frequency of hypoglycaemia

Hypoglycaemia is a fact of life for people with type 1 diabetes (Table 40.3) [1, 5, 110, 112, 132]. The average person has untold numbers of episodes of asymptomatic hypoglycaemia and experiences

on average, around two episodes of symptomatic hypoglycaemia per week – thousands of such episodes over a lifetime of diabetes – and one or more episodes of severe, temporarily disabling hypoglycaemia, often with seizure or coma, per year. There is little evidence that this problem has abated since it was highlighted by the Diabetes Control and Complications Trial (DCCT) in 1993 [116]. For example, in 2007 the UK Hypoglycaemia Study Group [74] reported an incidence of severe hypoglycaemia that was twice that in the DCCT in people with type 1 diabetes for <5 years, and an incidence fivefold higher than that in the DCCT in those with type 1 diabetes for >15 years (Table 40.3). An incidence comparable to the latter was also found in a large observational study [112].

Overall, hypoglycaemia is less frequent in type 2 diabetes (Table 40.3) [1, 5, 73–75, 112, 115, 118, 121, 122, 124–130, 133–136], but for the pathophysiological reasons discussed, hypoglycaemia becomes progressively more frequent as people approach the insulin-deficient end of the spectrum of type 2 diabetes [1, 5, 74, 75]. Indeed, its frequency has been reported to be similar in those with type 2 diabetes and type 1 diabetes matched for duration of insulin therapy [75]. When the UK Hypoglycaemia Study Group [74] contrasted people with type 2 diabetes treated with insulin for <2 years with those treated with insulin for >5 years, they found severe hypoglycaemia prevalence rates of 7% and 25% and incidence rates

Table 40.3 Event rates for severe hypoglycaemia (that requiring the assistance of another person), expressed as episodes per 100 person-years, in insulin-treated diabetes.

Study	n	Event rate	Comment
Type 1 diabetes			
UK Hypoglycaemia Study Group 2007 [74]	57 ^a	320	Prospective multicentre study
	50 ^b	110	
MacLeod et al. 1993 [121]	544	170	Retrospective clinic survey, randomly selected sample
Donnelly et al. 2005 [122]	94	115	Prospective study, population-based random sample
Reichard and Pihl 1994 [118]	48	110	Clinical trial, intensive insulin group
DCCT Research Group 1993 [116]	711	62	Clinical trial, intensive insulin group
Khunti et al. 2016 [123]	8022	490	Retrospective 6 mo and 4 wk self-reported prospective multinational survey
Type 2 diabetes			
MacLeod et al. 1993 [121]	56	73	Retrospective clinic survey, randomly selected sample
UK Hypoglycaemia Study Group 2007 [74]	77 ^c	70	Prospective multicentre study
	89 ^d	10	
Akram et al. 2006 [124]	401	44	Retrospective clinic survey
Donnelly et al. 2005 [122]	173	35	Prospective study, population-based random sample
Henderson et al. 2003 [73]	215	28	Retrospective clinic survey, randomly selected sample
Murata et al. 2005 [125]	344	21	Prospective study, random Veterans Affairs sample
Saudek et al. 1996 [126]	62 ^e	18	Clinical trial, multiple insulin injection group
Gürlek et al. 1999 [127]	114	15	Retrospective clinic survey
Abraira et al. 1995 [128]	75	3	Clinical trial, intensive insulin group
Yki-Järvinen et al. 1999 [129]	88	0	Clinical trial, initial insulin therapy
Ohkubo et al. 1995 [130]	52	0	Clinical trial, initial insulin therapy
Khunti et al. 2016 [123]	19 563	250	Retrospective 6 mo and 4 wk self-reported prospective multinational survey in insulin-treated type 2 diabetes

^a Insulin treatment for >15 yr.

^b Insulin treatment for <5 yr.

^c Insulin treatment for >5 yr.

^d Definite (8 per 100 person-years) plus suspected (10 per 100 person-years).

^e Insulin treatment for <2 yr.

Source: Adapted from Cryer et al. 2009 [131] by permission of the Endocrine Society.

of 10 and 70 episodes per 100 person-years, respectively. The pattern for self-treated hypoglycaemia was similar [74]. Thus, although the incidence of iatrogenic hypoglycaemia is relatively low (with current less than euglycemic goals) in the first few years of insulin treatment of type 2 diabetes, the risk increases substantially in advanced type 2 diabetes, approaching that in type 1 diabetes.

Because asymptomatic episodes will almost invariably be missed, and symptomatic episodes may not be recognized as the result of hypoglycaemia [66] and, even if they are, they are not long remembered [71, 137], estimates of the frequency of iatrogenic hypoglycaemia are underestimates. Although they represent only a small fraction of the total hypoglycaemic experience, because they are dramatic events that are more likely to be reported (by the person with diabetes or family or carers) [71, 137], estimates of the frequency of severe hypoglycaemia, requiring the assistance of another person, are more reliable, particularly if they are determined in population-based prospective studies focused on hypoglycaemia [1, 5].

The prospective population-based data of Donnelly et al. [122] indicate that the overall incidence of hypoglycaemia in insulin-treated type 2 diabetes is approximately one-third of that in type 1 diabetes (Table 40.3). The incidence of any and of severe hypoglycaemia was ~4300 and 115 episodes per 100 patient-years, respectively, in type 1 diabetes and ~1600 and 35 episodes per 100 patient-years, respectively, in insulin-treated type 2 diabetes. In addition, in population-based studies, the incidence of severe hypoglycaemia requiring emergency treatment in insulin-treated type 2 diabetes was ~40% [135] and ~100% [136] of that in type 1 diabetes. In the global Hypoglycaemia Awareness Tool study [123], using a six-month retrospective and four-week prospective self-adjustment questionnaire and diaries of 27 585 individuals with type 1 diabetes or insulin-treated type 2 diabetes worldwide, hypoglycaemia rates were three times higher than reported in population-based studies (Table 40.3). Because the prevalence of type 2 diabetes is ~20-fold greater than that of type 1 diabetes, and most people with type 2 diabetes ultimately require treatment with insulin, most episodes of iatrogenic hypoglycaemia, including severe hypoglycaemia, occur in people with type 2 diabetes.

Impact of hypoglycaemia

Iatrogenic hypoglycaemia causes recurrent physical and psychological morbidity, increases mortality, impairs defences against subsequent hypoglycaemia, and precludes maintenance of euglycaemia over a lifetime of diabetes [1, 5]. In the short term, it causes brain fuel deprivation that, if unchecked, results in functional brain failure that is typically corrected after the plasma glucose concentration is raised [3]. Rarely, it causes sudden, presumably cardiac arrhythmic [138, 139] death or, if it is profound and prolonged, brain death [3]. Three early reports indicated that 2–4% of people with diabetes die from hypoglycaemia [140–142]. More recent reports indicated that 6% [143], 7% [144], and 10% [145] of deaths of people with type 1 diabetes were the result of hypoglycaemia. In type 2 diabetes, mortality rates of up to 10% during episodes of severe sulfonylurea-induced hypoglycaemia have been reported [146]. In one trial of type 2 diabetes, between 1% and 9% of evaluable deaths were attributed to hypoglycaemia [147].

Excess mortality during intensive glycaemic therapy with increased rates of hypoglycaemia was found in randomized controlled trials (RCTs) in individuals in the intensive care unit [148] and in people with type 2 diabetes [119]. Overall, increased mortality has been consistently associated with severe hypoglycaemia in six

RCTs, two in individuals in the intensive care unit [148, 149] and four in people with type 2 diabetes [119, 120, 150, 151].

The physical morbidity of an episode of hypoglycaemia ranges from unpleasant symptoms to seizure and coma [1, 3, 5]. It can impair judgement, behaviour, and performance of physical tasks. Permanent neurological damage is rare, although there is concern that recurrent hypoglycaemia might cause chronic cognitive impairment. The developing brain is susceptible to effects of severe hypoglycaemia [152, 153], while from young adulthood to middle age the brain may be more resistant [154]. Cumulative exposure to severe hypoglycaemia in early-onset type 1 diabetes may be associated with poorer cognitive performance in adulthood. In the 32-year follow-up of the DCCT trial, both higher HbA_{1c} and a larger number of severe hypoglycaemic episodes were associated with greater cognitive decline [155]. There was notably a dose-response relationship, with a higher number of severe hypoglycaemic episodes linked to greater decrements in psychomotor function and mental efficiency that was most evident in later life [155, 156]. The psychological morbidity of fear of hypoglycaemia [157] should not be underestimated and can pose a barrier to optimal glycaemic levels.

Hypoglycaemia and cardiovascular disease

Hypoglycaemia can lead to cardiovascular consequences [158]. The role of tight glycaemic management in reducing microvascular complications in newly diagnosed type 2 diabetes was established in the UK Prospective Diabetes Study (UKPDS) in 1998 [134]. While there was a non-significant reduction in the relative risk of myocardial infarction ($p = 0.052$) in the original trial, a 10-year follow-up of the UKPDS cohort showed significant reductions in myocardial infarction and cardiovascular mortality in the intensively treated group [159]. Three, multicentre RCTs subsequently tested the hypothesis that intensive glycaemic management reduces cardiovascular events in type 2 diabetes by recruiting 23 182 participants globally with known cardiovascular disease or established risk factors [117, 118, 150]. In all trials, no significant reduction in major cardiovascular events was observed. Indeed, mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial actually increased [119]. Possible explanations for this include weight gain, specific medications, or simply the play of chance, but it is telling that compared to the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, where there was no increase in mortality, rates of severe hypoglycaemia in ACCORD were in the order of four to five times higher [158]. An association between hypoglycaemia and cardiovascular mortality has also been reported in type 1 diabetes, albeit less consistently [123, 160, 161]. It is uncertain, however, if the association between hypoglycaemia and cardiovascular mortality in diabetes is causal or due to confounding. Hypoglycaemia could be a marker for susceptibility by virtue of being more prevalent in those with comorbidities, including frailty, liver and kidney disease; these conditions are likely to lead to hypoglycaemia, but also independently increase the risk of cardiovascular mortality [162].

Concerns around confounding have led to additional *post hoc* analyses of global cohort studies (epidemiological and clinical trials) with tens and thousands of participants with type 1 diabetes and type 2 diabetes. Collectively, these studies demonstrate a 1.5–6-fold increased risk of cardiovascular events and mortality in those who experience hypoglycaemia compared with those who do not [158]. The association between hypoglycaemia and stroke,

however, is less convincing [163]. A large systematic review and meta-analysis of nearly a million people employed specific statistical adjustments to conclude that comorbidities alone cannot explain the relationship between hypoglycaemia and cardiovascular disease in type 2 diabetes [164]. Nonetheless, whether hypoglycaemia is a risk factor for cardiovascular disease or simply a risk marker is still debated [158]. A recent *post hoc* analysis of the DEVOTE trial population supports the hypothesis that hypoglycaemia is a risk factor for cardiovascular events in type 2 diabetes [165]. Further, Heller et al. recently conducted a *post hoc* analysis of the Liraglutide Effect and Action in Diabetes (LEADER) trial, first to test a potential association between non-severe and severe hypoglycaemia episodes; and second to test a potential association between hypoglycaemia severity and risk of subsequent cardiovascular events in those with type 2 diabetes [166]. Although non-severe hypoglycaemia episodes (>2 per year) were associated with an increased risk of severe hypoglycaemia, no association was found between lower rates (2–11 episodes per year) of non-severe hypoglycaemia and cardiovascular events; however, higher rates (≥ 12 episodes per year) of non-severe hypoglycaemia were associated with a higher risk of cardiovascular events and mortality, suggesting a dose-response relationship [166]. Overall, the true picture is likely to be multifactorial, with confounding and causality likely to be contributing and the magnitude of risk also influenced by the severity and frequency of hypoglycaemia, underlying cardiovascular risk, type and duration of diabetes, and potentially other as yet undetermined biological variables.

It is challenging to establish cause and effect between hypoglycaemia and cardiovascular events in diabetes through *post hoc* analyses. To definitively answer this question, a clinical trial would involve exposure of one group to severe hypoglycaemia while the other was not exposed, with cardiovascular events and mortality as key trial outcomes [158]. Such a study is impractical and clearly unethical, especially as intensive glycaemic management appears to confer a greater cardiovascular risk in those with a high pre-existing cardiovascular burden [167]. However, recent experimental studies have elucidated novel mechanisms through which hypoglycaemia could cause adverse cardiovascular events in those with diabetes [168–173]. These mechanisms are illustrated in Figure 40.9.

Clinical definition and classification of hypoglycaemia

The American Diabetes Association (ADA) and ADA/Endocrine Society Workgroups on Hypoglycaemia [174, 175] defined hypoglycaemia in diabetes as ‘all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm’. However, it is not possible to state a specific plasma glucose concentration that defines clinical hypoglycaemia; although symptoms typically develop at plasma glucose concentrations of 2.8–3.1 mmol/l (~50–55 mg/dl) (Figure 40.1) [176] in individuals without diabetes, the glycaemic threshold for symptoms (and also those for glucose counter-regulatory and cognitive dysfunction responses) shifts to lower plasma glucose concentrations in people with tightly managed diabetes and recurrent hypoglycaemia [59, 175], and to higher plasma glucose concentrations in those with suboptimally managed diabetes [59, 175, 177].

The ADA workgroups on hypoglycaemia with drug-treated diabetes (implicitly those treated with an insulin secretagogue or insulin) became concerned about the possibility of developing hypoglycaemia at a plasma glucose concentration of 3.9 mmol/l (≤ 70 mg/dl) [174, 175]. Within the error of self-monitoring of blood glucose (or continuous glucose sensing), that conservative alert value approximates the lower limit of the post-absorptive plasma glucose concentration range in people without diabetes [176] and the normal glycaemic thresholds for activation of physiological glucose counter-regulatory systems [176], and is low enough to reduce glycaemic defences against subsequent hypoglycaemia [61] in individuals without diabetes. Indeed, impairment of a complex function, driving, has been demonstrated at plasma glucose levels in this general range in type 1 diabetes [178]. It also generally provides some margin for the relative inaccuracy of glucose monitors at low plasma glucose concentrations.

The International Hypoglycaemia Study Group (IHSG) sought to standardize the definition of hypoglycaemia in clinical trials and proposed three levels of hypoglycaemia: level 1 (< 3.9 mmol/l); level 2 (< 3.0 mmol/l); and level 3, which corresponds to severe hypoglycaemia requiring external assistance (Table 40.4) [179]. The group recommended that glucose < 3.0 mmol/l should be regarded as

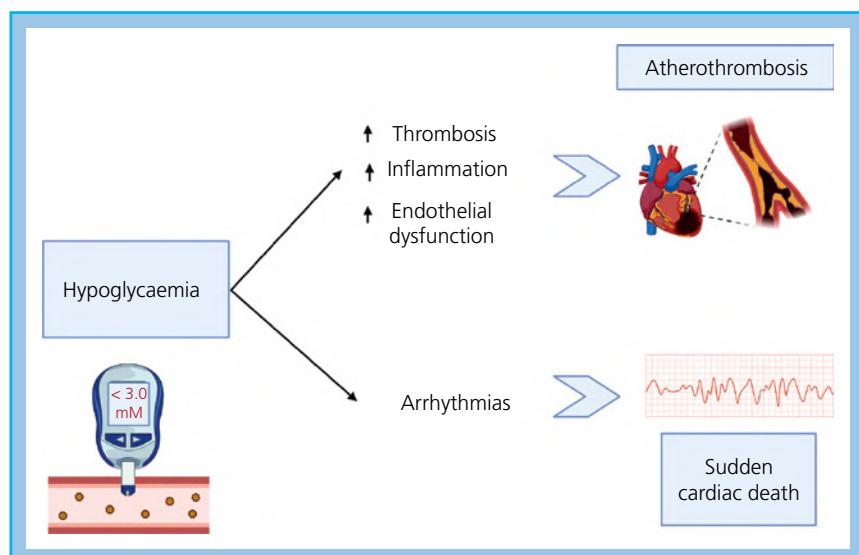


Figure 40.9 Mechanisms through which hypoglycaemia may cause adverse cardiovascular events. Source: Created by A. Iqbal in Biorender.com.

Table 40.4 International Hypoglycaemia Study Group definition of levels of hypoglycaemia that should be reported in clinical trials.

Level	Classification	Definition
1	Hypoglycaemia alert	Glucose <3.9 mmol/l (70 mg/dl)
2	Clinically important	Glucose <3.0 mmol/l (54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia Should be reported in clinical trials
3	Severe	Severe hypoglycaemia with as defined by American Diabetes Association [175] denotes severe cognitive impairment requiring external assistance for recovery

Source: Modified by permission from International Hypoglycaemia Study Group 2017 [179].

clinically significant and should be reported in clinical trials. The basis for the proposed new classification is as follows:

- The level of 3 mmol/l (54 mg/dl) represented a glucose level below which clinically relevant consequences can develop; these include cognitive impairment, cardiac arrhythmias, and evidence that repeated episodes of glucose levels below this concentration can lead to impaired awareness and counter-regulatory impairment.
- Agreeing a third level (level 2) that was not severe but was clinically important would increase the statistical power of studies comparing different interventions to prevent and treat hypoglycaemia.
- Agreeing a revised classification would permit researchers to combine trial data in systematic reviews and permit meta-analysis.
- Adding the phrase ‘cognitive impairment requiring the assistance of a third party’ would allow paediatricians to adopt the same classification as used in adult practice. Paediatric classifications previously had defined severe hypoglycaemia as coma or needing parenteral therapy, as all young children ‘need the help of another person’ when treating any episode of hypoglycaemia.

The classification was adopted by both the ADA and the European Association for the Study of Diabetes (EASD) and subsequently by other organizations, including the Juvenile Diabetes Research Foundation (JDRF), International Society for Paediatric and Adolescent Diabetes (ISPAD), Advanced Technologies and Treatments for Diabetes (ATT), and at least one regulator (European Medicines Agency, EMA).

Prevention and treatment of hypoglycaemia in diabetes: hypoglycaemia risk factor reduction

Iatrogenic hypoglycaemia is a barrier to glycaemic management in people with diabetes [1,5], but the barrier can be lowered in individuals with diabetes by the practice of hypoglycaemia risk factor reduction (Table 40.5) [1,5,108]. That involves four steps:

1. Acknowledge the problem.
2. Apply the principles of aggressive glycaemic therapy [1,5,108,180–184].
3. Consider the conventional risk factors for hypoglycaemia (Table 40.2).
4. Consider the risk factors for hypoglycaemia-associated counter-regulatory impairment in diabetes (Table 40.2).

Table 40.5 Hypoglycaemic risk factor reduction.

- 1 Acknowledge the problem
- 2 Apply the principles of aggressive glycaemic therapy
 - Diabetes self-management (patient education and empowerment)
 - Frequent self-monitoring of blood glucose and increasingly continuous glucose monitoring
 - Flexible and appropriate insulin (and other drug) regimens
 - Individualized glycaemic goals
 - Ongoing professional guidance and support
- 3 Consider the conventional risk factors for hypoglycaemia (Table 40.2)
- 4 Consider the risk factors indicative of hypoglycaemia-associated counter-regulatory impairment (Table 40.2)

The issue of hypoglycaemia should be addressed in every contact with people with diabetes, at least those treated with a sulfonylurea, a glinide, or insulin [1,5,108]. Acknowledging the problem allows the caregiver either to move on if hypoglycaemia is not an issue, or to address it, and keep it in perspective, if hypoglycaemia is an issue. Patient concerns about the reality, or even the possibility, of hypoglycaemia can be a barrier to glycaemic management [185,186]. It is often helpful also to question close associates of the person with diabetes, because they may have observed clues to episodes of hypoglycaemia not recognized by the individual with diabetes. Even if no concerns are expressed, examination of the self-monitoring of blood glucose or CGM records will often disclose that hypoglycaemia is a problem.

If hypoglycaemia is an issue, the principles of intensive glycaemic therapy in diabetes [1,5,108,180–184] should be reviewed and applied. These include diabetes self-management based on diabetes education and empowerment, frequent self-monitoring of blood glucose (and increasingly use of CGM), flexible and appropriate insulin (and other drug) regimens, individualized glycaemic goals, and ongoing professional guidance and support (Table 40.5).

Diabetes self-management education and empowerment are fundamentally important. As the therapeutic regimen becomes progressively more complex, both early in type 1 diabetes and later in type 2 diabetes, the success of glycaemic management becomes progressively more dependent on the many management decisions and skills of the well-informed person with diabetes. In addition to basic training about diabetes, people with insulin secretagogue or insulin-treated diabetes need to learn about hypoglycaemia [187]. They need to know the common symptoms of hypoglycaemia, and their individual most meaningful symptoms, and how to treat (and not overtreat) an episode. Close associates also need to be taught the symptoms and signs of hypoglycaemia, and when and how to administer glucagon. The individual needs to understand the relevant conventional risk factors for hypoglycaemia (Table 40.2), including the effects of the dose and timing of their individual secretagogue or insulin preparation(s) and also the effects of missed meals and the overnight fast, exercise, and alcohol ingestion. They also need to know that episodes of hypoglycaemia signal an increased likelihood of future, often more severe, hypoglycaemia [110,111,113,115,187–190]. Finally, individuals using an online glucose monitoring system need to apply those data critically to their attempts to minimize both hypoglycaemia and hyperglycaemia.

The core approach to virtually all individuals in whom iatrogenic hypoglycaemia becomes a problem is structured education (or often re-education), which reduces the rates of severe hypoglycaemia

[67, 191–193]. This is often coupled with short-term scrupulous avoidance of hypoglycaemia, which reverses impaired awareness of hypoglycaemia in most affected individuals [94–97]. The therapeutic objective is to minimize the number and the magnitude of episodes of hypoglycaemia, not to promote hyperglycaemia. Indeed, it is often possible to lower HbA_{1c}.

In people treated with an insulin secretagogue, and particularly those treated with insulin, frequent self-monitoring of blood glucose becomes progressively more key to diabetes self-management as the therapeutic regimen grows more complex, both early in type 1 diabetes and later in type 2 diabetes. Ideally, individuals should estimate their glucose levels whenever they suspect hypoglycaemia. That would not only confirm or exclude an episode of hypoglycaemia, it would also help the individual learn the key symptoms of their hypoglycaemic episodes and might lead to regimen adjustments. It is particularly important for people with impaired awareness of hypoglycaemia to monitor their glucose level before performing a critical task such as driving. Self-monitoring of blood glucose provides a glucose estimate only at one point in time; it does not indicate whether glucose levels are falling, stable, or rising. That limitation is addressed by evolving technologies for real-time CGM [194–196]. Subcutaneous glucose concentrations lag changes in plasma glucose by 10–15 minutes and their measurement suffers from some inaccuracy. Nonetheless, CGM is associated with an average HbA_{1c} reduction of 0.4–0.6% (4–6 mmol/mol) in adults with type 1 diabetes who used the device when prescribed without an increase in detected hypoglycaemia [194]. However, in one study, the sensitivity and specificity for the detection of low glucose levels were only 65% and 80%, respectively, and both false-negative and false-positive results were common [196].

Flexible and appropriate drug regimens are key components of hypoglycaemia risk factor reduction [1, 5, 108]. Hypoglycaemia is typically the result of relative or absolute therapeutic (endogenous or exogenous) insulin excess and compromised defences against falling plasma glucose concentrations. The relevant treatments include insulin or an insulin secretagogue such as a sulfonylurea (e.g. glibenclamide [glyburide], glipizide, glimepiride, and glipizide) or a glinide (e.g. repaglinide and nateglinide). Early in the course of type 2 diabetes, people may respond to drugs that do not raise insulin levels at low or normal plasma glucose concentrations and therefore should not, and probably do not, cause hypoglycaemia [1, 5]. These include the biguanide metformin, which nonetheless has been reported to cause self-reported hypoglycaemia [115], thiazolidinediones, α -glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium–glucose co-transporter 2 (SGLT-2) inhibitors. All these drugs require endogenous insulin secretion to lower plasma glucose concentrations, and insulin secretion declines appropriately as glucose levels fall into the normal range. That is true even for the GLP-1 receptor agonists and the DPP-4 inhibitors, which enhance glucose-stimulated insulin secretion (among other actions). They do not stimulate insulin secretion at normal or low plasma glucose concentrations (i.e. they increase insulin secretion in a glucose-dependent fashion). However, all five categories of drugs can increase the risk of hypoglycaemia if used with an insulin secretagogue or insulin.

Among the commonly used sulfonylureas, the longer-acting glibenclamide (glyburide) is more often associated with hypoglycaemia than the shorter-acting glimepiride [146, 197]. The use of long-acting insulin analogues (e.g. glargin or detemir), rather than neutral protamine Hagedorn (NPH) insulin, as the basal insulin in

a multiple daily injection insulin regimen reduces at least the incidence of nocturnal hypoglycaemia, and perhaps also that of total, symptomatic, and nocturnal hypoglycaemia, in type 1 diabetes and type 2 diabetes [197–199]. The use of a rapid-acting analogue (e.g. lispro, aspart, or glulisine) as the prandial insulin in a multiple daily injection regimen reduces the incidence of nocturnal hypoglycaemia, at least in type 1 diabetes [198–201]. Second-generation basal analogues (insulin degludec, insulin glargine 300 U/ml) have more consistent pharmacokinetic profiles. Compared with first-generation insulin glargine 100 U/ml, both are associated with a lower risk of hypoglycaemia, particularly nocturnal hypoglycaemia, while achieving similar HbA_{1c} [202–204]. In a randomized crossover trial, insulin degludec was associated with lower rates of symptomatic hypoglycaemic episodes in people with type 1 diabetes (2201 vs 2463 episodes per 100 person-years' exposure) compared with insulin glargine 100 U/ml [205].

Significant advances have been made in CGM systems, which detect interstitial glucose using enzymatic sensors, integrated with a mobile reader to deliver real-time glucose levels (real-time or rtCGM) or on scanning (intermittently scanned or isCGM). Such systems can warn the user or care partner of hypoglycaemia or impending hypoglycaemia. In RCTs, rtCGM reduced hypoglycaemia compared with self-monitoring of blood glucose in type 1 diabetes [204], including those with impaired awareness [207]. In type 2 diabetes, use of isCGM reduced hypoglycaemia in open-label trial settings [208]. Significant reductions in severe hypoglycaemic events with isCGM were also reported in real-world settings [209], although the accuracy of CGM sensors in the hypoglycaemia range remains a limiting factor.

Because the basal insulin infusion rate can be varied across the day, continuous subcutaneous insulin infusion using insulin pumps should be superior to multiple daily injections. It may reduce HbA_{1c}, the frequency of hypoglycaemia, or both, in selected capable and motivated individuals [210]. However, in the HypoCOMPaSS trial [68], neither pump therapy alone (compared with multiple daily injections) nor CGM (compared with self-monitoring of blood glucose) reduced severe hypoglycaemia or improved awareness of hypoglycaemia to a greater extent. Sensor-augmented pumps, which combine rtCGM with an insulin pump, achieve an ~0.5% (5 mmol/mol) greater decrease in HbA_{1c} than multiple daily injections alone without an increase in hypoglycaemia [211, 212]. A sensor-augmented pump that temporarily suspends insulin infusion for up to two hours when the CGM value falls below a preselected level (a low glucose suspend [LGS] feature) reduces the frequency of severe hypoglycaemia [213, 214].

Significant advances have been made in closed-loop insulin delivery, which combines CGM and insulin pump with an automated controller. Current commercially available systems are hybrid closed-loop systems that provide algorithm-driven automated insulin delivery, but still require manual or *announced* mealtime boluses. Compared with sensor-augmented pumps, hybrid closed-loop systems have been associated with significant reductions in HbA_{1c} and time in hypoglycaemia by CGM in adults and adolescents with type 1 diabetes [215–216]. Bihormonal pumps, with automated delivery of both insulin and glucagon, are actively under clinical development and may confer additional protection from hypoglycaemia [219–221]. Islet transplantation can restore α - and β -cell function in longstanding type 1 diabetes in individuals with impaired awareness of hypoglycaemia or recurrent severe hypoglycaemia with undetectable C-peptide. Long-term follow-up of transplant recipients has shown that they remained completely

free of severe hypoglycaemic episodes at 10 years with reduced insulin requirements [222]. Although closed-loop and islet transplantation may be effective in reducing hypoglycaemia, the cost and complexity of these technologies currently preclude them from being used widely. Patient motivation and education remain paramount in achieving the best outcomes with new technologies. Indeed, several psycho-educational interventions, including blood glucose awareness training [223], have demonstrated reduced numbers of severe hypoglycaemia in recent trials.

Given the evidence that optimal glycaemic management partially prevents or delays microvascular complications of diabetes, and may partially prevent or delay macrovascular complications, it follows that a lower HbA_{1c} is in the best interests of people with diabetes if it can be achieved and maintained safely [138]. Thus, a reasonable individualized glycaemic goal is the lowest HbA_{1c} that does not cause severe hypoglycaemia, preferably with little or no symptomatic or even asymptomatic hypoglycaemia, at a given stage in the evolution of the individual's diabetes [138]. That links the selection of a glycaemic goal to the risk of hypoglycaemia, as well as the use of drugs that can cause hypoglycaemia and the type and duration of diabetes, a surrogate for endogenous insulin deficiency. If the therapeutic regimen produces severe hypoglycaemia or impaired awareness of hypoglycaemia, or an unacceptable number of symptomatic or asymptomatic episodes, hypoglycaemia has become a problem that needs to be addressed.

Because the glycaemic management of diabetes is empirical, caregivers should work with each individual over time to find the most effective and safest method of glycaemic management at a given point in the course of that person's diabetes. Care is best accomplished by a team that includes, in addition to a physician, professionals trained in, and dedicated to, translating the standards of care into the care of the individual and making full use of modern communication and computing technologies.

Another step is to consider the conventional risk factors for hypoglycaemia, especially those that result in both relative and absolute therapeutic insulin excess. In addition to insulin secretagogue or insulin doses, timing, and type, these include conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization or sensitivity to insulin is increased, or insulin clearance is reduced (Table 40.2).

Finally, the risk factors for counter-regulatory impairment need to be considered. These include the degree of endogenous insulin deficiency, a history of severe hypoglycaemia, impaired hypoglycaemia awareness, or both, and also any relationship between hypoglycaemic episodes and recent antecedent hypoglycaemia, prior exercise or sleep, and lower HbA_{1c} levels (Table 40.2). Unless the cause is easily remediable, a history of severe hypoglycaemia should prompt consideration of a fundamental regimen adjustment. Without that, the risk of a subsequent episode of severe hypoglycaemia is high [110, 111, 113, 115, 187–190]. Given a history of impaired awareness of hypoglycaemia, a 2–3-week period of scrupulous avoidance of hypoglycaemia, without running glucose levels high, is advisable since it may improve awareness [94–98]. Interestingly, few of the reversal studies have led to significant restoration of impaired counter-regulatory hormone responses [95–98]. A history of late post-exercise hypoglycaemia, nocturnal hypoglycaemia, or both should prompt appropriately timed regimen adjustments (generally, less insulin action, more carbohydrate ingestion, or both).

When prevention fails, treatment of hypoglycaemia becomes necessary. Most episodes of asymptomatic hypoglycaemia (detected by self-monitoring of blood glucose or CGM) and of mild–moderate

symptomatic hypoglycaemia are effectively self-treated by ingestion of glucose tablets or carbohydrate-containing juice, soft drinks, other snacks, or a meal [224, 225]. A reasonable dose is 20 g of glucose [225]. Clinical improvement should occur in 15–20 minutes; however, in the setting of ongoing hyperinsulinaemia, the glycaemic response to oral glucose is transient, typically less than two hours [225]. Thus, ingestion of a more substantial snack or meal shortly after the plasma glucose concentration is raised is generally advisable.

Parenteral treatment is required when a hypoglycaemic patient is unwilling (because of neuroglycopenia) or unable to take carbohydrate orally. Glucagon, injected subcutaneously or intramuscularly (in a usual dose of 1.0 mg in adults) by an associate of the patient, may be used. That can be life-saving, but it often causes substantial, albeit transient, hyperglycaemia and it can cause nausea or even vomiting. Smaller doses of glucagon (e.g. 150 µg), repeated if necessary, are effective without side effects [226]. Because it acts by stimulating hepatic glycogenolysis, glucagon is ineffective in glycogen-depleted individuals (e.g. following a binge of alcohol ingestion). New formulations of nasal glucagon are now available that are easier to administer. In a real-world prospective study, hypoglycaemic episodes resolved within 30 minutes of nasal glucagon administration, and in 95% of individuals and severe hypoglycaemic episodes resolved without additional external help within 15 minutes of receiving glucagon [227]. New glucagon analogues are also entering clinical practice as pre-filled pens with a long shelf-life.

Although glucagon can be administered intravenously by medical personnel, intravenous glucose is the standard parenteral therapy [224]. The glycaemic response to intravenous glucose is, of course, transient in the setting of ongoing hyperinsulinaemia.

The duration of an episode of iatrogenic hypoglycaemia is a function of its cause. An episode caused by a rapid-acting insulin secretagogue or insulin analogue will be relatively brief, while that caused by a long-acting sulphonylurea or insulin analogue will be substantially longer. The latter can result in prolonged hypoglycaemia requiring hospitalization for monitoring and parenteral glucose infusion if required.

Hypoglycaemia in children and adolescents

The majority of individuals with type 1 diabetes are adults, but nearly three-quarters of new type 1 diabetes diagnoses occur in childhood and adolescence [228]. Despite recent advances in knowledge, education, and diabetes technologies and treatments, most children and adolescents with type 1 diabetes do not achieve recommended glycaemic targets [229, 230]. Specifically, only a quarter of young people achieve the internationally established recommended HbA_{1c} target of <53 mmol/mmol (<7%), known to be associated with reduced diabetes complications in adulthood [231]. Hypoglycaemia and the fear of hypoglycaemia remain significant barriers to achieving these targets.

Hypoglycaemia is a common complication in the management of type 1 diabetes in children and adolescents. It interferes with daily living and poses a constant perceived threat to the individual and their families. It has long been recognized as a limiting factor in achieving optimal glycaemic levels [232] with an impact on quality of life [233]. As with adults, minimizing hypoglycaemia and its impact is a key objective of paediatric diabetes care.

Although hypoglycaemia in the young person with type 1 diabetes has much in common with hypoglycaemia in adults, there are important differences, which will be highlighted in this section. For example, there are differences in the physiology of the symptomatic and hormonal counter-regulatory responses to hypoglycaemia, its epidemiology, and risk factors. Furthermore, the impact of hypoglycaemia may differ because the child's organs, in particular the brain, are developing. In addition, the effects of changing behaviour as the young person matures modify the impact and response to hypoglycaemia. Finally, more so than for adults, the role and responses of caregivers are crucial.

Definition of hypoglycaemia in children and young people

The definition and classification of hypoglycaemia in children have been aligned with those in adults (Table 40.4) [234]. An important consideration in young children is that they require assistance to correct even mild hypoglycaemia. As a result, to define a severe event accurately requires an assessment by the caregiver and clinician as to the presence (or not) of hypoglycaemia-induced cognitive dysfunction. A subgroup of severe hypoglycaemia is hypoglycaemic coma: this is a hypoglycaemic event resulting in coma or convulsion. These events should be recorded independently, as they are unequivocal and significant in outcome.

The increasing adoption of CGM into routine clinical care, particularly in children [235], has added a new dimension to assessing hypoglycaemia. Using CGM, hypoglycaemia can be reported as a proportion of time spent with a sensor glucose value below a certain value. A recent international consensus recommended targets for sensor glucose: for time with sensor glucose $<3.9\text{ mmol/l}$ (70 mg/dl) the target is $<4\%$ (1 h/d) and for time with sensor glucose $<3.0\text{ mmol/l}$ ($<54\text{ mg/dl}$) the target is $<1\%$ (15 min) [236].

Prevalence and incidence of hypoglycaemia in children and young people

Mild hypoglycaemia is common and its exact incidence is difficult to determine. Unless CGM is used, asymptomatic hypoglycaemia and hypoglycaemia during sleep are unreported. Symptomatic hypoglycaemia occurs on an average twice per week. In contrast, the accurate recall of severe hypoglycaemia is more likely to be robust, although variations in definitions, sample sizes, and retrospective surveys have made comparisons between studies difficult.

The DCCT was one of the first studies to prospectively document hypoglycaemia incidence. In that trial there was a threefold increased risk of severe hypoglycaemia events in individuals randomized to the intensive management arm of the study and rates were higher in adolescents both in the intensive and conventional treatment arms [110]. The incidence of severe hypoglycaemia requiring treatment assistance was 61 per 100 person-years in those intensively treated. Similar high rates were reported in contemporary observational cohorts from Colorado and Western Australia [237, 238].

More recently, rates have substantially reduced. Population-based studies from Western Australia, Denmark, and Germany/Austria (Diabetes-Patienten-Verlaufsdokumentation, DPV registry) demonstrated a reduction of severe hypoglycaemia rates (convulsions and coma) in children and young people by >50% over the last two decades [238–241]. Historically, severe hypoglycaemia was associated with lower HbA_{1c} [242, 243], although this relationship has weakened in recent years, as observed in a large longitudinal cohort study from Europe and Australia, with a reduction in the rates

of severe hypoglycaemia [244]. In that analysis, the severe hypoglycaemic coma rate decreased by an annual average of 2% and 6% in the European DPV and the Western Australian cohort, respectively. Likewise, younger age, historically a risk factor for severe events, did not increase the risk of severe hypoglycaemia, in spite of improved glycaemic levels [244, 245]. Similarly, a combined analysis from the US type 1 diabetes (T1D) Exchange and the DPV registry did not find increased rates of severe hypoglycaemic coma in those <6 years of age with HbA_{1c} $<7.5\%$ (58 mmol/mol) compared to those with higher HbA_{1c} [245]. The causes of these changes can only be subject to speculation, but improved knowledge and education along with increased use of insulin analogues and insulin pump therapy are likely contributors [240, 246–248]. Even though rates have reduced, hypoglycaemia continues to be a significant problem for young people living with diabetes and their families.

Signs and symptoms

As in adults, hypoglycaemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/or neurological dysfunction from glucose deprivation in the brain (neuroglycopenia). As the blood glucose falls, the initial symptoms result from activation of the autonomic nervous system and include shakiness, sweating, pallor, and palpitation. In healthy individuals with no diabetes, these symptoms occur at a higher blood glucose level in children than in adults ($3.2\text{--}3.4\text{ mmol/l}$ [$58\text{--}61\text{ mg/dl}$] vs $2.8\text{--}3.1\text{ mmol/l}$ [$50\text{--}56\text{ mg/dl}$], children vs adults) [249]. The threshold for symptoms in individuals with diabetes will depend on their glycaemic levels [178, 249, 250], with an adaptive shift of the glycaemic threshold for symptom onset to a higher glucose level with chronic hyperglycaemia and a lower glucose level with chronic hypoglycaemia.

Signs of hypoglycaemia in children include behavioural changes: irritability, agitation, quietness, stubbornness, and tantrums may be the prominent symptom particularly for preschool children, and may result from a combination of neuroglycopenic and autonomic responses [251]. In this younger age group, observed signs, such as pallor, are more important. The dominant symptoms of hypoglycaemia tend to differ depending on age, with neuroglycopenia more common than autonomic symptoms in the young [252].

Physiological responses in children and adolescents

Although many of the physiological responses to hypoglycaemia are similar throughout the lifespan, developmental and age-related differences have been described in children and adolescents. As described for symptoms, counter-regulatory hormone responses differ in adolescents, who release catecholamines, cortisol, and growth hormone at a higher blood glucose than adults [249]. Adolescents also have deficient glucagon responses to hypoglycaemia within three months from diagnosis of type 1 diabetes [253].

To date, nearly all studies have been conducted in adolescents and young adults, primarily due to the difficulty of studying a younger age group. As a result, little is known about whether responses in pre-adolescents demonstrate a similar or different effect.

Impact and consequences of hypoglycaemia in children and young people

Hypoglycaemia is a constant concern for children, adolescents, and their families. Symptoms may be distressing or embarrassing, potentially compromising academic, social, and physical activities. Transient cognitive dysfunction associated with neuroglycopenia can affect education and present a risk for the young person.

Furthermore, the daily requirement to adjust therapy to prevent hypoglycaemia is a significant ongoing burden for caregivers.

Psychological impact of hypoglycaemia

Severe hypoglycaemic episodes tend to have negative psychosocial consequences for the individual [254]. Fear of hypoglycaemia can induce anxiety and, although in some cases this anxiety can lead to appropriate vigilance in glucose management, high levels of anxiety can lead to disruptions in daily activities and suboptimal diabetes management [255]. Fear of hypoglycaemia can have impacts not only on the child but also the parents, and result in increased anxiety, poor sleep, and reduced quality of life [256]. This fear could lead families and/or physicians to accept high glucose levels, with behaviours directed towards avoiding hypoglycaemia leading to suboptimal glycaemic levels.

Neurological sequelae of hypoglycaemia

Although severe and prolonged hypoglycaemia has the potential to result in neurological impairment [257], multiple studies have only found subtle impacts of hypoglycaemia on the brain in children. Children with early-onset type 1 diabetes (<6 years of age) have cognitive defects on neuropsychological testing and changes on brain imaging [258]. This was assumed to be the result of hypoglycaemia, but detailed studies have not confirmed this and more recent evidence suggests that chronic hyperglycaemia [259,260] and even diabetic ketoacidosis [261] are more injurious to the brain in the young.

Impaired awareness of hypoglycaemia

Impaired awareness of hypoglycaemia may develop in children as well as adults, with a prevalence of between 19% and 37% [262,263]. As in adults, impaired awareness is associated with a significantly increased risk of a severe hypoglycaemia event [262]. Determining the level of hypoglycaemia awareness is an important component of routine clinical care.

Mortality

Mortality from hypoglycaemia in children and young people is rare, but has been reported [144,145]. Although rare, it is a common source of parental anxiety and fear of hypoglycaemia.

Risk factors for hypoglycaemia in children and young people

Undoubtedly, the most important risk factor for hypoglycaemia lies within insulin therapy itself and the mismatch between administered insulin and consumed food. An absolute excess of insulin could result from increased doses due to poor understanding of insulin type and action or accidental delivery. Similarly, a relative insulin excess is seen with reduced food intake or missed meals, and in situations where glucose utilization is increased (during exercise) or endogenous glucose production is decreased (after alcohol intake).

Managing type 1 diabetes and balancing the risk factors for hypoglycaemia in young children and young people present unique challenges owing to the child's developmental level, unpredictability of an infant or toddler's dietary intake, and the child's irregular activity level, emotional maturity, and behaviour.

Risk factors for recurrent hypoglycaemia

Most children with type 1 diabetes who experience severe hypoglycaemia have isolated events; however, a few experience recurrent episodes. After a severe episode, the risk of recurrent severe events

is increased, in one report for up to four years [264]. When hypoglycaemia is recurrent, it is important to exclude impaired awareness of hypoglycaemia and rule out coexisting autoimmune disorders, such as subclinical hypothyroidism, coeliac disease, and Addison's disease [265–267]. Unexplained hypoglycaemia particularly in adolescence may be factitious due to self-administration, often a sign of psychological distress [268].

Exercise

Glucose response to exercise is affected by many factors, including the duration, intensity, and type of exercise; the time of day when exercise is performed; plasma glucose and insulin levels; and the availability of supplemental and stored carbohydrates [269,270]. The risk of hypoglycaemia is increased immediately after or during exercise, but may also be delayed up to 12 hours after exercise due to changes in insulin sensitivity and muscle glycogen restoration [271]. A range of strategies may be used to prevent exercise-induced hypoglycaemia, including close glucose monitoring, altering insulin doses, and carbohydrate ingestion [269].

Alcohol

Alcohol inhibits gluconeogenesis and may lead to hypoglycaemia [272]. Furthermore, the symptoms of hypoglycaemia may be obscured or masked by the cerebral effects of alcohol.

Nocturnal hypoglycaemia

Hypoglycaemia during sleep is a major concern for parents, and children have more frequent and prolonged periods of hypoglycaemia at night [273]. Younger age, lower HbA_{1c}, antecedent exercise, and hypoglycaemia are associated with a greater frequency of nocturnal hypoglycaemia [274]. Counter-regulatory catecholamine responses to hypoglycaemia are suppressed during sleep.

Hypoglycaemia treatment in children and young people

A goal of diabetes education is the prevention of hypoglycaemia through awareness of the problem, recognition of risk factors, regular glucose monitoring, and self-care behaviours such as appropriate insulin dosing and food intake. Despite this, hypoglycaemia may occur and a treatment plan is a required component of management.

When the glucose level falls below 3.9 mmol/l (70 mg/dl), remedial actions to prevent a further drop in glucose are recommended. The amount of glucose required may vary between individuals, circumstances, and insulin treatment. One study found that in children, 0.3 g/kg of rapidly acting carbohydrate-containing preparations effectively resolves hypoglycaemia in most children and raises median blood glucose by 1–1.3 mmol/l (90–113 mg/dl) in 10 minutes and 2.0–2.1 mmol/l (180–190 mg/dl) in 15 minutes without rebound hyperglycaemia at the next meal [275]. For children using insulin pump therapy, a lower amount of glucose may be required along with suspension of insulin delivery [276].

Urgent treatment is required in the event of severe hypoglycaemia, which can be safely reversed by glucagon administered intravenously, intranasally, intramuscularly, or subcutaneously [277,278]. In hospital, intravenous glucose or glucagon may be given. Intravenous glucose should be administered by trained personnel over several minutes to reverse hypoglycaemia. If glucose is given in excessive concentration (50% dextrose) or too rapidly, there is a risk of brain injury due to rapid osmolar change and cerebral oedema [279].

Diabetes technology and hypoglycaemia in children and young people

The introduction of diabetes technologies into routine diabetes care has offered new approaches to reducing the impact of hypoglycaemia on young people with type 1 diabetes. Insulin pump therapy has been associated with lower hypoglycaemia rates in trials and real-world data reports [280, 281]. With pump therapy it is possible to adjust insulin delivery to more closely mimic physiological insulin delivery. CGM provides 24-hour glucose monitoring and allows the individual, or healthcare providers, to assess trends in glucose levels and early intervention to prevent hypoglycaemia. Trials and real-world outcome studies have shown reduced rates of hypoglycaemia with the use of these systems [281–283]. CGM that has the capacity for remote monitoring has the potential to provide caregivers with an alarm if glucose levels in a child are falling; in one trial their use was associated with improved parental quality of life and better sleep [284].

Sensor-augmented pump therapy with insulin suspension

The incorporation of algorithms that automatically suspend insulin delivery based on sensor glucose readings reduces the incidence of severe hypoglycaemia and the time spent in a low glucose range [214, 285, 286]. Current systems suspend on predicted hypoglycaemia.

Automated insulin delivery systems (hybrid closed-loop)

Automated insulin delivery, with continuous glucose sensing and insulin delivery without user intervention, offers the potential to reduce the significant glycaemic excursions associated with conventional therapy. These systems utilize a control algorithm that autonomously and continually increases and decreases the subcutaneous delivery of insulin on the basis of real-time sensor glucose levels. These devices improve the time in target glucose range and reduce the time spent in hypoglycaemia in clinical trials and observational studies [215, 287–289].

Perspective on hypoglycaemia in diabetes

Glycaemic management, a focus of this chapter, is but one aspect of the management of diabetes. It is now possible to drive plasma low-density lipoprotein (LDL) cholesterol concentrations to subphysiological levels and to normalize blood pressure pharmacologically, usually without major side effects, in most people with diabetes. Weight loss and smoking cessation are more challenging. Although it is not possible to maintain euglycaemia over a lifetime of diabetes, because of the barrier of hypoglycaemia, maintenance of the lowest mean glycaemia that can be accomplished safely is in the best interests of people with diabetes.

Despite the difficulty, people with diabetes and their caregivers should keep the problem of iatrogenic hypoglycaemia in perspective. Early in the course of type 2 diabetes, by far the most common type of diabetes, hyperglycaemia may respond to lifestyle changes, specifically weight loss, or to anti-diabetes drugs that do not raise insulin levels and therefore do not cause hypoglycaemia. In theory, when such drugs are effective in the absence of side effects, there is no reason not to accelerate their dosing until euglycaemia is achieved. Over time, however, as people with type 2 diabetes become progressively more insulin deficient, those drugs, even in combination, fail to maintain

glycaemic levels. Insulin secretagogues are also effective early in the course of type 2 diabetes, but they cause hyperinsulinaemia and therefore introduce both the risk of weight gain and hypoglycaemia. Euglycaemia is not an appropriate goal during therapy with an insulin secretagogue or with insulin. Nonetheless, the frequency of hypoglycaemia is relatively low during treatment with an insulin secretagogue or even with insulin early in the course of type 2 diabetes when glycaemic defences against falling plasma glucose concentrations are still intact. Therefore, over much of the course of the most common type of diabetes, it is possible to maintain a meaningful glycaemic level with a relatively low risk of hypoglycaemia.

The challenge is greater in people with advanced type 2 diabetes and type 1 diabetes caused by compromised defences against falling plasma glucose concentrations and the resulting higher barrier of iatrogenic hypoglycaemia. It is striking that it is 30 years since the recognition of the importance of repeated episodes of antecedent hypoglycaemia in damaging counter-regulatory mechanisms leading to impaired awareness of hypoglycaemia. Yet despite a substantial research effort in both basic and clinical arenas, our only effective therapeutic approaches involve therapeutic interventions that reduce the time individuals spend in hypoglycaemia. Nonetheless, concerns about hypoglycaemia should not be used as an excuse for suboptimal glycaemic levels. It should be recalled that the DCCT [110, 290] documented that the relationship between microvascular complications and mean glycaemia is curvilinear: some degree of glycaemic management puts the person with diabetes at substantially lower risk than little or no glycaemic management.

Diabetes will eventually be cured and prevented. Pending that, elimination of hypoglycaemia from the lives of people with diabetes will probably be accomplished by new treatment methods that provide plasma glucose-regulated insulin replacement or secretion. In the meantime, innovative research is needed if we are to improve the lives of all people affected by diabetes by lowering the barrier of iatrogenic hypoglycaemia.

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