

Type 2 diabetes mellitus

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Abstract | Type 2 diabetes mellitus (T2DM) is an expanding global health problem, closely linked to the epidemic of obesity. Individuals with T2DM are at high risk for both microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities), owing to hyperglycaemia and individual components of the insulin resistance (metabolic) syndrome. Environmental factors (for example, obesity, an unhealthy diet and physical inactivity) and genetic factors contribute to the multiple pathophysiological disturbances that are responsible for impaired glucose homeostasis in T2DM. Insulin resistance and impaired insulin secretion remain the core defects in T2DM, but at least six other pathophysiological abnormalities contribute to the dysregulation of glucose metabolism. The multiple pathogenetic disturbances present in T2DM dictate that multiple antidiabetic agents, used in combination, will be required to maintain normoglycaemia. The treatment must not only be effective and safe but also improve the quality of life. Several novel medications are in development, but the greatest need is for agents that enhance insulin sensitivity, halt the progressive pancreatic β -cell failure that is characteristic of T2DM and prevent or reverse the microvascular complications. For an illustrated summary of this Primer, visit: <http://go.nature.com/V2eGfN>

Type 2 diabetes mellitus (T2DM) is characterized by dysregulation of carbohydrate, lipid and protein metabolism, and results from impaired insulin secretion, insulin resistance or a combination of both. Of the three major types of diabetes, T2DM is far more common (accounting for more than 90% of all cases) than either type 1 diabetes mellitus (T1DM) or gestational diabetes. Over the past few decades, our understanding of the development and progression of T2DM has evolved rapidly. Its main cause is progressively impaired insulin secretion by pancreatic β -cells, usually upon a background of pre-existing insulin resistance in skeletal muscle, liver and adipose tissue¹ (BOX 1). Overt hyperglycaemia is preceded by prediabetes^{1,2}, a high-risk condition that predisposes individuals to T2DM development (TABLE 1). Prediabetes is characterized by any one of the following: impaired fasting glucose (IFG) levels, impaired glucose tolerance (IGT) or increased glycated haemoglobin A1c (HbA1c) levels. Individuals with IFG levels are characterized by fasting plasma glucose levels that are higher than normal but do not meet the criteria for the diagnosis of diabetes. IGT is characterized by insulin resistance in muscle and impaired late (second-phase) insulin secretion after a meal, whereas individuals with IFG levels manifest hepatic insulin resistance and impaired early (first-phase) insulin secretion². Individuals with prediabetes have HbA1c levels between 5.7–6.4%; they represent

a heterogeneous group with respect to pathophysiology and are clinically very diverse. Annual conversion rates of prediabetes to T2DM range from 3% to 11% per year³.

The clinical presentation, underlying pathophysiology and disease progression in patients with diabetes can vary considerably among individuals and, on occasion, atypical presentation of symptoms can make clear-cut classification of T2DM difficult. At the time of diagnosis, many patients with T2DM are asymptomatic, whereas others present with severe hyperglycaemia or even diabetic ketoacidosis. Latent autoimmune diabetes in adults⁴ and maturity-onset diabetes of the young⁵ can masquerade as T2DM. In asymptomatic individuals, the timing and frequency of testing for prediabetes or T2DM are based on the presence or absence of risk factors⁶. Screening in at-risk individuals is important because prediabetes is common and ~30% of individuals with T2DM are undiagnosed. Prevention of diabetes requires identification of individuals who have prediabetes and intervention with lifestyle modifications (weight loss and exercise) plus antidiabetic and anti-obesity medications^{7–9}. The American Diabetes Association (ADA) Consensus Conference¹⁰ recommended that high-risk individuals (HbA1c >6.5%; BMI ≥ 30 kg per m²; age ≤ 60 years) with IGT or IFG levels be treated with metformin. Pioglitazone¹¹ and combined low-dose metformin and rosiglitazone¹²

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also are very effective in preventing the conversion of prediabetes to diabetes. Lifestyle intervention (weight loss and exercise) alone, although initially effective, is associated with weight regain in most individuals^{13–15}. However, those individuals with prediabetes who successfully lose weight and maintain a physical activity programme can be expected to benefit from decreased conversion to diabetes¹⁶, an improved lipid profile and reduced cardiovascular risk, including a reduced risk of developing hypertension.

T2DM is a complex chronic disorder that requires continuous medical care, patient self-management for control of abnormal glucose levels, and multifactorial risk reduction strategies to normalize blood glucose levels, lipid profiles and blood pressure to prevent or

minimize acute and long-term microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as a heart attack and stroke)^{17–19} (TABLE 2). T2DM should be viewed and treated as a heterogeneous disorder with multiple pathophysiological abnormalities, varying susceptibility to complications and varying clinical response to therapeutic intervention^{17–19}. Ultimately, a true 'cure' for T2DM will require the elucidation of its molecular aetiology and effective interventions to combat the obesity epidemic. In this Primer, we discuss the epidemiology, diagnosis, pathophysiology and management (present and future) of T2DM.

Epidemiology

T2DM has become a major global public health concern (FIG. 1). The International Diabetes Federation estimated that, in 2013, 382 million adults aged 20–70 years worldwide had T2DM, with 80% of those affected living in low- and middle-income countries²⁰. This number is expected to rise to 592 million by 2035 (REF. 20). Areas particularly affected by this disease are China and India, where the prevalence of T2DM has increased dramatically despite the relatively low prevalence of obesity²¹. Given the same body mass index (BMI), Asians tend to have a higher percentage of body fat mass, greater abdominal obesity and less muscle mass²², which might explain their increased predisposition to T2DM. In addition, poor nutrition *in utero* and in early life, combined with overnutrition in later life, can contribute to the accelerated trajectory of the T2DM epidemic, especially in populations undergoing rapid nutrition transitions, involving changed food habits and reduced physical activity. Prevalence of T2DM is slightly higher in men than in women²⁰.

Epidemiological studies have improved our understanding of the behavioural, lifestyle and biological risk factors for T2DM (BOX 2). Increasing adiposity, as reflected by higher BMI levels, is the single most important risk factor for T2DM (FIG. 2). In addition, particular dietary components are associated with a reduced risk of T2DM, independent of body weight, including higher intake of whole grains, green leafy vegetables, nuts and coffee; lower intake of refined grains, red and processed meat, and sugar-sweetened beverages; and moderate intake of alcohol²³. Physical inactivity is a key behavioural risk factor, and both aerobic activity and resistance training are beneficial²⁴. Sedentary behaviour, such as prolonged television watching, is associated with increased risk²⁵. Both short (≤ 5 hours per night) and long (≥ 9 hours per night) duration of sleep are associated with increased risk²⁶, as is rotating shift work²⁷. In addition, cigarette smoking is a significant risk factor for developing T2DM, independent of body weight and other risk factors²¹. Although genetics play an important part in the development of T2DM²⁸, the ongoing diabetes epidemic cannot be explained by novel genetic mutations but is instead largely explained by the epidemic of obesity²⁹. Nevertheless, genes determine how we respond to changes in the environment, and vice versa.

Box 1 | Glucose homeostasis

Following a meal, insulin secretion is stimulated and glucagon secretion is inhibited by the combined actions of hyperinsulinaemia and hyperglycaemia. Approximately 60–70% of insulin secretion is dependent on the release of the incretin hormones, including glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP) by the L cells and the K cells in the gut, respectively. Collectively, the changes in glucose, insulin and glucagon levels suppress hepatic glucose production, stimulate muscle glucose uptake and inhibit lipolysis; the latter results in a reduction in the free fatty acid concentration in blood, which further enhances the effect of insulin on the liver and muscle. Type 2 diabetes mellitus is associated with major disturbances in all of the preceding physiological responses: insulin secretion is impaired; fasting plasma glucagon levels are increased and fail to suppress normally after a meal; basal hepatic glucose production is increased and fails to suppress normally after a meal; muscle glucose uptake is impaired; fasting plasma free fatty acid levels are increased and fail to suppress normally following a meal; and the post-meal rise in GLP1 and GIP is normal or modestly decreased. However, there is severe β -cell resistance to the stimulatory effect of both GLP1 and GIP on insulin secretion.

Table 1 | Diagnostic reference values

Parameters	Normal*	Prediabetes	T2DM
Haemoglobin A1c	<5.7% [‡] <6.0% [§]	5.7–6.4% [‡] 6.0–6.4% [§]	≥6.5%
Fasting plasma glucose	<100 mg per dl [‡] <110 mg per dl [§]	100–125 mg per dl [‡] 110–125 mg per dl [§]	≥126 mg per dl
Two-hour plasma OGTT	<140 mg per dl	140–199 mg per dl	≥200 mg per dl

OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus. *Normal glucose metabolism. [‡]American Diabetes Association. [§]World Health Organization.

Our understanding of the pathophysiology of T2DM has been aided by the discovery of novel disease biomarkers. High blood concentrations of pro-inflammatory cytokines, such as C-reactive protein, interleukin-6 (IL-6) and tumour necrosis factor (TNF), are associated with an increased risk of T2DM³⁰, whereas a high concentration of adiponectin, which has anti-inflammatory effects, is associated with a reduced risk³¹. Lower levels of sex hormone-binding globulin are associated with increased risk³², as are higher blood concentrations of branched-chain and aromatic amino acids³³. Gut flora metabolites might predict future risk of T2DM because the gut microbiota is involved in energy extraction from the diet, modification of host gene expression, and increasing metabolic endotoxaemia (the level of endotoxins in blood) and chronic inflammation³⁴.

In summary, up to 90% of T2DM cases are potentially preventable by following a healthy diet, maintaining a BMI of ≤25 kg per m², exercising for at least 30 minutes per day, avoiding smoking and consuming alcohol in moderation^{35,36}.

Table 2 | Multifactorial risk reduction outpatient goals of therapy in T2DM

Parameter	ADA	AACE	IDF (WDF)
Glucose			
Fasting glucose (mg per dl)	70–130*	<110	115
2 hour postprandial glucose (mg per dl)	<180*	<140	<160
Haemoglobin A1c (%)	<7	≤6.5	<7.0
Lipids			
LDL cholesterol (mg per dl)	<70 [‡]	70 [‡]	<70 [‡]
Non-HDL cholesterol (mg per dl)	NR	<130 <100 [‡]	<97
HDL cholesterol (mg per dl)	>40 in men >50 in women	>40 in men >50 in women	>39
Triglycerides (mg per dl)	<150	<150	<200
Blood pressure			
Systolic pressure/diastolic pressure (mm Hg)	<140/80*	<130/80	≤130/80 [§]

AACE, Association of Clinical Endocrinologists; ADA, American Diabetes Association; HDL, high-density lipoprotein; IDF, International Diabetes Federation; LDL, low-density lipoprotein; NR, no recommendation; T2DM, type 2 diabetes mellitus; WDF, World Diabetes Foundation. *Individualized goals. [‡]High-risk or established cardiovascular disease.

[§]Age 70–80 years goal <140/90 mmHg, and age >80 years goal <150/90 mmHg.

Mechanisms/pathophysiology

T2DM is a multifactorial disease involving genetic and environmental factors. The pathophysiological changes are characterized by β -cell dysfunction, insulin resistance and chronic inflammation, all of which progressively hamper control of blood glucose levels and lead to the development of micro- and macrovascular complications. With respect to hyperglycaemia, at least eight distinct pathophysiological abnormalities^{1,37} contribute to impaired glucose homeostasis (FIG. 3), and these factors are already well established early in the natural history of T2DM. To the 'ominous octet' we can add two additional pathophysiological abnormalities: activation of inflammatory pathways and impaired insulin-mediated vasodilation, which both contribute to muscle insulin resistance.

Genetic factors

T2DM clusters in families and is heritable. The relative risk of siblings of a patient with T2DM developing the disease compared with families in which none of the siblings has the disease is ~2–3, but this figure increases to 30 if two siblings have T2DM³⁸. The risk of developing T2DM is higher when the mother has the disease compared with when the father has the disease³⁹. The risk of developing T2DM is also markedly increased with a BMI of ≥30 or a non-normal fasting glucose concentration of >5.5 mmol l⁻¹ (REF. 40). By comparison, the relative risk for T1DM is ~15 and the relative risk for maturity-onset diabetes of the young is ~50. Identification of the genes that are responsible for complex polygenic diseases such as T2DM has been a challenge. A breakthrough came in 2007 with genome-wide association studies (GWASs) that reported common genetic variants associated with T2DM. A single-nucleotide polymorphism (SNP) in *TCF7L2* (already reported a year earlier on the basis of gene linkage analysis) showed the strongest association with T2DM^{41,42}, but SNPs in other genes have also been shown to be linked to T2DM, including in *SLC30A8*, *FTO*, *CDKAL1*, *CDKN2A*, *CDKN2B*, *HHEX*, *IGF2BP2*, *GCKR* and others^{42–44}. Subsequent GWASs have increased this list to more than 100 common variants associated with T2DM⁴⁵. Most variants are in introns, and it is more correct to talk about genetic loci than genes. Accordingly, defining the mechanisms by which these loci increase the risk of T2DM is difficult. Exceptions are a few variants in exons, which influence the function of the gene, such as *SLC30A8* (which encodes a zinc transporter that is required to store insulin)⁴⁶, *KCNJ11* (which encodes an ATP-dependent potassium channel) and *GCKR* (which encodes a glucokinase regulatory protein)^{43–45}. Intronic variants might influence the expression of a nearby gene (in *cis*) or a distant gene (in *trans*), but this has been verified only for a small number of genes, such as a variant in the *MTNR1B* gene (which encodes a melatonin receptor)⁴⁷. Cultured human islets carrying risk alleles have shown reduced β -cell function and survival. Gaining mechanistic insights into these SNPs has proved to be difficult, and animal data have not been very informative. For example, the human mutation in *SLC30A8* protects against T2DM, whereas it

predisposes to the disease in mice⁴⁶. Other animal data have been more rewarding. Linkage to impaired insulin secretion in a polygenic model for T2DM, the GK rat, was explained by a variant in the *ADRA2A* gene, resulting in overexpression of the $\alpha 2A$ -adrenergic receptor in islets⁴⁸. As pretreatment of human islet cells with an inhibitor of the receptor, yohimbine, normalized insulin secretion, the authors treated human carriers of the variant with the same inhibitor, which resulted in a dose-dependent improvement in insulin secretion⁴⁹. Impaired β -cell function has also been associated with epigenetic modifications⁵⁰ and microRNA patterns⁵¹ that are likely to increase the fraction of cases in which inheritance is a relevant pathogenetic factor⁴².

Notably, these genetic variants only have modest effects, increasing risk by 10–20%, and have thus been maintained during hundreds of generations. In fact, the majority of non-diabetic people carry risk variants for T2DM, and the average frequency of a T2DM-associated risk allele is 54%⁴⁵. Despite this high prevalence and only modest risk increase, these variants have provided novel

insights into the pathogenesis of T2DM. A prospective study of ~2,700 individuals, 150 of whom developed T2DM during 8 years of follow-up, tested the effect of a high genetic risk (highest quartile; ≥ 12 risk alleles) and low genetic risk (lowest quartile; ≤ 8 risk alleles) of T2DM and showed that all individuals became more obese and thereby insulin resistant regardless of high or low genetic risk. However, more high-risk people could not increase their insulin secretion to meet the demands imposed by insulin resistance and therefore developed T2DM⁵².

The majority of heritability (85%) cannot be explained by the currently identified SNPs. Alternative possibilities to explain the heritability are: disease heterogeneity (T2DM may not be a genetically uniform disease), gene–environment interactions and epigenetic mechanisms (DNA methylation and chromatin modifications). Some variants, such as those for *KCNQ1* (which encodes a voltage-gated potassium channel), show strong parent-of-origin effects; *KCNQ1* is methylated and imprinted in fetal but not in adult life when inherited from the mother⁵³.

β -cell function

Insulin resistance is the earliest detectable abnormality in individuals who are likely to develop T2DM^{1,54,55}. However, overt T2DM does not occur unless β -cells are unable to secrete sufficient amounts of insulin to offset the insulin resistance^{50,56,57}. Multiple factors contribute to β -cell failure, including ageing⁵⁸, genetic abnormalities⁴⁵, incretin hormone (glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP)) resistance and/or deficiency^{59,60}, lipotoxicity^{37,61,62}, glucotoxicity⁶³, insulin resistance leading to β -cell stress^{1,37}, hypersecretion of islet amyloid polypeptide (IAPP)⁶⁴, reactive oxygen stress⁶⁵ and activation of inflammatory pathways³⁷.

β -cell physiology. In human islets, β -cells constitute ~60% of cells and are intermingled with glucagon-producing α -cells (30%), somatostatin-producing δ -cells (10%) and pancreatic polypeptide-producing cells (1%)⁶⁶. Within the islet, β -cells form sparse sub-clusters, which show functional connectivity through gap junctions⁶⁷. Each islet contains 100–500 μ U of insulin, so that the whole endocrine pancreas (~1 million islets, weighing 0.9 g) contains 10 days' worth of supply for a healthy adult⁶⁸. β -cells communicate with each other and with the other islet endocrine cells through connexin proteins and other cell–cell adhesion complexes⁶⁷. Moreover, endocrine cells can influence one another via hormones released into the blood. Finally, non-hormonal endocrine cell products (such as ATP and zinc) and neurotransmitters influence β -cell function.

β -cells in T2DM. In post-mortem specimens from patients with T2DM, β -cell mass is reduced by 30–40% compared with specimens from non-diabetic subjects⁶⁹. Morphometric measures, however, overlap widely between individuals with or without T2DM, and β -cell mass quantification based on insulin immunostaining

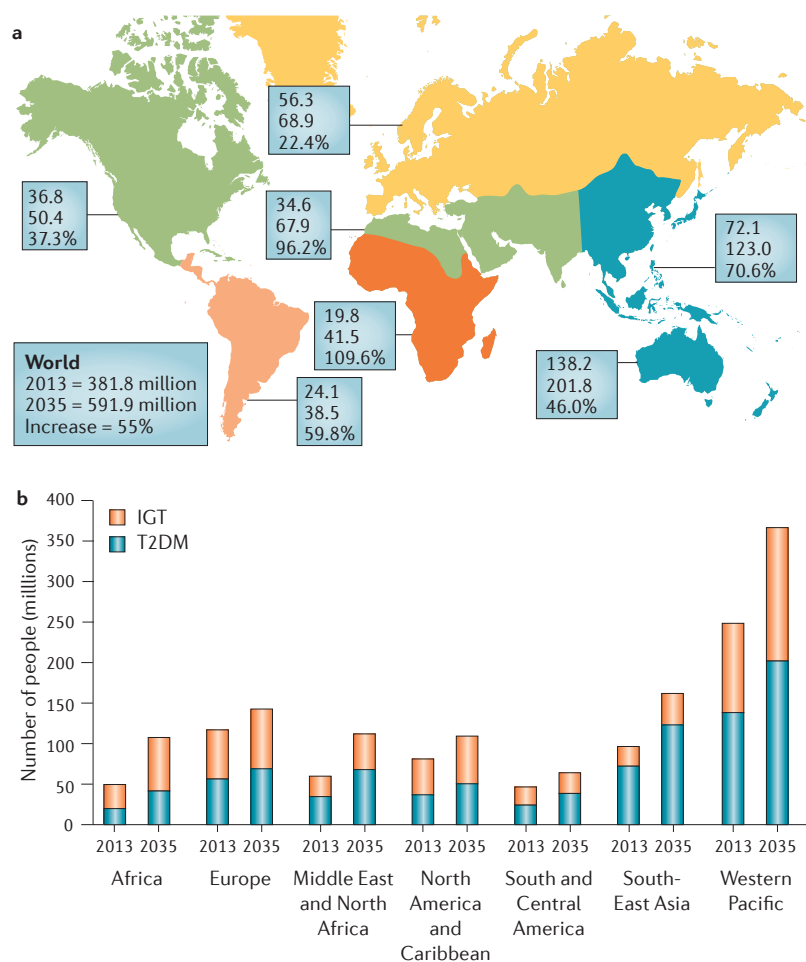


Figure 1 | Prevalence of T2DM and IGT. **a** | In each box, the top values are the number of people with type 2 diabetes mellitus (T2DM) (in millions) in 2013, and the middle numbers are an estimate of the number of people expected to have T2DM in 2035. The bottom value is the percentage increase from 2013 to 2035. **b** | The number of people with T2DM and impaired glucose tolerance (IGT) (in millions) by region for the years 2013 and 2035. Data are obtained from the International Diabetes Federation Diabetes Atlas.

Box 2 | Risk factors for T2DM

- Older age
- Non-white ancestry
- Family history of type 2 diabetes mellitus (T2DM)
- Genetic factors
- Components of the metabolic syndrome (increased waist circumference, increased blood pressure, increased plasma triglyceride levels, and low plasma high-density lipoprotein (HDL) cholesterol levels and small dense low-density lipoprotein (LDL) cholesterol particles)
- Overweight or obese (body mass index (BMI) of ≥ 25 kg per m²)
- Abdominal or central obesity (independent of BMI)
- Polycystic ovary syndrome
- History of atherosclerotic cardiovascular disease
- Unhealthy dietary factors (regular consumption of sugary beverages and red meats, and low consumption of whole grains and other fibre-rich foods)
- Cigarette smoking
- Sedentary lifestyle
- History of gestational diabetes or delivery of newborns >4 kg in weight
- Presence of acanthosis nigricans (hyperpigmentation of the skin)
- Some medications
- Short and long sleep duration and rotating shift work
- Psychosocial and economic factors

might lead to underestimation owing to β -cell degranulation⁷⁰. Loss of β -cells in T2DM is believed to occur via apoptosis⁷¹ and dysregulated autophagy⁷². β -cell proliferation does not seem to differ between diabetic and non-diabetic islets; whether neogenesis is impaired in T2DM is uncertain. Vascular disarray and amyloid deposition⁷³ contribute to altered cytoarchitecture in T2DM islets, especially in patients with long-standing disease. The quantitative functional impact of structural changes in human T2DM islets is still incompletely defined⁷³. Insulin resistance feeds back to the β -cell by raising its set point (more insulin is secreted at any serum level of glucose). This chronic adaptation is probably mediated by small increments in circulating glucose levels (such as those that occur in obese normal glucose-tolerant individuals) as well as by other factors, such as raised levels of free fatty acids (FFAs)⁷⁴. In addition, insulin resistance promotes a relative preponderance of α -cells over β -cells⁷⁴, possibly due to selective β -cell apoptosis as well as through a process of dedifferentiation and subsequent redifferentiation and to a progressive loss of β -cell mass. In culture, islets isolated from patients with T2DM show reduced insulin release in response to glucose and a higher threshold for the initiation of insulin secretion compared with islets isolated from healthy controls⁷⁵. Similar changes in insulin secretion can be induced in islets isolated from non-diabetic individuals by prolonged exposure to increased concentrations of FFAs (in particular, palmitate)⁷⁶ or glucose⁷⁵, and *in vivo*⁷⁷.

Insulin secretion. β -cells integrate inputs from substrates (such as glucose, FFAs, arginine, fructose and amino acids), hormones and nerve endings to adjust insulin release in response to changing demands (for example,

fasting–feeding cycles, exercise and stress) on a minute-to-minute basis in order to maintain normal blood glucose levels, and inter-individual differences affect this adjustment. For example, a lean, insulin-sensitive adult might need as little as 0.5 U of insulin to dispose of an oral load of 75 g of glucose over 2 hours, whereas an obese, insulin-resistant, glucose-intolerant person might require 45 U to perform the same task (~ 90 -fold inter-individual difference). *In vivo* tests in humans using intravenous or oral glucose, arginine, sulfonylureas (antidiabetic drugs) or mixed meals have demonstrated impaired β -cell function in overt T2DM. However, reliable quantitation of *in vivo* β -cell dysfunction requires some form of modelling⁷⁸. Absolute insulin secretion in response to an oral glucose challenge can be normal or even increased in T2DM (FIG. 4a), except in long-standing, poorly controlled disease, in which absolute insulin secretion is reduced. However, when insulin secretion rates are plotted against the concomitant plasma glucose concentrations, patients with T2DM secrete substantially less insulin than non-diabetic controls (FIG. 4b). This decline in β -cell glucose sensing occurs along a continuum extending from normoglycaemia through prediabetes to decompensated diabetes in adults⁷⁹ and children⁸⁰, and is a potent predictor of progression to diabetes independently of insulin resistance and classic phenotypic predictors⁷⁹. Absolute insulin secretion is a positive antecedent of deteriorating glucose tolerance. Furthermore, the ability of β -cells to respond to the rate of increase in plasma glucose concentration (rate sensitivity) is impaired in individuals with T2DM⁷⁹.

Antecedent hyperglycaemia and high levels of incretin hormones (GLP1 and GIP) potentiate glucose-stimulated insulin release in healthy individuals. In patients with T2DM, glucose-mediated potentiation of insulin release is increased compared with normal glucose-tolerant individuals (owing to the hyperglycaemia); incretin potentiation, however, is severely compromised⁸¹. The incretin defect is not reversed by reducing the plasma glucose concentration⁸².

Whenever an intervention results in a reduction in plasma glucose concentrations, fasting insulin secretion rate and total insulin output in response to glucose are reduced compared with the non-treated condition, but β -cell glucose sensitivity is improved. For example, successful bariatric surgery leads to partial recovery of β -cell function⁸³. This indicates that a β -cell mass deficit alone is unlikely to be the cause of diabetes and that, even in advanced T2DM, many β -cells are alive but ‘stunned’ or ‘disguised’, and therefore amenable to being revitalized by intervention⁸⁴ (FIG. 5).

Insulin resistance

Obesity and physical inactivity lead to insulin resistance, which together with a genetic predisposition⁴⁵, place stress on β -cells, leading to a failure of β -cell function and a progressive decline in insulin secretion^{1,2,7,57,85}. Insulin resistance precedes T2DM by many years^{1,2,54,55}. Insulin resistance is not only present in muscle and the liver^{1,84,85}, the two tissues responsible for the majority of glucose disposal following carbohydrate

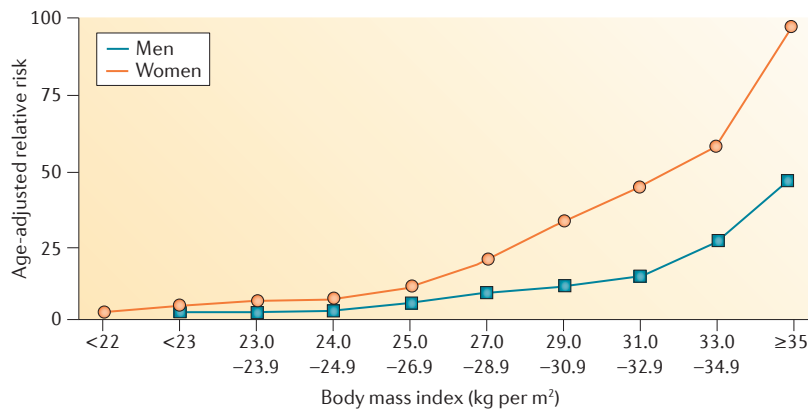


Figure 2 | **Association between BMI and T2DM.** Data obtained from REFS 321,322. BMI, body mass index; T2DM, type 2 diabetes mellitus.

ingestion, but also in adipose^{86,87}, kidney⁸⁸, gastro-intestinal tract⁸⁹, vasculature⁹⁰ and brain^{91,92} tissues, and pancreatic β -cells^{93–95}. In muscle, multiple abnormalities contribute to insulin resistance, including defects in insulin signalling, glucose transport, glucose phosphorylation, glycogen synthesis, pyruvate dehydrogenase complex activity and mitochondrial oxidative activity^{1,37,95}. In the liver, insulin resistance, together with insulin deficiency, hyperglucagonaemia, enhanced glucagon sensitivity and increased substrate (fatty acids, lactate, glycerol and amino acids) delivery^{96–99}, leads to increased gluconeogenesis, which is responsible for the increased basal rate of glucose production and fasting hyperglycaemia¹. Also, insulin resistance in the kidney and augmented renal gluconeogenesis⁸⁸ contribute to fasting hyperglycaemia. Impaired suppression of hepatic glucose production, decreased hepatic glucose uptake, muscle insulin resistance, reduced non-insulin-mediated glucose uptake^{100,101} and excessive renal glucose reabsorption¹⁰² contribute to postprandial hyperglycaemia in T2DM. In addition, insulin resistance in the vascular endothelium impairs the vasodilating effects of insulin, thereby further reducing not only its own delivery but also glucose delivery^{103,104}.

Molecular mechanisms of insulin resistance. Binding of insulin to its receptor activates insulin receptor tyrosine kinase and phosphorylation of a family of insulin receptor substrates (IRSs), especially IRS1 and IRS2 (REF. 105) (FIG. 6). These phosphorylated IRS proteins bind to and activate intracellular signalling molecules, most important of which is phosphatidylinositol 3-kinase (PI3K). PI3K promotes glucose transporter type 4 (GLUT4) translocation to the plasma membrane, resulting in glucose uptake into skeletal muscle, and phosphorylates and inactivates the transcription factor forkhead box protein O1 (FOXO1), altering transcription of downstream genes. Insulin also stimulates the RAS–mitogen-activated protein kinase (MAPK) pathway.

Insulin resistance in obesity and T2DM has mainly been linked to the PI3K pathway^{106,107}. Insulin resistance is usually associated with increased serine

phosphorylation of IRS proteins, which inhibits tyrosine phosphorylation, leading to insulin resistance^{108,109}. In some cases, serine phosphorylation also increases IRS degradation, further contributing to the insulin resistance¹¹⁰. The causes of increased serine phosphorylation are multifactorial, including ectopic lipid accumulation, mitochondrial dysfunction, inflammation and endoplasmic reticulum (ER) stress.

Ectopic lipids and PKCs. Ectopic lipid accumulation in muscle^{37,111} and the liver^{37,112–114} induces insulin resistance by increasing tissue diacylglycerol (DAG) levels¹¹⁵, which lead to activation of members of a class of protein kinase C (PKC): PKC θ in muscle¹⁰⁷, and PKC δ ¹¹⁶ and PKC ϵ ¹¹⁷ in the liver. These PKCs phosphorylate serine residues in IRS proteins, thereby inhibiting insulin signalling. Genetic knockdown of the genes encoding PKC θ in muscle¹¹⁸, PKC δ ¹¹⁶ or PKC ϵ ¹¹⁷ in the liver, or of the genes encoding one of the upstream enzymes involved in DAG production or accumulation¹¹⁹ ameliorates lipid-induced insulin resistance. Consistent with this observation, the levels of PKC θ in muscle and of PKC δ and PKC ϵ in the liver are increased in obesity and T2DM^{116,120,121}. In addition, animal models of obesity and T2DM have increased tissue levels of ceramides, which are linked to insulin resistance¹²². Ceramides and DAGs might have different roles in promoting insulin resistance depending on the length of fatty acid chains¹²³ and sites of cellular compartmentalization¹²⁴. Many treatments that improve insulin sensitivity, such as caloric restriction or thiazolidinediones, also reduce ectopic lipid content and tissue DAG content.

Mitochondrial dysfunction. Mitochondrial dysfunction has been observed in the liver, muscle, adipose tissue and even the brain, including the hypothalamus, in rodents and humans with obesity, T2DM and metabolic syndrome¹²⁵. The cause is both a reduction in mitochondrial density^{119,126} and impaired mitochondrial functioning secondary to aberrant expression of different components of the oxidative phosphorylation system^{127–129}. Altered mitochondrial function contributes to insulin resistance in multiple ways. In adipose tissue, mitochondrial dysfunction has been associated with impaired secretion of adiponectin, a potent insulin-sensitizing adipokine^{127,130,131}. In other tissues, mitochondrial dysfunction has been suggested to increase levels of reactive oxygen species, which activate redox-sensitive serine kinases to phosphorylate IRS proteins and produce insulin resistance¹³². Whether mitochondrial dysfunction is the cause or result of insulin resistance remains a topic of debate¹³³. However, given the key role of ectopic lipid deposition in causing insulin resistance, mitochondrial dysfunction associated with reduced mitochondrial fatty acid oxidation is at the very least an important exacerbating factor in this process¹³³.

Inflammation. Systemic inflammation is a well-documented contributor to insulin resistance. Increased levels of pro-inflammatory cytokines, such as IL-6 and TNF, and increased numbers of macrophages and other

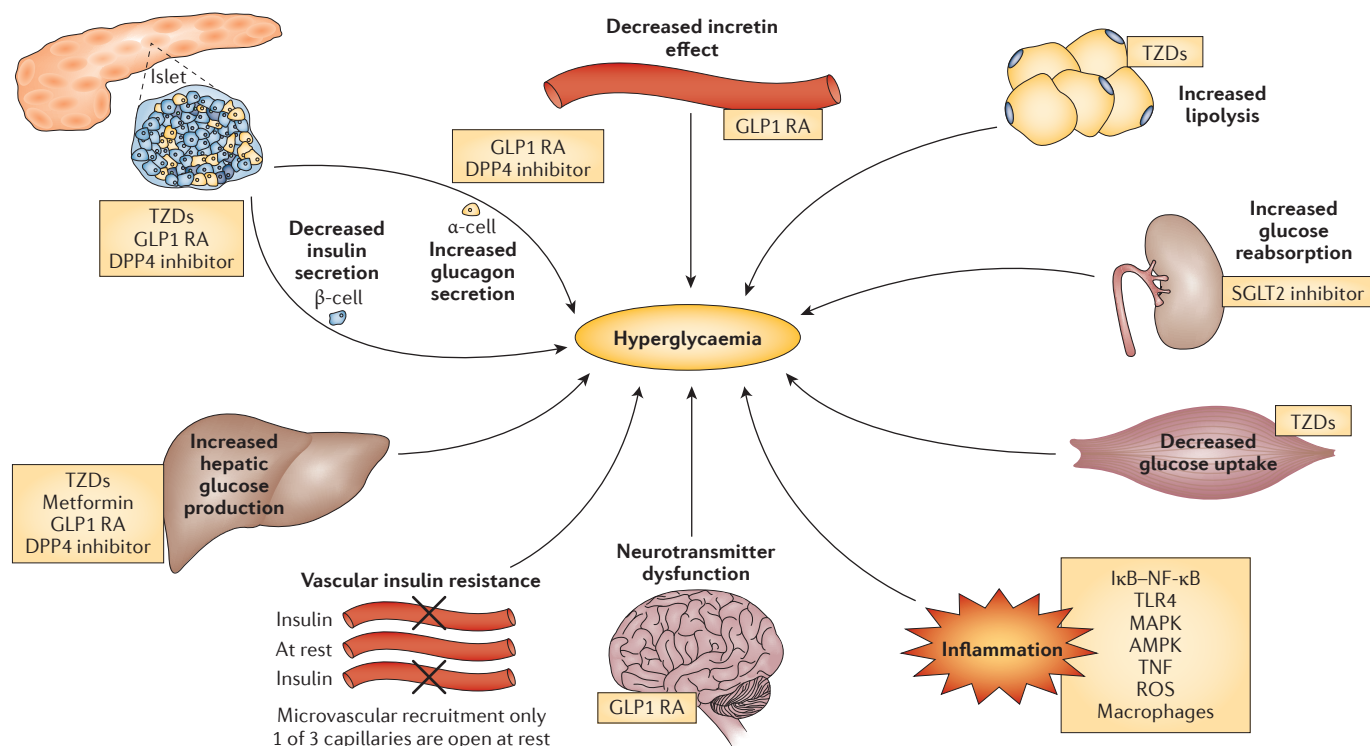


Figure 3 | The ‘ominous octet’ of hyperglycaemia in T2DM. Insulin resistance in muscle and the liver, and impaired insulin secretion by the pancreatic β -cells are the core defects in type 2 diabetes mellitus (T2DM). β -cell resistance to glucagon-like peptide 1 (GLP1) contributes to progressive failure in the function of β -cells, whereas increased glucagon levels and enhanced hepatic sensitivity to glucagon contribute to the excessive glucose production by the liver. Insulin resistance in adipocytes results in accelerated lipolysis and increased plasma free fatty acid (FFA) levels, both of which aggravate the insulin resistance in muscle and the liver and contribute to β -cell failure. Increased renal glucose reabsorption by the sodium/glucose co-transporter 2 (SGLT2) and the increased threshold for glucose spillage in the urine contribute to the maintenance of hyperglycaemia. Resistance to the appetite-suppressive effects of insulin, leptin, GLP1, amylin and peptide YY, as well as low brain dopamine and increased brain serotonin levels contribute to weight gain, which exacerbates the underlying resistance. To the ‘ominous octet’ must be added vascular insulin resistance and inflammation, making the ‘decadent decouplet’. AMPK, AMP-activated protein kinase; DPP4, dipeptidyl peptidase 4; I κ B, inhibitor of NF- κ B; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor- κ B; RA, receptor agonist; ROS, reactive oxygen species; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor; TZDs, thiazolidinediones.

inflammatory cells are observed in adipose tissue, livers and sera of patients and animals in insulin-resistant states¹³⁴. Pro-inflammatory cytokines induce insulin resistance by activating downstream kinases, including I κ B kinase- β (IKK β), JUN amino-terminal kinase 1 (JNK1; also known as MAPK8) and p38 MAPK, which can contribute to the phosphorylation of serine residues in IRS proteins^{135,136} and stimulate production of suppressors of cytokine signalling (SOCS), which block the action of IRS proteins^{137,138}. Blocking TNF activity with antibodies or knockout of its receptor improves insulin sensitivity in obese mice¹³⁹, but TNF-specific blocking agents do not improve glycaemic control in patients with T2DM¹⁴⁰. Conversely, pharmacological and genetic inhibition of the IKK β –nuclear factor- κ B (NF- κ B) pathway improves insulin sensitivity in mice^{135,141,142} and improves glycaemic control in patients with T2DM¹⁴³, albeit modestly.

Macrophage infiltration in adipose tissue is a key aspect of insulin resistance¹⁴⁴ and is characterized by an increase in the numbers of pro-inflammatory M1 macrophages (classic macrophages) as well as

T helper 1 (T_H1), T_H17 and CD8⁺ T cells, and a reduction in the numbers of less-inflammatory cells, such as M2 macrophages, regulatory T cells (T_{Reg} cells) and T_H2 cells^{145–147}. Inflammation occurs primarily in adipose tissue and the liver^{142,148}. Macrophage infiltration in adipose tissue stimulates lipolysis, and increased levels of IL-6 can stimulate hepatic gluconeogenesis and cause hepatic insulin resistance¹⁴⁹. Changes in adipose inflammation have been observed not only in obese mice but also in lean mice with differences in genetic predisposition to obesity and insulin resistance¹⁵⁰. These inflammatory cells themselves are insulin responsive, and knockout of the insulin receptor in these lineages protects against obesity-induced inflammation and systemic insulin resistance¹⁵¹.

Altered lipid metabolism can affect inflammation by activating Toll-like receptors (TLRs). Indeed, TLR4 is an important component of the innate immune response and is activated by fatty acids. Increased FFA levels can also increase the activity of IKK and JNK, cause serine phosphorylation of IRS proteins and block IRS tyrosine phosphorylation¹⁵².

ER stress and the UPR. The ER is the major site of synthesis and folding of secreted and integral membrane proteins. States that increase protein synthesis or disrupt normal processing create an imbalance between the demand and capacity of the ER, leading to ER stress and the unfolded protein response (UPR). As a result, three signalling pathways are activated — IRE1 α , PRKR-like ER kinase (PERK; also known as EIF2AK3) and ATF6 α ¹⁵³ — to reduce ER stress by ameliorating the UPR response. Pathophysiological states, including obesity, hyperlipidaemia and T2DM, disrupt this feedback loop by increasing phosphorylation of PERK and IRE1 α , enhancing splicing of X box-binding protein 1 (XBP1) and activating JNK^{154,155}. Conversely, weight loss¹⁵⁶ and administration of chemical chaperones that reduce ER stress¹⁵⁷ are associated with reduced UPR activation. Mechanistically, the UPR is thought to lead to insulin resistance through IRE1 α -dependent activation of JNK¹⁵⁸. Why ER stress develops in obesity is uncertain, but high fatty acid levels can cause ER stress and activate the UPR¹⁵⁹.

Another possible link between obesity and ER stress is the mammalian target of rapamycin (mTOR) signalling pathway. mTOR, which is involved in the regulation of a wide range of cellular functions, exists in two different complexes called mTORC1 and mTORC2 (REF. 160). Increased mTORC1 pathway activation blocks insulin signalling pathways by reducing insulin-induced tyrosine phosphorylation of IRS1 and IRS2 (REF. 161) and by increasing degradation of IRS1 (REF. 162). Recent studies have demonstrated that the p85 α regulatory subunit of PI3K interacts with XBP1s (the spliced, transcriptionally active isoform of XBP1) and promotes the translocation of XBP1s into the nucleus to initiate the ER stress response¹⁶³.

Diabetic complications

Diabetic microvascular complications are closely related to the severity and duration of hyperglycaemia^{164,165}. Hyperglycaemia promotes the development of microvascular complications through the activation of six major pathways, including enhanced polyol pathway flux, increased formation of advanced glycation end products (AGEs), increased AGE receptor expression, activation of PKC isoforms, enhanced hexosamine flux and increased intracellular reactive oxygen species^{166,167}. Genetic factors have a pivotal role in determining susceptibility to microvascular complications. T2DM also affects the macrovasculature, and the incidence of myocardial infarction, peripheral vascular disease and stroke is markedly increased^{137,168}. Reactive oxygen species impair angiogenesis, activate several pro-inflammatory pathways and cause epigenetic changes that result in long-lasting expression of pro-inflammatory genes that persists after glycaemia is normalized. These same biochemical and molecular mechanisms that contribute to the microvascular complications also contribute to the macrovascular complications^{166,167}.

Accelerated atherosclerotic cardiovascular disease is associated with several risk factors, including insulin resistance and hyperinsulinaemia, activation of inflammatory pathways and the presence of multiple cardiovascular risk factors (such as hypertriglyceridaemia, reduced high-density lipoprotein (HDL) cholesterol, small dense low-density lipoprotein (LDL) particles¹⁶⁹, hypertension, endothelial dysfunction, increased plasminogen activator inhibitor 1 levels, visceral obesity, and non-alcoholic steatohepatitis or non-alcoholic fatty liver disease)^{37,170}. Hypertension is twofold–threefold more common in people with T2DM and greatly increases the risk of macrovascular complications

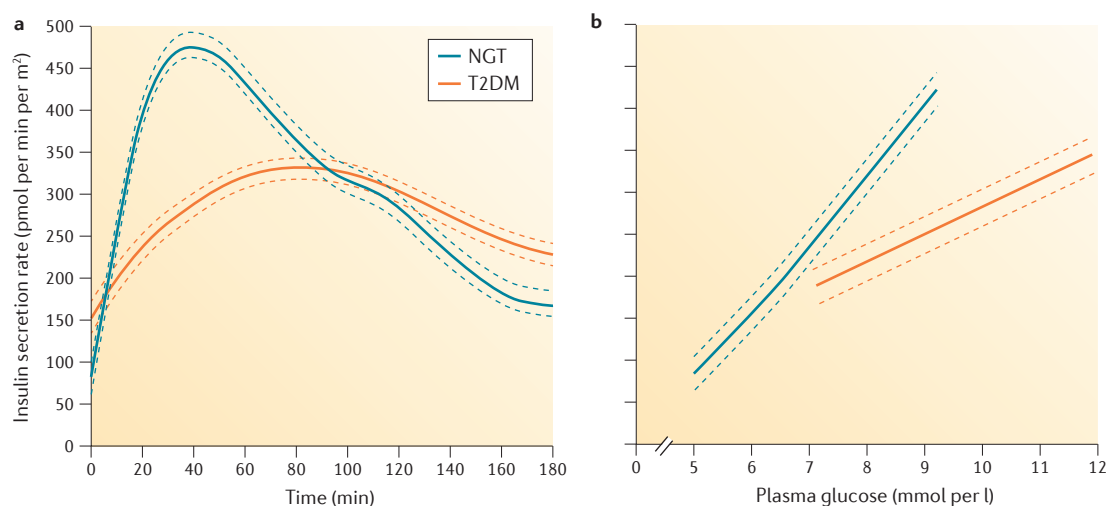


Figure 4 | Insulin secretion in response to glucose. **a** | Characteristic insulin secretory response (reconstructed by deconvolution of plasma C-peptide levels) to oral glucose in patients with type 2 diabetes mellitus (T2DM) and in body mass index (BMI)-matched non-diabetic individuals. Note the higher fasting secretion rate, the initial blunted secretory response and the later catch-up phase (due to higher glycaemia). **b** | The insulin secretion rates of panel **a** are here plotted against the concomitant plasma glucose concentrations to show the deficit in glucose sensing in patients versus normal glucose-tolerant (NGT) controls. Actual experimental data have been averaged and interpolated to produce these graphs.

(such as myocardial infarction, stroke, peripheral vascular disease and congestive heart failure), microvascular complications (including retinopathy and nephropathy) and premature death¹⁷¹. Multiple factors contribute to the increased incidence of hypertension in T2DM, including disturbed blood pressure circadian rhythms (higher nocturnal blood pressure), impaired blood flow autoregulation, stiffening of large arteries, increased intracellular sodium concentration, increased arterial sensitivity to angiotensin II, insulin resistance, endothelial dysfunction, obesity and genetic susceptibility^{172,173}.

Diagnosis, screening and prevention

Diagnosis

Diagnostic criteria for diabetes have traditionally relied on blood glucose levels. More recently, HbA1c has been added¹⁷⁴ as an integrated measure of long-term glycaemia (the lifespan of a red blood cell is ~120 days) (TABLE 1). However, haemolysis, which reduces red blood cell lifespan, can make HbA1c an invalid measure. Also, older age, non-white race, high dietary fat intake, alcohol consumption, cigarette smoking, liver disease, kidney disease and iron deficiency can affect HbA1c independently of glycaemia.

Although most clinicians agree that diabetes should be defined according to risk of complications, the level of hyperglycaemia associated with complications varies depending on the complication. Current criteria are based on maintaining fasting glucose, post-glucose-load glucose and HbA1c levels below the threshold that is associated with an increased risk of developing diabetic retinopathy¹⁷⁵.

T2DM diagnosis can be established on the basis of an elevated random plasma glucose test (≥ 200 mg per dl with classic symptoms of hyperglycaemia), fasting plasma glucose levels (≥ 126 mg per dl after at least an 8-hour fast), 2-hour post-glucose-load glucose level (≥ 200 mg per dl after 75 g oral glucose) or HbA1c ($\geq 6.5\%$) confirmed by repeat testing unless unequivocally elevated⁶ (TABLE 2). However, the risk of developing diabetic nephropathy and distal symmetric peripheral polyneuropathy is already increased with levels of hyperglycaemia lower than those associated with diabetic retinopathy¹⁷⁶. In addition, the relationship between glycaemia and cardiovascular disease seems to be linear, without a clear threshold, which demonstrates the difficulty in using single cut points to diagnose a complex disease state¹⁷⁷.

Screening

Screening for a disease is appropriate if the disease is serious; its natural history is understood; it is detectable in its preclinical stage; the screening test is acceptable, quick, inexpensive and valid; early treatment is more effective than late treatment; and screening improves outcomes¹⁷⁸. T2DM meets these criteria, and in 2014 the US Preventive Services Task Force (USPSTF) issued draft recommendations supporting screening for abnormal blood glucose levels and T2DM in adults¹⁷⁹. Specifically, the USPSTF recommended that adults ≥ 45 years of age and those who are overweight or obese, or who have

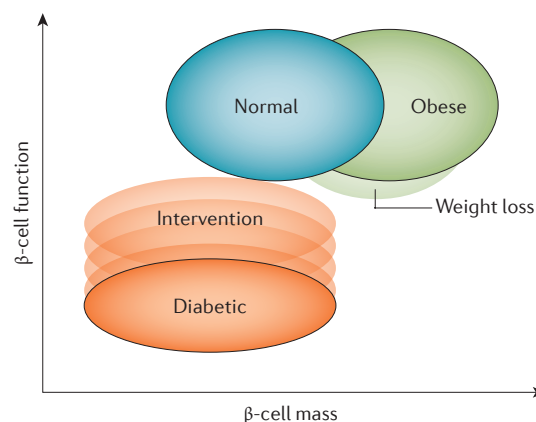


Figure 5 | **Schematic representation of the relationship between β -cell mass and β -cell function.**

In obese individuals who are not diabetic, β -cell mass is expanded (in some proportion to the degree of weight excess), but β -cell function is comparable to individuals with a normal body mass index (BMI). Preliminary data show that weight loss might cause some reduction in both β -cell mass and function in non-diabetic individuals. Average β -cell mass is reduced in type 2 diabetes mellitus (T2DM) regardless of obesity, but the inter-individual variation is large. β -cell function, however, is profoundly impaired. Intervention, such as weight loss and/or antihyperglycaemic treatment, improves β -cell function but without changes in β -cell mass.

a first-degree relative with diabetes be screened in primary care settings. They also pointed out that most racial and ethnic minority groups (African Americans, Latinos and Hispanics) are at increased risk compared with whites. Other diabetes professional societies have long recommended opportunistic screening for T2DM within established primary care guidelines in high-risk individuals.

Fasting glucose, post-glucose-load glucose and HbA1c have limitations as screening tests that are related to their acceptability (fasting), time consumption (2-hour post-glucose-load glucose level) and cost (HbA1c). Some organizations have recommended the use of risk models and random capillary glucose levels as initial screening tests, but these have not been widely adopted^{180,181}. In addition, different cut-off levels to define prediabetes have been proposed by international organizations¹⁸² (TABLE 1). The use of lower thresholds to define increased risk of future diabetes improves sensitivity (that is, the probability of a positive screening test given that the individual is at high risk) but lowers specificity (that is, the probability of a negative screening test given that the patient is at low risk), and decreases the positive predictive value of the test (that is, the probability of being at risk given a positive screening test). The 2-hour post-glucose-load glucose level of 140–199 mg per dl (IGT) is the most-studied marker for future diabetes risk, and essentially all randomized clinical trials (RCTs) that have evaluated the efficacy of interventions for diabetes prevention have been performed in patients with IGT. Data supporting cut-off levels for fasting glucose and HbA1c that define prediabetes are more controversial and differ among organizations.

Prevention

RCTs have conclusively demonstrated that intensive lifestyle interventions and medications are effective in delaying or preventing the development of T2DM in high-risk individuals. The evidence base for these interventions is extensive and robust (TABLE 3). Four large randomized, controlled clinical trials demonstrated that diet and moderate physical activity designed to achieve and maintain 5–7% body weight loss reduce T2DM risk by 29–58%^{16,183–185}. Lifestyle interventions are associated with improved quality of life (QOL) and are safe, cost-effective and effective across different ages, genders, and racial and ethnic groups, independent of the degree of obesity and hyperglycaemia. Metformin reduces the risk by 26–31%^{184,185}, α -glucosidase inhibitors (AGIs) reduce risk by 25–41%^{186,187}, and thiazolidinediones reduce risk by 55–72%^{11,188,189}. Observational follow-up of RCT participants has demonstrated that

the beneficial effects of lifestyle interventions may persist over time^{190–192}. Efforts are underway to implement lifestyle interventions in primary care and community settings. Pharmacological interventions have been less widely applied, perhaps owing to the fact that no medication is approved by the US FDA for diabetes prevention.

Management

Management of T2DM is complicated by multiple pathophysiological disturbances^{1,193} (FIG. 3) and the 'ABCDE' of diabetes management (Age, Body weight, Complications, Duration, Education and Expense, and Etiology)¹⁹. Prevention of microvascular complications focuses on glycaemic control^{164–166}, whereas prevention of macrovascular complications requires correction of classic cardiovascular risk factors that comprise the insulin resistance (metabolic) syndrome³⁷ (TABLE 3).

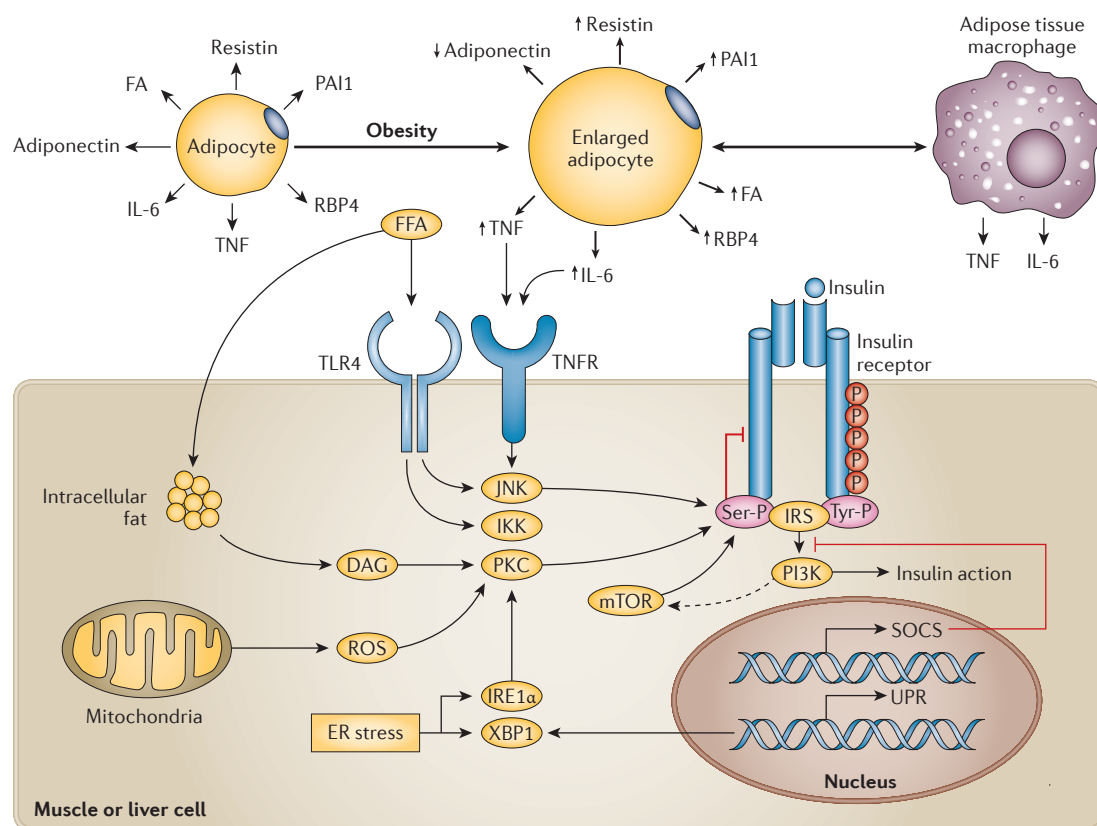


Figure 6 | Mechanisms of insulin resistance. In adipocytes, insulin resistance (also caused by increased insulin receptor substrate (IRS) serine phosphorylation) and inflammation lead to production and release of free fatty acids (FFAs) and insulin-resistance-provoking pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumour necrosis factor (TNF) and resistin. Insulin-sensitizing adipokines, such as adiponectin, conversely, ameliorate insulin resistance. Also, retinol-binding protein 4 (RBP4) increases and might contribute to insulin resistance. Plasminogen activator inhibitor 1 (PAI1) does not affect insulin resistance but has been implicated in complications of obesity, including accelerated atherosclerosis and type 2 diabetes. These factors contribute to the accumulation of toxic lipid metabolites (diacylglycerol (DAG), ceramides and acyl-CoAs) in myocytes and hepatocytes, which impair insulin signalling (IRS–phosphatidylinositol 3-kinase (PI3K) pathway) and activate inflammatory pathways (JUN amino-terminal kinase (JNK), I κ B kinase (IKK) and mitogen-activated protein kinase (MAPK)), which further impair the insulin signal transduction pathway. Mitochondrial dysfunction predisposing to DAG accumulation and nuclear protein kinase C (PKC) activation as well as generation of reactive oxygen species (ROS) and increased endoplasmic reticulum (ER) stress further exacerbate the insulin resistance^{95,125}. FA, fatty acid; mTOR, mammalian target of rapamycin; SOCS, suppressors of cytokine signalling; TLR4, Toll-like receptor 4; TNFR, TNF receptor; UPR, unfolded protein response; XBP1, X box-binding protein 1.

Table 3 | **Intervention to delay or prevent T2DM development***

Intervention	Risk reduction (%)	Refs
Lifestyle (body weight reduction of 5–7%)	29–58	183–185
Metformin	26–31	184,185
Lifestyle and metformin	28	185
Acarbose (α -glucosidase inhibitor)	25	186
Voglibose (α -glucosidase inhibitor)	41	187
Troglitazone	55	188
Rosiglitazone	60	189
Pioglitazone	72	11

T2DM, type 2 diabetes mellitus. *In people with impaired glucose tolerance.

Ideally, HbA1c should be reduced to as close to normal without causing adverse effects, of which hypoglycaemia is the greatest concern^{16,17,19,193,194}. Patients with T2DM with HbA1c levels persistently <6.5% do not develop retinopathy¹⁹⁵. Because obesity and physical inactivity are insulin-resistant states associated with tissue fat overload (lipotoxicity)^{37,61}, lifestyle modification should be a basic component of all intervention programmes^{16,17}. However, despite initial weight loss, most patients regain lost weight over the subsequent 1–2 years^{13–15}. Further, despite successful weight loss, ~50% of obese individuals with prediabetes still progress to overt diabetes¹⁹². Thus, most obesity experts recommend concomitant anti-obesity medications to help to promote and maintain weight loss. Mobilization of fat from the liver and muscle, and β -cells improves hepatic and muscle insulin sensitivity and β -cell function^{37,196,197}.

Antidiabetic medications

Achievement of durable glycaemic control requires antidiabetic medications that reverse the pathophysiological defects that are present in T2DM^{1,198}. Because no single medication reverses the multiple abnormalities, combination therapy has gained widespread acceptance and will continue to grow^{1,198–201}. Normalization of HbA1c at the time of diagnosis results in improved long-term glycaemic control^{17,8,200,202,203}. For prediabetes, pharmacological therapy with thiazolidinediones^{11,204}, GLP1 receptor agonists²⁰⁵, metformin¹⁹² and AGIs¹⁸⁶ effectively prevents or delays the progression of IGT to diabetes (TABLE 4).

Metformin. Metformin is the most commonly prescribed antidiabetic medication worldwide and works by suppressing hepatic glucose production, leading to a reduction in fasting plasma glucose levels and HbA1c²⁰⁶. Metformin has no effect on β -cell function^{206,207} and, in the absence of weight loss, does not improve muscle insulin sensitivity²⁰⁶; thus, after an initial decrease, HbA1c rises progressively^{207–209}. The mechanisms by which metformin suppresses hepatic glucose production remain unclear but include inhibition of mitochondrial complex I, activation of AMP-activated protein kinase (AMPK), and inhibition of glycolytic and/or gluconeogenic enzymes and mitochondrial

glycerophosphate dehydrogenase^{210,211}. In a study carried out in the United Kingdom and United States, cardiovascular events were significantly reduced in a small group of 344 obese patients with diabetes who were treated with metformin²¹².

Drugs that increase insulin secretion. Sulfonylureas augment insulin secretion, and the resulting hyperinsulinaemia overcomes insulin resistance, leading to a decline in fasting plasma glucose levels and HbA1c. However, after the initial decline, HbA1c rises progressively because sulfonylureas have no long-term protective effect on β -cell function^{1,207,209} and might even accelerate failure of β -cell function²¹³. Sulfonylureas commonly cause hypoglycaemia and are associated with weight gain, and some retrospective studies suggest that they might increase cardiovascular events^{214,215}. Compared with glibenclamide, the short-acting sulfonylurea, gliclazide has been associated with a reduced risk of all-cause mortality and cardiovascular death and is less likely to cause weight gain and hypoglycaemia²¹⁶. Stepwise addition of sulfonylurea to metformin, or vice versa, is associated with progressive failure of β -cell function and rise in HbA1c²¹⁷. However, because they are inexpensive, metformin and sulfonylureas remain the most commonly prescribed oral antidiabetic agents worldwide.

Meglitinides (repaglinide and nateglinide) are short-acting insulin secretagogues that require administration before each meal. Although related with less hypoglycaemia than sulfonylureas, they do not prevent the progressive decline in β -cell function and rise in HbA1c that is associated with T2DM.

Insulin sensitizers. Thiazolidinediones (pioglitazone and rosiglitazone) are the only true insulin-sensitizing agents^{1,37,217,218}. They enhance insulin action in skeletal and cardiac muscle, the liver and adipocytes^{1,37,217–219}, and exert a potent effect on β -cells to augment and preserve insulin secretion^{220–222}. Multiple mechanisms mediate their insulin-sensitizing effects: increased insulin signaling; stimulation of several intracellular steps involved in glucose metabolism (GLUT4, glycogen synthase and pyruvate dehydrogenase); stimulation of peroxisome proliferator-activated receptor- γ (PPAR γ); PPAR γ coactivator 1 (PGC1) activation leading to increased fat oxidation; proliferation of subcutaneous adipocytes and activation of genes involved in lipogenesis; fat redistribution from visceral to subcutaneous stores; reduced plasma levels of FFAs; a reduction in circulating inflammatory cytokines; and an increase in adiponectin levels^{1,61,217,218}. The combined insulin-sensitizing and β -cell stimulatory effects of thiazolidinediones explain their durable action, which was shown to be up to 5 years in the ADOPT study, and their ability to reduce HbA1c^{209,221,222}. Pioglitazone favourably affects many components of insulin resistance (metabolic) syndrome^{217,218} and reduced the MACE end points (myocardial infarction, stroke and cardiovascular death) in the PROactive study²²³. Adverse events (including fluid retention, fat mass gain and trauma-related fractures in post-menopausal women) are dose related, and doses >30 mg per day should be avoided²²⁴. Weight gain

is common with thiazolidinediones, but the greater the weight gain, the greater the decrease in HbA1c and the greater the improvements in insulin sensitivity and β -cell function^{220,221}. Concerns about the link between bladder cancer and pioglitazone have been dispelled by a 6-year follow-up in the PROactive study²²⁵ and a recently completed 10-year US FDA-mandated study²²⁶. In a review of approximately one million people from six populations, no increase in bladder cancer was observed with either pioglitazone (hazard ratio: 1.01–1.04) or rosiglitazone (hazard ratio: 1.00–1.01)²²⁷.

GLP1 modulators. T2DM is associated with severe GLP1 resistance in β -cells^{60,228,229}. Dipeptidyl peptidase 4 (DPP4) inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin) prolong the half-life of endogenously secreted GLP1. As DPP4 inhibitors do not increase (only prolong) plasma GLP1 levels, their ability to augment insulin secretion and reduce HbA1c is modest^{230,231}. Their primary effect to improve glycaemic control is mediated by inhibition of glucagon secretion and reduction in basal hepatic glucose production²³². DPP4 inhibitors have an excellent safety profile²³³. Concerns about pancreatitis have not been substantiated in prospective trials²³³. Two large cardiovascular outcome studies have demonstrated a hazard ratio of 1.0 for the primary end point (MACE) for both alogliptin²³⁴ and saxagliptin²³⁵, although a 27% increase in the incidence of hospitalization for congestive heart failure was observed with saxagliptin compared with placebo. The results of TECOS (sitagliptin) and ELIXIR (lixisenatide) presented at the ADA National Science Meeting (2015) also showed a hazard ratio of ~1.0 for the primary cardiovascular end point. Many cardiovascular outcome trials with the newer antidiabetic agents are ongoing, and results will be reported during the next 2–3 years.

GLP1 receptor agonists (exenatide, liraglutide, albiglutide, lixisenatide and dulaglutide) cause a pharmacological increase in plasma GLP1 levels, markedly augment insulin secretion and inhibit glucagon secretion^{236,237}. The increase in the levels of plasma insulin and the decrease in those of glucagon effectively suppress hepatic glucose production²³⁶ and cause a durable reduction — for up to 3 years — in HbA1c^{237,238}. GLP1 receptor agonists promote weight loss (resulting in improved insulin sensitivity), delay gastric emptying (which is accelerated in patients with new-onset diabetes), correct endothelial dysfunction, reduce blood pressure, improve the plasma lipid profile and reduce C-reactive protein levels^{238,239}. Combination therapy with a GLP1 receptor agonist plus basal insulin has been shown to be very effective in reducing HbA1c while preventing the weight gain associated with insulin therapy, without an increased risk of hypoglycaemia²⁴⁰. Nausea and vomiting are the most common side effects with GLP1 receptor agonists, but these are usually mild and dissipate within 4–8 weeks. An increased incidence of pancreatitis has not been observed in large healthcare databases^{234,235,241}.

Targeting intestinal and renal glucose absorption. AGIs (acarbose and voglibose) slow the rate of carbohydrate absorption in the intestine and increase meal-stimulated GLP1 secretion. The HbA1c-lowering effect of AGIs is modest and comparable to the effect of DPP4 inhibitors. In a review of 41 RCTs in the Cochrane Database²⁴², AGIs reduced HbA1c by 0.8%, which is similar to the HbA1c-lowering effect of gliptins (0.7–0.8%) in two different meta-analyses^{243,244}. However, AGIs have been shown to decrease the conversion of prediabetes to diabetes in the STOP NIDDM trial¹⁸⁶. Adverse effects of AGIs are related to the gastrointestinal tract (diarrhoea, abdominal pain, nausea and vomiting).

Table 4 | **Characteristics of major classes of currently available antidiabetic agents**

Drugs	Glycaemic efficacy (HbA1c)	Durability	Mechanism of action	Body weight	CV risk factors	CV safety	Side effects
Metformin	↓↓	No	↓↓ HGP	↓	↓	Possibly beneficial ¹²¹²	GI and lactic acidosis
Sulfonylureas	↓↓	No	↑↑ Insulin secretion	↑	Neutral	Possibly detrimental ^{1214,1216}	Hypoglycaemia
TZDs (pioglitazone)	↓↓	Yes	↑↑ Insulin sensitivity ↑↑ β -cell function	↑↑*	↓↓	Probably beneficial ¹²²³	Fluid retention Bone fractures
DPP4 inhibitors	↓	No	↓ Glucagon secretion ↑ Insulin secretion (weak)	Neutral	Neutral	Neutral ^{1234,1235}	None
SGLT2 inhibitors	↓↓	Not known	↓↓ Glucosuria ↓↓ Glucotoxicity	↓	↓	Unknown	Genital mycotic infections Volume-related
AGIs	↓	Not known	↓ Carbohydrate absorption	Neutral	Neutral	Possibly beneficial ¹¹⁸⁶	GI
GLP1 receptor agonists	↓↓	Yes	↑↑ Insulin secretion ↓↓ Glucagon secretion	↓↓	↓↓	Not known	Nausea and vomiting
Insulin	↓↓	Yes†	↓ HGP ↑ Glucose uptake in muscle	↑↑	Neutral	Neutral ¹²⁵⁷	Hypoglycaemia

↓, decreased; ↑, increased; AGIs, α -glucosidase inhibitors; CV, cardiovascular; DPP4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP1, glucagon-like peptide 1; HbA1c, haemoglobin A1c; HGP, hepatic glucose production; SGLT2, sodium/glucose co-transporter 2; TZDs, thiazolidinediones. *The greater the weight gain, the greater the improvements in insulin secretion and insulin sensitivity. †Requires increasing insulin dose. The number of arrows defines severity.

Sodium/glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin and empagliflozin) block glucose absorption in the proximal renal tubule^{245,246}. They decrease the maximum renal glucose reabsorptive capacity and, importantly, reduce the blood glucose threshold (to <40 mg per dl) at which glucose spills into the urine¹⁰². The increased glucose removal from the body via glucosuria leads to a reduction in plasma glucose, which results in the amelioration of glucotoxicity, with improved β -cell function and enhanced insulin sensitivity as a consequence^{247,248}. Their glucose-lowering efficacy is equivalent to that of metformin, and loss of calories in urine (4 calories per gram glucose) promotes weight loss of ~2.5–3.0 kg²⁴⁵. Because SGLT2 inhibitors also suppress sodium transport, they cause mild extracellular volume depletion and reduce blood pressure (~5–6 mmHg in systolic pressure and ~1–2 mmHg in diastolic pressure). Their glucose-lowering efficacy is offset by: increased glucose absorption by SGLT1, which can reabsorb ~30–40% of filtered glucose following SGLT2 blockade²⁴⁹, and ‘paradoxical’ stimulation of endogenous glucose production associated with increased glucagon and reduced insulin secretion^{247,248}. SGLT2 inhibitors can be combined with all antidiabetic medications, including insulin. The efficacy of SGLT2 inhibitors is reduced when the estimated glomerular filtration rate declines to <45–60 ml per min per 1.73 m². Adverse effects include genital mycotic infections in female patients, balanitis in uncircumcized male patients, urinary tract infections and volume-related side effects in older patients and individuals taking diuretics. Recently, cases of euglycaemic ketoacidosis have been described with SGLT2 inhibitors, primarily in T1DM, but also in T2DM. The potential of SGLT2 inhibitors to prevent diabetic nephropathy is being studied²⁵⁰. Combined SGLT2 and SGLT1 inhibitor therapy has considerable appeal. When SGLT2 is blocked, modest inhibition (~30%) of SGLT1 can increase glucosuria by ~80%²⁴⁹. Furthermore, 30% inhibition of gut SGLT1 produces an acarbose-like effect, which further reduces HbA1c by 0.5–0.6%²⁴⁹.

Adding insulin. If oral or injectable antidiabetic agents fail to normalize HbA1c, patients with T2DM can be treated with insulin, but large doses (>80–100 units per day) are often required²⁵¹. Combining insulin therapy with thiazolidinediones or metformin can improve glycaemic control and enable insulin dose reduction. The combination of GLP1 receptor agonists with basal insulin therapy causes robust HbA1c reduction, while reducing insulin dose and promoting weight loss²⁵². Combining SGLT2 inhibitors with insulin also effectively reduces HbA1c, decreases insulin dose, promotes weight loss and reduces hypoglycaemia²⁵³. In new-onset T2DM, intensive insulin therapy^{202,203} to reverse the metabolic decompensation, such as glucotoxicity and lipotoxicity, has proved effective in maintaining glycaemic control (HbA1c ~6.0%) for long periods.

Hypoglycaemia

Hypoglycaemia is a potential adverse effect of all antidiabetic agents, especially insulin secretagogues

(sulfonylureas) and insulin^{254,255}. According to the ADA, hypoglycaemia is defined as a plasma glucose level of <70 mg per dl. Most cases are mild, but severe hypoglycaemia (requiring third-party assistance for recovery) has been reported in 5–10% or more of individuals treated with sulfonylureas and insulin. Hypoglycaemia has been associated with myocardial infarction, ventricular arrhythmias, stroke and weight gain^{254–256}. In the ACCORD study, the incidence of severe hypoglycaemia and weight gain was 3.1% and 3.5%, respectively, in the intensively treated group, and the study was stopped early because of an increased incidence of sudden death²⁵⁷. Risk factors for hypoglycaemia include use of insulin or sulfonylureas, missed meals, strenuous exercise, alcohol consumption, interaction with other drugs, advanced age and renal or hepatic disease.

Cardiovascular comorbidities

Controversy has arisen about the optimal treatment goal for hypertension in T2DM based on results of the ACCORD trial²⁵⁸, which reported that targeting a systolic blood pressure of <120 mmHg did not reduce the composite primary outcome of cardiovascular events and was associated with more adverse events. This led to a reappraisal of optimal blood pressure levels to a less-stringent target of 140/90 mmHg²⁵⁹. However, in ACCORD, patients targeted to a systolic blood pressure of <120 mmHg experienced 40% fewer strokes²⁵⁸, and a meta-analysis of 40 RCTs ($n = 100,354$ participants) reported that a 10 mmHg decrease in systolic blood pressure was associated with a relative risk reduction (RRR) of 27% for stroke, 13% RRR for death, 12% RRR for coronary heart disease events, 13% RRR for retinopathy and 17% RRR for albuminuria²⁶⁰. Hyperglycaemia is a relatively weak risk factor for cardiovascular disease in T2DM¹⁶⁴, and the anti-atherogenic effect of HbA1c reduction might take >10 years to manifest¹⁶⁵. Dyslipidaemia is a major risk factor for cardiovascular disease in T2DM, and hypercholesterolaemia should be treated aggressively (TABLE 2).

Quality of life

T2DM imposes a substantial physical and psychological burden on patients, resulting in reduced health status and QOL. The relationship between improvements in HbA1c, reduced symptoms of hypoglycaemia and hyperglycaemia, and enhanced QOL was clearly demonstrated more than 15 years ago²⁶¹. Since then, many classes of glucose-lowering medications and different types of insulin have been approved, but few comparative-effectiveness studies exist to guide treatment choices on the basis of patient-centred outcomes such as QOL²⁶².

The complexity, burden and adverse effects of diabetes therapies reduce QOL, satisfaction and adherence to therapy, often leading to suboptimal glycaemic control. However, comparative longitudinal studies assessing patient-centred outcomes are relatively rare. Moreover, when they are used, assessments often lack the measurement properties such as sensitivity, responsiveness and ability to detect changes that are meaningful to patients²⁶³. As the number of approved diabetes treatments increases, therapeutic decisions will be made on

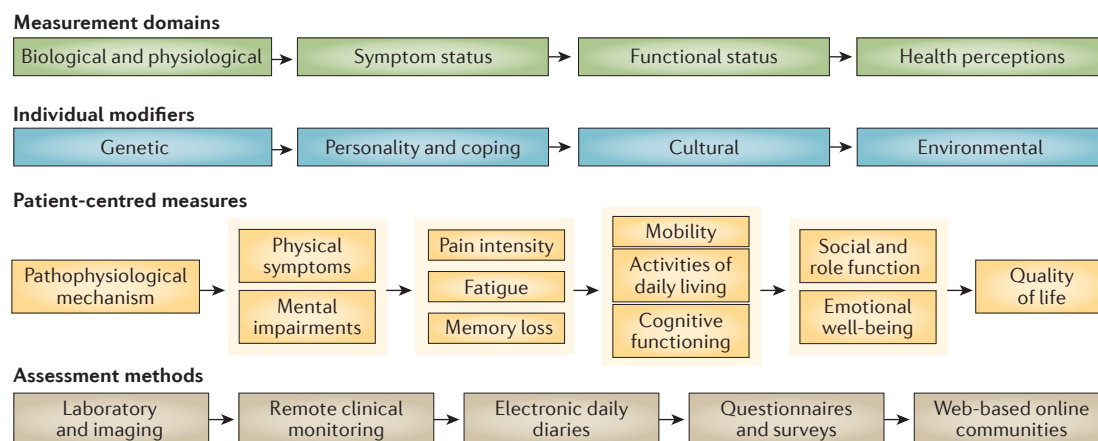


Figure 7 | **Illustration of the four major concepts in patient-reported outcomes.** The domains, individual modifiers and assessment methods for the multidimensional quality-of-life construct are shown in relation to selected patient-centred measures.

the basis of outcomes such as QOL, satisfaction and treatment adherence. Therefore, future diabetes research should be designed to gather high-quality scientific evidence of comparative treatment effectiveness on the basis of patient-centred outcomes.

QOL is multifaceted and can be assessed using several techniques (FIG. 7). Effective measurement of patient-centred outcomes poses challenges for clinical researchers, when deciding among the hundreds of available generic and disease-specific questionnaires (for example, see PROQOLID (<http://www.qolid.org/proqolid>)). Although QOL outcomes measured through structured, clinic-based, self-administered questionnaires have been found to be responsive to the effects of therapeutic interventions — such as symptoms of diabetes, changes in HbA1c, adverse effects, weight changes and glycaemic variability^{264,265} — they are artificially restrictive and typically undertaken in the clinic at relatively infrequent intervals.

Using newer electronic and mobile computing technologies, monitoring QOL in real time is now feasible, and offers a more efficient and accurate way to collect data and broaden the scientific assessment of QOL data to real-time surveillance and remote monitoring. Smartphones and tablets are much more effective for reporting acute diabetes-related and treatment-related events such as hypoglycaemia, gastrointestinal symptoms, cognitive problems and sleep disturbances than older technologies²⁶⁶. Furthermore, they allow for ‘dynamic’ questionnaires, bridging the gap between more-sensitive but more-burdensome longer ‘static’ questionnaires and less-sensitive but less-burdensome shorter forms by using item response theory and computer adaptive testing²⁶⁷. Most recently, big data methods have been used in patient-centred outcomes research for analysing electronic health records, web-based, crowd-sourced social media databanks, and intensively longitudinal, electronic remote patient-monitoring databases transmitted through glucose, blood pressure, weight and activity devices. These methods provide promising research opportunities for capturing patient functioning and feelings in real time and in real-life environments.

Outlook

Long-term normalization of blood glucose levels in T2DM depends on delaying or reversing failure of β -cell function to ensure appropriate insulin secretion and on improving insulin resistance. New avenues for treatment are currently in development²⁶⁸ and might, in combination with existing drugs, bring change and enhance our ability to control glycaemia. Our ability to prevent and reverse advanced microvascular and macrovascular complications is limited, and new strategies, some currently under investigation, will be required to close this gap (FIG. 8).

Insulin secretion

Progression from altered glucose metabolism to overt diabetes occurs as the reduction in β -cell mass and function is further aggravated. Thus, an attractive intervention is one that will halt the progressive decline in β -cell mass and function and prevent the need for exogenous insulin replacement that otherwise follows¹. Agents that suppress inflammation, including IL-1 β blockers and salsalate (a potent inhibitor of NF- κ B), have shown some promise in improving glycaemic control and β -cell function^{143,269,270}. MicroRNAs play a pivotal part in the physiological and pathological processes involved in glucose metabolism by post-transcriptional regulation of gene expression. Particular microRNAs can regulate β -cell function²⁷¹, exposing key regulatory signalling pathways involved in restoration of β -cell mass, and provide a promising strategy for improving insulin secretion and β -cell health in T2DM. Identification of novel insulin secretagogues that act directly on β -cells and enteroendocrine K cells and L cells in the intestine are under investigation, and members of the G protein-coupled class of receptors have shown promise²⁷². GLP1 receptor agonists induce β -cell proliferation in rodents²⁷³, but studies in humans have not demonstrated a similar effect²³⁷. A series of novel signalling pathways have been reported to be strongly associated with β -cell mass restoration. For example, the PI3K–PKC ζ pathway has been shown to augment glucose-mediated β -cell proliferation, and activation of PKC ζ may provide a novel approach to increase human β -cell proliferation²⁷⁴.

Glucose-stimulated insulin secretion

Mitochondrial metabolism is essential for normal β -cell function²⁷⁵. APPL1 proteins are reported to influence mitochondrial function and β -cells by maintaining the expression of several key genes involved in mitochondrial biogenesis²⁷⁶. APPL1 also contributes to the regulation of both first and second phases of glucose-stimulated insulin secretion²⁷⁶ and therefore has potential as a therapeutic target for anti-T2DM drug discovery. Other agents that improve mitochondrial function, including the regulators of NAD-dependent protein deacetylase sirtuin 1, peroxisome proliferator-activated protein kinase and uncoupling protein 2 (UCP2), may prove to be effective in the therapeutic intervention of T2DM^{277–279}.

Glucokinase is a key therapeutic target and serves as the 'glucose sensor' and glycolysis activator in β -cells.

However, multiple glucokinase activators have failed because of lack of efficacy or adverse effects²⁸⁰. Glucagon receptor antagonists have shown good clinical efficacy, although α -cell hyperplasia and increased levels of hepatic aminotransferases may limit their usefulness²⁸¹. Gluconeogenic inhibitors have shown some efficacy^{282–284}, but safety issues (hypoglycaemia and lactic acidosis) are a concern.

Islet transplantation faces many hurdles²⁸⁵, but encapsulated islets hold promise²⁸⁶. The practicality of transforming stem cells into insulin-secreting β -cells that are responsive to glucose²⁸⁷ is a long way off. The creation of stem cells that imitate natural healthy β -cells represents another option²⁸⁷. However, the concept that stressed β -cells in patients with diabetes dedifferentiate into other islet cells raises hopes for reversing this process²⁸⁸.

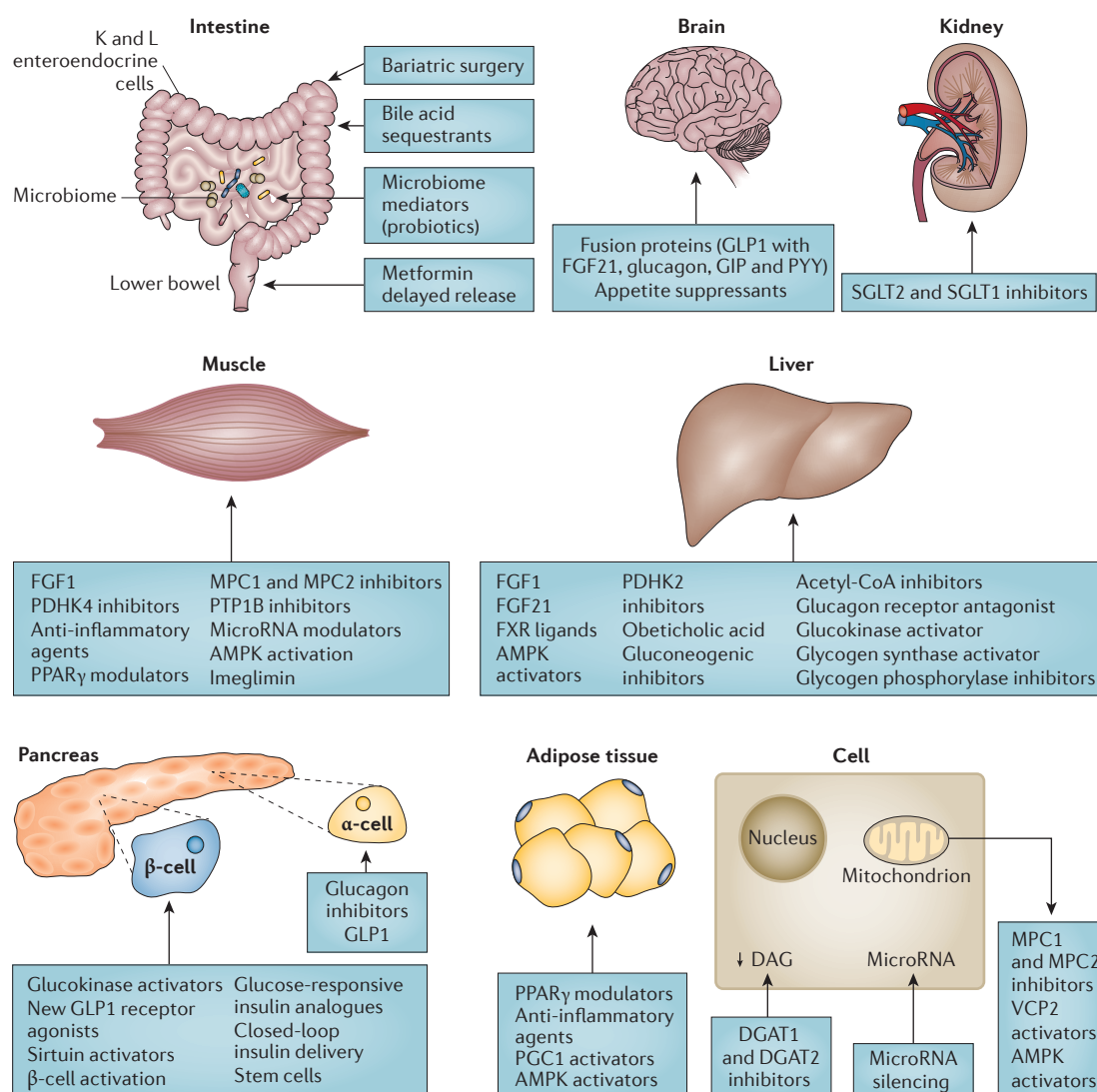


Figure 8 | Potential therapeutic targets in T2DM management. Schematic representation of the different targets in type 2 diabetes mellitus (T2DM) organized per tissue. AMPK, AMP-activated protein kinase; DAG, diacylglycerol; DGAT, DAG acyltransferase; FGF, fibroblast growth factor; FXR, farnesoid X nuclear receptor; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide 1; MPC, mitochondrial pyruvate carrier; PDHK, pyruvate dehydrogenase kinase; PGC1, PPAR γ coactivator 1; PPAR γ , peroxisome proliferator-activated receptor- γ ; PTP1B, protein tyrosine phosphatase 1B; PYY, peptide YY; SGLT, sodium/glucose co-transporter; VCP2, viral citrullinated peptide 2.

In patients with T2DM who have minimal β -cell reserves, intensive continuous subcutaneous insulin infusion has proved to be very effective²⁸⁹. In contrast to the accuracy needed for insulin delivery in insulin-sensitive T1DM, the larger doses of insulin and underlying insulin resistance in T2DM enable the use of much simpler pump devices. Hopefully, this will result in the introduction of less-sophisticated and low-price pumps into the market. Conversely, closed-loop insulin delivery systems that consist of an insulin pump that delivers insulin based on an algorithm whose inputs are derived from a continuous glucose monitor are advancing quickly in clinical studies^{289,290}, and this might be an attractive option for insulin-dependent, poorly controlled T2DM. Insulin administration via injection is a limiting factor for its broader use. Inhaled insulin with improved pharmacokinetic and pharmacodynamic profiles makes this option more appealing to patients²⁹¹. Another attractive option is oral insulin, which is currently in clinical trials and hopefully will mature into a simple and safe alternative for insulin delivery²⁹².

Insulin sensitivity

There is a major need for novel insulin-sensitizing agents, and many new agents show promise in humans. New metformin preparations target the lower bowel, effectively reducing HbA1c while minimizing metformin exposure²⁹³. In addition, selective PPAR γ modulators have shown some efficacy as insulin sensitizers²⁹⁴. Compounds targeting mitochondrial proteins (mitochondrial pyruvate carrier 1 (MPC1) and MPC2) have shown efficacy²⁹⁵. Derivatives of fibroblast growth factor 1 improve hepatic and muscle insulin sensitivity in animals²⁹⁶ and reduce plasma glucose levels in patients with T2DM²⁹⁷. Inhibitors of pyruvate dehydrogenase kinase 4 (PDHK4) increase pyruvate oxidation in muscle and reduce the supply of gluconeogenic precursors (lactate and alanine) to the liver, whereas inhibition of PDHK2 in the liver decreases gluconeogenesis²⁹⁸. Imeglimin, the first member of a new tetrahydrotriazine-containing class of oral antidiabetics (glimins), has modest HbA1c-lowering efficacy and augments both insulin sensitivity and insulin secretion^{299,300}. UCP2 activators have similarly been shown to improve hepatic and muscle insulin sensitivity in rodents.

Accumulation of toxic lipid metabolites (DAG, fatty acid acyl-CoAs and ceramides) in muscle and the liver causes severe insulin resistance. Inhibitors of DAG acyltransferase 1 (DGAT1) and DGAT2 have yielded conflicting results^{301,302}. Blockade of *de novo* lipogenesis with inhibitors of acetyl-CoA carboxylase reduces liver fat and increases hepatic insulin sensitivity in preclinical studies³⁰³. Liver-targeted mitochondrial uncouplers have been shown to reduce liver fat and content and improve insulin sensitivity in mice^{304,305}. Weight loss drugs (topiramate and phentermine extended-release, lorcaserin, bupropion and naltrexone, and high-dose liraglutide) promote fat removal from muscle and the liver and improve insulin sensitivity and glycaemic control in T2DM³⁰⁶. Bariatric surgery provides long-term remission of T2DM³⁰⁷. The farnesoid X nuclear receptor ligand obeticholic acid³⁰⁸

and bile acid sequestrants³⁰⁹ might prove to be useful in treating T2DM. Novel fusion proteins, including GLP1 with fibroblast growth factor 21, glucagon, GIP or peptide YY, which promote weight loss and enhance insulin sensitivity in rodents, are in development³¹⁰. Inhibitors of protein tyrosine phosphatase 1B, a cytosolic non-receptor PTPase that has been implicated as a negative regulator of insulin signal transduction, have received interest³¹¹. Several microRNAs are upregulated in diabetes and obesity, and their silencing improves insulin sensitivity³¹².

Specific microbiome profiles render individuals prone to develop obesity and altered glucose metabolism³¹³. The ability to identify protective microbiome profiles might provide a key to the development of obesity and diabetes interventions. It remains to be determined whether specific dietary components are involved in microbiome changes and induce unfavourable transitions. Probiotics or pharmacological manipulation of microbiome elements that favour more 'healthy' flora may prove to be useful in stemming the 'twin epidemics' of obesity and T2DM³¹³. Surgical rearrangement of the gastrointestinal tract has shown remarkable efficacy in treating obese patients with T2DM^{307,314}. Development of minimally invasive reversible procedures, such as the duodenal sleeve and temporary mucosal barriers, might replace surgery in the near future.

Comorbidities

There is great need to address short- and long-term diabetic complications. The most promising therapy for the near future is the use of drug combinations (dual or triple) that address the pathophysiological abnormalities responsible for β -cell dysfunction and insulin resistance and that normalize plasma glucose levels^{198–200} (FIG. 3). The optimal candidates for this therapy are patients at the very early stage of their disease or at the prediabetes state⁷.

Hypoglycaemia remains a critical barrier for intensification of care, especially in patients who require insulin, and poses serious immediate and long-term risks. Continuous glucose monitoring with pre-set alarms and use of therapeutic agents or regimens that minimize the risk of hypoglycaemia are available options. A self-regulating insulin that is responsive to blood sugar levels (*SmartCells*) is currently under development.

Treatment of established microvascular complications remains a major unmet need. Anti-VEGF (vascular endothelial growth factor) therapy has changed the outcome in many patients with advanced retinopathy, but more novel therapies are needed. C-peptide replacement therapy³¹⁵ and ocular inhibition of kallikreins and kinin receptor antagonists offer new therapeutic avenues³¹⁶. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers slow progression of nephropathy but do not reverse it³¹⁷. Endothelin inhibitors or agents that prevent AGE accumulation are in Phase III studies for prevention of microvascular complications^{318,319}. SGLT2 inhibitors also are being investigated for the prevention of diabetic nephropathy²⁵⁰. Although we have agents that can ameliorate symptoms of diabetic neuropathy, there is a need for molecules that will prevent its development and progression.

Cardiovascular morbidity and mortality, the major cause of death in T2DM, is increased twofold–threefold in patients with T2DM³²⁰. Hyperglycaemia is a weak risk factor for cardiovascular disease, and the factors (other than hypertension, dyslipidaemia and enhanced coagulation) that are responsible for the increased

cardiovascular risk in T2DM remain obscure. As T2DM is an inflammatory disease, an anti-inflammatory approach initiated early in combination with normalization of cardiovascular risk factors¹⁷ before the clinical appearance of macrovascular disease may prove to be effective.

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Introduction (R.R.H.); Epidemiology (F.B.H.); Mechanisms/pathophysiology (L.C.G., C.R.K., E.F., G.I.S. and R.A.D.); Diagnosis, screening and prevention (W.H.H.); Management (R.A.D.); Quality of life (D.C.S. and M.A.T.); Outlook (I.R., J.J.H. and R.W.); overview of Primer (R.A.D.).

Competing interests

The authors declare the following potential COI: (1) R.A.D.: Research Grant Support - AstraZeneca, Bristol Myers Squibb, Janssen, Speakers Bureau - AstraZeneca, Novo Nordisk, Advisory Board/Consultant - AstraZeneca, Janssen, Novo Nordisk, Boehringer Ingelheim, Lexicon, Intarcia; (2) E.F.: Research Grant Support - Boehringer Ingelheim, Eli Lilly; Consultant/Speaker Bureau-Boehringer Ingelheim, Eli Lilly, Sanofi, Novo Nordisk, Janssen, AstraZeneca, Takeda, Medtronic, Intarcia; (3) C.R.K. serves as a consultant for Medimmune, Merck, Five Prime Therapeutics, CohBar, Antriabio, and Catabasis; (4) L.G. has no conflict of interest; (5) R.H. has received grant support from Hitachi, Janssen, Eli Lilly, Sanofi-Aventis and Viacety and is a consultant/advisory board member for Alere, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Clin Met, Eisai, Elcelyx, Gilead, Intarcia, Isis, Janssen, Merck, Novo Nordisk, Sanofi-Aventis, and Vivus; (6) W.H.H. has no conflict of interest; (7) J.J.H. has received grant support from Novartis and Merck and is a consultant/advisory board member for Glaxo, Smith, Kline, Novo Nordisk, and Zealand Pharmaceuticals; (8) M.A.T. has no conflict of interest; (9) R.W. serves as a consultant for Medtronic and Kamada and is on the speaker's bureau for Medtronic and Novo Nordisk; (10) F.H. has received research support from California Walnut Commission and Metegenics; (11) G.I.S. serves on scientific advisory boards for Merck and Novartis and he has received research grant support from Gilead Pharmaceuticals; (12) D.C.S. has no conflict of interest; (13) I.R. – Advisory Board: Novo Nordisk, Astra Zeneca/BMS, MSD, Eli Lilly, Sanofi, Medscape Cardiology; Consultant: Astra Zeneca/BMS, Insuline; Speaker's Bureau: Eli Lilly, Novo Nordisk, Astra Zeneca/BMS, J&J, Sanofi, MSD, Novartis, Teva; Shareholder: Insuline, Labstyle.