4. Lifestyle Management

American Diabetes Association

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Lifestyle management is a fundamental aspect of diabetes care and includes diabetes self-management education (DSME), diabetes self-management support (DSMS), nutrition therapy, physical activity, smoking cessation counseling, and psychosocial care. Patients and care providers should focus together on how to optimize lifestyle from the time of the initial comprehensive medical evaluation, throughout all subsequent evaluations and follow-up, and during the assessment of complications and management of comorbid conditions in order to enhance diabetes care.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

- In accordance with the national standards for diabetes self-management education and support, all people with diabetes should participate in diabetes self-management education to facilitate the knowledge, skills, and ability necessary for diabetes self-care and in diabetes self-management support to assist with implementing and sustaining skills and behaviors needed for ongoing self-management, both at diagnosis and as needed thereafter. B
- Effective self-management and improved clinical outcomes, health status, and quality of life are key goals of diabetes self-management education and support that should be measured and monitored as part of routine care. C
- Diabetes self-management education and support should be patient centered, respectful, and responsive to individual patient preferences, needs, and values and should help guide clinical decisions. A
- Diabetes self-management education and support programs have the necessary elements in their curricula to delay or prevent the development of type 2 diabetes. Diabetes self-management education and support programs should therefore be able to tailor their content when prevention of diabetes is the desired goal. B
- Because diabetes self-management education and support can improve outcomes and reduce costs B, diabetes self-management education and support should be adequately reimbursed by third-party payers. E

DSME and DSMS programs facilitate the knowledge, skills, and abilities necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes. The overall objectives of DSME and DSMS are to support informed decision making, self-care behaviors, problem solving, and active collaboration with the health care team to improve clinical outcomes, health status, and quality of life in a cost-effective manner (1). Providers should consider the burden of treatment and the patient's level of confidence/self-efficacy for management behaviors as well as the level of social and family support when providing DSME or DSMS. Monitor patient performance of self-management behaviors as well as psychosocial factors impacting the person's self-management.

DSME and DSMS, and the current national standards guiding them (1,2), are based on evidence of their benefits. Specifically, DSME helps people with diabetes to identify and implement effective self-management strategies and cope with diabetes at the four critical time points (described below) (1). Ongoing DSMS helps people with diabetes to maintain effective self-management throughout a lifetime of diabetes as they face new challenges and as advances in treatment become available (3).

Suggested citation: American Diabetes Association. Lifestyle management. Sec. 4. In Standards of Medical Care in Diabetes—2017. *Diabetes Care 2017;40(Suppl. 1):S33–S43*

Four critical time points have been defined when the need for DSME and DSMS should be evaluated by the medical care provider and/or multidisciplinary team, with referrals made as needed (1):

1. At diagnosis
2. Annually for assessment of education, nutrition, and emotional needs
3. When new complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) arise that influence self-management
4. When transitions in care occur

DSME focuses on supporting patient empowerment by providing people with diabetes the tools to make informed self-management decisions (4). Diabetes care has shifted to an approach that is more patient centered and places the person with diabetes and his or her family at the center of the care model, working in collaboration with health care professionals. Patient-centered care is respectful of and responsive to individual patient preferences, needs, and values. It ensures that patient values guide all decision making (5).

Evidence for the Benefits

Studies have found that DSME is associated with improved diabetes knowledge and self-care behaviors (2), lower A1C (6–9), lower self-reported weight (10,11), improved quality of life (8,12), healthy coping (13,14), and reduced health care costs (15,16). Better outcomes were reported for DSME interventions that were over 10 h in total duration, included follow-up with DSMS (3,17), were culturally (18,19) and age appropriate (20,21), were tailored to individual needs and preferences, and addressed psychosocial issues and incorporated behavioral strategies (4,13,22,23). Individual and group approaches are effective (11,24). Emerging evidence is pointing to the benefit of Internet-based DSME programs for diabetes prevention and the management of type 2 diabetes (25,26). There is growing evidence for the role of community health workers (27), as well as peer (27–29) and lay (30) leaders, in providing ongoing support.

DSME is associated with an increased use of primary care and preventive services (15,31,32) and less frequent use of acute care and inpatient hospital services (10). Patients who participate in DSME are more likely to follow best practice treatment recommendations, particularly among the Medicare population, and have lower Medicare and insurance claim costs (16,31). Despite these benefits, reports indicate that only 5–7% of individuals eligible for DSME through Medicare or a private insurance plan actually receive it (33,34). This low participation may be due to lack of referral or other identified barriers such as logistical issues (timing, costs) and the lack of a perceived benefit (35). Thus, alternative and innovative models of DSME delivery need to be explored and evaluated.

Reimbursement

Medicare reimburses DSME and DSMS, when provided by a program that meets the national standards (2) and is recognized by the American Diabetes Association (ADA) or other approval bodies. DSME is also covered by most health insurance plans. DSMS has been shown to be instrumental for improving outcomes when it follows the completion of a DSME program. DSME and DSMS are frequently reimbursed when performed in person. However, although DSME and DSMS can also be provided via phone calls and telehealth, these remote versions may not always be reimbursed.

NUTRITION THERAPY

For many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat and following a food plan. There is not a one-size-fits-all eating pattern for individuals with diabetes. Nutrition therapy has an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with his or her health care team, including the collaborative development of an individualized eating plan (36,37). All individuals with diabetes should receive individualized medical nutrition therapy (MNT), preferably provided by a registered dietitian who is knowledgeable and skilled in providing diabetes-specific MNT. MNT delivered by a registered dietitian is associated with A1C decreases of 0.3–1% for people with type 1 diabetes (38–40) and 0.5–2% for people with type 2 diabetes (41–44).

It is important that each member of the health care team be knowledgeable about nutrition therapy principles for people with all types of diabetes and be supportive of their implementation. Emphasis should be on healthful eating patterns containing nutrient-dense, high-quality foods with less focus on specific nutrients. The Mediterranean (45), Dietary Approaches to Stop Hypertension (DASH) (46,47), and plant-based diets (48) are all examples of healthful eating patterns. See **Table 4.1** for specific nutrition recommendations.

For complete discussion and references, see the ADA position statement "Nutrition Therapy Recommendations for the Management of Adults With Diabetes" (37).

Goals of Nutrition Therapy for Adults With Diabetes

1. To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, in order to improve overall health and specifically to:
   - Achieve and maintain body weight goals
   - Attain individualized glycemic, blood pressure, and lipid goals
   - Delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and barriers to change
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Weight Management

Body weight management is important for overweight and obese people with type 1 and type 2 diabetes. Lifestyle intervention programs should be intensive and have frequent follow-up to achieve significant reductions in excess body weight and improve clinical indicators. There is strong and consistent evidence that modest persistent weight loss can delay the progression from prediabetes to type 2 diabetes (49,50) and is beneficial to the management of type 2 diabetes (see Section 7 "Obesity Management for the Treatment of Type 2 Diabetes").

In overweight and obese patients with type 2 diabetes, modest weight loss, defined as sustained reduction of

5% of initial body weight, has been shown to improve glycemic control and to reduce the need for glucose-lowering medications (51–53). Sustaining weight loss can be challenging (54). Weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit or provide ~1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, adjusted for the individual's baseline body weight. For many obese individuals with type 2 diabetes, weight loss >5% is needed to produce beneficial outcomes in glycemic control, lipids, and blood pressure, and sustained weight loss of ≥7% is optimal (54).

The diets used in intensive lifestyle management for weight loss may differ in the types of foods they restrict (e.g., high-fat vs. high-carbohydrate foods), but their emphasis should be on nutrient-dense foods, such as whole grains, vegetables, fruits, legumes, low-fat dairy, lean meats, nuts, and seeds, as well as on achieving the desired energy deficit (55–58). The diet choice should be based on the patients' health status and preferences.

Carbohydrates

Studies examining the ideal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake and considering the blood glucose response to dietary carbohydrate are key for improving postprandial glucose control (59,60). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, though in some studies lowering the glycemic load of consumed carbohydrates has demonstrated A1C reductions of −0.2% to −0.5% (61,62). A systematic review (61) found that whole-grain consumption was not associated with improvements in glycemic control in type 2 diabetes. One study did find a potential benefit of whole-grain intake in reducing mortality and cardiovascular disease (CVD) among individuals with type 2 diabetes (63).

As for all Americans, individuals with diabetes should be encouraged to replace refined carbohydrates and added sugars with whole grains, legumes, vegetables, and fruits. The consumption of sugar-sweetened beverages and processed "low-fat" or "nonfat" food products with high amounts of refined grains and added sugars should be strongly discouraged (64).

Individuals with type 1 or type 2 diabetes taking insulin at mealtimes should be offered intensive education on the need to couple insulin administration with carbohydrate intake. For people whose meal schedules or carbohydrate consumption is variable, regular counseling to help them understand the complex relationship between carbohydrate intake and insulin needs is important. In addition, education regarding the carbohydrate-counting approach to meal planning can assist them with effectively modifying insulin dosing from meal to meal and improving glycemic control (39,59,65–67). Individuals who consume meals containing more protein and fat than usual may also need to make mealtime insulin dose adjustments to compensate for delayed postprandial glycemic excursions (68,69). For individuals on a fixed daily insulin schedule, meal planning should emphasize a relatively fixed carbohydrate consumption pattern with respect to both time and amount (37). By contrast, a simpler diabetes meal planning approach emphasizing portion control and healthful food choices may be better suited for some elderly individuals, those with cognitive dysfunction, and those for whom there are concerns over health literacy and numeracy (37–39,41,59,65). The modified plate method (which uses measuring cups to assist with portion measurement) may be an effective alternative to carbohydrate counting for some patients in improving glycemia (70).

Protein

There is no evidence that adjusting the daily level of protein ingestion (typically 1–1.5 g/kg body weight/day or 15–20% total calories) will improve health in individuals without diabetic kidney disease, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic control or CVD risk (61). Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety (47).

For those with diabetic kidney disease (with albuminuria and/or reduced estimated glomerular filtration rate), dietary protein should be maintained at the recommended daily allowance of 0.8 g/kg body weight/day. Reducing the amount of dietary protein below the recommended daily allowance is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines (71,72).

In individuals with type 2 diabetes, ingested protein may enhance the insulin response to dietary carbohydrates (73). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia.

Fats

The ideal amount of dietary fat for individuals with diabetes is controversial. The Institute of Medicine has defined an acceptable macronutrient distribution for total fat for all adults to be 20–35% of energy (74). The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk (64,75–78). Multiple randomized controlled trials including patients with type 2 diabetes have reported that a Mediterranean-style eating pattern (75,79–82), rich in monounsaturated fats, can improve both glycemic control and blood lipids. However, supplements do not seem to have the same effects. A systematic review concluded that dietary supplements with ω-3 fatty acids did not improve glycemic control in individuals with type 2 diabetes (61). Randomized controlled trials also do not support recommending ω-3 supplements for primary or secondary prevention of CVD (83–87). People with diabetes should be advised to follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and *trans* fat (64). In general, *trans* fats should be avoided.

Sodium

As for the general population, people with diabetes should limit their sodium consumption to <2,300 mg/day. Lowering sodium intake (i.e., 1,500 mg/day) may benefit blood pressure in certain circumstances (88). However, other studies (89,90) have recommended caution for universal sodium restriction to 1,500 mg in people with diabetes. Sodium intake recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet (91).

6. Glycemic Targets

American Diabetes Association

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ASSESSMENT OF GLYCEMIC CONTROL

Patient self-monitoring of blood glucose (SMBG) and A1C are available to health care providers and patients to assess the effectiveness and safety of the management plan on glycemic control. Continuous glucose monitoring (CGM) also has an important role in assessing the effectiveness and safety of treatment in subgroups of patients with type 1 diabetes and in selected patients with type 2 diabetes.

Recommendations

- Most patients using intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should perform self-monitoring of blood glucose (SMBG) prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. B
- When prescribed as part of a broad educational program, SMBG may help to guide treatment decisions and/or self-management for patients taking less frequent insulin injections B or noninsulin therapies. E
- When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique, SMBG results, and their ability to use SMBG data to adjust therapy. E
- When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥25 years) with type 1 diabetes. A
- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. B
- CGM may be a useful tool in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. C
- Given the variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing. E
- When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use. E
- People who have been successfully using CGM should have continued access after they turn 65 years of age. E

Self-monitoring of Blood Glucose

Major clinical trials of insulin-treated patients have included SMBG as part of the multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications. SMBG is thus an integral component of effective therapy (1). SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Integrating SMBG results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, and adjusting medications (particularly prandial insulin doses). Among patients with type 1 diabetes, there is a correlation between greater SMBG frequency and lower A1C (2). The patient's specific needs and goals should dictate SMBG frequency and timing.

Optimization

SMBG accuracy is dependent on the instrument and user, so it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper review and interpretation of the data, by both the patient and the provider. Among patients who check their blood

Suggested citation: American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetes—2017. *Diabetes Care 2017;40(Suppl. 1):S48–S56*

glucose at least once daily, many report taking no action when results are high or low. In a yearlong study of insulin-naive patients with suboptimal initial glycemic control, a group trained in structured SMBG (a paper tool was used at least quarterly to collect and interpret 7-point SMBG profiles taken on 3 consecutive days) reduced their A1C by 0.3 percentage points more than the control group (3). Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. The ongoing need for and frequency of SMBG should be reevaluated at each routine visit to avoid overuse (4–6). SMBG is especially important for insulin-treated patients to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia.

For Patients on Intensive Insulin Regimens

Most patients using intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should perform SMBG prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. For many patients, this will require testing 6–10 (or more) times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjustment for multiple confounders, increased daily frequency of SMBG was significantly associated with lower A1C (–0.2% per additional test per day) and with fewer acute complications.

For Patients Using Basal Insulin or Oral Agents

The evidence is insufficient regarding when to prescribe SMBG and how often testing is needed for patients who do not use intensive insulin regimens, such as those with type 2 diabetes using oral agents or basal insulin. For patients using basal insulin, lowering of A1C has been demonstrated for those who adjust their dose to attain a fasting glucose as determined by SMBG within a targeted range (7,8).

For individuals with type 2 diabetes on less intensive insulin therapy, more frequent SMBG (e.g., fasting, before/after meals) may be helpful, as increased frequency is associated with meeting A1C targets (9).

Several randomized trials have called into question the clinical utility and cost-effectiveness of routine SMBG in noninsulin-treated patients (10–12). Meta-analyses have suggested that SMBG can reduce A1C by 0.25–0.3% at 6 months (10,13), but the effect was attenuated at 12 months in one analysis (13). A key consideration is that performing SMBG alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Continuous Glucose Monitoring

CGM measures interstitial glucose (which correlates well with plasma glucose) and includes sophisticated alarms for hypo- and hyperglycemic excursions. The U.S. Food and Drug Administration (FDA) has not yet approved these devices as a sole device to monitor glucose. CGMs require calibration with SMBG, and SMBG is still required to make treatment decisions. An FDA advisory panel recently recommended approval for use of one CGM device alone (without SMBG) to make treatment decisions, but the final FDA decision is still pending.

A 26-week randomized trial of 322 patients with type 1 diabetes showed that adults aged ≥25 years using intensive insulin therapy and CGM experienced a 0.5% reduction in A1C (from ~7.6% to 7.1% [~60 mmol/mol to 54 mmol/mol]) compared with those using intensive insulin therapy with SMBG (14). CGM use in those aged <25 years (children, teens, and adults) did not result in significant A1C lowering, and there was no significant difference in hypoglycemia in any group. The greatest predictor of A1C lowering for all age-groups was frequency of sensor use, which was highest in those aged ≥25 years and lower in younger age-groups. Other small, short-term studies have demonstrated similar A1C reductions using CGM compared with SMBG in adults with A1C levels ≥7% (53 mmol/mol) (15,16).

A registry study of 17,317 participants confirmed that more frequent CGM use is associated with lower A1C (17), whereas another study showed that children with >70% sensor use (i.e., ≥5 days per week) missed fewer school days (18). Small randomized controlled trials in adults and children with baseline A1C <7.0–7.5% (53–58 mmol/mol) have confirmed favorable outcomes including a reduced frequency of hypoglycemia (defined as a blood glucose level <70 mg/dL [3.9 mmol/L]) and maintaining A1C <7% (53 mmol/mol) during the study period in groups using CGM, suggesting that CGM may provide further benefit for individuals with type 1 diabetes who already have good glycemic control (19–21).

A meta-analysis suggests that compared with SMBG, CGM is associated with short-term A1C lowering of ~0.26% in insulin-treated patients (22). The long-term effectiveness of CGM needs to be determined. This technology may be particularly useful in insulin-treated patients with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not shown consistent reductions in severe hypoglycemia (22–24). A CGM device equipped with an automatic low glucose suspend feature has been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 patients with type 1 diabetes and documented nocturnal hypoglycemia showed that sensor-augmented insulin pump therapy with a low glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (25). These devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. In September 2016, the FDA approved the first hybrid closed-loop system, which may be considered as an option in those already on an insulin pump when it is available on the market. The safety of hybrid closed-loop systems has been supported in the literature (26).

Due to variable adherence, optimal CGM use requires an assessment of individual readiness for the technology as well as initial and ongoing education and support (17,27). Additionally, providers need to provide robust diabetes education, training, and support for optimal CGM implementation and ongoing use. As people with type 1 or type 2 diabetes are living longer healthier lives, individuals who have been successfully using CGM should have continued access to these devices after they turn 65 years of age (28).

A1C TESTING

Recommendations

- Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). E
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. E
- Point-of-care testing for A1C provides the opportunity for more timely treatment changes. E

8. Pharmacologic Approaches to Glycemic Treatment

American Diabetes Association

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PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. A
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. A
- Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. E
- Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. E

Insulin Therapy

Insulin is the mainstay of therapy for individuals with type 1 diabetes. Generally, the starting insulin dose is based on weight, with doses ranging from 0.4 to 1.0 units/kg/day of total insulin with higher amounts required during puberty. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in patients who are metabolically stable, with higher weight-based dosing required immediately following presentation with ketoacidosis (1), and provides detailed information on intensification of therapy to meet individualized needs. The American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" additionally provides a thorough overview of type 1 diabetes treatment and associated recommendations (2).

Education regarding matching prandial insulin dosing to carbohydrate intake, premeal glucose levels, and anticipated activity should be considered, and selected individuals who have mastered carbohydrate counting should be educated on fat and protein gram estimation (3–5). Although most studies of multiple daily injections (MDI) versus continuous subcutaneous insulin infusion (CSII) have been small and of short duration, a systematic review and meta-analysis concluded that there are minimal differences between the two forms of intensive insulin therapy in A1C (combined mean between-group difference favoring insulin pump therapy −0.30% [95% CI −0.58 to −0.02]) and severe hypoglycemia rates in children and adults (6). A 3-month randomized trial in patients with type 1 diabetes with nocturnal hypoglycemia reported that sensor-augmented insulin pump therapy with the threshold suspend feature reduced nocturnal hypoglycemia without increasing glycated hemoglobin levels (7). Intensive management using CSII and continuous glucose monitoring (CGM) should be encouraged in selected patients when there is active patient/family participation (8–10).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive therapy with MDI or CSII delivered by multidisciplinary teams of physicians, nurses, dietitians, and behavioral scientists improved glycemia and resulted in better long-term outcomes (11–13). The study was carried out with short-acting and intermediate-acting human insulins. Despite better microvascular, macrovascular, and all-cause mortality outcomes, intensive therapy was associated with a high rate of severe hypoglycemia (61 episodes per 100 patient-years of therapy). Since the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia in type 1 diabetes, while matching the A1C lowering of human insulins (14,15).

Suggested citation: American Diabetes Association. Pharmacologic approaches to glycemic treatment. Sec. 8. In Standards of Medical Care in Diabetes—2017. *Diabetes Care 2017; 40(Suppl. 1):S64–S74*

Rapid-acting inhaled insulin used before meals in type 1 diabetes was shown to be noninferior when compared with aspart insulin for A1C lowering, with less hypoglycemia observed with inhaled insulin therapy (16). However, the mean reduction in A1C was greater with aspart (−0.21% vs. −0.40%, satisfying the noninferiority margin of 0.4%), and more patients in the insulin aspart group achieved A1C goals of ≤7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol). Because inhaled insulin cartridges are only available in 4, 8, and 12 unit doses, people with type 1 diabetes may have limited dosing increments to fine-tune prandial insulin doses when using this therapy.

Postprandial glucose excursions may be better controlled by adjusting the timing of prandial (bolus) insulin dose administration. The optimal time to administer prandial insulin varies, based on the type of insulin used (regular, rapid-acting analog, inhaled, etc.), the measured blood glucose level, timing of meals, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized.

Pramlintide

Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is U.S. Food and Drug Administration (FDA)–approved for use in adults with type 1 diabetes. It has been shown to induce weight loss and lower insulin doses. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia.

Pancreas and Islet Transplantation

Pancreas and islet transplantation have been shown to normalize glucose levels but require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (17). Islet transplantation remains investigational. Autoislet transplantation may be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis.

Investigational Agents

Metformin

Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled type 1 diabetes. In a meta-analysis, metformin in type 1 diabetes was found to reduce insulin requirements (6.6 units/day, $P < 0.001$) and led to small reductions in weight and total and LDL cholesterol but not to improved glycemic control (absolute A1C reduction 0.11%, $P = 0.42$) (18). Metformin is not FDA-approved for use in patients with type 1 diabetes.

Incretin-Based Therapies

Due to their potential protection of β-cell mass and suppression of glucagon release, glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are being studied in patients with type 1 diabetes but are not currently FDA-approved for use in patients with type 1 diabetes.

Sodium–Glucose Cotransporter 2 Inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in type 2 diabetes. There are three FDA-approved agents for patients with type 2 diabetes, but none are FDA-approved for the treatment of patients with type 1 diabetes (2). The FDA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic diabetic ketoacidosis) in patients with type 1 and type 2 diabetes treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain. Patients should be instructed to stop taking SGLT2 inhibitors and seek medical attention immediately if they have symptoms or signs of ketoacidosis (19).

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C ≥10% (86 mmol/mol) and/or blood glucose levels ≥300 mg/dL (16.7 mmol/L). E
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. A
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences. E
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. B
- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B

The use of metformin as first-line therapy was supported by findings from a large meta-analysis, with selection of second-line therapies based on patient-specific considerations (20). An ADA/European Association for the Study of Diabetes position statement (21) recommended a patient-centered approach, including assessment of efficacy, hypoglycemia risk, impact on weight, side effects, costs, and patient preferences. Renal effects may also be considered when selecting glucose-lowering medications for individual patients. Lifestyle modifications that improve health

(see Section 4 "Lifestyle Management") should be emphasized along with any pharmacologic therapy.

Initial Therapy

Metformin monotherapy should be started at diagnosis of type 2 diabetes unless there are contraindications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (22). Metformin may be safely used in patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m^2 (23), and the U.S. label for metformin was recently revised to reflect its safety in patients with eGFR ≥30 mL/min/1.73 m^2 (24). Patients should be advised to stop the medication in cases of nausea, vomiting, or dehydration. Metformin is associated with vitamin B12 deficiency, with a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting that periodic testing of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy (25).

In patients with metformin contraindications or intolerance, consider an initial drug from another class depicted in **Fig. 8.1** under "Dual Therapy" and proceed accordingly. When A1C is ≥9% (75 mmol/mol), consider initiating dual combination therapy (**Fig. 8.1**) to more expeditiously achieve the target A1C level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features (weight loss, ketosis) are present. Consider initiating combination insulin injectable therapy (**Fig. 8.2**) when blood glucose is ≥300 mg/dL (16.7 mmol/L) or A1C is ≥10% (86 mmol/mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia). As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

Combination Therapy

Although there are numerous trials comparing dual therapy with metformin alone,

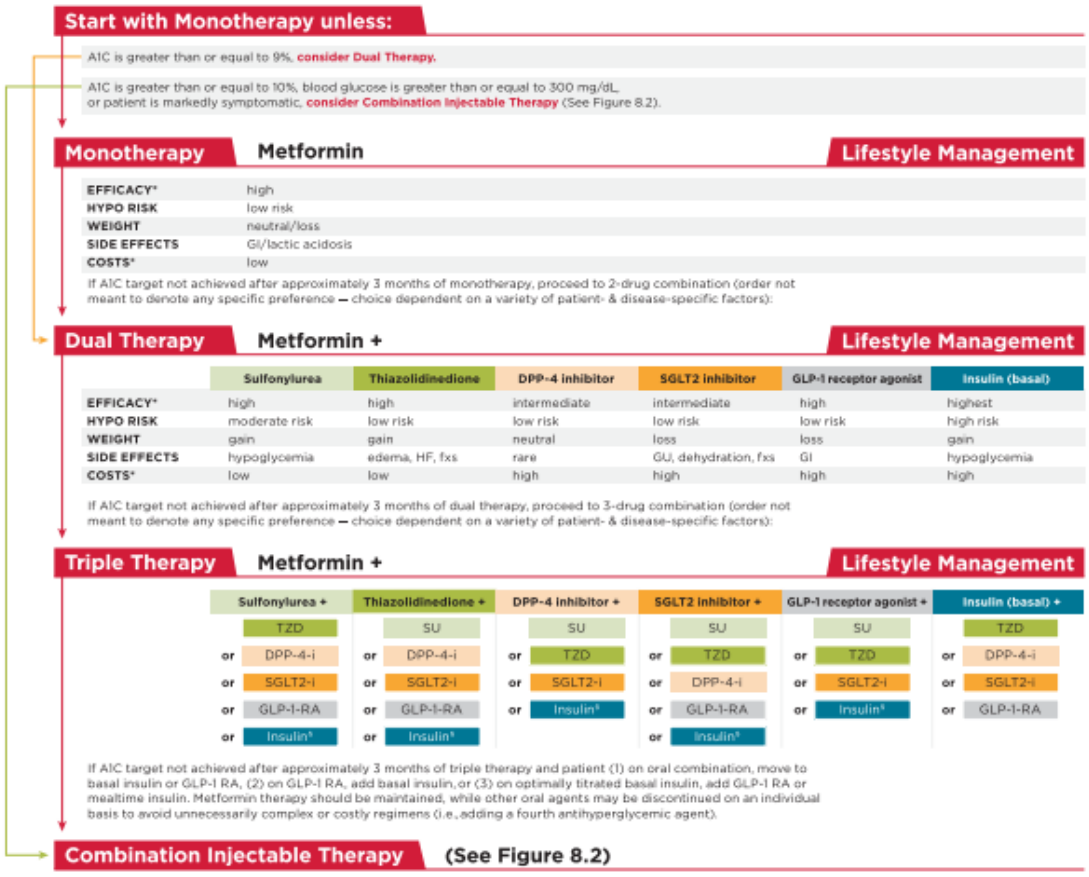

Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations. The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 21 for description of efficacy and cost categorization. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (21).