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AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2017

American Diabetes Association®

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Standards of Medical Care in Diabetes—2017

American Diabetes Association®

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[T]he simple word *Care* may suffice to express [the journal's] philosophical mission. The new journal is designed to promote better patient care by serving the expanded needs of all health professionals committed to the care of patients with diabetes. As such, the American Diabetes Association views *Diabetes Care* as a reaffirmation of Francis Weld Peabody's contention that "the secret of the care of the patient is in caring for the patient."

—Norbert Freinkel, *Diabetes Care*, January-February 1978

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Introduction

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Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association's (ADA's) "Standards of Medical Care in Diabetes," referred to as the "Standards of Care," is intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care. The Standards of Care recommendations are not intended to preclude clinical judgment and must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about management of diabetes, please refer to *Medical Management of Type 1 Diabetes* (1) and *Medical Management of Type 2 Diabetes* (2).

The recommendations include screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. Many of these interventions have also been shown to be cost-effective (3).

The ADA strives to improve and update the Standards of Care to ensure that clinicians, health plans, and policymakers can continue to rely on them as the most authoritative and current guidelines for diabetes care.

ADA STANDARDS, STATEMENTS, AND REPORTS

The ADA has been actively involved in the development and dissemination of diabetes care standards, guidelines, and related documents for over 25 years. ADA's clinical practice recommendations are viewed as important resources for health care professionals who care for people with diabetes. ADA's Standards of Care, position statements, and scientific statements undergo a formal review process by ADA's Professional Practice Committee (PPC) and the Board of Directors. Readers who wish to comment on the 2017 Standards of Care are invited to do so at http://professional.diabetes.org/SOC.

Standards of Care

Standards of Care: ADA position statement that provides key clinical practice recommendations. The PPC performs an extensive literature search and updates the Standards of Care annually based on the quality of new evidence.

ADA Position Statement

A position statement is an official ADA point of view or belief that contains clinical or research recommendations. Position statements are issued on scientific or medical issues related to diabetes. They are published in the ADA journals and other scientific/medical publications. ADA position statements are typically based on a systematic review or other review of published literature. Position statements undergo a formal review process. They are updated every 5 years or as needed.

ADA Scientific Statement

A scientific statement is an official ADA point of view or belief that may or may not contain clinical or research recommendations. Scientific statements contain scholarly synopsis of a topic related to diabetes. Workgroup reports fall into this category. Scientific statements are published in the ADA journals and other scientific/medical publications, as appropriate. Scientific statements also undergo a formal review process.

Consensus Report

A consensus report contains a comprehensive examination by an expert panel (i.e., consensus panel) of a scientific or medical issue related to diabetes. A consensus report is not an ADA position and represents expert opinion only. The category may also include task force and expert committee reports. The need for a consensus report arises when clinicians or scientists desire guidance on a subject for which the evidence is contradictory or incomplete. A consensus report is developed following a consensus conference where the controversial issue is extensively discussed. The report represents the panel's collective analysis, evaluation, and opinion at that point in time based in part on the conference proceedings. A consensus report does not undergo a formal ADA review process.

GRADING OF SCIENTIFIC EVIDENCE

Since the ADA first began publishing practice guidelines, there has been considerable evolution in the evaluation of scientific evidence and in the development of evidence-based guidelines. In 2002, the ADA developed a classification system to grade the quality of scientific evidence supporting ADA recommendations for all new and revised ADA position statements. A recent analysis of the evidence cited in the Standards of Care found steady improvement in quality over the past 10 years, with the 2014 Standards of Care for the first time having the majority of bulleted recommendations supported by **A**- or **B**-level evidence (4). A grading system (**Table 1**) developed by the ADA and modeled after existing methods was used to clarify and codify the evidence that forms the basis for the recommendations. ADA recommendations are assigned ratings of **A**, **B**, or **C**, depending on the quality

"Standards of Medical Care in Diabetes" was originally approved in 1988. Most recent review/revision: December 2015.

Table 1—ADA evidence-grading system for "Standards of Medical Care in Diabetes"

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

of evidence. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, in which clinical trials may be impractical, or in which there is conflicting evidence. Recommendations with an **A** rating are based on large well-designed clinical trials or well-done meta-analyses. Generally, these recommendations have the best chance of improving outcomes when applied to the population to which they are appropriate. Recommendations with lower levels of evidence may be equally important but are not as well supported. Of course, evidence is only one component of clinical decision making. Clinicians care for patients, not populations; guidelines must always be interpreted with the individual patient in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and, above all, patients' values and preferences, must be considered and may lead to different treatment targets and strategies. Furthermore, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

References

1. American Diabetes Association. *Medical Management of Type 1 Diabetes*. 6th ed. Kaufman FR, Ed. Alexandria, VA, American Diabetes Association, 2012
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Professional Practice Committee

Diabetes Care 2017;40(Suppl. 1):S3 | DOI: 10.2337/dc17-S002

The Professional Practice Committee (PPC) of the American Diabetes Association (ADA) is responsible for the "Standards of Medical Care in Diabetes" position statement, referred to as the "Standards of Care." The PPC is a multidisciplinary expert committee comprised of physicians, diabetes educators, registered dietitians, and others who have expertise in a range of areas, including adult and pediatric endocrinology, epidemiology, public health, lipid research, hypertension, preconception planning, and pregnancy care. Appointment to the PPC is based on excellence in clinical practice and research. Although the primary role of the PPC is to review and update the Standards of Care, it is also responsible for overseeing the review and revision of ADA's position statements and scientific statements.

The ADA adheres to the Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines. All members of the PPC are required to disclose potential conflicts of interest with industry and/or other relevant organizations. These disclosures are discussed at the onset of each Standards of Care revision meeting. Members of the committee, their employer, and their disclosed conflicts of interest are listed in the "Professional Practice Committee Disclosures" table (see p. S130).

For the current revision, PPC members systematically searched MEDLINE for human studies related to each section and published since 1 January 2016. Recommendations were revised based on new evidence or, in some cases, to clarify the prior recommendation or match the strength of the wording to the strength of the evidence. A table linking the changes in recommendations to new evidence can be reviewed at http://professional.diabetes.org/SOC. As for all position statements, the Standards of Care position statement was approved by the Executive Committee of ADA's Board of Directors, which includes health care professionals, scientists, and lay people.

Feedback from the larger clinical community was valuable for the 2017 revision of the Standards of Care. Readers who wish to comment on the 2017 Standards of Care are invited to do so at http://professional.diabetes.org/SOC.

The ADA funds development of the Standards of Care and all ADA position statements out of its general revenues and does not use industry support for these purposes. The PPC would like to thank the following individuals who provided their expertise in reviewing and/or consulting with the committee: *Conor J. Best, MD; William T. Cefalu, MD; Mary de Groot, PhD; Gary D. Hack, DDS; Silvio E. Inzucchi, MD; Meghan Jardine, MS, MBA, RD, LD, CDE; Victor R. Lavis, MD; Mark E. Molitch, MD; Antoinette Moran, MD; Matt Petersen; Sean Petrie; Louis H. Philipson, MD, PhD; Margaret A. Powers, PhD, RD, CDE; Desmond Schatz, MD; Philip R. Schauer, MD; Sonali N. Thosani, MD; and Guillermo E. Umpierrez, MD.*

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Standards of Medical Care in Diabetes—2017: Summary of Revisions

Diabetes Care 2017;40(Suppl. 1):S4–S5 | DOI: 10.2337/dc17-S003

GENERAL CHANGES

In light of the American Diabetes Association's (ADA's) new position statement on psychosocial care in the treatment of diabetes, the "Standards of Medical Care in Diabetes," referred to as the "Standards of Care," has been updated to address psychosocial issues in all aspects of care including self-management, mental health, communication, complications, comorbidities, and life-stage considerations.

*Although levels of evidence for several recommendations have been updated, these changes are not addressed below as the clinical recommendations have remained the same. Changes in evidence level from, for example, **E** to **C** are not noted below. The 2017 Standards of Care contains, in addition to many minor changes that clarify recommendations or reflect new evidence, the following more substantive revisions.*

SECTION CHANGES

Section 1. Promoting Health and Reducing Disparities in Populations

This section was renamed and now focuses on improving outcomes and reducing disparities in populations with diabetes.

Recommendations were added to assess patients' social context as well as refer to local community resources and provide self-management support.

Section 2. Classification and Diagnosis of Diabetes

The section was updated to include a new consensus on the staging of type 1 diabetes (**Table 2.1**) and a discussion of a proposed unifying diabetes classification scheme that focuses on β-cell dysfunction and disease stage as indicated by glucose status.

Language was added to clarify screening and testing for diabetes. Screening approaches were described, and **Fig. 2.1** was included to provide an example of a validated tool to screen for prediabetes and previously undiagnosed type 2 diabetes.

Due to recent data, delivering a baby weighing 9 lb or more is no longer listed as an independent risk factor for the development of prediabetes and type 2 diabetes.

A section was added that discusses recent evidence on screening for diabetes in dental practices.

The recommendation to test women with gestational diabetes mellitus for persistent diabetes was changed from 6–12 weeks' postpartum to 4–12 weeks' postpartum to allow the test to be scheduled just before the standard 6-week postpartum obstetrical checkup so that the results can be discussed with the patient at that time of the visit or to allow the test to be rescheduled at the visit if the patient did not get the test.

Additional detail was added to the section on monogenic diabetes syndromes, and a new table was added (**Table 2.7**) describing the most common forms of monogenic diabetes.

A new section was added on post-transplantation diabetes mellitus.

Section 3. Comprehensive Medical Evaluation and Assessment of Comorbidities

This new section, including components of the 2016 section "Foundations of Care and Comprehensive Medical Evaluation," highlights the importance of assessing comorbidities in the context of a patient-centered comprehensive medical evaluation.

A new discussion of the goals of provider-patient communication is included.

The Standards of Care now recommends the assessment of sleep pattern and duration as part of the comprehensive medical evaluation based on emerging evidence suggesting a relationship between sleep quality and glycemic control.

An expanded list of diabetes comorbidities now includes autoimmune diseases, HIV, anxiety disorders, depression, disordered eating behavior, and serious mental illness.

Section 4. Lifestyle Management

This section, previously entitled "Foundations of Care and Comprehensive Medical Evaluation," was refocused on lifestyle management.

The recommendation for nutrition therapy in people prescribed flexible insulin therapy was updated to include fat and protein counting in addition to carbohydrate counting for some patients to reflect evidence that these dietary factors influence insulin dosing and blood glucose levels.

Based on new evidence of glycemic benefits, the Standards of Care now recommends that prolonged sitting be interrupted every 30 min with short bouts of physical activity.

A recommendation was added to highlight the importance of balance and flexibility training in older adults.

A new section and table provide information on situations that might warrant referral to a mental health provider.

Section 5. Prevention or Delay of Type 2 Diabetes

To help providers identify those patients who would benefit from prevention efforts, new text was added emphasizing the importance of screening for prediabetes using an assessment tool or informal assessment of risk factors and performing a diagnostic test when appropriate.

To reflect new evidence showing an association between B12 deficiency and long-term metformin use, a recommendation was added to consider periodic measurement of B12 levels and supplementation as needed.

Section 6. Glycemic Targets

Based on recommendations from the International Hypoglycaemia Study Group, serious, clinically significant hypoglycemia is now defined as glucose <54 mg/dL (3.0 mmol/L), while the glucose alert value is defined as ≤70 mg/dL (3.9 mmol/L) (**Table 6.3**). Clinical implications are discussed.

Section 7. Obesity Management for the Treatment of Type 2 Diabetes

To be consistent with other ADA position statements and to reinforce the role of surgery in the treatment of type 2 diabetes, bariatric surgery is now referred to as metabolic surgery.

To reflect the results of an international workgroup report endorsed by the ADA and many other organizations, recommendations regarding metabolic surgery have been substantially changed, including those related to BMI thresholds for surgical candidacy (**Table 7.1**), mental health assessment, and appropriate surgical venues.

Section 8. Pharmacologic Approaches to Glycemic Treatment

The title of this section was changed from "Approaches to Glycemic Treatment" to "Pharmacologic Approaches to Glycemic Treatment" to reinforce that the section focuses on pharmacologic therapy alone. Lifestyle management and obesity management are discussed in separate chapters.

To reflect new evidence showing an association between B12 deficiency and long-term metformin use, a recommendation was added to consider periodic measurement of B12 levels and supplementation as needed.

A section was added describing the role of newly available biosimilar insulins in diabetes care.

Based on the results of two large clinical trials, a recommendation was added to consider empagliflozin or liraglutide in patients with established cardiovascular disease to reduce the risk of mortality.

Figure 8.1, antihyperglycemic therapy in type 2 diabetes, was updated to acknowledge the high cost of insulin.

The algorithm for the use of combination injectable therapy in patients with type 2 diabetes (**Fig. 8.2**) has been changed to reflect studies demonstrating the noninferiority of basal insulin plus glucagon-like peptide 1 receptor agonist versus basal insulin plus rapid-acting insulin versus two daily injections of premixed insulin, as well as studies demonstrating the noninferiority of multiple dose premixed insulin regimens versus basal-bolus therapy.

Due to concerns about the affordability of antihyperglycemic agents, new tables were added showing the median costs of noninsulin agents (**Table 8.2**) and insulins (**Table 8.3**).

Section 9. Cardiovascular Disease and Risk Management

To better align with existing data, the hypertension treatment recommendation for diabetes now suggests that, for patients without albuminuria, any of the four classes of blood pressure medications (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers) that have shown beneficial cardiovascular outcomes may be used.

To optimize maternal health without risking fetal harm, the recommendation for the treatment of pregnant patients with diabetes and chronic hypertension was changed to suggest a blood pressure target of 120–160/80–105 mmHg.

A section was added describing the cardiovascular outcome trials that demonstrated benefits of empagliflozin and liraglutide in certain high-risk patients with diabetes.

Section 10. Microvascular Complications and Foot Care

A recommendation was added to highlight the importance of provider communication regarding the increased risk of retinopathy in women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant.

The section now includes specific recommendations for the treatment of neuropathic pain.

A new recommendation highlights the benefits of specialized therapeutic footwear for patients at high risk for foot problems.

Section 12. Children and Adolescents

Additional recommendations highlight the importance of assessment and referral for psychosocial issues in youth.

Due to the risk of malformations associated with unplanned pregnancies and poor metabolic control, a new recommendation was added encouraging preconception counseling starting at puberty for all girls of childbearing potential.

To address diagnostic challenges associated with the current obesity epidemic, a discussion was added about distinguishing between type 1 and type 2 diabetes in youth.

A section was added describing recent nonrandomized studies of metabolic surgery for the treatment of obese adolescents with type 2 diabetes.

Section 13. Management of Diabetes in Pregnancy

Insulin was emphasized as the treatment of choice in pregnancy based on concerns about the concentration of metformin on the fetal side of the placenta and glyburide levels in cord blood.

Based on available data, preprandial self-monitoring of blood glucose was deemphasized in the management of diabetes in pregnancy.

In the interest of simplicity, fasting and postprandial targets for pregnant women with gestational diabetes mellitus and preexisting diabetes were unified.

Section 14. Diabetes Care in the Hospital

This section was reorganized for clarity.

A treatment recommendation was updated to clarify that either basal insulin or basal plus bolus correctional insulin may be used in the treatment of noncritically ill patients with diabetes in a hospital setting, but not sliding scale alone.

The recommendations for insulin dosing for enteral/parenteral feedings were expanded to provide greater detail on insulin type, timing, dosage, correctional, and nutritional considerations.

1. Promoting Health and Reducing Disparities in Populations

American Diabetes Association

Diabetes Care 2017;40(Suppl. 1):S6–S10 | DOI: 10.2337/dc17-S004

Recommendations

- Treatment decisions should be timely, rely on evidence-based guidelines, and be made collaboratively with patients based on individual preferences, prognoses, and comorbidities. **B**
- Providers should consider the burden of treatment and self-efficacy of patients when recommending treatments. **E**
- Treatment plans should align with the Chronic Care Model, emphasizing productive interactions between a prepared proactive practice team and an informed activated patient. **A**
- When feasible, care systems should support team-based care, community involvement, patient registries, and decision support tools to meet patient needs. **B**

DIABETES AND POPULATION HEALTH

Clinical practice guidelines are key to improving population health; however, for optimal outcomes, diabetes care must be individualized for each patient. Thus, efforts to improve population health will require a combination of system-level and patient-level approaches. With such an integrated approach in mind, the American Diabetes Association (ADA) highlights the importance of *patient-centered care*, defined as care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions (1). Practice recommendations, whether based on evidence or expert opinion, are intended to guide an overall approach to care. The science and art of medicine come together when the clinician is faced with making treatment recommendations for a patient who may not meet the eligibility criteria used in the studies on which guidelines are based. Recognizing that one size does not fit all, the standards presented here provide guidance for when and how to adapt recommendations for an individual.

Care Delivery Systems

Over the last 10 years, there has been steady improvement in the proportion of patients with diabetes who are treated with statins and who achieve recommended hemoglobin A1C (A1C), blood pressure, and LDL cholesterol levels (2). The mean A1C nationally among people with diabetes has declined from 7.6% (60 mmol/mol) in 1999–2002 to 7.2% (55 mmol/mol) in 2007–2010 based on the National Health and Nutrition Examination Survey (NHANES), with younger adults less likely to meet treatment targets than older adults (2). This has been accompanied by improvements in cardiovascular outcomes and has led to substantial reductions in end-stage microvascular complications.

Nevertheless, 33–49% of patients still do not meet targets for glycemic, blood pressure, or cholesterol control, and only 14% meet targets for all three measures while also avoiding smoking (2). Evidence suggests that progress in cardiovascular risk factor control (particularly tobacco use) may be slowing (2,3). Certain segments of the population, such as young adults and patients with complex comorbidities, financial or other social hardships, and/or limited English proficiency, face particular challenges to goal-based care (4–6). Even after adjusting for these patient factors, the persistent variability in the quality of diabetes care across providers and practice settings indicates that substantial system-level improvements are still needed.

Chronic Care Model

Numerous interventions to improve adherence to the recommended standards have been implemented. However, a major barrier to optimal care is a delivery

Suggested citation: American Diabetes Association. Promoting health and reducing disparities in populations. Sec. 1. In Standards of Medical Care in Diabetes—2017. *Diabetes Care 2017; 40(Suppl. 1):S6–S10*

system that is often fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care. The Chronic Care Model (CCM) takes these factors into consideration, and is an effective framework for improving the quality of diabetes care (7).

Six Core Elements. The CCM includes six core elements to optimize the care of patients with chronic disease:

1. Delivery system design (moving from a *reactive* to a *proactive* care delivery system where planned visits are coordinated through a team-based approach)
2. Self-management support
3. Decision support (basing care on evidence-based, effective care guidelines)
4. Clinical information systems (using registries that can provide patient-specific and population-based support to the care team)
5. Community resources and policies (identifying or developing resources to support healthy lifestyles)
6. Health systems (to create a quality-oriented culture)

Redefining the roles of the health care delivery team and empowering patient self-management are fundamental to the successful implementation of the CCM (8). Collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management (9–11).

Strategies for System-Level Improvement

Optimal diabetes management requires an organized, systematic approach and the involvement of a coordinated team of dedicated health care professionals working in an environment where patient-centered high-quality care is a priority (6). The National Diabetes Education Program (NDEP) maintains an online resource (www.betterdiabetescare.nih.gov) to help health care professionals to design and implement more effective health care delivery systems for those with diabetes. Three specific objectives, with references to literature outlining practical strategies to achieve each, are as follows.

Objective 1: Optimize Provider and Team Behavior. The care team, which includes the patient, should prioritize timely and appropriate intensification of lifestyle and/or pharmacological therapy for patients who have not achieved the recommended metabolic targets (12–14). To inform this process, providers should routinely assess medication adherence. At a system level, "adequate" adherence is defined as 80% (calculated as the number of pills taken by the patient in a given time period divided by the number of pills prescribed by the physician in that same time period) (15). If adherence is 80% or above, then treatment intensification should be considered (e.g., up-titration). Additional strategies shown to improve care team behavior and thereby catalyze reductions in A1C, blood pressure, and/or LDL cholesterol include explicit and collaborative goal setting with patients (16,17); identifying and addressing language, numeracy, or cultural barriers to care (18–20); integrating evidence-based guidelines and clinical information tools into the process of care (21–23); soliciting performance feedback, setting reminders, and providing structured care (e.g., guidelines, formal case management, and patient education resources) (6); and incorporating care management teams including nurses, dietitians, pharmacists, and other providers (24,25).

Objective 2: Support Patient Self-management. Successful diabetes care requires a systematic approach to supporting patients' behavior change efforts, including the following:

1. Healthy lifestyle choices (healthy eating, physical activity, tobacco cessation, weight management, and effective strategies for coping with stress)
2. Disease self-management (taking and managing medications and, when clinically appropriate, self-monitoring of glucose and blood pressure)
3. Prevention of diabetes complications (self-monitoring of foot health; active participation in screening for eye, foot, and renal complications; and immunizations)
4. Identification of self-management problems and development of strategies to solve those problems, including self-selected behavioral goal setting

High-quality diabetes self-management education (DSME) has been shown to improve patient self-management, satisfaction, and glucose outcomes. National DSME standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem solving), and engagement with psychosocial concerns (26).

In devising approaches to support disease self-management, it is notable that in 23% of cases, uncontrolled A1C, blood pressure, or lipids were associated with poor medication adherence (15). Barriers to adherence may include patient factors (remembering to obtain or take medications, fear, depression, or health beliefs), medication factors (complexity, multiple daily dosing, cost, or side effects), and system factors (inadequate follow-up or support). A patient-centered, nonjudgmental communication style can help providers to identify barriers to adherence as well as motivation for self-care (17). Nurse-directed interventions, home aides, diabetes education, and pharmacy-derived interventions improved adherence but had a very small effect on outcomes, including metabolic control (27). Success in overcoming barriers to adherence may be achieved if the patient and provider agree on a targeted approach for a specific barrier (10). For example, simplifying a complex treatment regimen may improve adherence in those who identify complexity as a barrier.

Objective 3: Change the Care System. A characteristic of most successful care systems is making high-quality care an institutional priority (28). Changes that increase the quality of diabetes care include providing care on evidence-based guidelines (21); expanding the role of teams to implement more intensive disease management strategies (6,24,29); tracking medication adherence at a system level (15); redesigning the care process (30); implementing electronic health record tools (31,32); empowering and educating patients (33,34); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, self-monitoring of blood glucose, and necessary medications (6); assessing and addressing psychosocial issues (26,35); and identifying/developing/engaging community resources and public policy that support healthy lifestyles (36).

Initiatives such as the Patient-Centered Medical Home show promise for improving outcomes by coordinating primary care and offering new opportunities for team-based chronic disease management (37). Additional strategies to improve diabetes care include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care to achieve metabolic goals (38), and incentives that accommodate personalized care goals (6,39).

TAILORING TREATMENT TO REDUCE DISPARITIES

Recommendations

- Providers should assess social context, including potential food insecurity, housing stability, and financial barriers, and apply that information to treatment decisions. A
- Patients should be referred to local community resources when available. B
- Patients should be provided with self-management support from lay health coaches, navigators, or community health workers when available. A

The causes of health disparities are complex and include societal issues such as institutional racism, discrimination, socioeconomic status, poor access to health care, education, and lack of health insurance. Social determinants of health can be defined as the economic, environmental, political, and social conditions in which people live, and are responsible for a major part of health inequality worldwide (40). Given the tremendous burden that obesity, unhealthy eating, physical inactivity, and smoking place on the health of patients with diabetes, efforts are needed to address and change the societal determinants of these problems (41).

The ADA recognizes the association between social and environmental factors and the development of obesity and type 2 diabetes and has issued a call for research that seeks to better understand how these social determinants influence behaviors and how the relationships between these variables might be modified for the prevention and management of diabetes (42).

Ethnic/Cultural/Sex Differences

Ethnic, cultural, and sex differences may affect diabetes prevalence and outcomes. Despite advances over the last several decades in medical knowledge around diabetes management, racial and ethnic minorities remain at higher risk for microvascular complications than nonminorities. Type 2 diabetes develops more frequently in women with prior gestational diabetes mellitus (43) and in certain racial/ethnic groups (African American, Native American, Hispanic/Latino, and Asian American) (44). Women with diabetes are also at greater risk of coronary heart disease than men with diabetes (45).

Access to Health Care

Socioeconomic and ethnic inequalities exist in the provision of health care to individuals with diabetes (46). For example, children with type 1 diabetes from racial/ethnic minority populations with lower socioeconomic status are at risk for poor metabolic control and poor emotional functioning (47). Significant racial differences and barriers exist in self-monitoring and outcomes (48).

Lack of Health Insurance

Not having health insurance affects the processes and outcomes of diabetes care. Individuals without insurance coverage for blood glucose monitoring supplies have a 0.5% higher A1C than those with coverage (49). In a recent study of predominantly African American or Hispanic uninsured patients with diabetes, 50–60% had hypertension, but only 22–37% had systolic blood pressure controlled by treatments to under 130 mmHg (50). The Affordable Care Act has improved access to health care; however, many remain without coverage (www.cdc.gov/nchs/fastats/health-insurance.htm).

System-Level Interventions

Eliminating disparities will require individualized, patient-centered, and culturally appropriate strategies as well as system-level interventions. Structured interventions that are developed for diverse populations and that integrate culture, language, finance, religion, and literacy and numeracy skills positively influence patient outcomes (51). All providers and health care systems are encouraged to use the National Quality Forum's National Voluntary Consensus Standards for Ambulatory Care—Measuring Healthcare Disparities (52).

Community Support

Identification or development of resources to support healthy lifestyles is a core element of the CCM (7). Health care community linkages are receiving increasing attention from the American Medical Association, the Agency for Healthcare Research and Quality, and others as a means of promoting translation of clinical recommendations for lifestyle modification in real-world settings (53). To overcome disparities, community health workers (54), peers (55,56), and lay leaders (57) may assist in the delivery of DSME and diabetes self-management support services (58), particularly in underserved communities. Strong social support leads to improved clinical outcomes, a reduction in psychosocial issues, and adoption of healthier lifestyles (59).

Food Insecurity

Food insecurity (FI) is the unreliable availability of nutritious food and the inability to consistently obtain food without resorting to socially unacceptable practices. Over 14% (or one of every seven people in the U.S.) are food insecure. The rate is higher in some racial/ethnic minority groups including African American and Latino populations, in low-income households, and in homes headed by a single mother. FI may involve a tradeoff between purchasing more expensive nutritious food and less expensive energy- and carbohydrate-dense processed foods, which may contribute to obesity.

The risk for type 2 diabetes is increased twofold in those with FI (42). Therefore, in people with FI, interventions should focus on preventing diabetes. In those with diabetes and FI, the priority is mitigating the increased risk for uncontrolled hyperglycemia and severe hypoglycemia. Reasons for the increased risk of hyperglycemia include the steady consumption of inexpensive carbohydrate-rich processed foods, binge eating, financial constraints to the filling of diabetes medication prescriptions, and anxiety/depression leading to poor diabetes self-care behaviors. Hypoglycemia can occur as a result of inadequate or erratic carbohydrate consumption following administration of sulfonylureas or insulin. Providers should recognize that FI complicates diabetes management and seek local resources that can help patients and the parents of patients with diabetes to more regularly obtain nutritious food (60).

Treatment Options

If using a sulfonylurea in patients with FI, glipizide may be considered due to its relatively short half-life. It can be taken immediately before meals, thus obviating the need to plan meals to an extent that may be unreachable for those with FI.

For those needing insulin, short-acting insulin analogs, preferably delivered by a pen, may be used immediately after meal consumption, whenever food becomes available. While such insulin analogs may be costly, many pharmaceutical companies provide access to free medications through patient assistance programs. If short-acting insulin analogs are not options for those with FI who need insulin therapy, a relatively low dose of an ultra-long-acting insulin analog may be prescribed simply to prevent marked hyperglycemia, while recognizing that tight control may not be possible in such cases.

Language Barriers

Diabetes is more common among non-English speaking individuals in the U.S., as is FI. Therefore, it is important to consider screening for diabetes and FI in this population. Providers that care for non-English speakers should develop or offer educational programs and materials in multiple languages with the specific goal of preventing diabetes and building diabetes awareness in people who cannot easily read or write in English.

Homelessness

Homelessness often accompanies many barriers to diabetes self-management, including FI, literacy and numeracy deficiencies, lack of insurance, cognitive dysfunction, and mental health issues. Therefore, providers who care for homeless individuals should be well versed or have access to social workers to facilitate temporary housing for their patients as a means to prevent and control diabetes. Additionally, patients with diabetes who are homeless need secure places to keep their diabetes supplies and refrigerator access to properly store their insulin and have access to take it on a regular schedule.

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2. Classification and Diagnosis of Diabetes

American Diabetes Association

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CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (1).

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both cohorts. Occasionally, patients with type 2 diabetes may present with diabetic ketoacidosis (DKA), particularly ethnic minorities (2). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with DKA (3). The onset of type 1 diabetes may be more variable in adults, and they may not present with the classic symptoms seen in children. Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the true diagnosis becomes more obvious over time.

In October 2015, the ADA, JDRF, the European Association for the Study of Diabetes, and the American Association of Clinical Endocrinologists convened the Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis Research Symposium (4). The goals of the symposium were to discuss the genetic and environmental determinants of type 1 and type 2 diabetes risk and progression, to determine appropriate therapeutic approaches based on disease pathophysiology and stage, and to define research gaps hindering a personalized approach to treatment. The experts agreed that in both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, patients with all forms of diabetes are at risk for developing the same complications, although rates of progression may differ. They concluded that the identification of individualized therapies for diabetes in the future will require better characterization of the many paths to β-cell demise or dysfunction.

Characterization of the underlying pathophysiology is much more developed in type 1 diabetes than in type 2 diabetes. It is now clear from studies of first-degree relatives of patients with type 1 diabetes that the persistent presence of two or

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more autoantibodies is an almost certain predictor of clinical hyperglycemia and diabetes. The rate of progression is dependent on the age at first detection of antibody, number of antibodies, antibody specificity, and antibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (**Table 2.1**) and serve as a framework for future research and regulatory decision making (4,5).

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion frequently in the setting of insulin resistance appears to be the common denominator. Characterization of subtypes of this heterogeneous disorder have been developed and validated in Scandinavian and Northern European populations, but have not been confirmed in other ethnic and racial groups. Type 2 diabetes is primarily associated with insulin secretory defects related to inflammation and metabolic stress among other contributors including genetic factors. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction and the stage of disease as indicated by glucose status (normal, impaired, or diabetes) (4).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) or A1C criteria (1,6) (**Table 2.2**).

FPG, 2-h PG after 75-g OGTT, and A1C are equally appropriate for diagnostic testing. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes (7,8) has primarily been demonstrated among individuals with impaired glucose tolerance (IGT), not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria.

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes. Diabetes may be identified anywhere along the spectrum of clinical scenarios: in seemingly low-risk individuals who happen to have glucose testing, in individuals tested based on diabetes risk assessment, and in symptomatic patients.

Fasting and 2-Hour Plasma Glucose

The FPG and 2-h PG may be used to diagnose diabetes (**Table 2.2**). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Numerous studies have confirmed that, compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with diabetes.

A1C

The A1C test should be performed using a method that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of point-of-care assays for diagnostic purposes is not recommended but may be considered in the future if proficiency testing is performed and documented.

The A1C has several advantages compared with the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of ≥6.5% (48 mmol/mol) identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥126 mg/dL (7.0 mmol/L) (9).

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia including age, race/ethnicity, and anemia/hemoglobinopathies.

Age

The epidemiological studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations. Therefore, it remains unclear if A1C and the same A1C cut point should be used to diagnose diabetes in children and adolescents (9,10).

Race/Ethnicity

A1C levels may vary with race/ethnicity independently of glycemia (11,12). For example, African Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and post-glucose load glucose levels (13). Though there is some conflicting data, African Americans may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (14,15). The association of A1C with risk for complications appears to be similar in African Americans and non-Hispanic whites (16).

Table 2.1—Staging of type 1 diabetes (4,5)

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Hemoglobinopathies/Red Blood Cell Turnover

Interpreting A1C levels in the presence of certain hemoglobinopathies may be problematic. For patients with an abnormal hemoglobin but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used. An updated list of interferences is available at www.ngsp.org/interf.asp.

In conditions associated with increased red blood cell turnover, such as pregnancy (second and third trimesters), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only blood glucose criteria should be used to diagnose diabetes.

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL [11.1 mmol/L]), a second test is required for confirmation. It is recommended that the same test be repeated without delay using a new blood sample for confirmation because there will be a greater likelihood of concurrence. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the A1C (two results ≥6.5% [48 mmol/mol]) but not FPG (<126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Since all the tests have preanalytic and analytic variability, it is possible that an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients have test results near the margins of the diagnostic threshold, the health care professional should follow the patient closely and repeat the test in 3–6 months.

CATEGORIES OF INCREASED RISK FOR DIABETES (PREDIABETES)

Recommendations

- Screening for prediabetes and risk for future diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**
- Testing for prediabetes and risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes. **B**
- For all people, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for prediabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. **B**
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. **B**
- Testing for prediabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

Description

In 1997 and 2003, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (17,18) recognized a group of individuals whose glucose levels did not meet the criteria for diabetes but were too high to be considered normal. "Prediabetes" is the term used for individuals with IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol). Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes (**Table 2.3**) and cardiovascular disease (CVD). Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (17,18) defined IFG as FPG levels between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels between 140 and 199 mg/dL (between 7.8 and 11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5 and 6.0% (between 37 and 42 mmol/mol)

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors: • A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing • first-degree relative with diabetes • high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) • women who were diagnosed with GDM • history of CVD • hypertension (≥140/90 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) • women with polycystic ovary syndrome • physical inactivity • other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
2. For all patients, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

had a substantially increased risk of diabetes (5-year incidence from 9 to 25%). An A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25 and 50% and a relative risk 20 times higher compared with A1C of 5.0% (31 mmol/mol) (19). In a community-based study of African American and non-Hispanic white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (20). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (21), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (22).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 5 "Prevention or Delay of Type 2 Diabetes"). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (19). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [42 mmol/mol]).

Table 2.4 summarizes the categories of prediabetes and **Table 2.3** the criteria for prediabetes testing. The ADA diabetes risk test is an additional option for screening (**Fig. 2.1**). For recommendations regarding risk factors and screening for prediabetes, see pp. S17–S18 ("Screening and Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults" and "Screening and Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents").

TYPE 1 DIABETES

Recommendations

- Blood glucose rather than A1C should be used to diagnose the acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia. **E**
- Screening for type 1 diabetes with a panel of autoantibodies is currently recommended only in the setting of a research trial or in first-degree family members of a proband with type 1 diabetes. **B**
- Persistence of two or more autoantibodies predicts clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial. Outcomes may include reversion of autoantibody status, prevention of glycemic progression within the normal or prediabetes range, prevention of clinical diabetes, or preservation of residual C-peptide secretion. **A**

Diagnosis

In a patient with classic symptoms, measurement of blood glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥200 mg/dL [11.1 mmol/L]). In these cases, knowing the blood glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some providers may also want to know the A1C to determine how long a patient has had hyperglycemia.

Immune-Mediated Diabetes

This form, previously called "insulin-dependent diabetes" or "juvenile-onset diabetes," accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (GAD65), insulin, the tyrosine phosphatases IA-2 and IA-2β, and ZnT8. Type 1 diabetes is defined by the presence of one or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the *DQA* and *DQB* genes. These HLA-DR/DQ alleles can be either predisposing or protective.

The rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia

Table 2.4—Categories of increased risk for diabetes (prediabetes)*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7−6.4% (39−47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

ARE YOU AT RISK FOR

TYPE 2 DIABETES?

American Diabetes Association.

Diabetes Risk Test

Write your score in the box.

1. **How old are you?**
   - Less than 40 years (0 points)
   - 40—49 years (1 point)
   - 50—59 years (2 points)
   - 60 years or older (3 points)
2. **Are you a man or a woman?**
   Man (1 point) Woman (0 points)
3. **If you are a woman, have you ever been diagnosed with gestational diabetes?**
   Yes (1 point) No (0 points)
4. **Do you have a mother, father, sister, or brother with diabetes?**
   Yes (1 point) No (0 points)
5. **Have you ever been diagnosed with high blood pressure?**
   Yes (1 point) No (0 points)
6. **Are you physically active?**
   Yes (0 points) No (1 point)
7. **What is your weight status?** *(see chart at right)*

Height	Weight (lbs.)		
4′ 10″	119-142	143-190	191+
4′ 11″	124-147	148-197	198+
5′ 0″	128-152	153-203	204+
5′ 1″	132-157	158-210	211+
5′ 2″	136-163	164-217	218+
5′ 3″	141-168	169-224	225+
5′ 4″	145-173	174-231	232+
5′ 5″	150-179	180-239	240+
5′ 6″	155-185	186-246	247+
5′ 7″	159-190	191-254	255+
5′ 8″	164-196	197-261	262+
5′ 9″	169-202	203-269	270+
5′ 10″	174-208	209-277	278+
5′ 11″	179-214	215-285	286+
6′ 0″	184-220	221-293	294+
6′ 1″	189-226	227-301	302+
6′ 2″	194-232	233-310	311+
6′ 3″	200-239	240-318	319+
6′ 4″	205-245	246-327	328+
	(1 Point)	(2 Points)	(3 Points)

You weigh less than the amount in the left column (0 points)

Adapted from Bang et al., Ann Intern Med 151:775-783, 2009.
Original algorithm was validated without gestational diabetes as part of the model.

Add up your score.

If you scored 5 or higher:
You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes (a condition that precedes type 2 diabetes in which blood glucose levels are higher than normal). Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, American Indians, and Asian Americans and Pacific Islanders.

Higher body weights increase diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weights than the rest of the general public (about 15 pounds lower).

For more information, visit us at diabetes.org or call 1-800-DIABETES (1-800-342-2383)

Lower Your Risk

The good news is that you can manage your risk for type 2 diabetes. Small steps make a big difference and can help you live a longer, healthier life.

If you are at high risk, your first step is to see your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (1-800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Visit us on Facebook
Facebook.com/AmericanDiabetesAssociation

Figure 2.1—ADA risk test.

that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient β-cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity should not preclude the diagnosis. Patients with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, Addison disease, celiac disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 3 "Comprehensive Medical Evaluation and Assessment of Comorbidities").

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of β-cell autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may be intermittent.

Testing for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes is increasing (23). Patients with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and approximately one-third are diagnosed with life-threatening ketoacidosis (3). Several studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes (5). Such testing, coupled with education about diabetes symptoms and close follow-up, may enable earlier identification of type 1 diabetes onset. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (24). These findings are highly significant because, while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (25–27).

Although there is currently a lack of accepted screening programs, one should consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study (http://www.diabetestrialnet.org). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. Individuals who test positive will be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of autoimmunity (www.clinicaltrials.gov).

TYPE 2 DIABETES

Recommendations

- Screening for type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. B
- Testing for type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI $\geq$25 kg/m^2 or $\geq$23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes. B
- For all people, testing should begin at age 45 years. B
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. C
- To test for type 2 diabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. B
- In patients with diabetes, identify and treat other cardiovascular disease risk factors. B
- Testing for type 2 diabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. E

Description

Type 2 diabetes, previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, patients with type 2 diabetes are overweight or obese. Excess weight itself causes some degree of insulin resistance. Patients who are not obese or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

Ketoacidosis seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection. Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms. Nevertheless, even undiagnosed patients are at increased risk of developing macrovascular and microvascular complications.

Whereas patients with type 2 diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these patients would be expected to result in even higher insulin values had their β-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal.

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM, in those with hypertension or dyslipidemia, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition, more so than type 1 diabetes. However, the genetics of type 2 diabetes is poorly understood. In adults without traditional risk factors for type 2 diabetes and/or younger age, consider antibody testing for type 1 diabetes (i.e., GAD).

Screening and Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the ADA risk test (**Fig. 2.1**), is recommended to guide providers on whether performing a diagnostic test (**Table 2.2**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available. The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes (see Section 5 "Prevention or Delay of Type 2 Diabetes") and reduce the risk of diabetes complications (see Section 9 "Cardiovascular Disease and Risk Management" and Section 10 "Microvascular Complications and Foot Care").

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed (28). Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur.

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (29). General practice patients between the ages of 40 and 69 years were screened for diabetes and randomly assigned by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (29). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes (30); moreover, screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (<$11,000 per quality-adjusted life-year gained) (31).

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic patients include the following.

Age

Screening recommendations for diabetes in asymptomatic adults are listed in **Table 2.3**. Age is a major risk factor for diabetes. Testing should begin at age 45 years for all patients. Screening should be considered in overweight or obese adults of any age with one or more risk factors for diabetes.

BMI and Ethnicity

In general, BMI $\geq$25 kg/m^2 is a risk factor for diabetes. Data and recommendations from the ADA position statement "BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening" (32,33) suggest that the BMI cut point should be lower for the Asian American population. The BMI cut points fall consistently between 23 and 24 kg/m^2 (sensitivity of 80%) for nearly all Asian American subgroups (with levels slightly lower for Japanese Americans). This makes a rounded cut point of 23 kg/m^2 practical. In determining a single BMI cut point, it is important to balance sensitivity and specificity so as to provide a valuable screening tool without numerous false positives. An argument can be made to push the BMI cut point to lower than 23 kg/m^2 in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from the WHO also suggest that a BMI of $\geq$23 kg/m^2 should be used to define increased risk in Asian Americans (34). The finding that half of diabetes in Asian Americans is undiagnosed suggests that testing is not occurring at lower BMI thresholds (28).

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m^2 in non-Hispanic whites was equivalent to a BMI of 26 kg/m^2 in African Americans (35).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (36), are known to increase the risk of diabetes and should be considered when deciding whether to screen.

Testing Interval

The appropriate interval between screening tests is not known (37). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced and individuals with false-negative tests will be retested before substantial time elapses and complications develop (37).

Community Screening

Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. Community screening outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Community testing may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (38).

Screening in Dental Practices

Because periodontal disease is associated with diabetes, the utility of chairside screening and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (39–41), with one study estimating that 30% of patients $\geq$30 years of age seen in general dental practices had dysglycemia (41). Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in racial and ethnic minority populations (23). Recent studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (42). However, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (43). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this cohort (44,45). The modified recommendations of the ADA consensus report "Type 2 Diabetes in Children and Adolescents" are summarized in **Table 2.5** (46).

Table 2.5—Testing for type 2 diabetes or prediabetes in asymptomatic children* (46)

Criteria • Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors: • Family history of type 2 diabetes in first- or second-degree relative • Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) • Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) • Maternal history of diabetes or GDM during the child's gestation
Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency: every 3 years

*Persons aged ≤18 years.

GESTATIONAL DIABETES MELLITUS

Recommendations

- Test for undiagnosed diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. **B**
- Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously known to have diabetes. **A**
- Test women with gestational diabetes mellitus for persistent diabetes at 4–12 weeks' postpartum, using the oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **E**
- Women with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**
- Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions or metformin to prevent diabetes. **A**

Definition

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy (17), regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but it was limited by imprecision.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, with an increase in the number of pregnant women with undiagnosed type 2 diabetes (47). Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes (**Table 2.3**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.2**). Women diagnosed with diabetes in the first trimester should be classified as having preexisting pregestational diabetes (type 2 diabetes or, very rarely, type 1 diabetes). GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes (see Section 13 "Management of Diabetes in Pregnancy"). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT were not derived from data in the first half of pregnancy, so the diagnosis of GDM in early pregnancy by either FPG or OGTT values is not evidence based (48).

Diagnosis

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (49), a large-scale multinational cohort study completed by more than 23,000 pregnant women, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. GDM diagnosis (**Table 2.6**) can be accomplished with either of two strategies:

1. "One-step" 75-g OGTT or
2. "Two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading some experts to debate, and disagree on, optimal strategies for the diagnosis of GDM.

One-Step Strategy

In the 2011 Standards of Care (50), the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g

Table 2.6—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24−28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥130 mg/dL, 135 mg/dL, or 140 mg/dL* (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (59)	or	NDDG (60)
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *The ACOG recommends either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L). A systematic review determined that a cutoff of 130 mg/dL (7.2 mmol/L) was more sensitive but less specific than 140 mg/dL (7.8 mmol/L) (55).

OGTT at 24–28 weeks of gestation, based on a recommendation of the IADPSG (51). The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h plasma glucose values in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis. The ADA recognized that the anticipated increase in the incidence of GDM would have a substantial impact on costs and medical infrastructure needs and had the potential to "medicalize" pregnancies previously categorized as normal. Nevertheless, the ADA recommended these changes in diagnostic criteria with the intent of optimizing gestational outcomes because these criteria were the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits to the offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria. Those trials found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (52,53). It is important to note that 80–90% of women being treated for mild GDM in two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped with the thresholds recommended by the IADPSG, and in one trial (53), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]). No randomized controlled trials of identifying and treating GDM using the IADPSG criteria versus older criteria have been published to date. Data are also lacking on how the treatment of lower levels of hyperglycemia affects a mother's future risk for the development of type 2 diabetes and her offspring's risk for obesity, diabetes, and other metabolic disorders. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of women with GDM diagnosed by the one-step strategy.

Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (54). The 15-member panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screened positive. Commonly used cutoffs for the 1-h 50-g GLT include 130, 135, and 140 mg/dL (7.2, 7.5, and 7.8 mmol/L). The American College of Obstetricians and Gynecologists (ACOG) recommends either 135 or 140 mg/dL (45). A systematic review for the U.S. Preventive Services Task Force compared GLT cutoffs of 130 mg/dL (7.2 mmol/L) and 140 mg/dL (7.8 mmol/L) (55). The higher cutoff yielded sensitivity of 70–88% and specificity of 69–89%, while the lower cutoff was 88–99% sensitive and 66–77% specific. Data regarding a cutoff of 135 mg/dL are limited. As for other screening tests, choice of a cutoff is based upon the tradeoff between sensitivity and specificity. The use of A1C at 24–28 weeks as a screening test for GDM does not function as well as the GLT (56).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of women with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. Treatment of higher threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (57), and shoulder dystocia, without increasing small-for-gestational-age births. ACOG updated its guidelines in 2013 and supported the two-step approach (58). The ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT (59,60). Each is based on different mathematical conversions of the original recommended thresholds, which used whole blood and nonenzymatic methods for glucose determination. A recent secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (61) demonstrated that treatment was similarly beneficial in patients meeting only the lower thresholds (59) and in those meeting only the higher thresholds (60). If the two-step approach is used, it would appear advantageous to use the lower diagnostic thresholds as shown in Step 2 in **Table 2.6**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A cost-benefit estimation comparing the two strategies concluded that the one-step approach is cost-effective only if patients with GDM receive postdelivery counseling and care to prevent type 2 diabetes (62). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

As the IADPSG criteria ("one-step strategy") have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (63) and may be the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (64,65). In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria (66,67). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently under way.

MONOGENIC DIABETES SYNDROMES

Recommendations

- All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. A
- Children and adults, diagnosed in early adulthood, who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. A
- In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. E

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). **Table 2.7** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (68).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed "neonatal" or "congenital" diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (69). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β-cell K_{ATP} channel. Correct diagnosis has critical implications because most patients with K_{ATP}-related neonatal diabetes will exhibit improved glycemic control when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and, while treatment presently is intensive insulin management, there are important genetic considerations as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date. The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

Clinically, patients with GCK-MODY exhibit mild, stable, fasting hyperglycemia and do not require antihyperglycemic therapy except sometimes during pregnancy. Patients with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy. Mutations or deletions in *HNF1B* are associated with renal cysts and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes including *PDX1* (*IPF1*) and *NEUROD1*.

Diagnosis

A diagnosis of one of the three most common forms of MODY including GCK-MODY, HNF1A-MODY, and HNF4A-MODY allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members.

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes, although admittedly "atypical diabetes" is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes. In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in patients with monogenic diabetes has been reported (70). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation if available, and consultation is available from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (71), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. It

Table 2.7—Most common causes of monogenic diabetes (68)

	Gene	Inheritance	Clinical features
MODY			
	GCK	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes			
	KCNJ11	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Transient or permanent: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1, HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes; autoimmune thyroid disease; exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction.

is critical to correctly diagnose one of the monogenic forms of diabetes because these patients may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment regimens and delays in diagnosing other family members (72). The information is especially critical for GCK-MODY mutations where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (73). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations) (69,74)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes–associated autoantibodies; nonobese, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6 and 7.6% (between 38 and 60 mmol/mol), especially if nonobese

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

- Annual screening for cystic fibrosis–related diabetes with oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with cystic fibrosis–related diabetes. B
- A1C as a screening test for cystic fibrosis–related diabetes is not recommended. B
- Patients with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. A
- Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. E

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults. Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. Continuous glucose monitoring may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking continuous glucose monitoring results to long-term outcomes is lacking, and its use is not recommended for screening (75).

CFRD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (76). There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in cystic fibrosis patients with diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and patients gained 0.39 (± 0.21) BMI units ($P = 0.02$). The repaglinide-treated group had initial weight gain, but this was not sustained by 6 months. The placebo group continued to lose weight (77). Insulin remains the most widely used therapy for CFRD (78).

Recommendations for the clinical management of CFRD can be found in the ADA position statement "Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes: A Position Statement of the American Diabetes Association and a Clinical Practice Guideline of the Cystic Fibrosis Foundation, Endorsed by the Pediatric Endocrine Society" (79).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

- Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of posttransplantation diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection. **E**
- The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. **B**
- Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation. "New-onset diabetes after transplantation" (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes patients with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (80). Another term, "posttransplantation diabetes mellitus" (PTDM) (80), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (80,81). In most cases, such stress or steroid-induced hyperglycemia resolves by the time of discharge. Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents. Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance immunosuppression and in the absence of acute infection.

The OGTT is considered the gold standard test for the diagnosis of PTDM (80,82–84). However, screening patients using fasting glucose and/or A1C can identify high-risk patients requiring further assessment and may reduce the number of overall OGTTs required (85). There is currently a lack of clinical data examining the use of antidiabetes agents in the setting of PTDM to inform specific recommendations for use in this population. Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM and the role of the diabetes care provider is to treat hyperglycemia appropriately regardless of the type of immunosuppression (80).

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3. Comprehensive Medical Evaluation and Assessment of Comorbidities

American Diabetes Association

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PATIENT-CENTERED COLLABORATIVE CARE

Recommendation

- A patient-centered communication style that uses active listening, elicits patient preferences and beliefs, and assesses literacy, numeracy, and potential barriers to care should be used to optimize patient health outcomes and health-related quality of life. **B**

A successful medical evaluation depends on beneficial interactions between the patient and the care team. The Chronic Care Model (1–3) (see Section 1 "Promoting Health and Reducing Disparities in Populations") is a patient-centered approach to care that requires a close working relationship between the patient and clinicians involved in treatment planning. People with diabetes should receive health care from a team that may include physicians, nurse practitioners, physician assistants, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. Individuals with diabetes must assume an active role in their care. The patient, family or support persons, physician, and health care team should formulate the management plan, which includes lifestyle management (see Section 4 "Lifestyle Management").

Treatment goals and plans should be created with the patients based on their individual preferences, values, and goals. The management plan should take into account the patient's age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy) skills, diabetes complications, comorbidities, health priorities, other medical conditions, preferences for care, and life expectancy. Various strategies and techniques should be used to support patients' self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Provider communications with patients/families should acknowledge that multiple factors impact glycemic management, but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–7). Thus, the goal of provider-patient communication is to establish a collaborative relationship and to assess and address self-management barriers without blaming patients for "noncompliance" or "nonadherence" when the outcomes of self-management are not optimal (8). The familiar terms "noncompliance" and "nonadherence" denote a passive, obedient role for a person with diabetes in "following doctor's orders" that is at odds with the active role people with diabetes take in directing the day-to-day decision making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in self-management may help minimize patients' resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the patient said can help facilitate communication. Patients' perceptions about their own ability, or self-efficacy, to self-manage diabetes are one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes

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(9–13) and should be a target of ongoing assessment, patient education, and treatment planning.

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

A complete medical evaluation should be performed at the initial visit to

- Confirm the diagnosis and classify diabetes. B
- Detect diabetes complications and potential comorbid conditions. E
- Review previous treatment and risk factor control in patients with established diabetes. E
- Begin patient engagement in the formulation of a care management plan. B
- Develop a plan for continuing care. B

The comprehensive medical evaluation (**Table 3.1**) includes the initial and ongoing evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, and engagement of the patient throughout the process. The goal is to provide the health care team information to optimally support a patient. In addition to the medical history, physical examination, and laboratory tests, providers should assess diabetes self-management behaviors, nutrition, and psychosocial health (see Section 4 "Lifestyle Management") and give guidance on routine immunizations. Consider the assessment of sleep pattern and duration; a recent meta-analysis found that poor sleep quality, short sleep, and long sleep were associated with higher A1C in people with type 2 diabetes (14).

Lifestyle management and psychosocial care are the cornerstones of diabetes management. Patients should be referred for diabetes self-management education (DSME), diabetes self-management support (DSMS), medical nutrition therapy (MNT), and psychosocial/emotional health concerns if indicated. Patients should receive recommended preventive care services (e.g., immunizations, cancer screening, etc.); smoking cessation counseling; and ophthalmological, dental, and podiatric referrals. Additional referrals should be arranged as necessary (**Table 3.2**). Clinicians should ensure that individuals with diabetes are appropriately screened for complications and comorbidities. Discussing and implementing an approach to glycemic control with the patient is a part, not the sole goal, of care.

Immunization

Recommendations

- Provide routine vaccinations for children and adults with diabetes according to age-related recommendations. C
- Annual vaccination against influenza is recommended for all persons with diabetes ≥6 months of age. C
- Vaccination against pneumonia is recommended for all people with diabetes 2 through 64 years of age with pneumococcal polysaccharide vaccine (PPSV23). At age ≥65 years, administer the pneumococcal conjugate vaccine (PCV13) at least 1 year after vaccination with PPSV23, followed by another dose of vaccine PPSV23 at least 1 year after PCV13 and at least 5 years after the last dose of PPSV23. C
- Administer 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes who are age 19–59 years. C
- Consider administering 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes who are age ≥60 years. C

As for the general population, all children and adults with diabetes should receive vaccinations (15,16) according to age-specific recommendations. The child and adolescent vaccination schedule is available at http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html, and the adult vaccination schedule is available at http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends influenza and pneumococcal vaccines for individuals with diabetes (http://www.cdc.gov/vaccines/schedules).

Influenza

Influenza is a common, preventable infectious disease associated with high mortality and morbidity in vulnerable populations including the young and the elderly and people with chronic diseases. In a case-control study, the influenza vaccine was found to reduce diabetes-related hospital admission by as much as 79% during flu epidemics (17).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes may be at increased risk for the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, with a mortality rate as high as 50% (18). All patients with diabetes 2 years of age and older should receive the pneumococcal polysaccharide vaccine (PPSV23). There is sufficient evidence to support that adults with diabetes <65 years of age have appropriate serologic and clinical responses to these vaccinations (19). The American Diabetes Association (ADA) endorses recommendations from the CDC ACIP that all adults 65 years of age or older receive a dose of pneumococcal conjugate vaccine (PCV13) followed by a dose of PPSV23 at least 1 year later (and at least 5 years after their previous PPSV23 dose).

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis B. This may be due to contact with infected blood or through improper equipment use (glucose monitoring devices or infected needles). Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes.

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and their patients need to be aware of common comorbidities that affect people with diabetes and may complicate management (20–24). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. The list below includes many of the common comorbidities observed in patients with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Autoimmune Diseases

Recommendation

- Consider screening patients with type 1 diabetes for autoimmune thyroid disease and celiac disease soon after diagnosis. E

People with type 1 diabetes are at increased risk for other autoimmune diseases including thyroid disease, primary adrenal insufficiency, celiac disease, autoimmune gastritis, autoimmune hepatitis, dermatomyositis, and myasthenia gravis

Table 3.1—Components of the comprehensive diabetes medical evaluation*

Medical history
- Age and characteristics of onset of diabetes (e.g., diabetic ketoacidosis, asymptomatic laboratory finding)
- Eating patterns, nutritional status, weight history, sleep behaviors (pattern and duration), and physical activity habits; nutrition education and behavioral support history and needs
- Complementary and alternative medicine use
- Presence of common comorbidities and dental disease
- Screen for depression, anxiety, and disordered eating using validated and appropriate measures**
- Screen for diabetes distress using validated and appropriate measures**
- Screen for psychosocial problems and other barriers to diabetes self-management, such as limited financial, logistical, and support resources
- History of tobacco use, alcohol consumption, and substance use
- Diabetes education, self-management, and support history and needs
- Review of previous treatment regimens and response to therapy (A1C records)
- Assess medication-taking behaviors and barriers to medication adherence
- Results of glucose monitoring and patient's use of data
- Diabetic ketoacidosis frequency, severity, and cause
- Hypoglycemia episodes, awareness, and frequency and causes
- History of increased blood pressure, abnormal lipids
- Microvascular complications: retinopathy, nephropathy, and neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
- Macrovascular complications: coronary heart disease, cerebrovascular disease, and peripheral arterial disease
- For women with childbearing capacity, review contraception and preconception planning

Physical examination
- Height, weight, and BMI; growth and pubertal development in children and adolescents
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination
- Thyroid palpation
- Skin examination (e.g., for acanthosis nigricans, insulin injection or infusion set insertion sites)
- Comprehensive foot examination
  - Inspection
  - Palpation of dorsalis pedis and posterior tibial pulses
  - Presence/absence of patellar and Achilles reflexes
  - Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation
- A1C, if the results are not available within the past 3 months
- If not performed/available within the past year
  - Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides, as needed
  - Liver function tests
  - Spot urinary albumin–to–creatinine ratio
  - Serum creatinine and estimated glomerular filtration rate
  - Thyroid-stimulating hormone in patients with type 1 diabetes

*The comprehensive medical evaluation should ideally be done on the initial visit, although different components can be done as appropriate on follow-up visits. **Refer to the ADA position statement "Psychosocial Care for People With Diabetes" for additional details on diabetes-specific screening measures (65).

(25,26). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (27). In autoimmune diseases, the immune system fails to maintain self-tolerance to specific peptides within target organs. It is likely that many factors trigger autoimmune disease; however, common triggering factors are known for only some autoimmune conditions (i.e., gliadin peptides in celiac disease) (see Section 12 "Children and Adolescents").

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (28). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (29), such as underlying disease physiology or diabetes treatments, although evidence for these links is scarce. Patients with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking).

Cognitive Impairment/Dementia

Recommendation

- In people with cognitive impairment/dementia, intensive glucose control cannot be expected to remediate deficits. Treatment should be tailored to avoid significant hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of

Table 3.2—Referrals for initial care management
- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for MNT
- DSME/DSMS
- Dentist for comprehensive dental and periodontal examination
- Mental health professional, if indicated

dementia (30,31). A recent meta-analysis of prospective observational studies in people with diabetes showed a 73% increased risk of all types of dementia, a 56% increased risk of Alzheimer dementia, and 127% increased risk of vascular dementia compared with individuals without diabetes (32). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer disease, and vascular dementia compared with rates in those with normal glucose tolerance (33).

Hyperglycemia

In those with type 2 diabetes, the degree and duration of hyperglycemia are related to dementia. More rapid cognitive decline is associated with both increased A1C and longer duration of diabetes (34). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that each 1% higher A1C level was associated with lower cognitive function in individuals with type 2 diabetes (35). However, the ACCORD study found no difference in cognitive outcomes in participants randomly assigned to intensive and standard glycemic control, supporting the recommendation that intensive glucose control should not be advised for the improvement of cognitive function in individuals with type 2 diabetes (36).

Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. In a long-term study of older patients with type 2 diabetes, individuals with one or more recorded episode of severe hypoglycemia had a stepwise increase in risk of dementia (37). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (38). Tailoring glycemic therapy may help to prevent hypoglycemia in individuals with cognitive dysfunction.

Nutrition

In one study, adherence to the Mediterranean diet correlated with improved cognitive function (39). However, a recent Cochrane review found insufficient evidence to recommend any dietary change for the prevention or treatment of cognitive dysfunction (40).

Statins

A systematic review has reported that data do not support an adverse effect of statins on cognition (41). The U.S. Food and Drug Administration (FDA) postmarketing surveillance databases have also revealed a low reporting rate for cognitive-related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (41). Therefore fear of cognitive decline should not be a barrier to statin use in individuals with diabetes and a high risk for cardiovascular disease.

Fatty Liver Disease

Elevations of hepatic transaminase concentrations are associated with higher BMI, waist circumference, and triglyceride levels and lower HDL cholesterol levels. In a prospective analysis, diabetes was significantly associated with incident nonalcoholic chronic liver disease and with hepatocellular carcinoma (42). Interventions that improve metabolic abnormalities in patients with diabetes (weight loss, glycemic control, and treatment with specific drugs for hyperglycemia or dyslipidemia) are also beneficial for fatty liver disease (43,44).

Fractures

Age-specific hip fracture risk is significantly increased in people with both type 1 (relative risk 6.3) and type 2 (relative risk 1.7) diabetes in both sexes (45). Type 1 diabetes is associated with osteoporosis, but in type 2 diabetes, an increased risk of hip fracture is seen despite higher bone mineral density (BMD) (46). In three large observational studies of older adults, femoral neck BMD T score and the World Health Organization Fracture Risk Assessment Tool (FRAX) score were associated with hip and nonspine fractures. Fracture risk was higher in participants with diabetes compared with those without diabetes for a given T score and age for a given FRAX score (47). Providers should assess fracture history and risk factors in older patients with diabetes and recommend measurement of BMD if appropriate for the patient's age and sex. Fracture prevention strategies for people with diabetes are the same as for the general population and include vitamin D supplementation. For patients with type 2 diabetes with fracture risk factors, thiazolidinediones (48) and sodium–glucose cotransporter 2 inhibitors (49) should be used with caution.

Hearing Impairment

Hearing impairment, both in high-frequency and low/mid-frequency ranges, is more common in people with diabetes than in those without, perhaps due to neuropathy and/or vascular disease. In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes compared with those without, after adjusting for age and other risk factors for hearing impairment (50).

HIV

Recommendation

- Patients with HIV should be screened for diabetes and prediabetes with a fasting glucose level every 6–12 months before starting antiretroviral therapy and 3 months after starting or changing antiretroviral therapy. If initial screening results are normal, checking fasting glucose every year is advised. If prediabetes is detected, continue to measure fasting glucose levels every 3–6 months to monitor for progression to diabetes. **E**

Diabetes risk is increased with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs). New-onset diabetes is estimated to occur in more than 5% of patients infected with HIV on PIs, whereas more than 15% may have prediabetes (51). PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance.

Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies, so a screening protocol is recommended (52). The A1C test underestimates glycemia in people with HIV and is not recommended for diagnosis and may present challenges for monitoring (53). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among patients with HIV and diabetes, preventive health care using an approach similar to that used in patients without HIV is critical to reduce the risks of microvascular and macrovascular complications.

For patients with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (54). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Low Testosterone in Men

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (55). Treatment in asymptomatic men is controversial. The evidence that testosterone replacement affects outcomes is mixed, and recent guidelines do not recommend testing or treating men without symptoms (56).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (57). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep disordered breathing may be as high as 58% (58,59). In obese participants enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (60). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure control. The evidence for a treatment effect on glycemic control is mixed (61).

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in patients with diabetes than in those without (62,63). Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (24).

Psychosocial/Emotional Disorders

Prevalence of clinically significant psychopathology in people with diabetes ranges across diagnostic categories, and some diagnoses are considerably more common in people with diabetes than for those without the disease (64). Symptoms, both clinical and subclinical, that interfere with the person's ability to carry out diabetes self-management must be addressed. Diabetes distress is addressed in Section 4 "Lifestyle Management," as this state is very common and distinct from a psychological disorder (65).

Anxiety Disorders

Recommendations

- Consider screening for anxiety in people exhibiting anxiety or worries regarding diabetes complications, insulin injections or infusion, taking medications, and/or hypoglycemia that interfere with self-management behaviors and those who express fear, dread, or irrational thoughts and/or show anxiety symptoms such as avoidance behaviors, excessive repetitive behaviors, or social withdrawal. Refer for treatment if anxiety is present. **B**
- Persons with hypoglycemic unawareness, which can co-occur with fear of hypoglycemia, should be treated using blood glucose awareness training (or other evidence-based similar intervention) to help re-establish awareness of hypoglycemia and reduce fear of hyperglycemia. **A**

Anxiety symptoms and diagnosable disorders (e.g., generalized anxiety disorder, body dysmorphic disorder, obsessive-compulsive disorder, specific phobias, and posttraumatic stress disorder) are common in people with diabetes (66). The Behavioral Risk Factor Surveillance System (BRFSS) estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes (67). Common diabetes-specific concerns include fears related to hyperglycemia (68,69), not meeting blood glucose targets (66), and insulin injections or infusion (70). Onset of complications presents another critical point when anxiety can occur (71). People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic targets may be experiencing symptoms of obsessive-compulsive disorder (72).

General anxiety is a predictor of injection-related anxiety and associated with fear of hypoglycemia (69,73). Fear of hypoglycemia and hypoglycemia unawareness often co-occur, and interventions aimed at treating one often benefit both (74). Fear of hypoglycemia may explain avoidance of behaviors associated with lowering glucose such as increasing insulin doses or frequency of monitoring. If fear of hypoglycemia is identified and a person does not have symptoms of hypoglycemia, a structured program, blood glucose awareness training, delivered in routine clinical practice, can improve A1C, reduce the rate of severe hypoglycemia, and restore hypoglycemia awareness (75,76).

Depression

Recommendations

- Providers should consider annual screening of all patients with diabetes, especially those with a self-reported history of depression, for depressive symptoms with age-appropriate depression screening measures, recognizing that further evaluation will be necessary for individuals who have a positive screen. **B**
- Beginning at diagnosis of complications or when there are significant changes in medical status, consider assessment for depression. **B**
- Referrals for treatment of depression should be made to mental health providers with experience using cognitive behavioral therapy, interpersonal therapy, or other evidence-based treatment approaches in conjunction with collaborative care with the patient's diabetes treatment team. **A**

History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors such as obesity and family history of type 2 diabetes (77–79). Elevated depressive symptoms and depressive disorders affect one in four patients with type 1 or type 2 diabetes (80). Thus, routine screening for depressive symptoms is indicated in this high-risk population including people with prediabetes (particularly those who are overweight), type 1 or type 2 diabetes, gestational diabetes mellitus and postpartum diabetes. Regardless of diabetes type, women have significantly higher rates of depression than men (81).

Routine monitoring with patient-appropriate validated measures can help to identify if referral is warranted. Remission of depressive symptoms or disorder in adult patients suggests the need for ongoing monitoring of depression recurrence within the context of routine care (77). Integrating mental and physical health care can improve outcomes. When a patient is in psychological therapy (talk therapy), the mental health provider should be incorporated into the diabetes treatment team (82).

Disordered Eating Behavior

Recommendations

- Providers should consider reevaluating the treatment regimen of people with diabetes who present with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating. **B**
- Consider screening for disordered or disrupted eating using validated screening measures when hyperglycemia and weight loss are unexplained based on self-reported behaviors related to medication dosing, meal plan, and physical activity. In addition, a review of the medical regimen is recommended to identify potential treatment-related effects on hunger/caloric intake. **B**

Estimated prevalence of disordered eating behaviors and diagnosable eating disorders in people with diabetes varies (83–85). For people with type 1 diabetes, insulin omission causing glycosuria in order to lose weight is the most commonly reported disordered eating behavior (86,87); in people with type 2 diabetes, bingeing (excessive food intake with an accompanying sense of loss of control) is most commonly reported. For people with type 2 diabetes treated with insulin, intentional omission is also frequently reported (88). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (89). People with type 1 diabetes and eating disorders have high rates of diabetes distress and fear of hypoglycemia (90).

When evaluating symptoms of disordered or disrupted eating in people with diabetes, etiology and motivation for the behavior should be considered (85,91). Adjunctive medication such as glucagon-like peptide 1 receptor agonists (92) may help individuals to not only meet glycemic targets but also to regulate hunger and food intake, thus having the potential to reduce uncontrollable hunger and bulimic symptoms.

Serious Mental Illness

Recommendations

- Annually screen people who are prescribed atypical antipsychotic medications for prediabetes or diabetes. **B**
- If a second-generation antipsychotic medication is prescribed for adolescents or adults with diabetes, changes in weight, glycemic control, and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed. **C**
- Incorporate monitoring of diabetes self-care activities into treatment goals in people with diabetes and serious mental illness. **B**

Studies of individuals with serious mental illness, particularly schizophrenia and other thought disorders, show significantly increased rates of type 2 diabetes (93). People with schizophrenia should be monitored for type 2 diabetes because of the known comorbidity. Disordered thinking and judgment can be expected to make it difficult to engage in behaviors that reduce risk factors for type 2 diabetes, such as restrained eating for weight management. Coordinated management of diabetes or prediabetes and serious mental illness is recommended to achieve diabetes treatment targets. In addition, those taking second-generation (atypical) antipsychotics such as olanzapine require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (94).

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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).

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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

Table 4.1—MNT recommendations

Topic	Recommendations	Evidence rating
Effectiveness of nutrition therapy	• An individualized MNT program, preferably provided by a registered dietitian, is recommended for all people with type 1 or type 2 diabetes.	A
	• For people with type 1 diabetes and those with type 2 diabetes who are prescribed a flexible insulin therapy program, education on how to use carbohydrate counting and in some cases fat and protein gram estimation to determine mealtime insulin dosing can improve glycemic control.	A
	• For individuals whose daily insulin dosing is fixed, having a consistent pattern of carbohydrate intake with respect to time and amount can result in improved glycemic control and a reduced risk of hypoglycemia.	B
	• A simple and effective approach to glycemia and weight management emphasizing portion control and healthy food choices may be more helpful for those with type 2 diabetes who are not taking insulin, who have limited health literacy or numeracy, and who are elderly and prone to hypoglycemia.	B
	• Because diabetes nutrition therapy can result in cost savings B and improved outcomes (e.g., A1C reduction) A, MNT should be adequately reimbursed by insurance and other payers. E	B, A, E
Energy balance	• Modest weight loss achievable by the combination of reduction of calorie intake and lifestyle modification benefits overweight or obese adults with type 2 diabetes and also those with prediabetes. Intervention programs to facilitate this process are recommended.	A
Eating patterns and macronutrient distribution	• As there is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for people with diabetes, macronutrient distribution should be individualized while keeping total calorie and metabolic goals in mind.	E
	• A variety of eating patterns are acceptable for the management of type 2 diabetes and prediabetes including Mediterranean, DASH, and plant-based diets.	B
	• Carbohydrate intake from whole grains, vegetables, fruits, legumes, and dairy products, with an emphasis on foods higher in fiber and lower in glycemic load, should be advised over other sources, especially those containing sugars.	B
	• People with diabetes and those at risk should avoid sugar-sweetened beverages in order to control weight and reduce their risk for CVD and fatty liver B and should minimize the consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices A	B, A
Protein	• In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia.	B
Dietary fat	• Whereas data on the ideal total dietary fat content for people with diabetes are inconclusive, an eating plan emphasizing elements of a Mediterranean-style diet rich in monounsaturated fats may improve glucose metabolism and lower CVD risk and can be an effective alternative to a diet low in total fat but relatively high in carbohydrates.	B
	• Eating foods rich in long-chain ω-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA) is recommended to prevent or treat CVD B; however, evidence does not support a beneficial role for ω-3 dietary supplements. A	B, A
Micronutrients and herbal supplements	• There is no clear evidence that dietary supplementation with vitamins, minerals, herbs, or spices can improve outcomes in people with diabetes who do not have underlying deficiencies, and there may be safety concerns regarding the long-term use of antioxidant supplements such as vitamins E and C and carotene.	C
Alcohol	• Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men).	C
	• Alcohol consumption may place people with diabetes at increased risk for hypoglycemia, especially if taking insulin or insulin secretagogues. Education and awareness regarding the recognition and management of delayed hypoglycemia are warranted.	B
Sodium	• As for the general population, people with diabetes should limit sodium consumption to $<$2,300 mg/day, although further restriction may be indicated for those with both diabetes and hypertension.	B
Nonnutritive sweeteners	• The use of nonnutritive sweeteners has the potential to reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners and without compensation by intake of additional calories from other food sources. Nonnutritive sweeteners are generally safe to use within the defined acceptable daily intake levels.	B

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).

Micronutrients and Supplements

There continues to be no clear evidence of benefit from herbal or nonherbal (i.e., vitamin or mineral) supplementation for people with diabetes without underlying deficiencies (37). 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, particularly in those with anemia or peripheral neuropathy (92). Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. In addition, there is insufficient evidence to support the routine use of herbals and micronutrients, such as cinnamon (93) and vitamin D (94), to improve glycemic control in people with diabetes (37,95).

Alcohol

Moderate alcohol consumption does not have major detrimental effects on long-term blood glucose control in people with diabetes. Risks associated with alcohol consumption include hypoglycemia (particularly for those using insulin or insulin secretagogue therapies), weight gain, and hyperglycemia (for those consuming excessive amounts) (37,95).

Nonnutritive Sweeteners

For people who are accustomed to sugar-sweetened products, nonnutritive sweeteners have the potential to reduce overall calorie and carbohydrate intake and may be preferred to sugar when consumed in moderation. Regulatory agencies set acceptable daily intake levels for each nonnutritive sweetener, defined as the amount that can be safely consumed over a person's lifetime (37,96).

PHYSICAL ACTIVITY

Recommendations

- Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week. C
- Most adults with with type 1 C and type 2 B diabetes should engage in 150 min or more of moderate-to-vigorous intensity physical activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.
- Adults with type 1 C and type 2 B diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.
- All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. B Prolonged sitting should be interrupted every 30 min for blood glucose benefits, particularly in adults with type 2 diabetes. C
- Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. C

Physical activity is a general term that includes all movement that increases energy use and is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important. Exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Physical activity is as important for those with type 1 diabetes as it is for the general population, but its specific role in the prevention of diabetes complications and the management of blood glucose is not as clear as it is for those with type 2 diabetes.

Structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even without a significant change in BMI (97). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, greater muscle strength, improved insulin sensitivity, etc.) of regular exercise for those with type 1 diabetes (98). Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness (99). Other benefits include slowing the decline in mobility among overweight patients with diabetes (100). The ADA position statement "Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association" reviews the evidence for the benefits of exercise in people with diabetes (101).

Exercise and Children

All children, including children with diabetes or prediabetes, should be encouraged to engage in at least 60 min of physical activity each day. Children should engage in at least 60 min of moderate-to-vigorous aerobic activity every day with muscle- and bone-strengthening activities at least 3 days per week (102). In general, youth with type 1 diabetes benefit from being physically active, and an active lifestyle should be recommended to all.

Frequency and Type of Physical Activity

The U.S. Department of Health and Human Services' physical activity guidelines for Americans (103) suggest that adults over age 18 years engage in 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of the two. In addition, the guidelines suggest that adults do muscle-strengthening activities that involve all major muscle groups 2 or more days/week. The guidelines suggest that adults over age 65 years and those with disabilities follow the adult guidelines if possible or, if not possible, be as physically active as they are able.

Recent evidence supports that all individuals, including those with diabetes, should be encouraged to reduce the amount of time spent being sedentary (e.g., working at a computer, watching TV), by breaking up bouts of sedentary activity ($>$30 min) by briefly standing, walking, or performing at other light physical activities (104,105). Avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk and may also aid in glycemic control for those with diabetes.

Physical Activity and Glycemic Control

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (106) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (107). If not contraindicated, patients with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (exercise with free weights or weight machines), with each session consisting of at least one set (group of consecutive repetitive exercise motions) of five or more different resistance exercises involving the large muscle groups (106).

For type 1 diabetes, although exercise in general is associated with improvement in disease status, care needs to be taken in titrating exercise with respect to glycemic management. Each individual with type 1 diabetes has a variable glycemic response to exercise. This variability should be taken into consideration when recommending the type and duration of exercise for a given individual (98).

Women with preexisting diabetes, particularly type 2 diabetes, and those at risk for or presenting with gestational diabetes mellitus should be advised to engage in regular moderate physical activity prior to and during their pregnancies as tolerated (101).

Pre-exercise Evaluation

As discussed more fully in Section 9 "Cardiovascular Disease and Risk Management," the best protocol for assessing asymptomatic patients with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (108) concluded that routine testing is not recommended. However, providers should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease in patients with diabetes. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration. Providers should assess patients for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, peripheral neuropathy, and a history of foot ulcers or Charcot foot. The patient's age and previous physical activity level should be considered. The provider should customize the exercise regimen to the individual's needs. Those with complications may require a more thorough evaluation (98).

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not altered. Individuals on these therapies may need to ingest some added carbohydrate if pre-exercise glucose levels are <100 mg/dL (5.6 mmol/L), depending on whether they can lower insulin levels during the workout (such as with an insulin pump or reduced pre-exercise insulin dosage), the time of day exercise is done, and the intensity and duration of the activity (98,101). Hypoglycemia is less common in patients with diabetes who are not treated with insulin or insulin secretagogues, and no routine preventive measures for hypoglycemia are usually advised in these cases. In some patients, hypoglycemia after exercise may occur and last for several hours due to increased insulin sensitivity. Intense activities may actually raise blood glucose levels instead of lowering them, especially if pre-exercise glucose levels are elevated (109).

Exercise in the Presence of Specific Long-term Complications of Diabetes

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (110). Consultation with an ophthalmologist prior to engaging in an intense exercise regimen may be appropriate.

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities result in an increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. Studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear (111). In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with prediabetic neuropathy (112). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia (113). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (114). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Diabetic Kidney Disease

Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise increases the rate of progression of diabetic kidney disease, and there appears to be no need for specific exercise restrictions for people with diabetic kidney disease (110).

SMOKING CESSATION: TOBACCO AND e-CIGARETTES

Recommendations

- Advise all patients not to use cigarettes and other tobacco products **A** or e-cigarettes. **E**
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **B**

Results from epidemiological, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks (115). Recent data show tobacco use is higher among adults with chronic conditions (116). Other studies of individuals with diabetes consistently demonstrate that smokers (and people exposed to secondhand smoke) have a heightened risk of CVD, premature death, and microvascular complications. Smoking may have a role in the development of type 2 diabetes (117). One study in smokers with newly diagnosed type 2 diabetes found that smoking cessation was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria at 1 year (118).

The routine and thorough assessment of tobacco use is essential to prevent smoking or encourage cessation. Numerous large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of brief counseling in smoking cessation, including the use of telephone quit lines, in reducing tobacco use. For the patient motivated to quit, the addition of pharmacological therapy to counseling is more effective than either treatment alone. Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (119). Although some patients may gain weight in the period shortly after smoking cessation, recent research has demonstrated that this weight gain does not diminish the substantial CVD benefit realized from smoking cessation (120).

Nonsmokers should be advised not to use e-cigarettes. There are no rigorous studies that have demonstrated that e-cigarettes are a healthier alternative to smoking or that e-cigarettes can facilitate smoking cessation. More extensive research of their short- and long-term effects is needed to determine their safety and their cardiopulmonary effects in comparison with smoking and standard approaches to smoking cessation (121–123).

PSYCHOSOCIAL ISSUES

Recommendations

- Psychosocial care should be integrated with a collaborative, patient-centered approach and provided to all people with diabetes, with the goals of optimizing health outcomes and health-related quality of life. **A**
- Psychosocial screening and follow-up may include, but are not limited to, attitudes about the illness, expectations for medical management and outcomes, affect or mood, general and diabetes-related quality of life, available resources (financial, social, and emotional), and psychiatric history. **E**
- Providers should consider assessment for symptoms of diabetes distress, depression, anxiety, disordered eating, and cognitive capacities using patient-appropriate standardized and validated tools at the initial visit, at periodic intervals, and when there is a change in disease, treatment, or life circumstance. Including caregivers and family members in this assessment is recommended. **B**
- Consider screening older adults (aged $\geq$65 years) with diabetes for cognitive impairment and depression. **B**

Please refer to the ADA position statement "Psychosocial Care for People with Diabetes" for a list of assessment tools and additional details (124).

Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (125–127) or family's (128) ability to carry out diabetes care tasks and therefore potentially compromise health status. There are opportunities for the clinician to routinely assess psychosocial status in a timely and efficient manner for referral to appropriate services. A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference –0.29%) and mental health outcomes (129). However, there was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes.

Screening

Key opportunities for psychosocial screening occur at diabetes diagnosis, during regularly scheduled management visits, during hospitalizations, with new onset of complications, or when problems with glucose control, quality of life, or self-management are identified (1). Patients are likely to exhibit psychological vulnerability at diagnosis, when their medical status changes (e.g., end of the honeymoon period), when the need for intensified treatment is evident, and when complications are discovered.

Providers can start with informal verbal inquires, for example, by asking if there have been changes in mood during the past 2 weeks or since their last visit. Providers should consider asking if there are new or different barriers to treatment and self-management, such as feeling overwhelmed or stressed by diabetes or other life stressors. Standardized and validated tools for psychosocial monitoring and assessment can also be used by providers, with positive findings leading to referral to a mental health provider specializing in diabetes for comprehensive evaluation, diagnosis, and treatment.

Diabetes Distress

Recommendation

- Routinely monitor people with diabetes for diabetes distress, particularly when treatment targets are not met and/or at the onset of diabetes complications. **B**

Table 4.2—Situations that warrant referral of a person with diabetes to a mental health provider for evaluation and treatment

- If self-care remains impaired in a person with diabetes distress after tailored diabetes education
- If a person has a positive screen on a validated screening tool for depressive symptoms
- In the presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
- If intentional omission of insulin or oral medication to cause weight loss is identified
- If a person has a positive screen for anxiety or fear of hypoglycemia
- If a serious mental illness is suspected
- In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, or significant distress
- If a person screens positive for cognitive impairment
- Declining or impaired ability to perform diabetes self-care behaviors
- Before undergoing bariatric or metabolic surgery and after surgery if assessment reveals an ongoing need for adjustment support

Diabetes distress (DD) is very common and is distinct from other psychological disorders (130–132). DD refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a severe, complicated, and demanding chronic disease such as diabetes (131–133). The constant behavioral demands (medication dosing, frequency, and titration; monitoring blood glucose, food intake, eating patterns, and physical activity) of diabetes self-management and the potential or actuality of disease progression are directly associated with reports of DD (131). The prevalence of DD is reported to be 18–45% with an incidence of 38–48% over 18 months (133). In the second Diabetes Attitudes, Wishes and Needs (DAWN2) study, significant DD was reported by 45% of the participants, but only 24% reported that their health care teams asked them how diabetes affected their lives (130). High levels of DD significantly impact medication-taking behaviors and are linked to higher A1C, lower self-efficacy, and poorer dietary and exercise behaviors (14,131,133). DSME has been shown to reduce DD (14). It may be helpful to provide counseling regarding expected diabetes-related versus generalized psychological distress at diagnosis and when disease state or treatment changes (134).

DD should be routinely monitored (135) using patient-appropriate validated measures. If DD is identified, the person should be referred for specific diabetes education to address areas of diabetes self-care that are most relevant to the patient and impact clinical management. People whose self-care remains impaired after tailored diabetes education should be referred by their care team to a behavioral health provider for evaluation and treatment.

Other psychosocial issues known to affect self-management and health outcomes include attitudes about the illness, expectations for medical management and outcomes, available resources (financial, social, and emotional) (136), and psychiatric history. For additional information on psychiatric comorbidities (depression, anxiety, disordered eating, and serious mental illness), please refer to Section 3 "Comprehensive Medical Evaluation and Assessment of Comorbidities."

Referral to a Mental Health Specialist

Indications for referral to a mental health specialist familiar with diabetes management may include positive screening for overall stress related to work-life balance, DD, diabetes management difficulties, depression, anxiety, disordered eating, and cognitive functioning difficulties (see **Table 4.2** for a complete list). It is preferable to incorporate psychosocial assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status to occur (22,130). Providers should identify behavioral and mental health providers, ideally those who are knowledgeable about diabetes treatment and the psychosocial aspects of diabetes, to whom they can refer patients. Ideally, psychosocial care providers should be embedded in diabetes care settings. Although the clinician may not feel qualified to treat psychological problems (137), optimizing the patient–provider relationship as a foundation may increase the likelihood of the patient accepting referral for other services. Collaborative care interventions and a team approach have demonstrated efficacy in diabetes self-management and psychosocial functioning (14).

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5. Prevention or Delay of Type 2 Diabetes

American Diabetes Association

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For guidelines related to screening for increased risk for type 2 diabetes (prediabetes), please refer to Section 2 "Classification and Diagnosis of Diabetes."

Recommendations

- At least annual monitoring for the development of diabetes in those with prediabetes is suggested. **E**
- Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**
- Technology-assisted tools including Internet-based social networks, distance learning, DVD-based content, and mobile applications may be useful elements of effective lifestyle modification to prevent diabetes. **B**
- Given the cost-effectiveness of diabetes prevention, such intervention programs should be covered by third-party payers. **B**

Screening for prediabetes and type 2 diabetes through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the American Diabetes Association risk test (**Fig. 2.1**), is recommended to guide providers on whether performing a diagnostic test for prediabetes (**Table 2.4**) and previously undiagnosed type 2 diabetes (**Table 2.2**) is appropriate (see Section 2 "Classification and Diagnosis of Diabetes"). Those determined to be at high risk for type 2 diabetes, including people with A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose, are ideal candidates for diabetes prevention efforts. At least annual monitoring for the development of diabetes in those with prediabetes is suggested.

LIFESTYLE INTERVENTIONS

The Diabetes Prevention Program

The strongest evidence for diabetes prevention comes from the Diabetes Prevention Program (DPP) (1). The DPP demonstrated that an intensive lifestyle intervention could reduce the incidence of type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention has shown sustained reduction in the rate of conversion to type 2 diabetes: 43% reduction at 20 years in the Da Qing study (2), 43% reduction at 7 years in the Finnish Diabetes Prevention Study (DPS) (1), and 34% reduction at 10 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS) (3).

The two major goals of the DPP intensive, behavioral, lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min of physical activity per week similar in intensity to brisk walking. The DPP lifestyle intervention was a goal-based intervention: all participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (4).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve the 7% weight loss during the first 6 months of the intervention. The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body

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weight). The initial focus was on reducing total dietary fat. After several weeks, the concept of calorie balance and the need to restrict calories as well as fat was introduced (4).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week with at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (4).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for tailoring of interventions to reflect the diversity of the population (4).

The DPP intervention was administered as a structured core curriculum followed by a more flexible maintenance program of individual sessions, group classes, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program and included sections on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors, and psychological, social, and motivational challenges. For further details on the core curriculum sessions, refer to ref. 4.

Nutrition

Reducing caloric intake is of paramount importance for those at high risk for developing type 2 diabetes, though recent evidence suggests that the quality of fats consumed in the diet is more important than the total quantity of dietary fat (5–7). For example, the Mediterranean diet, which is relatively high in monounsaturated fats, may help to prevent type 2 diabetes (8–10).

Whereas overall healthy low-calorie eating patterns should be encouraged, there is also some evidence that particular dietary components impact diabetes risk. Data suggest that whole grains may help to prevent type 2 diabetes (11). Higher intakes of nuts (12), berries (13), yogurt (14), coffee, and tea (15) are associated with reduced diabetes risk. Conversely, red meats and sugar-sweetened beverages are associated with an increased risk of type 2 diabetes (6).

As is the case for those with diabetes, individualized medical nutrition therapy (see Section 4 "Lifestyle Management" for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (16).

Physical Activity

Just as 150 min/week of moderate-intensity physical activity, such as brisk walking, showed beneficial effects in those with prediabetes (17), moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (18,19). On the basis of these findings, providers are encouraged to promote a DPP-style program, including its focus on physical activity, to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, an exercise regimen designed to prevent diabetes may include resistance training (1,20). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (21,22). The preventative effects of exercise appear to extend to the prevention of gestational diabetes mellitus (GDM) (23).

Technology Assistance to Deliver Lifestyle Interventions

New information technology platforms may effectively deliver the core components of the DPP (24–26). Initial studies have validated DVD-based content delivery (27). This has been corroborated in a primary care patient population (28). Recent studies support content delivery through virtual small groups (29), Internet-driven social networks (30,31), cellular phones, and other mobile devices. Mobile applications for weight loss and diabetes prevention have been validated for their ability to reduce A1C in the setting of prediabetes (31). The Centers for Disease Control and Prevention (CDC) Diabetes Prevention Recognition Program (DPRP) (http://www.cdc.gov/diabetes/prevention/recognition/index.htm) has begun to certify electronic and mobile health-based modalities as effective vehicles for DPP-based interventions that may be considered alongside more traditional face-to-face and coach-driven programs. A recent study showed that an all-mobile approach to administering DPP content can be effective as a prevention tool, at least over the short term, in overweight and obese individuals at high risk for diabetes (32).

Cost-effectiveness

A cost-effectiveness model suggested that the lifestyle intervention used in the DPP was cost-effective (33). Actual cost data from the DPP and DPPOS confirmed this (34). Group delivery of DPP content in community settings has the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (35,36). The CDC helps to coordinate the National Diabetes Prevention Program, a resource designed to bring evidence-based lifestyle change programs for preventing type 2 diabetes to communities (http://www.cdc.gov/diabetes/prevention/index.htm). On 7 July 2016, the Centers for Medicare and Medicaid Services (CMS) proposed expanded Medicare reimbursement coverage for DPP programs in an effort to expand preventive services using a cost-effective model (https://www.cms.gov/site-search/search-results.html?q=diabetes%20prevention).

PHARMACOLOGIC INTERVENTIONS

Recommendations

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI $\geq$35 kg/m^2, those aged $<$60 years, women with prior gestational diabetes mellitus, and/or those with rising A1C despite lifestyle intervention. **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**

Pharmacologic agents including metformin, α-glucosidase inhibitors, orlistat, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones have each been shown to decrease incident diabetes to various degrees in those with prediabetes. Metformin has the strongest evidence base and demonstrated long-term safety as pharmacologic therapy for diabetes prevention (37). For other drugs, cost, side effects, and durable efficacy require consideration.

Metformin was less effective than lifestyle modification in the DPP and DPPOS but may be cost-saving over a 10-year period (34). It was as effective as lifestyle modification in participants with BMI $\geq$35 kg/m^2 but not significantly better than placebo in those over 60 years of age (17). In the DPP, for women with history of GDM, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (38), and both interventions remained highly effective during a 10-year follow-up period (39). Metformin should be recommended as an option for high-risk individuals (e.g., those with a history of GDM, those who are very obese, and/or those with relatively more hyperglycemia) and/or those with rising A1C despite lifestyle intervention. Consider monitoring B12 levels in those taking metformin chronically to check for possible deficiency (see Section 8 "Pharmacologic Approaches to Glycemic Treatment" for more details).

PREVENTION OF CARDIOVASCULAR DISEASE

Recommendation

- Screening for and treatment of modifiable risk factors for cardiovascular disease is suggested for those with prediabetes. B

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia, and are at increased risk for cardiovascular disease (40). Although treatment goals for people with prediabetes are the same as for the general population, increased vigilance is warranted to identify and treat these and other cardiovascular risk factors (e.g., smoking).

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendation

- Diabetes self-management education and support programs may be appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the development of diabetes. B

As for those with established diabetes, the standards for diabetes self-management education and support (see Section 4 "Lifestyle Management") can also apply to people with prediabetes. Currently, there are significant barriers to the provision of education and support to those with prediabetes. However, the strategies for supporting successful behavior change, and the healthy behaviors recommended for people with prediabetes are comparable to those for diabetes. Although reimbursement remains a barrier, studies show that providers of diabetes self-management education and support are particularly well equipped to assist people with prediabetes in developing and maintaining behaviors that can prevent or delay the development of diabetes (16,41).

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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

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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 $\geq$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 $\geq$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 $\geq$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., $\geq$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**

A1C reflects average glycemia over approximately 3 months and has strong predictive value for diabetes complications (29,30). Thus, A1C testing should be performed routinely in all patients with diabetes—at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained. The frequency of A1C testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment. The use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters between patients and providers. Patients with type 2 diabetes with stable glycemia well within target may do well with A1C testing only twice per year. Unstable or intensively managed patients (e.g., pregnant women with type 1 diabetes) may require testing more frequently than every 3 months (31).

A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. Conditions that affect red blood cell turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's SMBG levels. For patients in whom A1C/estimated average glucose (eAG) and measured blood glucose appear discrepant, clinicians should consider the possibilities of altered red blood cell turnover. Options for monitoring include more frequent and/or different timing of SMBG or CGM use. Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol (1,5-AG) are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C (see Section 2 "Classification and Diagnosis of Diabetes").

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially patients with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from SMBG and A1C. A1C may also confirm the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

A1C and Mean Glucose

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on two studies: the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between A1C and frequent SMBG and CGM in 507 adults (83% non-Hispanic whites) with type 1, type 2, and no diabetes (32), and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial (27). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the eAG result when a clinician orders the A1C test (**Table 6.1**). Clinicians should note that the mean plasma glucose numbers in the table are based on ~2,700 readings per A1C in the ADAG trial.

A1C Differences in Ethnic Populations and Children

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although the study was underpowered to detect a difference and there was a trend toward a difference between the African/African American and non-Hispanic white cohorts, with higher values observed in Africans/African Americans compared with non-Hispanic whites. Other studies have also demonstrated higher A1C levels in African Amercans than in whites (33). A small study comparing A1C to CGM data in children with type 1 diabetes found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation (r = 0.7) was significantly lower than in the ADAG trial (34). Whether there are clinically meaningful differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (35,36). For the time being, the question has not led to different recommendations about testing A1C or to different interpretations of the clinical meaning of given levels of A1C in those populations. Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of both individualized SMBG and A1C results.

A1C GOALS

For glycemic goals in children, please refer to Section 12 "Children and Adolescents." For glycemic goals in pregnant women, please refer to Section 13 "Management of Diabetes in Pregnancy."

Recommendations

- A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). A
- Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C
- Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (1), a prospective randomized controlled trial of intensive versus standard glycemic control in patients with type 1 diabetes, showed definitively that better glycemic control is associated with significantly decreased rates of development and progression of microvascular (retinopathy [37] and diabetic kidney disease) and neuropathic complications. Follow-up of the

Table 6.1—Mean glucose levels for specified A1C levels (27,32)

A1C	Mean plasma glucose*		Mean fasting glucose		Mean premeal glucose		Mean postmeal glucose		Mean bedtime glucose	
% (mmol/mol)	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L
6 (42)	126 (100–152)	7.0 (5.5–8.5)								
5.5–6.49 (37–47)			122 (117–127)	6.8 (6.5–7.0)	118 (115–121)	6.5 (6.4–6.7)	144 (139–148)	8.0 (7.7–8.2)	136 (131–141)	7.5 (7.3–7.8)
6.5–6.99 (47–53)			142 (135–150)	7.9 (7.5–8.3)	139 (134–144)	7.7 (7.4–8.0)	164 (159–169)	9.1 (8.8–9.4)	153 (145–161)	8.5 (8.0–8.9)
7 (53)	154 (123–185)	8.6 (6.8–10.3)								
7.0–7.49 (53–58)			152 (143–162)	8.4 (7.9–9.0)	152 (147–157)	8.4 (8.2–8.7)	176 (170–183)	9.8 (9.4–10.2)	177 (166–188)	9.8 (9.2–10.4)
7.5–7.99 (58–64)			167 (157–177)	9.3 (8.7–9.8)	155 (148–161)	8.6 (8.2–8.9)	189 (180–197)	10.5 (10.0–10.9)	175 (163–188)	9.7 (9.0–10.4)
8 (64)	183 (147–217)	10.2 (8.1–12.1)								
8.0–8.5 (64–69)			178 (164–192)	9.9 (9.1–10.7)	179 (167–191)	9.9 (9.3–10.6)	206 (195–217)	11.4 (10.8–12.0)	222 (197–248)	12.3 (10.9–13.8)
9 (75)	212 (170–249)	11.8 (9.4–13.9)								
10 (86)	240 (193–282)	13.4 (10.7–15.7)								
11 (97)	269 (217–314)	14.9 (12.0–17.5)								
12 (108)	298 (240–347)	16.5 (13.3–19.3)								

Data in parentheses represent 95% CI, unless otherwise noted. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at http://professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92 (32).

DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (38) demonstrated persistence of these microvascular benefits despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (39) and UK Prospective Diabetes Study (UKPDS) (40,41) confirmed that intensive glycemic control significantly decreased rates of microvascular and neuropathic complications in patients with type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (42).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of diabetes. Epidemiological analyses of the DCCT (1) and UKPDS (43) demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. These analyses also suggest that further lowering of A1C from 7% to 6% [53 mmol/mol to 42 mmol/mol] is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycemia in type 1 diabetes trials and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets outweigh the potential benefits on microvascular complications.

ACCORD, ADVANCE, and VADT

Three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) showed that lower A1C levels were associated with reduced onset or progression of microvascular complications (44–46).

The concerning mortality findings in the ACCORD trial (47), discussed below, and the relatively intense efforts required to achieve near-euglycemia should also be considered when setting glycemic targets. However, on the basis of physician judgment and patient preferences, select patients, especially those with little comorbidity and long life expectancy, may benefit from adopting more intensive glycemic targets (e.g., A1C target <6.5% [48 mmol/mol]) as long as significant hypoglycemia does not become a barrier.

A1C and Cardiovascular Disease Outcomes

Cardiovascular Disease and Type 1 Diabetes

Cardiovascular disease (CVD) is a more common cause of death than microvascular complications in populations with diabetes. There is evidence for a cardiovascular benefit of intensive glycemic control after long-term follow-up of cohorts treated early in the course of type 1 and type 2 diabetes. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or cardiovascular death compared with those previously randomized to the standard arm (48). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (49) and to be associated with a modest reduction in all-cause mortality (50).

Cardiovascular Disease and Type 2 Diabetes

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. During the UKPDS, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance ($P = 0.052$), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). However, after 10 years of observational follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (42).

The ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for 3.5–5.6 years who had more advanced type 2 diabetes than UKPDS participants. All three trials were conducted in relatively older participants with longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. The target A1C among intensive control subjects was <6% (42 mmol/mol) in ACCORD, <6.5% (48 mmol/mol) in ADVANCE, and a 1.5% reduction in A1C compared with control subjects in VADT, with achieved A1C of 6.4% versus 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% versus 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% versus 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in the ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association" (51).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]), with a similar increase in cardiovascular deaths. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive treatment arm (47).

Longer-term follow-up has shown no evidence of cardiovascular benefit or harm in the ADVANCE trial (52). The end-stage renal disease rate was lower in the intensive treatment group over follow-up. However, 10-year follow-up of the VADT cohort (53) showed a reduction in the risk of cardiovascular events (52.7 [control group] vs. 44.1 [intervention group] events per 1,000 person-years) with no benefit in cardiovascular or overall mortality. Heterogeneity of mortality effects across studies was noted, which may reflect differences in glycemic targets, therapeutic approaches, and population characteristics (54).

Mortality findings in ACCORD (47) and subgroup analyses of VADT (55) suggest that the potential risks of intensive glycemic control may outweigh its benefits in higher-risk patients. In all three trials, severe hypoglycemia was significantly more likely in participants who were randomly assigned to the intensive glycemic control arm. Those patients with long duration of diabetes, a known history of hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (56,57).

Providers should be vigilant in preventing hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such targets cannot be safely and reasonably achieved. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals. Many factors, including patient preferences, should be taken into account when developing a patient's individualized goals (**Table 6.2**)

A1C and Glycemic Targets

Numerous aspects must be considered when setting glycemic targets. The ADA proposes optimal targets, but each target must be individualized to the needs of each patient and his or her disease factors.

When possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. **Figure 6.1** is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making (58), both in type 1 and type 2 diabetes.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.2**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7% (53 mmol/mol). The issue of preprandial versus postprandial SMBG targets is complex (59). Elevated post-challenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiological studies, but intervention trials have not shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In subjects with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7% (53 mmol/mol). However, outcome studies have clearly shown A1C to be the primary predictor of complications, and landmark trials

Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

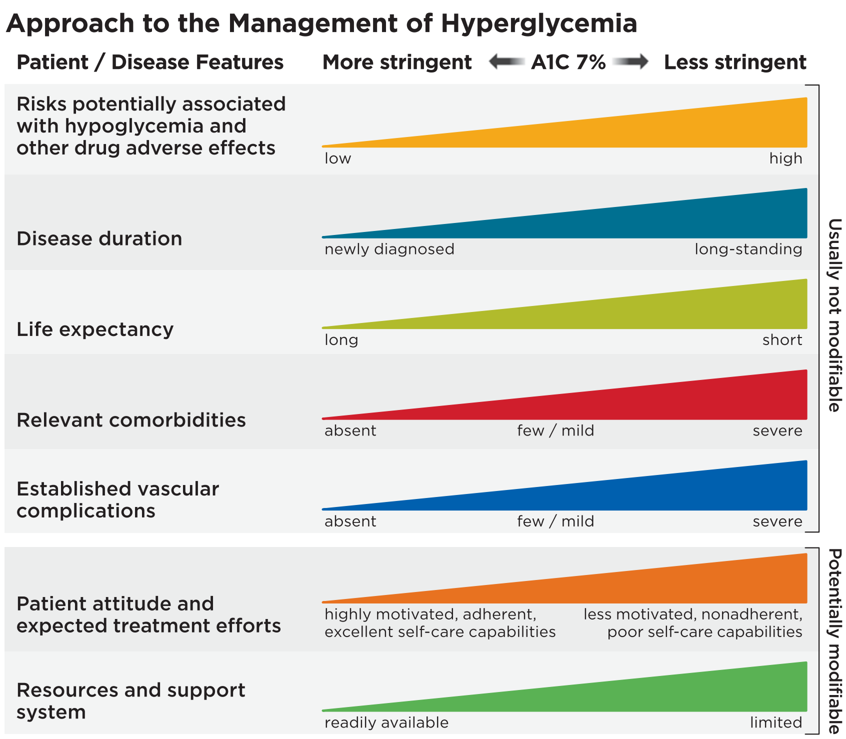

Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (58).

of glycemic control such as the DCCT and UKPDS relied overwhelmingly on preprandial SMBG. Additionally, a randomized controlled trial in patients with known CVD found no CVD benefit of insulin regimens targeting postprandial glucose compared with those targeting preprandial glucose (60). Therefore, it is reasonable for postprandial testing to be recommended for individuals who have premeal glucose values within target but have A1C values above target. Measuring postprandial plasma glucose 1–2 h after the start of a meal and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10.0 mmol/L) may help to lower A1C.

An analysis of data from 470 participants in the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that actual average glucose levels associated with conventional A1C targets were higher than older DCCT and ADA targets (**Table 6.1**) (27,29). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data prompted the revision in the ADA-recommended premeal glucose target to 80–130 mg/dL (4.4–7.2 mmol/L) but did not affect the definition of hypoglycemia.

HYPOGLYCEMIA

Recommendations

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. C
- Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia (glucose alert value of ≤70 mg/dL [3.9 mmol/L]), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. E
- Glucagon should be prescribed for all individuals at increased risk of clinically significant hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. E
- Hypoglycemia unawareness or one or more episodes of severe hypoglycemia should trigger reevaluation of the treatment regimen. E
- Insulin-treated patients with hypoglycemia unawareness or an episode of clinically significant hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. A
- Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. B

Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations from the International Hypoglycaemia Study Group regarding the classification of hypoglycemia are outlined in **Table 6.3** (61). Of note, this classification scheme considers a blood glucose <54 mg/dL (3.0 mmol/L) detected by SMBG, CGM (for at least 20 min), or laboratory measurement of plasma glucose as sufficiently low to indicate serious, clinically significant hypoglycemia that should be included in reports of clinical trials of glucose-lowering drugs for the treatment of diabetes (61). However, a glucose alert value of ≥70 mg/dL (3.9 mmol/L) can be important for therapeutic dose adjustment of glucose-lowering drugs in clinical care and is often related to symptomatic hypoglycemia. Severe hypoglycemia is defined as severe cognitive impairment requiring assistance from another person for recovery (62).

Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, and hunger. Hypoglycemia may be inconvenient or frightening to patients with diabetes. Severe hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. It is reversed by administration of rapid-acting glucose or glucagon. Clinically significant hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle

Table 6.3—Classification of hypoglycemia (61)

Level	Glycemic criteria	Description
Glucose alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

accidents, or other injury. A large cohort study suggested that among older adults with type 2 diabetes, a history of severe hypoglycemia was associated with greater risk of dementia (63). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of severe hypoglycemia (64). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of severe hypoglycemia and cognitive decline (65), as discussed in Section 12 "Children and Adolescents."

Severe hypoglycemia was associated with mortality in participants in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward. An association of severe hypoglycemia with mortality was also found in the ADVANCE trial (66). An association between self-reported severe hypoglycemia and 5-year mortality has also been reported in clinical practice (67).

Young children with type 1 diabetes and the elderly are noted as particularly vulnerable to clinically significant hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glucose targets, patient education, dietary intervention (e.g., bedtime snack to prevent overnight hypoglycemia), exercise management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (62).

In 2015, the ADA changed its preprandial glycemic target from 70–130 mg/dL (3.9–7.2 mmol/L) to 80–130 mg/dL (4.4–7.2 mmol/L). This change reflects the results of the ADAG study, which demonstrated that higher glycemic targets corresponded to A1C goals (27). An additional goal of raising the lower range of the glycemic target was to limit overtreatment and provide a safety margin in patients titrating glucose-lowering drugs such as insulin to glycemic targets.

Hypoglycemia Treatment

Providers should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the blood glucose alert value of 70 mg/dL (3.9 mmol/L) or less. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless further food is ingested after recovery. Once the glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, child care providers, correctional institution staff, or coworkers) should be instructed on the use of glucagon kits including where the kit is and when and how to administer glucagon. An individual does not need to be a health care professional to safely administer glucagon. Care should be taken to ensure that glucagon kits are not expired.

Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management. SMBG and, for some patients, CGM are essential tools to assess therapy and detect incipient hypoglycemia. Patients should understand situations that increase their risk of hypoglycemia, such as fasting for tests or procedures, delayed meals, during or after intense exercise, and during sleep. Hypoglycemia may increase the risk of harm to self or others, such as with driving. Teaching people with diabetes to balance insulin use and carbohydrate intake and exercise are necessary, but these strategies are not always sufficient for prevention.

In type 1 diabetes and severely insulin-deficient type 2 diabetes, hypoglycemia unawareness (or hypoglycemia-associated autonomic failure) can severely compromise stringent diabetes control and quality of life. This syndrome is characterized by deficient counterregulatory hormone release, especially in older adults, and a diminished autonomic response, which both are risk factors for, and caused by, hypoglycemia. A corollary to this "vicious cycle" is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counterregulation and hypoglycemia awareness in many patients (68). Hence, patients with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets.

INTERCURRENT ILLNESS

For further information on management of patients with hyperglycemia in the hospital, please refer to Section 14 "Diabetes Care in the Hospital."

Stressful events (e.g., illness, trauma, surgery, etc.) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or alteration in the level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment regimen and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or medical nutrition therapy alone may temporarily require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration is more likely to necessitate hospitalization of the person with diabetes than the person without diabetes.

A physician with expertise in diabetes management should treat the hospitalized patient. For further information on the management of diabetic ketoacidosis and the hyperglycemic nonketotic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (69).

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7. Obesity Management for the Treatment of Type 2 Diabetes

American Diabetes Association

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There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (1,2) and may be beneficial in the treatment of type 2 diabetes (3–8). In overweight and obese patients with type 2 diabetes, modest and sustained weight loss has been shown to improve glycemic control and to reduce the need for glucose-lowering medications (3–5). Small studies have demonstrated that in obese patients with type 2 diabetes more extreme dietary energy restriction with very low-calorie diets can reduce A1C to <6.5% (48 mmol/mol) and fasting glucose to <126 mg/dL (7.0 mmol/L) in the absence of pharmacological therapy or ongoing procedures (7,9,10). Weight loss–induced improvements in glycemia are most likely to occur early in the natural history of type 2 diabetes when obesity-associated insulin resistance has caused reversible β-cell dysfunction but insulin secretory capacity remains relatively preserved (5,8,10). The goal of this section is to provide evidence-based recommendations for dietary, pharmacological, and surgical interventions for obesity management as treatments for hyperglycemia in type 2 diabetes.

ASSESSMENT

Recommendation

- At each patient encounter, BMI should be calculated and documented in the medical record. **B**

At each routine patient encounter, BMI should be calculated from the height and weight. BMI should be classified to determine the presence of overweight or obesity, discussed with the patient, and documented in the patient record. In Asian Americans, the BMI cutoff points to define overweight and obesity are lower than in other populations (**Table 7.1**) (11,12). Providers should advise overweight and obese patients that higher BMIs increase the risk of cardiovascular disease and all-cause mortality. Providers should assess each patient's readiness to achieve weight loss and jointly determine weight loss goals and intervention strategies. Strategies include diet, physical activity, behavioral therapy, pharmacological therapy, and metabolic surgery (**Table 7.1**). The latter two strategies may be prescribed for carefully selected patients as adjuncts to diet, physical activity, and behavioral therapy.

DIET, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

- Diet, physical activity, and behavioral therapy designed to achieve >5% weight loss should be prescribed for overweight and obese patients with type 2 diabetes ready to achieve weight loss. **A**
- Such interventions should be high intensity (≥16 sessions in 6 months) and focus on diet, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit. **A**
- Diets should be individualized, as those that provide the same caloric restriction but differ in protein, carbohydrate, and fat content are equally effective in achieving weight loss. **A**
- For patients who achieve short-term weight loss goals, long-term (≥1-year) comprehensive weight maintenance programs should be prescribed. Such programs should provide at least monthly contact and encourage ongoing monitoring of body weight (weekly or more frequently), continued

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Table 7.1—Treatment for overweight and obesity in type 2 diabetes

	BMI category (kg/m²)				
Treatment	23.0* or 25.0–26.9	27.0–29.9	27.5* or 30.0–34.9	35.0–39.9	≥40
Diet, physical activity, and behavioral therapy	┼	┼	┼	┼	┼
Pharmacotherapy		┼	┼	┼	┼
Metabolic surgery			┼	┼	┼

*Cutoff points for Asian American individuals.
┼Treatment may be indicated for selected motivated patients.

consumption of a reduced calorie diet, and participation in high levels of physical activity (200–300 min/week). A

- To achieve weight loss of >5%, short-term (3-month) interventions that use very low-calorie diets (≤800 kcal/day) and total meal replacements may be prescribed for carefully selected patients by trained practitioners in medical care settings with close medical monitoring. To maintain weight loss, such programs must incorporate long-term comprehensive weight maintenance counseling. B

Among overweight or obese patients with type 2 diabetes and inadequate glycemic, blood pressure, and lipid control and/or other obesity-related medical conditions, lifestyle changes that result in modest and sustained weight loss produce clinically meaningful reductions in blood glucose, A1C, and triglycerides (3–5). Greater weight loss produces even greater benefits, including reductions in blood pressure, improvements in LDL and HDL cholesterol, and reductions in the need for medications to control blood glucose, blood pressure, and lipids (13,14).

Look AHEAD Trial

Although the Action for Health in Diabetes (Look AHEAD) trial did not show that an intensive lifestyle intervention reduced cardiovascular events in overweight or obese adults with type 2 diabetes (13), it did show the feasibility of achieving and maintaining long-term weight loss in patients with type 2 diabetes. In the Look AHEAD intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years (14). Approximately 50% of intensive lifestyle intervention participants lost ≥5% and 27% lost ≥10% of their initial body weight at 8 years (14). Participants randomly assigned to the intensive lifestyle group achieved equivalent risk factor control but required fewer glucose-, blood pressure–, and lipid-lowering medications than those randomly assigned to standard care. Secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document other benefits of weight loss in patients with type 2 diabetes, including improvements in mobility, physical and sexual functioning, and health-related quality of life (15).

Lifestyle Interventions

Weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit or provide approximately 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. Although benefits may be seen with as little as 5% weight loss, sustained weight loss of ≥7% is optimal.

These diets may differ in the types of foods they restrict (such as high-fat or high-carbohydrate foods) but are effective if they create the necessary energy deficit (16–19). Use of meal replacement plans prescribed by trained practitioners, with close patient monitoring, can be beneficial. Within the intensive lifestyle intervention group of the Look AHEAD trial, for example, use of a partial meal replacement plan was associated with improvements in diet quality (20). The diet choice should be based on the patient's health status and preferences.

Intensive behavioral lifestyle interventions should include ≥16 sessions in 6 months and focus on diet, physical activity, and behavioral strategies to achieve an ~500–750 kcal/day energy deficit. Interventions should be provided by trained interventionists in either individual or group sessions (21).

Overweight and obese patients with type 2 diabetes who have lost weight during the 6-month intensive behavioral lifestyle intervention should be enrolled in long-term (≥1-year) comprehensive weight loss maintenance programs that provide at least monthly contact with a trained interventionist and focus on ongoing monitoring of body weight (weekly or more frequently), continued consumption of a reduced calorie diet, and participation in high levels of physical activity (200–300 min/week). Some commercial and proprietary weight loss programs have shown promising weight loss results (22).

When provided by trained practitioners in medical care settings with close medical monitoring, short-term (3-month) interventions that use very low-calorie diets (defined as ≤800 kcal/day) and total meal replacements may achieve greater short-term weight loss (10–15%) than intensive behavioral lifestyle interventions that typically achieve 5% weight loss. Weight regain following the cessation of very low-calorie diets is greater than following intensive behavioral lifestyle interventions unless a long-term comprehensive weight loss maintenance program is provided (23,24).

PHARMACOTHERAPY

Recommendations

- When choosing glucose-lowering medications for overweight or obese patients with type 2 diabetes, consider their effect on weight. E
- Whenever possible, minimize the medications for comorbid conditions that are associated with weight gain. E
- Weight loss medications may be effective as adjuncts to diet, physical activity, and behavioral counseling for selected patients with type 2 diabetes and BMI ≥27 kg/m^2. Potential benefits must be weighed against the potential risks of the medications. A
- If a patient's response to weight loss medications is <5% weight loss after 3 months or if there are any safety or tolerability issues at

any time, the medication should be discontinued and alternative medications or treatment approaches should be considered. A

Antihyperglycemic Therapy

When evaluating pharmacological treatments for overweight or obese patients with type 2 diabetes, providers should first consider their choice of glucose-lowering medications. Whenever possible, medications should be chosen to promote weight loss or to be weight neutral. Agents associated with weight loss include metformin, α-glucosidase inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and amylin mimetics. Dipeptidyl peptidase 4 inhibitors appear to be weight neutral. Unlike these agents, insulin secretagogues, thiazolidinediones, and insulin have often been associated with weight gain (see Section 8 "Pharmacologic Approaches to Glycemic Treatment").

Concomitant Medications

Providers should carefully review the patient's concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Medications associated with weight gain include atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, etc.) and antidepressants (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, oral contraceptives that contain progestins, anticonvulsants including gabapentin, and a number of antihistamines and anticholinergics.

Approved Weight Loss Medications

The U.S. Food and Drug Administration (FDA) has approved five weight loss medications (or combination medications) for long-term use (more than a few weeks) by patients with BMI $\geq$27 kg/m^2 with one or more obesity-associated comorbid conditions (e.g., type 2 diabetes. hypertension, and dyslipidemia) and by patients with BMI $\geq$30 kg/m^2 who are motivated to lose weight (25–27). Medications approved for long-term weight loss and weight loss maintenance and their advantages and disadvantages are summarized in **Table 7.2**. The rationale for weight loss medications is to help patients to more consistently adhere to low-calorie diets and to reinforce lifestyle changes including physical activity. Providers should be knowledgeable about the product label and should balance the potential benefits of successful weight loss against the potential risks of the medication for each patient. These medications are contraindicated in women who are or may become pregnant. Women in their reproductive years must be cautioned to use a reliable method of contraception.

Assessing Efficacy and Safety

Efficacy and safety should be assessed at least monthly for the first 3 months of treatment. If a patient's response is deemed insufficient (weight loss $<$5%) or if there are any safety or tolerability issues at any time, the medication should be discontinued and alternative medications or treatment approaches should be considered.

In general, pharmacological treatment of obesity has been limited by low adherence, modest efficacy, adverse effects, and weight regain after medication cessation (25).

METABOLIC SURGERY

Recommendations

- Metabolic surgery should be recommended to treat type 2 diabetes in appropriate surgical candidates with BMI $\geq$40 kg/m^2 (BMI $\geq$37.5 kg/m^2 in Asian Americans), regardless of the level of glycemic control or complexity of glucose-lowering regimens, and in adults with BMI 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in Asian Americans) when hyperglycemia is inadequately controlled despite lifestyle and optimal medical therapy. A
- Metabolic surgery should be considered for adults with type 2 diabetes and BMI 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asian Americans) if hyperglycemia is inadequately controlled despite optimal medical control by either oral or injectable medications (including insulin). B
- Metabolic surgery should be performed in high-volume centers with multidisciplinary teams that understand and are experienced in the management of diabetes and gastrointestinal surgery. C
- Long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided to patients after surgery, according to guidelines for postoperative management of metabolic surgery by national and international professional societies. C
- People presenting for metabolic surgery should receive a comprehensive mental health assessment. B Surgery should be postponed in patients with histories of alcohol or substance abuse, significant depression, suicidal ideation, or other mental health conditions until these conditions have been fully addressed. E
- People who undergo metabolic surgery should be evaluated to assess the need for ongoing mental health services to help them adjust to medical and psychosocial changes after surgery. C

Several gastrointestinal (GI) operations promote dramatic and durable improvement of type 2 diabetes. Given the magnitude and rapidity of the effect of GI surgery on hyperglycemia, and experimental evidence that rearrangements of GI anatomy similar to those in some metabolic procedures directly affect glucose homeostasis (28), GI interventions have been suggested as treatments for type 2 diabetes, and in that context are termed "metabolic surgery."

A substantial body of evidence has now accumulated, including data from numerous randomized controlled clinical trials, demonstrating that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk factors in obese patients with type 2 diabetes compared with various lifestyle/medical interventions (29). Improvements in micro- and macrovascular complications of diabetes, cardiovascular disease, and cancer have been observed only in nonrandomized observational studies (30–37). Cohort studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality (31).

On the basis of this mounting evidence, several organizations and government agencies have recommended expanding the indications for metabolic surgery to include patients with inadequately controlled type 2 diabetes and BMI as low as 30 kg/m^2 (27.5 kg/m^2 for

Table 7.2—Medications approved by the FDA for the long-term (more than a few weeks) treatment of obesity

Generic drug name (proprietary name[s]) and dosage strength and form	Adult dosing frequency	Average wholesale price (per month)[1]	1-Year weight change status[2–5]: Average weight loss relative to placebo	1-Year weight change status[2–5]: % Patients with ≥5% loss of baseline weight	Adverse effects[2,6–12]: Common[7]	Adverse effects[2,6–12]: Serious[7]
Lipase inhibitor						
Orlistat (Alli) 60 mg caps or orlistat (Xenical) 120 mg caps	60 mg or 120 mg t.i.d. (during or up to 1 h after a low-fat meal)	\$43–86 (60 mg); \$670 (120 mg)	2.5 kg (60 mg); 3.4 kg (120 mg)	35–73%	Abdominal pain/discomfort, oily spotting/stool, fecal urgency, flatulence, malabsorption of fat-soluble vitamins (A, D, E, K) and medications (e.g., cyclosporine, thyroid hormone replacement, or anticonvulsants), potentiation of the effects of warfarin	Liver failure and oxalate nephropathy
Selective serotonin (5-HT) 5-HT_{2C} receptor agonist						
Lorcaserin (Belviq) 10 mg tabs	10 mg b.i.d.	\$263	3.2 kg	38–48%	Hypoglycemia, headache, fatigue	Serotonin syndrome or NMS-like reactions, suicidal ideation, heart valve disorder (<2.4%), bradycardia
Sympathomimetic amine anorectic/antiepileptic combination						
Phentermine/topiramate ER (Qsymia) 3.75 mg/23 mg caps, 7.5 mg/46 mg caps, 11.25 mg/69 mg caps, 15 mg/92 mg caps	Recommended dose: 3.75 mg/23 mg q.d. for 14 days, then increase to 7.5 mg/46 mg q.d. Maximum dose: 15 mg/92 mg q.d.	\$239 (maximum dose using the highest strength)	6.7 kg (7.5 mg/46 mg); 8.9 kg (15 mg/92 mg)	45–70%	Paresthesia, xerostomia, constipation, headache	Topiramate is teratogenic and has been associated with cleft lip/palate
Opioid antagonist/aminoketone antidepressant combination						
Naltrexone/bupropion (Contrave) 8 mg/90 mg tabs	Maximum dose: two tablets of Contrave b.i.d. for a total daily dosage of naltrexone 32 mg/bupropion 360 mg	\$251 (maximum dose)	2.0–4.1 kg (32 mg/360 mg)	36–57%	Nausea, constipation, headache, vomiting	Depression, precipitation of mania, contraindicated in patients with a seizure disorder
Acylated human glucagon-like peptide 1 receptor agonist						
Liraglutide (Saxenda) 6 mg/mL prefilled pen	Maintenance dose: 3 mg s.c. q.d.	\$1,385	5.8–5.9 kg	51–73%	Hypoglycemia, nausea, vomiting, diarrhea, constipation, headache	Pancreatitis, thyroid C-cell tumors in rodents, contraindicated in patients with personal/family history of MTC or MEN2, acute renal failure

All medications are contraindicated in women who are or may become pregnant. Women in their reproductive years must be cautioned to use a reliable method of contraception. Caps, capsules; ER, extended release; MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid carcinoma; NMS, neuroleptic malignant syndrome; s.c., subcutaneous; tabs, tablets.

[1]RED BOOK Online. Micromedex 2.0 (electronic version). Truven Health Analytics, Greenwood Village, CO.

[2]Physicians' Desk Reference. PDR Network, LLC (electronic version). Truven Health Analytics, Greenwood Village, CO.

[3]Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA 2014;311:74–86.

[4]Astrup A, Carraro R, Finer N, et al.; NN8022–1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond) 2012;36:843–854.

[5]Wadden TA, Hollander P, Klein S, et al.; NN8022–1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37:1443–1451.

[6]DrugPoints System (electronic version). Truven Health Analytics, Greenwood Village, CO.

[7]Selective common (defined as an incidence of >5%) and serious adverse effects are noted. Refer to the medication package inserts for full information about adverse effects, cautions, and contraindications.

[8]Data of common adverse effects for Xenical were derived from seven double-blind, placebo-controlled clinical trials in mixed-type study populations (i.e., patients with or without type 2 diabetes), but the percentage of patients with type 2 diabetes was not reported. In clinical trials in obese patients with diabetes, hypoglycemia and abdominal distension were also observed.

[9]Data of common adverse effects for Belviq were derived from placebo-controlled clinical trials in patients with type 2 diabetes.

[10]Data of common adverse effects for Qsymia were derived from four clinical trials in mixed-type study populations (i.e., patients with or without type 2 diabetes); 13% had type 2 diabetes.

[11]Data of common adverse effects for Contrave were derived from five double-blind, placebo-controlled clinical trials in mixed-type study populations (i.e., patients with or without type 2 diabetes); 13% had type 2 diabetes.

[12]Data of common adverse effects for Saxenda were derived from clinical trials in mixed-type study populations (i.e., patients with or without type 2 diabetes). Percentage of patients with type 2 diabetes was not reported.

Asian Americans) (38–41). Please refer to the American Diabetes Association consensus report "Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations" for a thorough review (29).

Randomized controlled trials with postoperative follow-up ranging from 1 to 5 years have documented sustained diabetes remission in 30–63% of patients (29). Available data suggest an erosion of diabetes remission over time: 35–50% or more of patients who initially achieve remission of diabetes eventually experience recurrence. However, the median disease-free period among such individuals following Roux-en-Y gastric bypass (RYGB) is 8.3 years (42,43). With or without diabetes relapse, the majority of patients who undergo surgery maintain substantial improvement of glycemic control from baseline for at least 5 (44) to 15 (31,32,43,45–47) years.

Younger age, shorter duration of diabetes (e.g., <8 years) (48), nonuse of insulin, and better glycemic control are consistently associated with higher rates of diabetes remission and/or lower risk of recidivism (31,46,48). Greater baseline visceral fat area may also help to predict better postoperative outcomes, especially among Asian American patients with type 2 diabetes, who typically have more visceral fat compared with Caucasians with diabetes of the same BMI (49).

Beyond improving glycemia, metabolic surgery has been shown to confer additional health benefits in randomized controlled trials, including greater reductions in cardiovascular disease risk factors (29) and enhancements in quality of life (44,48,50).

The safety of metabolic surgery has improved significantly over the past two decades, with continued refinement of minimally invasive approaches (laparoscopic surgery), enhanced training and credentialing, and involvement of multidisciplinary teams. Mortality rates with metabolic operations are typically 0.1–0.5%, similar to cholecystectomy or hysterectomy (51–55). Morbidity has also dramatically declined with laparoscopic approaches. Major complications rates are 2–6%, with minor complications in up to 15% (51–59), comparing favorably with other commonly performed elective operations (55). Empirical data suggest that proficiency of the operating surgeon is an important factor for determining mortality, complications, reoperations, and readmissions (60).

Although metabolic surgery has been shown to improve the metabolic profiles of morbidly obese patients with type 1 diabetes, establishing the role of metabolic surgery in such patients will require larger and longer studies (61).

Retrospective analyses and modeling studies suggest that metabolic surgery may be cost-effective or even cost-saving for patients with type 2 diabetes, but the results are largely dependent on assumptions about the long-term effectiveness and safety of the procedures (62,63).

Adverse Effects

Metabolic surgery is costly and has associated risks. Longer-term concerns include dumping syndrome (nausea, colic, diarrhea), vitamin and mineral deficiencies, anemia, osteoporosis, and, rarely (64), severe hypoglycemia from insulin hypersecretion. Long-term nutritional and micronutrient deficiencies and related complications occur with variable frequency depending on the type of procedure and require lifelong vitamin/nutritional supplementation (65,66). Postprandial hypoglycemia is most likely to occur with RYGB (66,67). The exact prevalence of symptomatic hypoglycemia is unknown. In one study, it affected 11% of 450 patients who had undergone RYGB or vertical sleeve gastrectomy (67). Patients who undergo metabolic surgery may be at increased risk for substance use, including drug and alcohol use and cigarette smoking (68).

People with diabetes presenting for metabolic surgery also have increased rates of depression and other major psychiatric disorders (69). Candidates for metabolic surgery with histories of alcohol or substance abuse, significant depression, suicidal ideation, or other mental health conditions should therefore first be assessed by a mental health professional with expertise in obesity management prior to consideration for surgery (70). Individuals with preoperative psychopathology should be assessed regularly following metabolic surgery to optimize mental health management and to ensure psychiatric symptoms do not interfere with weight loss and lifestyle changes.

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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).

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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,

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — **Metformin** — **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — **Metformin +** — **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — **Metformin +** — **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy **(See Figure 8.2)**

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).

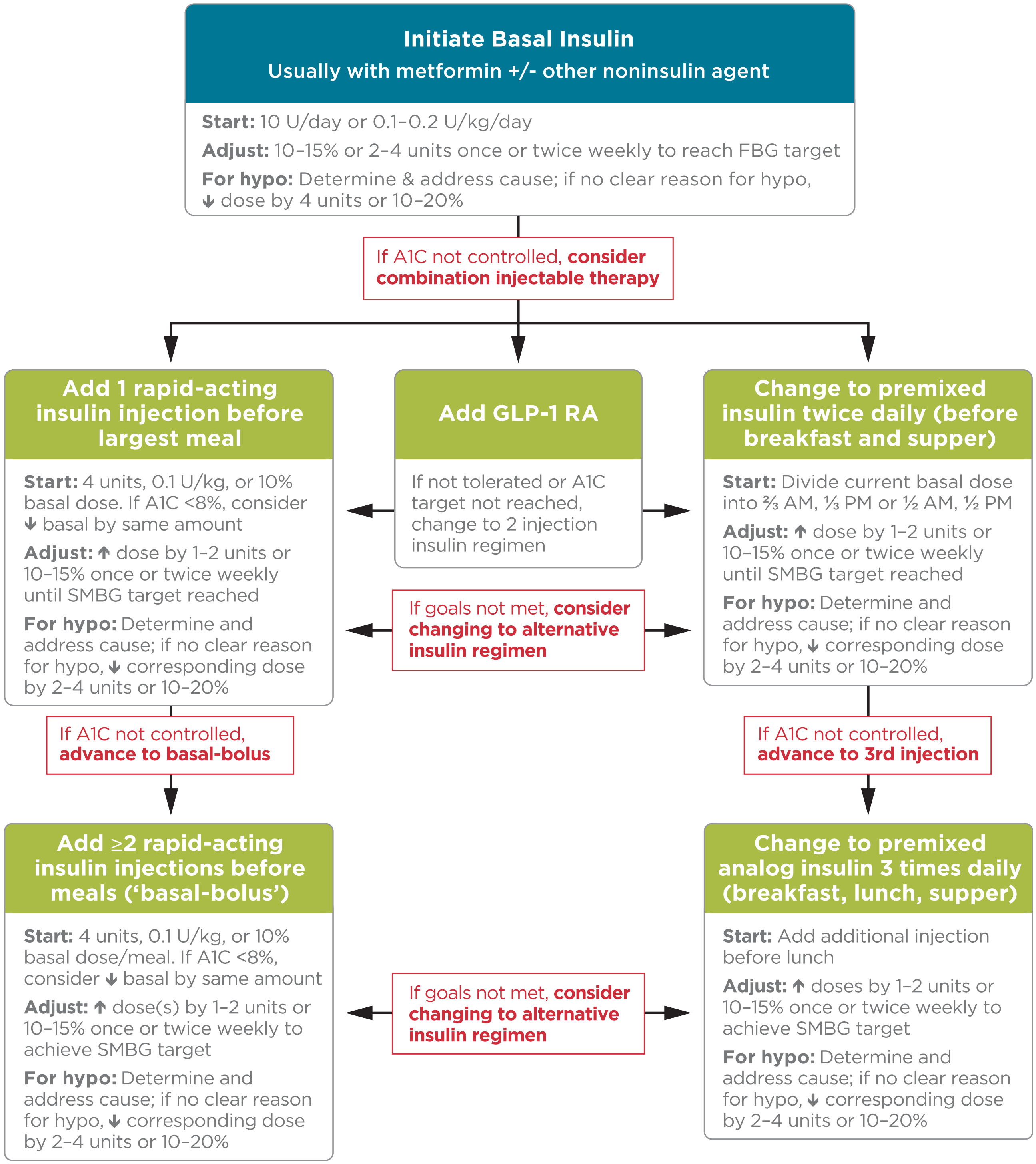

Figure 8.2—Combination injectable therapy for type 2 diabetes. FBG, fasting blood glucose; GLP-1 RA, GLP-1 receptor agonist; hypo, hypoglycemia. Adapted with permission from Inzucchi et al. (21).

few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis (23) suggests that each new class of noninsulin agents added to initial therapy generally lowers A1C approximately 0.9–1.1%. If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of the six available treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin (**Fig. 8.1**). If A1C target is still not achieved after ~3 months of dual therapy, proceed to three-drug combination (**Fig. 8.1**). Again, if A1C target is not achieved after ~3 months of triple therapy, proceed to combination injectable therapy (**Fig. 8.2**).

Drug choice is based on patient preferences (26), as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially

Table 8.1—Properties of available glucose-lowering agents in the U.S. that may guide individualized treatment choices in patients with type 2 diabetes (21)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR $<$30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Relatively higher A1C efficacy	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• Rare hypoglycemia • Relatively higher A1C efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone) • ↓ Risk of stroke and MI in patients without diabetes and with *insulin resistance* and history of recent stroke or TIA (IRIS study [42], pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• Rare hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin; ? alogliptin)	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• Rare hypoglycemia • ↓ LDL-C	• Modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High

Continued on p. S69

Table 8.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Rare hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER) (30)	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Training requirements • Patient and provider reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	High#

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Table 8.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
	• Basal insulin analogs - Glargine - Detemir - Degludec • Premixed insulin products - NPH/Regular 70/30 −70/30 aspart mix −75/25 lispro mix −50/50 lispro mix					

CVD, cardiovascular disease; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (29); GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; IRIS, Insulin Resistance Intervention After Stroke Trial; LDL-C, LDL cholesterol; PPAR-γ, peroxisome proliferator–activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (43); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (44); TIA, transient ischemic attack; TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study (45,46). Cycloset trial of quick-release bromocriptine (47). *Cost is based on lowest-priced member of the class (21). ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analogs > human insulins) and dosage. Adapted with permission from Inzucchi et al. (21).

hypoglycemia. **Table 8.1** lists drugs commonly used in the U.S. Cost-effectiveness models have suggested that some of the newer agents may be of relatively lower clinical utility based on high cost and moderate glycemic effect (27). **Table 8.2** provides cost information for currently approved noninsulin therapies. *Of note, prices listed are average wholesale prices (AWP) and do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. While there are alternative means to estimate medication prices, AWP was utilized to provide a comparison of list prices with the primary goal of highlighting the importance of cost considerations when prescribing antihyperglycemic treatments*. The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) will compare four drug classes (sulfonylurea, DPP-4 inhibitor, GLP-1 receptor agonist, and basal insulin) when added to metformin therapy over 4 years on glycemic control and other medical, psychosocial, and health economic outcomes (28).

Rapid-acting secretagogues (meglitinides) may be used instead of sulfonylureas in patients with sulfa allergies, irregular meal schedules, or those who develop late postprandial hypoglycemia when taking a sulfonylurea. Other drugs not shown in **Fig. 8.1** (e.g., inhaled insulin, α-glucosidase inhibitors, colesevelam, bromocriptine, and pramlintide) may be tried in specific situations but are not often used due to modest efficacy in type 2 diabetes, the frequency of administration, the potential for drug interactions, and/or side effects.

Cardiovascular Outcome Trials

Several recently published cardiovascular outcome trials (CVOTs) have provided data on patients with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease. The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a SGLT2 inhibitor, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99%

Table 8.2—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S. (48)

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($5, $94)	2,000 mg
		850 mg (IR)	$108 ($5, $108)	2,550 mg
		1,000 mg (IR)	$86 ($4, $87)	2,000 mg
		500 mg (ER)	$90 ($82, $6,672)	2,000 mg
		750 mg (ER)	$72 ($65, $92)	1,500 mg
		1,000 mg (ER)	$1,028 ($1,010, $7,213)	2,000 mg
Sulfonylureas (2nd Gen)	• Glyburide	5 mg 6 mg (micronized)	$94 ($64, $103) $50 ($48, $71)	20 mg 12 mg (micronized)
	• Glipizide	10 mg (IR) 10 mg (XL)	$74 ($67, $97) $97	40 mg (IR) 20 mg (XL)
	• Glimepiride	4 mg	$74 ($71, $198)	8 mg
Meglitinides (glinides)	• Repaglinide	2 mg	$799 ($163, $878)	16 mg
	• Nateglinide	120 mg	$156	360 mg
TZDs	• Pioglitazone	45 mg	$349 ($348, $349)	45 mg
	• Rosiglitazone	4 mg	$355	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$104 ($104, 105)	300 mg
	• Miglitol	100 mg	$241	300 mg
DPP-4 inhibitors	• Sitagliptin	100 mg	$436	100 mg
	• Saxagliptin	5 mg	$436	5 mg
	• Linagliptin	5 mg	$428	5 mg
	• Alogliptin	25 mg	$436	25 mg
Bile acid sequestrant	• Colesevelam	625 mg tabs 1.875 g suspension	$679 $1,357	3.75 g 3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$719	4.8 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$470	300 mg
	• Dapagliflozin	10 mg	$470	10 mg
	• Empagliflozin	25 mg	$470	25 mg
GLP-1 receptor agonists	• Exenatide	10 μg pen	$729	20 μg
	• Exenatide (extended-release)	2 mg powder for suspension or pen	$692	2 mg**
	• Liraglutide	18 mg/3 mL pen	$831	1.8 mg
	• Albiglutide	50 mg pen	$527	50 mg**
	• Dulaglutide	1.5/0.5 mL pen	$690	1.5 mg**
Amylin mimetics	• Pramlintide	120 μg pen	$2,124	120 μg/injection††

ER and XL, extended release; IR, immediate release; TZD, thiazolidinedione. †Calculated for 30 day supply (AWP unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP listed alone when only one product and/or price. *Utilized to calculate median AWP (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP calculated based on 120 μg three times daily.

had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%) (29). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results: A Long Term Evaluation (LEADER) trial was a randomized double-blind trial that assessed the effect of liraglutide, a GLP-1 receptor agonist, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease inclusive of a prior myocardial infarction (MI), prior stroke or transient ischemic attack, prior revascularization procedure, or ≥50% stenosis of coronary, carotid, or lower-extremity arteries. LEADER showed that the composite primary outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) after a median follow-up of 3.8 years (30). Whether other GLP-1 receptor agonists will have the same effect in high-risk patients or if this drug class will have similar effects in lower-risk patients with diabetes remains unknown.

CVOT data for the DPP-4 inhibitors sitagliptin (31), saxagliptin (32), and alogliptin (33) have also been reported, with no significant difference in rates of major cardiovascular events noted between treatment and placebo groups in any of these trials.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients. *Providers* *should avoid using insulin as a threat or describing it as a sign of personal failure or punishment.*

Equipping patients with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) improves glycemic control in patients with type 2 diabetes initiating insulin (34). Comprehensive education regarding SMBG, diet, and the avoidance of and appropriate treatment of hypoglycemia are critically important in any patient using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units per day or 0.1–0.2 units/kg/day, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and sometimes one additional noninsulin agent. While there is evidence for reduced risk of hypoglycemia with newer, longer-acting basal insulin analogs, people with type 2 diabetes without a history of hypoglycemia may use NPH insulin safely and at much lower cost (27,35). **Table 8.3** provides average wholesale price information (cost per 1,000 units) for currently available insulin products in the U.S. There have been substantial increases in the price of insulin over the past decade and the cost-effectiveness of different antihyperglycemic agents is an important consideration when selecting therapies (36). A follow-on U-100 (100 units/mL) glargine product (basaglar) is now available in the U.S. This product was approved through an abbreviated FDA approval pathway based, in part, on the FDA's finding of safety and effectiveness for the reference U-100 glargine product.

Bolus Insulin

Many individuals with type 2 diabetes may require mealtime bolus insulin dosing in addition to basal insulin. Rapid-acting analogs are preferred due to their prompt onset of action after dosing. The recommended starting dose of mealtime insulin is 4 units, 0.1 U/kg, or 10% of the basal dose. If A1C is $<$8% (64 mmol/mol) when starting mealtime bolus insulin, consideration should be given to decreasing the basal insulin dose.

Premixed Insulin

Premixed insulin products contain both a basal and prandial component, allowing coverage of both basal and prandial needs with a single injection. NPH/Regular 70/30 insulin, for example, is composed of 70% NPH insulin and 30% regular insulin. The use of premixed insulin products has its advantages and disadvantages, as discussed below in COMBINATION INJECTABLE THERAPY.

Concentrated Insulin Products

Several concentrated insulin preparations are currently available. U-500 regular insulin, by definition, is five times as concentrated as U-100 regular insulin and has a delayed onset and longer duration of

Table 8.3—Median cost of insulins in the U.S. calculated as average wholesale price per 1,000 units of specified dosage form/product (48)

Insulins	Compounds	Dosage form/product	Median AWP package price (min, max)*
Rapid-acting analogs			
	• Lispro	U-100 vial	$306
		U-100 3 mL cartridges	$306 ($306, $379)
		U-100 prefilled pen; U-200 prefilled pen	$394
	• Aspart	U-100 vial	$306
		U-100 3 mL cartridges	$380
		U-100 prefilled pen	$395
	• Glulisine	U-100 vial	$283
		U-100 prefilled pen	$365
	• Inhaled insulin	Inhalation cartridges	$557 ($453, $754)
Short-acting			
	• Human Regular	U-100 vial	$165
Intermediate-acting			
	• Human NPH	U-100 vial	$165
		U-100 prefilled pen	$350
Concentrated Human Regular insulin			
	• U-500 Human Regular insulin	U-500 vial	$165
		U-500 prefilled pen	$213
Basal analogs			
	• Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	$298
	• Detemir	U-100 vial; U-100 prefilled pen	$323
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$355
Premixed products			
	• NPH/Regular 70/30	U-100 vial	$165
		U-100 prefilled pen	$350
	• Lispro 50/50	U-100 vial	$317
		U-100 prefilled pen	$394
	• Lispro 75/25	U-100 vial	$317
		U-100 prefilled pen	$394
	• Aspart 70/30	U-100 vial	$318
		U-100 prefilled pen	$395

AWP listed alone when only one product and/or price.

action than U-100 regular, posessing both prandial and basal properties. U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations, have longer durations of action, and allow higher doses of basal insulin administration per volume used. The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL). These concentrated preparations may be more comfortable for the patient and may improve adherence for patients with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials (a dedicated syringe was FDA approved in July 2016), other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Inhaled Insulin

Inhaled insulin is available for prandial use with a more limited dosing range. It is contraindicated in patients with chronic lung disease such as asthma and chronic obstructive pulmonary disease and is not recommended in patients who smoke or who recently stopped smoking. It requires spirometry (FEV_1) testing to identify potential lung disease in all patients prior to and after starting therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day) and A1C remains above target, consider advancing to combination injectable therapy (**Fig. 8.2**). When initiating combination injectable therapy, metformin therapy should be maintained while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent). In general, GLP-1 receptor agonists should not be discontinued with the initiation of basal insulin. Sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonists are typically stopped once more complex insulin regimens beyond basal are used. In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once an insulin regimen is initiated, dose titration is important with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control).

Studies have demonstrated the noninferiority of basal insulin plus a single injection of rapid-acting insulin at the largest meal relative to basal insulin plus a GLP-1 receptor agonist relative to two daily injections of premixed insulins (**Fig. 8.2**). Basal insulin plus GLP-1 receptor agonists are associated with less hypoglycemia and with weight loss instead of weight gain but may be less tolerable and have a greater cost (37,38). In November 2016, the FDA approved two different once-daily combination products containing basal insulin plus a GLP-1 receptor agonist: insulin glargine plus lixisenatide and insulin degludec plus liraglutide. Other options for treatment intensification include adding a single injection of rapid-acting insulin analog (lispro, aspart, or glulisine) before the largest meal or stopping the basal insulin and initiating a premixed (or biphasic) insulin (NPH/Regular 70/30, 70/30 aspart mix, 75/25 or 50/50 lispro mix) twice daily, usually before breakfast and before dinner. Each approach has its advantages and disadvantages. For example, providers may wish to consider regimen flexibility when devising a plan for the initiation and adjustment of insulin therapy in people with type 2 diabetes, with rapid-acting insulin offering greater flexibility in terms of meal planning than premixed insulin. If one regimen is not effective (i.e., basal insulin + GLP-1 receptor agonist), consider switching to another regimen to achieve A1C targets (i.e., basal insulin + single injection of rapid-acting insulin or premixed insulin twice daily) (39,40). Regular human insulin and human NPH/Regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogs and premixed insulin analogs, respectively, but their pharmacodynamic profiles may make them less optimal.

Figure 8.2 outlines these options, as well as recommendations for further intensification, if needed, to achieve glycemic goals. If a patient is still above the A1C target on premixed insulin twice daily, consider switching to premixed analog insulin three times daily (70/30 aspart mix, 75/25 or 50/50 lispro mix). In general, three times daily premixed analog insulins have been found to be noninferior to basal-bolus regimens with similar rates of hypoglycemia (41). If a patient is still above the A1C target on basal insulin + single injection of rapid-acting insulin before the largest meal, advance to a basal-bolus regimen with ≥2 injections of rapid-acting insulin before meals. Consider switching patients from one regimen to another (i.e., premixed analog insulin three times daily to basal-bolus regimen or vice-versa) if A1C targets are not being met and/or depending on other patient considerations (39,40).

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9. Cardiovascular Disease and Risk Management

American Diabetes Association

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For prevention and management of diabetes complications in children and adolescents, please refer to Section 12 "Children and Adolescents."

Atherosclerotic cardiovascular disease (ASCVD)—defined as acute coronary syndromes (ACSs), a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed simultaneously. There is evidence that measures of 10-year coronary heart disease (CHD) risk among U.S. adults with diabetes have improved significantly over the past decade (1) and that ASCVD morbidity and mortality have decreased (2–4).

In all patients with diabetes, cardiovascular risk factors should be systematically assessed at least annually. These risk factors include hypertension, dyslipidemia, smoking, a family history of premature coronary disease, and the presence of albuminuria. Abnormal risk factors should be treated as described in these guidelines.

HYPERTENSION/BLOOD PRESSURE CONTROL

Recommendations

Screening and Diagnosis

- Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. **B**

Goals

- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. **A**
- Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. **C**
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. **E**

Treatment

- Patients with confirmed office-based blood pressure >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. **A**
- Patients with confirmed office-based blood pressure >160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. **A**

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- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). **A**
- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine (**A**) or 30–299 mg/g creatinine (**B**). If one class is not tolerated, the other should be substituted. **B**
- For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. **B**
- For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. **B**

Hypertension, defined as a sustained blood pressure ≥140/90 mmHg, is a common comorbidity of type 1 and type 2 diabetes. The prevalence of hypertension depends on type of diabetes, age, sex, BMI, and race/ethnicity. Hypertension is a major risk factor for both ASCVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying diabetic kidney disease, while in type 2 diabetes, it usually coexists with other cardiometabolic risk factors. Please refer to the American Diabetes Association (ADA) position statement "Diabetes and Hypertension" for a detailed review (5).

Screening and Diagnosis

Blood pressure should be measured by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should be confirmed on a separate day. Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white-coat hypertension, masked hypertension, or other discrepancies between office and "true" blood pressure. Studies in individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (6,7). However, most of the evidence of benefits of hypertension treatment in people with diabetes is based on office measurements.

Treatment Goals

Epidemiological analyses show that blood pressure >115/75 mmHg is associated with increased cardiovascular event rates and mortality in individuals with diabetes (8). Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and diabetic kidney disease) of lowering blood pressure to <140 mmHg systolic and <90 mmHg diastolic in individuals with diabetes (9,10). There is limited prespecified clinical trial evidence for the benefits of lower systolic blood pressure (SBP) or diastolic blood pressure (DBP) targets (11). A meta-analysis of randomized trials of adults with type 2 diabetes comparing intensive blood pressure targets (upper limit of 130 mmHg systolic and 80 mmHg diastolic) with standard targets (upper limit of 140–160 mmHg systolic and 85–100 mmHg diastolic) found no significant reduction in mortality or nonfatal MI. There was a statistically significant 35% relative risk (RR) reduction in stroke with intensive targets, but the absolute risk reduction was only 1%, and intensive targets were associated with an increased risk for adverse events such as hypotension and syncope (12).

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

Given the epidemiological relationship between lower blood pressure and better long-term clinical outcomes, two landmark trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure (ADVANCE-BP), examined the benefit of tighter blood pressure control in patients with type 2 diabetes. Additional studies, such as the Systolic Blood Pressure Intervention Trial (SPRINT) and the Hypertension Optimal Treatment (HOT) trial, also examined the potential benefits of intensive versus standard control, though the relevance of their results to people with diabetes is less clear.

ACCORD. The ACCORD trial examined whether an SBP of <120 mmHg in patients with type 2 diabetes at high risk for ASCVD provided greater cardiovascular protection than an SBP of 130–140 mmHg (13). The study did not find a benefit in the primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive blood pressure treatment (intensive BP; goal <120 mmHg, average blood pressure achieved 119/64 mmHg on 3.4 medications) with standard treatment (standard BP; average blood pressure achieved 143/70 mmHg on 2.1 medications). However, a follow-up analysis found a strong interaction between glycemic control and blood pressure control. Compared with the standard glycemia/standard BP control group in the blood pressure trial, the intensive BP/intensive glycemia, intensive BP/standard glycemia, and standard BP/intensive glycemia groups all showed benefit for reducing the risk of major cardiovascular disease (14). Stroke was significantly reduced in the intensive BP treatment groups, but the intensive BP/intensive glycemia group showed no evidence of incremental benefit compared with either single intensive intervention (14). Thus, more intensive blood pressure control may be reasonable in certain motivated, ACCORD-like patients (40–79 years of age with prior evidence of cardiovascular disease or multiple cardiovascular risk factors) who have been educated about the added treatment burden, side effects, and costs of more intensive blood pressure control and for patients who prefer to lower their risk of stroke beyond what can be achieved through standard care.

ADVANCE. In ADVANCE, the active blood pressure intervention arm (a single-pill, fixed-dose combination of perindopril and indapamide) showed a significant reduction in the risk of the primary composite end point (major macrovascular or microvascular event) and significant reductions in the risk of death from any cause and of death from cardiovascular causes (15). The baseline blood pressure among the study subjects was 145/81 mmHg. Compared with the placebo group, the patients treated with a single-pill, fixed-dose combination of perindopril and indapamide experienced an average reduction of 5.6 mmHg in SBP and 2.2 mmHg in DBP. The final blood pressure in the treated group was 136/73 mmHg, not quite the intensive or tight control achieved in ACCORD. The recently published 6-year follow-up of the ADVANCE trial, the ADVANCE–Post-Trial Observational Study (ADVANCE-ON), reported that the reductions in the risk of death from any cause and of death from cardiovascular causes in the intervention group were attenuated but remained significant (16).

HOT. The Hypertension Optimal Treatment (HOT) trial included patients with and without diabetes and compared DBP targets of ≤90, ≤85, and ≤80 mmHg. Post hoc analyses found cardiovascular benefit with more intensive targets in the subpopulation with diabetes (17). The HOT trial results, taken together with the higher quality data from ACCORD and ADVANCE, support the current recommendation to achieve blood pressure levels <140/90 mmHg, with lower targets in selected patients.

SPRINT. The Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter, randomized controlled trial that compared two strategies for treating SBP with either the standard target of <140 mmHg or an intensive target of <120 mmHg; primary outcomes were MI, ACS, stroke, heart failure, and death due to cardiovascular disease. Patients assigned to the intensive SBP target of <120 mmHg, compared with a target SBP of 140 mmHg, had reduced RR of cardiovascular events by almost a third and of death by almost a quarter, though risks of electrolyte abnormalities and acute kidney injury were increased (18). *Of note, patients with diabetes were excluded from participating in this trial, so the results have no direct implications for blood pressure management in patients with diabetes.*

Systolic Blood Pressure

The evidence that SBP >140 mmHg is harmful is irrefutable, suggesting that clinicians promptly initiate and titrate therapy to achieve and maintain SBP <140 mmHg in most patients. For some patients, lower SBP targets closer to 130 mmHg are appropriate. A recent systematic review and meta-analysis evaluating SBP lowering in adults with type 2 diabetes showed that each 10 mmHg reduction of SBP was associated with significantly lower risk of mortality, cardiovascular events, CHD, stroke, albuminuria, and retinopathy. However, when trials were stratified by mean baseline SBP ≥140 mmHg or <140 mmHg, blood pressure–lowering treatment was associated with lower risks of stroke and albuminuria, regardless of initial SBP (9). Therefore, individuals in whom cardiovascular disease risk, particularly stroke, is a concern may, as part of shared decision making, have lower systolic targets than 140 mmHg. This is especially true if lower blood pressure can be achieved with few drugs and without side effects of therapy. For older adults, treating to an SBP of <130 mmHg has not been shown to improve cardiovascular outcomes (19).

Diastolic Blood Pressure

Similarly, strong evidence from randomized clinical trials supports DBP targets of <90 mmHg. These targets are in harmony with the Eighth Joint National Committee (JNC 8) recommendation of a DBP threshold of <90 mmHg for individuals over 18 years of age with diabetes (11). A DBP of <80 mmHg may still be appropriate for patients with long life expectancy, chronic kidney disease, elevated urinary albumin excretion, evidence of cardiovascular disease, or additional risk factors such as dyslipidemia, smoking, or obesity (17). In older adults, treating to a DBP of <70 mmHg has been associated with a greater risk of mortality (20).

Treatment Strategies

Lifestyle Intervention

Although there are no well-controlled studies of diet and exercise in the treatment of elevated blood pressure or hypertension in individuals with diabetes, the Dietary Approaches to Stop Hypertension (DASH) study evaluated the impact of healthy dietary patterns in individuals without diabetes and has shown antihypertensive effects similar to those of pharmacologic monotherapy.

Lifestyle therapy consists of reducing excess body weight through caloric restriction, restricting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (21), and increasing activity levels (11).

These lifestyle (nonpharmacologic) strategies may also positively affect glycemia and lipid control and should be encouraged in those with even mildly elevated blood pressure, although the impact of lifestyle therapy on cardiovascular events has not been established. Nonpharmacologic therapy is reasonable in individuals with diabetes and mildly elevated blood pressure (SBP >120 mmHg or DBP >80 mmHg). If the blood pressure is confirmed to be ≥140 mmHg systolic and/or ≥90 mmHg diastolic, pharmacologic therapy should be initiated along with nonpharmacologic therapy (11). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management.

Pharmacologic Interventions

Lowering of blood pressure with regimens based on a variety of antihypertensive agents, including ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, and calcium channel blockers has been shown to be effective in reducing cardiovascular events (9,22).

In people with diabetes and albuminuria, ACE inhibitors or ARBs may have unique advantages for initial or early treatment of hypertension. In a trial of individuals at high risk for ASCVD, including a large subset with diabetes, an ACE inhibitor reduced ASCVD outcomes and the development of albuminuria when compared with placebo, even after adjustment for differences in blood pressure, an effect that has been termed a “blood pressure independent effect” (23). In patients with congestive heart failure, including subgroups with diabetes, ARBs have been shown to reduce major ASCVD outcomes (24–26). Among patients with type 2 diabetes, urine albumin–to–creatinine ratio (UACR)

≥300 mg/g creatinine, and elevated serum creatinine concentration, an ARB significantly reduced progression of kidney disease compared with placebo (27). A meta-analysis confirmed that treatment of patients with diabetic kidney disease with an ACE inhibitor or ARB reduces the risk of progressing to end-stage renal disease, though strong evidence of benefit was limited to participants with baseline UACR ≥300 mg/g creatinine (28). Smaller trials also suggest reduction in composite cardiovascular events and reduced progression of advanced nephropathy (29–31).

However, the superiority of ACE inhibitors or ARBs over other antihypertensive agents for prevention of cardiovascular outcomes has not been consistently shown for all patients with diabetes (22,28,32,33). In particular, a recent meta-analysis suggests that thiazide-type diuretics or dihydropyridine calcium channel blockers have cardiovascular benefit similar to that of ACE inhibitors or ARBs (22). Therefore, among patients without albuminuria for whom cardiovascular disease prevention is the primary goal of blood pressure control, a thiazide-like diuretic or dihydropyridine calcium channel blocker may be considered instead of or in addition to an ACE inhibitor or ARB.

There are no adequate head-to-head comparisons of ACE inhibitors and ARBs, but there is clinical trial support for each of the following statements: In patients with type 1 diabetes with hypertension and any degree of albuminuria, ACE inhibitors have been shown to reduce loss of glomerular filtration rate and delay the progression of nephropathy. In patients with type 2 diabetes, hypertension, and UACR 30–299 mg/g creatinine, ACE inhibitors and ARBs have been shown to delay the progression to UACR ≥300 mg/g creatinine. The use of both ACE inhibitors and ARBs in combination is not recommended given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (34,35).

Combination Drug Therapy

The blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed-dose combination of the ACE inhibitor perindopril and the thiazide-like diuretic indapamide significantly reduced combined microvascular and macrovascular outcomes, as well as death from cardiovascular causes and total mortality. The improved outcomes could also have been due to lower achieved blood pressure in the perindopril–indapamide arm (15). Another trial showed a decrease in morbidity and mortality in those receiving ACE inhibitor benazepril and calcium channel blocker amlodipine versus benazepril and thiazide-like diuretic hydrochlorothiazide (36,37). If needed to achieve blood pressure targets, amlodipine and indapamide or hydrochlorothiazide or thiazide-like diuretic chlorthalidone can be added. If estimated glomerular filtration rate is <30 mL/min/1.73 m^2, a loop diuretic should be prescribed. Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome clinical inertia in achieving blood pressure targets.

Bedtime Dosing

Growing evidence suggests that there is an association between absence of nocturnal blood pressure dipping and the incidence of ASCVD. A randomized controlled trial of 448 participants with type 2 diabetes and hypertension demonstrated reduced cardiovascular events and mortality with median follow-up of 5.4 years if at least one antihypertensive medication was given at bedtime (38). Consider administering one or more antihypertensive medications at bedtime (39).

Other Considerations

An important caveat is that most patients with diabetes and hypertension require multiple-drug therapy to reach blood pressure treatment goals (21). Identifying and addressing barriers to medication adherence (such as cost and side effects) should routinely be done. If blood pressure remains uncontrolled despite confirmed adherence to optimal doses of at least three antihypertensive agents of different classes, one of which should be a diuretic, clinicians should consider an evaluation for secondary causes of hypertension.

Pregnancy and Antihypertensive Medications

Since there is a lack of randomized controlled trials of antihypertensive therapy in pregnant women with diabetes, recommendations for the management of hypertension in pregnant women with diabetes should be similar to those for all pregnant women. The American College of Obstetricians and Gynecologists (ACOG) has recommended that women with mild gestational hypertension (SBP <160 mmHg or DBP <110 mmHg) do not need to be treated with antihypertensive medications as there is no benefit identified that clearly outweighs potential risks of therapy (40). A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (41). For pregnant women who require antihypertensive therapy, SBP levels of 120–160 mmHg and DBP levels of 80–105 mmHg are suggested to optimize maternal health without risking fetal harm. Lower targets (SBP 110–119 mmHg and DBP 65–79 mmHg) may contribute to improved long-term maternal health; however, they may be associated with impaired fetal growth. Pregnant women with hypertension and evidence of end-organ damage from cardiovascular and/or renal disease may be considered for lower blood pressure targets to avoid progression of these conditions during pregnancy.

During pregnancy, treatment with ACE inhibitors, ARBs, and spironolactone are contraindicated as they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, hydralazine, carvedilol, clonidine, and long-acting nifedipine (40). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (40,42). ACOG also recommends that postpartum patients with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these women as they have increased lifetime cardiovascular risk (43).

LIPID MANAGEMENT

Recommendations

- In adults not taking statins, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter, or more frequently if indicated. E
- Obtain a lipid profile at initiation of statin therapy and periodically thereafter as it may help to monitor the response to therapy and inform adherence. E
- Lifestyle modification focusing on weight loss (if indicated); the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of dietary ω-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. A
- Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). C
- For patients with fasting triglyceride levels ≥500 mg/dL (5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C
- For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. A
- For patients with diabetes aged <40 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity or high-intensity statin and lifestyle therapy. C
- For patients with diabetes aged 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin and lifestyle therapy. A
- For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using high-intensity statin and lifestyle therapy. B
- For patients with diabetes aged >75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin therapy and lifestyle therapy. B
- For patients with diabetes aged >75 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity or high-intensity statin therapy and lifestyle therapy. B
- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). E
- The addition of ezetimibe to moderate-intensity statin therapy has been shown to provide additional cardiovascular benefit compared with moderate-intensity statin therapy alone for patients with recent acute coronary syndrome and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) and should be considered for these patients A and also in patients with diabetes and history of ASCVD who cannot tolerate high-intensity statin therapy. E
- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. A However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≤34 mg/dL (0.9 mmol/L). B
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended. A
- Statin therapy is contraindicated in pregnancy. B

Lifestyle Intervention

Lifestyle intervention, including weight loss, increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each patient's age, diabetes type, pharmacologic treatment, lipid levels, and medical conditions. Recommendations should focus on reducing saturated fat, cholesterol, and *trans* fat intake and increasing plant stanols/sterols, ω-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus). Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control.

Statin Treatment

Initiating Statin Therapy Based on Risk

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of pharmacologic (statin) therapy on ASCVD outcomes in subjects with and without CHD (44,45). Subgroup analyses of patients with diabetes in larger trials (46–50) and trials in patients with diabetes (51,52) showed significant primary and secondary prevention of ASCVD events and CHD death in patients with diabetes. Meta-analyses, including data from over 18,000 patients with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each mmol/L (39 mg/dL) reduction in LDL cholesterol (53).

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (54,55). Statins are the drugs of choice for LDL cholesterol lowering and cardioprotection.

Most trials of statins and ASCVD outcomes tested specific doses of statins against placebo or other statins rather than aiming for specific LDL cholesterol goals (56), suggesting that the initiation and intensification of statin therapy be based on risk profile (**Table 9.1** and **Table 9.2**).

The Risk Calculator. The American College of Cardiology/American Heart Association ASCVD risk calculator may be a useful tool to estimate 10-year ASCVD risk (http://my.americanheart.org). As diabetes itself confers increased risk for ASCVD, the risk calculator has limited

Table 9.1—Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy. **ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

use for assessing cardiovascular risk in individuals with diabetes.

Age 40–75 Years

In low-risk patients with diabetes aged 40–75 years, moderate-intensity statin treatment should be considered in addition to lifestyle therapy. Clinical trials in high-risk patients with increased cardiovascular risk (e.g., LDL cholesterol ≥100 mg/dL [2.6 mmol/L], high blood pressure, smoking, albuminuria, and family history of premature ASCVD) and with ASCVD (57–59) have demonstrated that more aggressive therapy with high doses of statins led to a significant reduction in cardiovascular events. High-intensity statins are recommended in all such patients.

Age >75 Years

For adults with diabetes >75 years of age, there are limited data regarding the benefits and risks of statin therapy. Statin therapy should be individualized based on risk profile. High-intensity statins, if well tolerated, are still appropriate and recommended for older adults with ASCVD. High-intensity statin therapy may also be appropriate in adults with diabetes >75 years of age with additional ASCVD risk factors. However, the risk–benefit profile should be routinely evaluated in this population, with downward titration (e.g., high to moderate intensity) performed as needed. See Section 11 "Older Adults" for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes

Very little clinical trial evidence exists for patients with type 2 diabetes under the age of 40 years or for patients with type 1 diabetes of any age. In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 patients with type 1 diabetes had a proportionately similar, although not statistically significant, reduction in risk as patients with type 2 diabetes (47). Even though the data are not definitive, similar statin treatment approaches should be considered for patients with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (60) for additional discussion.

High-intensity statin therapy is recommended for all patients with diabetes and ASCVD. Treatment with a moderate dose of statin should be considered if the patient does not have ASCVD but has additional ASCVD risk factors.

Table 9.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to <50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

Ongoing Therapy and Monitoring With Lipid Panel

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, testing for LDL cholesterol may be considered on an individual basis (e.g., to monitor for adherence and efficacy). In cases where patients are adherent but the LDL cholesterol level is not responding, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (61). When maximally tolerated doses of statins fail to substantially lower LDL cholesterol (<30% reduction from the patient's baseline), there is no strong evidence that combination therapy should be used. Clinicians should attempt to find a dose or alternative statin that is tolerable, if side effects occur. There is evidence for benefit from even extremely low, less than daily, statin doses (62).

Increased frequency of LDL cholesterol monitoring should be considered for patients with new-onset ACS. Increased frequency of LDL cholesterol monitoring may also be considered in adults with heterozygous familial hypercholesterolemia who require additional lowering of LDL cholesterol.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone. Individuals were ≥50 years of age, had experienced an ACS within the preceding 10 days, and had an LDL cholesterol level ≥50 mg/dL (1.3 mmol/L). In those with diabetes (27%), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45%) and RR reduction of 14% (RR 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (63). Therefore, for people meeting IMPROVE-IT eligibility criteria, ezetimibe should be added to moderate-intensity statin therapy. Though not explicitly studied, these results may also suggest that the addition of ezetimibe should be considered for any patient with diabetes and history of ASCVD who cannot tolerate high-intensity statin therapy.

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximally tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36% to 59%. These agents may therefore be considered as adjunctive therapy for patients with diabetes at high risk for ASCVD events who require additional lowering of LDL cholesterol or who require but are intolerant to high-intensity statin therapy (64,65). It is important to note that the effects of this novel class of agents on ASCVD outcomes are unknown as phase 4 studies are currently under way.

Treatment of Other Lipoprotein Fractions or Targets

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including abstinence from alcohol (66). Severe hypertriglyceridemia (>1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) to reduce the risk of acute pancreatitis.

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in individuals with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (67). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (68).

Combination Therapy

Statin and Fibrate

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (69).

In the ACCORD study, in patients with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke as compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (0.9 mmol/L) (70).

Statin and Niacin

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 patients (about one-third with diabetes) with established ASCVD, low LDL cholesterol levels (<180 mg/dL [4.7 mmol/L]), low HDL cholesterol levels (men <40 mg/dL [1.0 mmol/L] and women <50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (71). Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes, possible increase in risk of ischemic stroke, and side effects.

Diabetes With Statin Use

Several studies have reported an increased risk of incident diabetes with statin use (72,73), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statins were linked to diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (74). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (74). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 patients (73).

Statins and Cognitive Function

A recent systematic review of the U.S. Food and Drug Administration's postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition. Therefore, a concern that statins might cause cognitive dysfunction or dementia should not deter their use in individuals with diabetes at high risk for ASCVD (75).

ANTIPLATELET AGENTS

Recommendations

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**
- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome and may have benefits beyond this period. **B**

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased cardiovascular risk. This includes most men and women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding. **C**
- Aspirin should not be recommended for atherosclerotic cardiovascular disease prevention for adults with diabetes at low atherosclerotic cardiovascular disease risk, such as in men or women with diabetes aged <50 years with no other major atherosclerotic cardiovascular disease risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. **C**
- When considering aspirin therapy in patients with diabetes <50 years of age with multiple other atherosclerotic cardiovascular disease risk factors, clinical judgment is required. **E**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial both for patients with diabetes and for patients without diabetes (76,77). Previous randomized controlled trials of aspirin specifically in patients with diabetes failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (78–80).

The Antithrombotic Trialists' (ATT) collaborators published an individual patient-level meta-analysis of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (RR 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (RR 0.95 [95% CI 0.78–1.15]) or total stroke. There was some evidence of a difference in aspirin effect by sex: aspirin significantly reduced ASCVD events in men but not in women. Conversely, aspirin had no effect on stroke in men but significantly reduced stroke in women. However, there was no heterogeneity of effect by sex in the risk of serious vascular events ($P = 0.9$).

Sex differences in aspirin's effects have not been observed in studies of secondary prevention (76). In the six trials examined by the ATT collaborators, the effects of aspirin on major vascular events were similar for patients with or without diabetes: RR 0.88 (95% CI 0.67–1.15) and RR 0.87 (95% CI 0.79–0.96), respectively. The confidence interval was wider for those with diabetes because of smaller numbers.

Aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effects appear to be an increased risk of gastrointestinal bleeding. The excess risk may be as high as 1–5 per 1,000 per year in real-world settings. In adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to or greater than the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (81).

Treatment Considerations

In 2010, a position statement of the ADA, the American Heart Association, and the American College of Cardiology Foundation recommended that low-dose (75–162 mg/day) aspirin for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased ASCVD risk and who are not at increased risk for bleeding (82). This previous statement included sex-specific recommendations for use of aspirin therapy as primary prevention persons with diabetes. However, since that time, multiple recent well-conducted studies and meta-analyses have reported a risk of heart disease and stroke that is equivalent if not higher in women compared with men with diabetes, including among nonelderly adults. Thus, current recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria) who are not at increased risk of bleeding (83–86). While risk calculators such as those from the American College of Cardiology/American Heart Association (http://my.americanheart.org) may be a useful tool to estimate 10-year ASCVD risk, diabetes itself confers increased risk for ASCVD. As a result, such risk calculators have limited utility in helping to assess the potential benefits of aspirin therapy in individuals with diabetes. Noninvasive imaging techniques such as coronary computed tomography angiography may potentially help further tailor aspirin therapy, particularly in those at low risk (87), but are not generally recommended. Sex differences in the antiplatelet effect of aspirin have been suggested in the general population (88); however, further studies are needed to investigate the presence of such differences in individuals with diabetes.

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (89). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects (90). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from patients with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in the patient with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus not sensitive to the effects of aspirin (91). "Aspirin resistance" has been described in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (88), but other studies suggest no impairment in aspirin response among patients with diabetes (92). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (93); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Use

A P2Y12 receptor antagonist in combination with aspirin should be used for at least 1 year in patients following an ACS and may have benefits beyond this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (94). In patients with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and coronary heart disease death (95). More studies are needed to investigate the longer-term benefits of these therapies after ACS among patients with diabetes.

CORONARY HEART DISEASE

Recommendations

Screening

- In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**
- Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

Treatment

- In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) **A** and consider ACE inhibitor therapy **C** to reduce the risk of cardiovascular events.
- In patients with prior myocardial infarction, β-blockers should be continued for at least 2 years after the event. **B**
- In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. **A**
- In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. **B**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (96), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (97,98). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (99). In prospective trials, coronary artery calcium has been established as an independent predictor of future ASCVD events in patients with diabetes and is superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (100–102). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (103). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (104,105). Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven. Although asymptomatic patients with diabetes with higher coronary disease burden have more future cardiac events (100,106,107), the role of these tests beyond risk stratification is not clear. Their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (108). Patients at increased ASCVD risk should receive aspirin and a statin and ACE inhibitor or ARB therapy if the patient has hypertension, unless there are contraindications to a particular drug class. While clear benefit exists for ACE inhibitor and ARB therapy in patients with nephropathy or hypertension, the benefits in patients with ASCVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (109,110). In patients with prior MI, β-blockers should be continued for at least 2 years after the event (111).

Diabetes and Heart Failure

As many as 50% of patients with type 2 diabetes may develop heart failure (112). Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with heart failure (113–115). Therefore, thiazolidinedione use should be avoided in patients with symptomatic heart failure.

Recent studies have also examined the relationship between dipeptidyl peptidase 4 (DPP-4) inhibitors and heart failure and have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with saxagliptin (a DPP-4 inhibitor) were more likely to be hospitalized for heart failure than were those given placebo (3.5% vs. 2.8%, respectively) (116). Two other recent multicenter, randomized, double-blind, noninferiority trials, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), did not show associations between DPP-4 inhibitor use and heart failure. EXAMINE reported that the hospital admission rate for heart failure was 3.1% for patients randomly assigned to alogliptin compared with 2.9% for those randomly assigned to placebo (hazard ratio 1.07 [95% CI 0.79–1.46]) (117). Alogliptin had no effect on the composite end point of cardiovascular death and hospital admission for heart failure in the post hoc analysis (hazard ratio 1.00 [95% CI 0.82–1.21]) (117). TECOS showed a nonsignificant difference in the rate of heart failure hospitalization for the sitagliptin group (3.1%; 1.07 per 100 person-years) compared with the placebo group (3.1%; 1.09 per 100 person-years) (118).

Antihyperglycemic Therapies and Cardiovascular Outcomes

Recently published cardiovascular outcome trials have provided additional data on cardiovascular outcomes in patients with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease. The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, versus placebo and standard care on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%) (119). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 receptor agonist, versus placebo and standard care on cardiovascular outcomes in patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease inclusive of a prior MI, prior stroke or transient ischemic attack, prior revascularization procedure, or ≥50% stenosis of coronary, carotid, or lower-extremity arteries. LEADER showed that the composite primary outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) after a median follow-up of 3.8 years (120). Whether other glucagon-like peptide 1 receptor agonists will have the same effect in high-risk patients or if this drug class will have similar effects in lower-risk patients with diabetes remains unknown.

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10. Microvascular Complications and Foot Care

American Diabetes Association

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DIABETIC KIDNEY DISEASE

Recommendations

Screening

- At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of ≥5 years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. B

Treatment

- Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. A
- Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. A
- For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered. B
- In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30–299 mg/g creatinine) B and is *strongly* recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. A
- Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. E
- Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. E
- An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. B
- When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. E
- Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. A
- Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. B

Assessment of Albuminuria and Estimated Glomerular Filtration Rate

Chronic kidney disease (CKD) is diagnosed by the presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). Diabetic kidney disease, or CKD attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading

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cause of end-stage renal disease (ESRD) (1). Diabetic kidney disease typically develops after a diabetes duration of 10 years, or at least 5 years in type 1 diabetes, but may be present at diagnosis of type 2 diabetes.

Screening for albuminuria can be most easily performed by urinary albumin–to–creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine (Cr) is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration.

Normal UACR is generally defined as $<$30 mg/g Cr, and increased urinary albumin excretion is defined as $\geq$30 mg/g Cr. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes. Furthermore, because of biological variability in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have albuminuria. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage.

eGFR should be calculated from serum Cr using a validated formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred (2). eGFR is routinely reported by laboratories with serum Cr, and eGFR calculators are available from http://www.nkdep.nih.gov. An eGFR $<$60 mL/min/1.73 m^2 is generally considered abnormal, though optimal thresholds for clinical diagnosis are debated (3).

Urinary albumin excretion and eGFR each vary within people over time, and abnormal results should be confirmed to stage CKD (1,2). Since 2003, stage 1–2 CKD has been defined by evidence of kidney damage (usually albuminuria) with eGFR $\geq$60 mL/min/1.73 m^2, while stages 3–5 CKD have been defined by progressively lower ranges of eGFR (4) (**Table 10.1**). More recently, Kidney Disease: Improving Global Outcomes (KDIGO) recommended a more comprehensive CKD staging that incorporates albuminuria and is more closely associated with risks of cardiovascular disease (CVD) and CKD progression (2). It has not been determined whether application of the more complex system aids clinical care or improves health outcomes.

Table 10.1—Stages of CKD

Stage	Description	eGFR (mL/min/1.73 m^2)
1	Kidney damage* with normal or increased eGFR	$\geq$90
2	Kidney damage* with mildly decreased eGFR	60–89
3	Moderately decreased eGFR	30–59
4	Severely decreased eGFR	15–29
5	Kidney failure	$<$15 or dialysis

*Kidney damage is defined as UACR persistently $\geq$30 mg/g Cr or other abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (4).

Diagnosis of Diabetic Kidney Disease

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without hematuria, and gradually progressive kidney disease. However, signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes, and reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (5–8).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) may suggest alternative or additional causes of kidney disease. For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for patients with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (9).

Surveillance

Albuminuria and eGFR should be monitored regularly to enable timely diagnosis of diabetic kidney disease, monitor progression of diabetic kidney disease, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed (**Table 10.2**). Albuminuria and eGFR may change due to progression of diabetic kidney disease, development of superimposed kidney disease, or the effects of medication, including many antihypertensive medications (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs], and diuretics) and some glucose-lowering medications (e.g., sodium–glucose cotransporter 2 [SGLT2] inhibitors). For patients with eGFR $<$60 mL/min/1.73 m^2, appropriate medication dosing should be verified, exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and potential CKD complications should be evaluated.

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy, and achieving blood pressure control is a subject of debate. Continued surveillance can assess both response to therapy and disease progression and may aid in assessing adherence to ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria from levels $\geq$300 mg/g Cr has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to minimize UACR. However, this approach has not been formally evaluated in prospective trials, and in type 1 diabetes, remission of albuminuria may occur spontaneously and is not associated with improved clinical outcomes (10). The prevalence of CKD complications correlates with eGFR. When eGFR is $<$60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 10.2**). Early vaccination

Table 10.2—Management of CKD in diabetes

eGFR (mL/min/1.73 m^2)	Recommended management
All patients	Yearly measurement of UACR, serum Cr, potassium
45–60	Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes <10 years, persistent albuminuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in eGFR, or active urinary sediment on urine microscopic examination) Consider the need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, and parathyroid hormone at least yearly Assure vitamin D sufficiency Vaccinate against Hep B virus Consider bone density testing Referral for dietary counseling
30–44	Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, and weight every 3–6 months Consider the need for dose adjustment of medications
<30	Referral to a nephrologist

against hepatitis B virus is indicated in patients likely to progress to ESRD.

Interventions

Nutrition

For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline.

Glycemia

Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 diabetes (11,12) and type 2 diabetes (1,13–17). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that glycemic control itself helps prevent diabetic kidney disease and its progression. The effects of glucose-lowering therapies on diabetic kidney disease have helped define hemoglobin A1C targets (**Table 6.2**).

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (18–20). Glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (21,22). Renal effects may be considered among other factors when selecting glucose-lowering medications for individual patients (see Section 8 "Pharmacologic Approaches to Glycemic Treatment").

The presence of diabetic kidney disease affects the risks and benefits of intensive glycemic control and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline (23,24). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (17,25,26). Therefore, in some patients with prevalent diabetic kidney disease and substantial comorbidity, target A1C levels should be >7% (53 mmol/mol) (1,27). The glucose-lowering effects of SGLT2 inhibitors are blunted with reduced eGFR, but the renal and cardiovascular benefits of empagliflozin, compared with placebo, were not reduced among trial participants with baseline eGFR 30–59 mL/min/1.73 m^2, compared with participants with baseline eGFR ≥60 mL/min/1.73 m^2 (19,28).

With reduced eGFR, drug dosing may require modification (1). The U.S. Food and Drug Administration (FDA) revised guidance for the use metformin in diabetic kidney disease in 2016 (29), recommending use of eGFR instead of serum Cr to guide treatment and expanding the pool of patients with kidney disease for whom metformin treatment should be considered. Revised FDA guidance states that metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2, eGFR should be monitored while taking metformin, the benefits and risks of continuing treatment should be reassessed when eGFR falls <45 mL/min/1.73 m^2, metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m^2, and metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m^2. Other glucose-lowering medications also require dose adjustment or discontinuation at low eGFR (1).

Cardiovascular Disease and Blood Pressure

Patients with diabetic kidney disease are at high risk of CVD. To reduce cardiovascular risk, statin therapy and blood pressure treatment should be considered in patients with diabetic kidney disease. Blood pressure control reduces risk of cardiovascular events (30).

Hypertension is a strong risk factor for the development and progression of diabetic kidney disease. Antihypertensive therapy reduces the risk of albuminuria (30–32), and among patients with type 1 or 2 diabetes with established diabetic kidney disease (eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g Cr), ACE inhibitor or ARB therapy reduce the risk of progression to ESRD (33–35).

Blood pressure levels <140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression. In individuals with albuminuria, who are at increased risk of CVD and CKD progression, lower blood pressure targets (e.g., <130/80 mmHg) may be considered (36). Of note, there is an adverse safety signal in clinical trials of diabetic kidney disease when diastolic blood pressure is treated to <70 mmHg and especially <60 mmHg in older populations. As a result, clinical judgment should be used when attempting to achieve systolic blood pressure targets <130 mmHg to avoid diastolic blood pressure levels <60–70 mmHg.

ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes, hypertension, eGFR <60 mL/min/1.73 m^2, and UACR ≥300 mg/g Cr because of their proven benefits for prevention of CKD progression and major CVD events (37). In general, ACE inhibitors and ARBs are considered to have similar benefits (38) and risks. In the setting of lower levels of albuminuria (30–299 mg/g Cr), ACE inhibitor or ARB therapy has been demonstrated to reduce progression to more advanced albuminuria (≥300 mg/g Cr) and cardiovascular events but not progression to ESRD (37,39). While ACE inhibitors or ARB are often prescribed for albuminuria without hypertension, clinical trials have not been performed in this setting to determine whether this improves renal outcomes.

Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but may not be superior to alternative classes of antihypertensive therapy (40). In a trial of people with type 2 diabetes and normal urine albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (41). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (42). *Therefore, ACE inhibitors or ARBs are not recommended for patients without hypertension to prevent the development of diabetic kidney disease.*

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or diabetic kidney disease, and the drug combination had higher adverse event rates (hyperkalemia and/or acute kidney injury) (43). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone) in combination with ACE inhibitors or ARBs remain an area of great interest. Mineralocorticoid receptor antagonists are effective for management of resistant hypertension, have been shown to reduce albuminuria in short-term studies of diabetic kidney disease, and may have additional cardiovascular benefits (44–46). There has been, however, an increase in hyperkalemic episodes in those on dual therapy, and larger, longer trials with clinical outcomes are needed before recommending such therapy.

Diuretics, calcium channel blockers, and β-blockers can be used as add-on therapy to achieve blood pressure goals in patients treated with maximum doses of ACE inhibitors or ARBs (47) or as alternate therapy in the rare individual unable to tolerate ACE inhibitors and ARBs.

Referral to a Nephrologist

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease, difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal replacement therapy for ESRD. The threshold for referral may vary depending on the frequency with which a provider encounters patients with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR ≤30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (48). However, other specialists and providers should also educate their patients about the progressive nature of diabetic kidney disease, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

DIABETIC RETINOPATHY

Recommendations

- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Screening

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then exams every 2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam. **E**
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

Treatment

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**
- Laser photocoagulation therapy is indicated to reduce the risk of vision

loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. A

- Intravitreal injections of anti–vascular endothelial growth factor are indicated for central-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision. A
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. A

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (49), nephropathy (50), hypertension (51), and dyslipidemia (52). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy and potentially improve patient-reported visual function (14,53–55).

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (54). ACE inhibitors and ARBs are both effective treatments in diabetic retinopathy (56). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy (NPDR) at baseline (52). Several case series and a controlled prospective study suggest that pregnancy in patients with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor at the time of conception (57,58). Laser photocoagulation surgery can minimize the risk of vision loss (58).

Screening

The preventive effects of therapy and the fact that patients with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy.

An ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy should perform the examinations. If diabetic retinopathy is present, prompt referral to an ophthalmologist is recommended. Subsequent examinations for patients with type 1 or type 2 diabetes are generally repeated annually for patients with minimal to no retinopathy. Exams every 2 years may be cost-effective after one or more normal eye exams, and in a population with well-controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (59). More frequent examinations by the ophthalmologist will be required if retinopathy is progressing.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (60,61). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (62). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for comprehensive eye exams, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (63).

Type 2 Diabetes

Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Pregnancy is associated with a rapid progression of diabetic retinopathy (64,65). Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (58). Women who develop gestational diabetes mellitus do not require eye examinations during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (66).

Treatment

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (67) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe NPDR or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications.

Anti–Vascular Endothelial Growth Factor Treatment

While the ETDRS (68) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or within 500 μm of the center of the macula), current data from well-designed clinical trials demonstrate that intravitreal anti–vascular endothelial growth factor (anti-VEGF) agents provide a more effective treatment regimen for central-involved diabetic macular edema than monotherapy or even combination therapy with laser (69–71).

In both trials, laser photocoagulation surgery was beneficial in reducing the risk of further visual loss in affected patients but generally not beneficial in reversing already diminished acuity. Now, anti-VEGF improves vision and has replaced the need for laser photocoagulation in the vast majority of patients with diabetic macular edema in most cases (72). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema. Intravitreous anti-VEGF therapy is also a potentially viable alternative treatment for PDR (73). Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation.

NEUROPATHY

Recommendations

Screening

- All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. B
- Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. B
- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular and neuropathic complications. E

Treatment

- Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes A and to slow the progression of neuropathy in patients with type 2 diabetes. B
- Assess and treat patients to reduce pain related to diabetic peripheral neuropathy B and symptoms of autonomic neuropathy and to improve quality of life. E
- Either pregabalin or duloxetine are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. A

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important.

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. Numerous treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathy (DPN) may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
4. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control can effectively prevent DPN and cardiac autonomic neuropathy (CAN) in type 1 diabetes (74,75) and may modestly slow their progression in type 2 diabetes (16) but does not reverse neuronal loss. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (76) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests. Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesias (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation
2. Large-fiber function: vibration perception, 10-g monofilament, and ankle reflexes
3. Protective sensation: 10-g monofilament

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical or the diagnosis is unclear.

In all patients with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (alcohol), neurotoxic medications (chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (multiple myeloma, bronchogenic carcinoma), infections (HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (77).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

Cardiac Autonomic Neuropathy

CAN is associated with mortality independently of other cardiovascular risk factors (78,79). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies

Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is emerging as a viable alternative.

Genitourinary Disturbances

Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (76). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (80). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in patients with type 1 diabetes (81–84). Although the evidence for the benefit of near-normal glycemic control is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (16,85). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (86).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (87). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions.

Pregabalin and duloxetine have received regulatory approval by the FDA, Health Canada, and the European Medicines Agency for the treatment of neuropathic pain in diabetes. The opioid tapentadol has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker (88). Comparative effectiveness studies and trials that include quality-of-life outcomes are rare, so treatment decisions must consider each patient's presentation and comorbidities and often follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and stepwise pharmacologic strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (89–91).

Pregabalin, a calcium channel α2-δ subunit ligand, is the most extensively studied drug for DPN. The majority of studies testing pregabalin have reported favorable effects on the proportion of participants with at least 30–50% improvement in pain (88,90,92–95). However, not all trials with pregabalin have been positive (88,90,96,97), especially when treating patients with advanced refractory DPN (94). Adverse effects may be more severe in older patients (98) and may be attenuated by lower starting doses and more gradual titration.

Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DPN in multicenter randomized trials, although some of these had high drop-out rates (88,90,95,97). Duloxetine also appeared to improve neuropathy-related quality of life (99). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (100). Adverse events may be more severe in older people, but may be attenuated with lower doses and slower titrations of duloxetine.

Tapentadol is a centrally acting opioid analgesic that exerts its analgesic effects through both μ-opioid receptor agonism and noradrenaline reuptake inhibition. Extended-release tapentadol was approved by the FDA for the treatment of neuropathic pain associated with diabetes based on data from two multicenter clinical trials in which participants titrated to an optimal dose of tapentadol were randomly assigned to continue that dose or switch to placebo (101,102). However, both used a design enriched for patients who responded to tapentadol and therefore their results are not generalizable. A recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain found the evidence supporting the effectiveness of tapentadol in reducing neuropathic pain to be inconclusive (88). Therefore, given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of tapentadol ER is not generally recommended as a first- or second-line therapy.

Tricyclic antidepressants, gabapentin, venlafaxine, carbamazepine, tramadol, and topical capsaicin, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (76,88,90).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. Dietary changes may be useful, such as eating multiple small meals and decreasing dietary fat and fiber intake. Withdrawing drugs with adverse effects on gastrointestinal motility including opioids, anticholinergics, tricyclic antidepressants, glucagon-like peptide 1 receptor agonists, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (103,104). In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 5 days is no longer recommended by the FDA or the European Medicines Agency. It should be reserved for severe cases that are unresponsive to other therapies (104).

Erectile Dysfunction

Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve the patient's quality of life.

FOOT CARE

Recommendations

- Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**
- All patients with diabetes should have their feet inspected at every visit. **C**
- Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**
- The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration, or ankle reflexes), and vascular assessment including pulses in the legs and feet. **B**
- Patients who are 50 years or older and any patients with symptoms of claudication or decreased and/or absent pedal pulses should be referred for further vascular assessment as appropriate. **C**
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot, prior ulcers, or amputation). **B**
- Refer patients who smoke or who have histories of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Provide general preventive foot self-care education to all patients with diabetes. **B**
- The use specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, or history of amputation. **B**

Foot ulcers and amputation, which are consequences of diabetic neuropathy and/or peripheral arterial disease (PAD), are common and represent major causes of morbidity and mortality in people with diabetes. Early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- Poor glycemic control
- Peripheral neuropathy with LOPS
- Cigarette smoking
- Foot deformities
- Preulcerative callus or corn
- PAD
- History of foot ulcer
- Amputation
- Visual impairment
- Diabetic nephropathy (especially patients on dialysis)

Clinicians are encouraged to review American Diabetes Association screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (105).

Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually. Detailed foot assessments may occur more frequently in patients with histories of ulcers or amputations, foot deformities, insensate feet, and PAD (106). Foot inspections should occur at every visit in all patients with diabetes. To assess risk, clinicians should ask about history of foot ulcers or amputation, neuropathic and peripheral vascular symptoms, impaired vision, renal disease, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be performed. Vascular assessment should include inspection and palpation of pedal pulses.

The neurological exam performed as part of the foot examination is designed to identify LOPS rather than early neuropathy. The 10-g monofilament is the most useful test to diagnose LOPS. Ideally, the 10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration sensation using a 128-Hz tuning fork, or ankle reflexes). Absent monofilament sensation suggests LOPS, while at least two normal tests (and no abnormal test) rules out LOPS.

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of decreased walking speed, leg fatigue, claudication, and an assessment of the pedal pulses. Ankle-brachial index testing should be performed in patients with symptoms or signs of PAD.

Patient Education

All patients with diabetes and particularly those with high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) and their families should be provided general education about risk factors and appropriate management (107). Patients at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot monitoring on a daily basis. Patients with LOPS should be educated on ways to substitute other sensory modalities (palpation or visual inspection using an unbreakable mirror) for surveillance of early foot problems.

The selection of appropriate footwear and footwear behaviors at home should also be discussed. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

Treatment

People with neuropathy or evidence of increased plantar pressures (e.g., erythema, warmth, or calluses) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extrawide or deep shoes. People with bony deformities, including Charcot foot, who cannot be accommodated with commercial therapeutic footwear, will require custom-molded shoes. Special consideration and a thorough workup should be performed when patients with neuropathy present with the acute onset of a red, hot, swollen foot or ankle, and Charcot neuroarthropathy should be excluded. Early diagnosis and treatment of Charcot neuroarthropathy is the best way to prevent deformities that increase the risk of ulceration and amputation. The routine prescription of therapeutic footwear is not generally recommended. However, patients should be provided adequate information to aid in selection of appropriate footwear. General footwear recommendations include a broad and square toe box, laces with three or four eyes per side, padded tongue, quality lightweight materials, and sufficient size to accommodate a cushioned insole. Use of custom therapeutic footwear can help reduce the risk of future foot ulcers in high-risk patients (106,108).

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. *Staphylococci* and *Streptococci* are the most common causative organisms. Wounds without evidence of soft-tissue or bone infection do not require antibiotic therapy. Empiric antibiotic therapy can be narrowly targeted at gram-positive cocci in many patients with acute infections, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader-spectrum regimens and should be referred to specialized care centers (109). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes (109).

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11. Older Adults

American Diabetes Association

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Recommendations

- Consider the assessment of medical, mental, functional, and social geriatric domains in older adults to provide a framework to determine targets and therapeutic approaches for diabetes management. C
- Screening for geriatric syndromes may be appropriate in older adults experiencing limitations in their basic and instrumental activities of daily living, as they may affect diabetes self-management and be related to health-related quality of life. C
- Annual screening for early detection of mild cognitive impairment or dementia is indicated for adults 65 years of age or older. B
- Older adults (≥65 years of age) with diabetes should be considered a high-priority population for depression screening and treatment. B
- Hypoglycemia should be avoided in older adults with diabetes. It should be assessed and managed by adjusting glycemic targets and pharmacologic interventions. B
- Older adults who are cognitively and functionally intact and have significant life expectancy may receive diabetes care with goals similar to those developed for younger adults. C
- Glycemic goals for some older adults might reasonably be relaxed using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. C
- Screening for diabetes complications should be individualized in older adults. Particular attention should be paid to complications that would lead to functional impairment. C
- Treatment of hypertension to individualized target levels is indicated in most older adults. C
- Treatment of other cardiovascular risk factors should be individualized in older adults considering the time frame of benefit. Lipid-lowering therapy and aspirin therapy may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials. E
- When palliative care is needed in older adults with diabetes, strict blood pressure control may not be necessary, and withdrawal of therapy may be appropriate. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. E
- Consider diabetes education for the staff of long-term care facilities to improve the management of older adults with diabetes. E
- Patients with diabetes residing in long-term care facilities need careful assessment to establish glycemic goals and to make appropriate choices of glucose-lowering agents based on their clinical and functional status. E
- Overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity are primary goals for diabetes management at the end of life. E

Diabetes is an important health condition for the aging population; approximately one-quarter of people over the age of 65 years have diabetes (1), and this proportion is expected to increase rapidly in the coming decades. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses, such as hypertension, coronary heart disease, and stroke, than those without diabetes. Older adults with diabetes also are at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, urinary incontinence, injurious falls, and persistent pain.

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Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact therapeutic approaches and targets. Older adults are at increased risk for depression and should therefore be screened and treated accordingly (2). Diabetes management may require assessment of medical, mental, functional, and social domains. This may provide a framework to determine targets and therapeutic approaches. Particular attention should be paid to complications that can develop over short periods of time and/or that would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association (ADA) consensus report "Diabetes in Older Adults" for details (3).

NEUROCOGNITIVE FUNCTION

Older adults with diabetes are at higher risk of cognitive decline and institutionalization (4,5). The presentation of cognitive impairment ranges from subtle executive dysfunction to memory loss and overt dementia. People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia than people with normal glucose tolerance (6). The effects of hyperglycemia and hyperinsulinemia on the brain are areas of intense research. Clinical trials of specific interventions—including cholinesterase inhibitors and glutamatergic antagonists—have not shown positive therapeutic benefit in maintaining or significantly improving cognitive function or in preventing cognitive decline (7). Recent pilot studies in patients with mild cognitive impairment evaluating the potential benefits of intranasal insulin therapy and metformin therapy provide insights for future clinical trials and mechanistic studies (8–10).

The presence of cognitive impairment can make it challenging for clinicians to help their patients to reach individualized glycemic, blood pressure, and lipid targets. Cognitive dysfunction makes it difficult for patients to perform complex self-care tasks, such as glucose monitoring and adjusting insulin doses. It also hinders their ability to appropriately maintain the timing and content of diet. When clinicians are managing these types of patients, it is critical to simplify drug regimens and to involve caregivers in all aspects of care.

Poor glycemic control is associated with a decline in cognitive function (11), and longer duration of diabetes worsens cognitive function. There are ongoing studies evaluating whether preventing or delaying diabetes onset may help to maintain cognitive function in older adults. However, studies examining the effects of intensive glycemic and blood pressure control to achieve specific targets have not demonstrated a reduction in brain function decline (12).

Older adults with diabetes should be carefully screened and monitored for cognitive impairment (3). Several organizations have released simple assessment tools, such as the Mini-Mental State Examination (13) and the Montreal Cognitive Assessment (14), which may help to identify patients requiring neuropsychological evaluation, particularly those in whom dementia is suspected (i.e., experiencing memory loss and decline in their basic and instrumental activities of daily living). Annual screening for cognitive impairment is indicated for adults 65 years of age or older for early detection of mild cognitive impairment or dementia (15). People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health provider for formal cognitive/neuropsychological evaluation (16).

HYPOGLYCEMIA

It is important to prevent hypoglycemia to reduce the risk of cognitive decline (17) and other major adverse outcomes. It is also important to carefully assess and reassess patients' risk for worsening of glycemic control and functional decline. Older adults are at higher risk of hypoglycemia for many reasons, including insulin deficiency necessitating insulin therapy and progressive renal insufficiency. In addition, older adults tend to have higher rates of unidentified cognitive deficits, causing difficulty in complex self-care activities (e.g., glucose monitoring, adjusting insulin doses, etc.). These cognitive deficits have been associated with increased risk of hypoglycemia, and, conversely, severe hypoglycemia has been linked to increased risk of dementia. Therefore, it is important to routinely screen older adults for cognitive dysfunction and discuss findings with the patients and their caregivers. Hypoglycemic events should be diligently monitored and avoided, whereas glycemic targets and pharmacologic interventions may need to be adjusted to accommodate for the changing needs of the older adult (3).

TREATMENT GOALS

Rationale

The care of older adults with diabetes is complicated by their clinical, mental, and functional heterogeneity. Some older individuals may have developed diabetes years earlier and have significant complications, others are newly diagnosed and may have had years of undiagnosed diabetes with resultant complications, and still other older adults may have truly recent-onset disease with few or no complications (18). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (19,20). Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable but are often longer than clinicians realize. Providers caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (21) (**Table 11.1**). In addition, older adults with diabetes should be assessed for disease treatment and self-management knowledge, health literacy, and mathematical literacy (numeracy) at the onset of treatment.

Healthy Patients With Good Functional Status

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid control. Patients who can be expected to live long enough to reap the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes. As with all patients with diabetes, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care

Table 11.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By "multiple," we mean at least three, but many patients may have five or more (40). **The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. †A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

for older adults and their caregivers. Self-management knowledge and skills should be reassessed when regimen changes are made or an individual's functional abilities diminish. In addition, declining or impaired ability to perform diabetes self-care behaviors may be an indication for referral of older adults with diabetes for cognitive and physical functional assessment using age-normalized evaluation tools (16,22).

Patients With Complications and Reduced Functionality

For patients with advanced diabetes complications, life-limiting comorbid illnesses, or substantial cognitive or functional impairments, it is reasonable to set less intensive glycemic goals. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. However, patients with poorly controlled diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals at a minimum should avoid these consequences.

Vulnerable Patients at the End of Life

For patients receiving palliative care and end-of-life care, the focus should be to avoid symptoms and complications from glycemic management. Thus, when organ failure develops, several agents will have to be titrated or discontinued. For the dying patient, most agents for type 2 diabetes may be removed. There is, however, no consensus for the management of type 1 diabetes in this scenario (23,24).

Beyond Glycemic Control

Although hyperglycemia control may be important in older individuals with diabetes, greater reductions in morbidity and mortality are likely to result from control of other cardiovascular risk factors rather than from tight glycemic control alone. There is strong evidence from clinical trials of the value of treating hypertension in older adults (25,26). There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary prevention and secondary intervention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials.

PHARMACOLOGIC THERAPY

Special care is required in prescribing and monitoring pharmacologic therapies in older adults (27). Cost may be an important consideration, especially as older adults tend to be on many medications.

Metformin

Metformin is the first-line agent for older adults with type 2 diabetes. Recent studies have indicated that it may be used safely in patients with estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 (28). However, it is contraindicated in patients with advanced renal insufficiency or significant heart failure. Metformin may be temporarily discontinued before procedures, during hospitalizations, and when acute illness may compromise renal or liver function.

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in those with, or at risk for, congestive heart failure and those at risk for falls or fractures.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues are associated with hypoglycemia and should be used with caution. If used, shorter-duration sulfonylureas such as glipizide are preferred. Glyburide is a longer-duration sulfonylurea and contraindicated in older adults (29).

Incretin-Based Therapies

Oral dipeptidyl peptidase 4 inhibitors have few side effects and minimal hypoglycemia, but their costs may be a barrier to some older patients. A systematic review concluded that incretin-based agents do not increase major adverse cardiovascular events (30).

Glucagon-like peptide 1 receptor agonists are injectable agents, which require visual, motor, and cognitive skills. They may be associated with nausea, vomiting, and diarrhea. Also, weight loss with GLP-1 receptor agonists may not be desirable in some older patients, particularly those with cachexia.

Sodium–Glucose Cotransporter 2 Inhibitors

Sodium–glucose cotransporter 2 inhibitors offer an oral route, which may be convenient for older adults with diabetes; however, long-term experience is limited despite the initial efficacy and safety data reported with these agents.

Insulin Therapy

The use of insulin therapy requires that patients or their caregivers have good visual and motor skills and cognitive ability. Insulin therapy relies on the ability of the older patient to administer insulin on their own or with the assistance of a caregiver. Insulin doses should be titrated to meet individualized glycemic targets and to avoid hypoglycemia. Once-daily basal insulin injection therapy is associated with minimal side effects and may be a reasonable option in many older patients. Multiple daily injections of insulin may be too complex for the older patient with advanced diabetes complications, life-limiting comorbid illnesses, or limited functional status.

Other Factors to Consider

The needs of older adults with diabetes and their caregivers should be evaluated to construct a tailored care plan. Social difficulties may impair their quality of life and increase the risk of functional dependency (31). The patient's living situation must be considered, as it may affect diabetes management and support. Social and instrumental support networks (e.g., adult children, caretakers) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision making.

Older adults in assisted living facilities may not have support to administer their own medications, whereas those living in a nursing home (community living centers) may rely completely on the care plan and nursing support. Those receiving palliative care (with or without hospice) may require an approach that emphasizes comfort and symptom management, while deemphasizing strict metabolic and blood pressure control.

TREATMENT IN SKILLED NURSING FACILITIES AND NURSING HOMES

Management of diabetes in the long-term care (LTC) setting (i.e., nursing homes and skilled nursing facilities) is unique. Individualization of health care is important in all patients; however, practical guidance is needed for medical providers as well as the LTC staff and caregivers (32). The American Medical Directors Association guidelines offer a 12-step program for staff (33). This training includes diabetes detection and institutional quality assessment. The guidelines also recommend that LTC facilities develop their own policies and procedures for prevention and management of hypoglycemia.

Resources

Staff of LTC facilities should receive appropriate diabetes education to improve the management of older adults with diabetes. Treatments for each patient should be individualized. Special management considerations include the need to avoid both hypoglycemia and the metabolic complications of diabetes and the need to provide adequate diabetes training to LTC staff (3,34). For more information, see the ADA position statement "Management of Diabetes in Long-term Care and Skilled Nursing Facilities: A Position Statement of the American Diabetes Association" (32).

Nutritional Considerations

An older adult residing in an LTC facility may have irregular and unpredictable meal consumption, undernutrition, anorexia, and impaired swallowing. Furthermore, therapeutic diets may inadvertently lead to decreased food intake and contribute to unintentional weight loss and undernutrition. Diets tailored to a patient's culture, preferences, and personal goals might increase quality of life, satisfaction with meals, and nutrition status (35).

Hypoglycemia

Older adults with diabetes in LTC are especially vulnerable to hypoglycemia. They have a disproportionately high number of clinical complications and comorbidities that can increase hypoglycemia risk: impaired cognitive and renal function, slowed hormonal regulation and counterregulation, suboptimal hydration, variable appetite and nutritional intake, polypharmacy, and slowed intestinal absorption (36).

Another consideration for the LTC setting is that unlike the hospital setting, medical providers are not required to evaluate the patients daily. According to federal guidelines, assessments should be done at least every 30 days for the first 90 days after admission and then at least once every 60 days. Although in practice the patients may actually be seen more frequently, the concern is that patients may have uncontrolled glucose levels or wide excursions without the practitioner being notified. Providers may make adjustments to treatment regimens by telephone, fax, or order directly at the LTC facilities provided they are given timely notification from a standardized alert system.

The following alert strategy could be considered:

1. **Call provider immediately**: in case of low blood glucose levels (<70 mg/dL [3.9 mmol/L]). Low finger-stick blood glucose values should be confirmed by laboratory glucose measurement.
2. **Call as soon as possible**: a) glucose values between 70 and 100 mg/dL (between 3.9 and 5.6 mmol/L) (regimen may need to be adjusted), b) glucose values greater than 250 mg/dL (13.9 mmol/L) within a 24-h period, c) glucose values greater than 300 mg/dL (16.7 mmol/L) within 2 consecutive days, d) when any reading is too high, or e) the patient is sick, with vomiting or other malady that can reflect hyperglycemic crisis and may lead to poor oral intake, thus requiring regimen adjustment.

END-OF-LIFE CARE

The management of the older adult at the end of life receiving palliative medicine or hospice care is a unique situation. Overall, palliative medicine promotes comfort, symptom control and prevention (pain, hypoglycemia, hyperglycemia, and dehydration) and preservation of dignity and quality-of-life in patients with limited life expectancy (34,37). A patient has the right to refuse testing and treatment, whereas providers may consider withdrawing treatment and limiting diagnostic testing, including a reduction in the frequency of finger-stick testing (38). Glucose targets should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be mindful of quality of life. Careful monitoring of oral intake is warranted. The decision process may need to involve the patient, family, and caregivers, leading to a care plan that is both convenient and effective for the goals of care (39). The pharmacologic therapy may include oral agents as first line, followed by a simplified insulin regimen. If needed, basal insulin can be implemented, accompanied by oral agents and without rapid-acting insulin. Agents that can cause gastrointestinal symptoms such as nausea or excess weight loss may not be good choices in this setting. As symptoms progress, some agents may be slowly tapered and discontinued.

Strata have been proposed for diabetes management in those with advanced disease (24).

1. **A stable patient**: continue with the patient's previous regimen, with a focus on the prevention of hypoglycemia and the management of hyperglycemia using blood glucose testing, keeping levels below the renal threshold of glucose. There is very little role for A1C monitoring and lowering.
2. **A patient with organ failure**: preventing hypoglycemia is of greater significance. Dehydration must be prevented and treated. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases but should not be stopped. For those with type 2 diabetes, agents that may cause hypoglycemia should be titrated. The main goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired target range.
3. **A dying patient**: for patients with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as patients are unlikely to have any oral intake. In patients with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications.

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12. Children and Adolescents

American Diabetes Association

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TYPE 1 DIABETES

Three-quarters of all cases of type 1 diabetes are diagnosed in individuals <18 years of age (although recent data using genetic risk scoring would suggest that over 40% of patients with autoimmune diabetes are diagnosed over the age of 30 years) (1). The provider must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the child care and school environment, and neurological vulnerability to hypoglycemia and hyperglycemia in young children, as well as possible adverse neurocognitive effects of diabetic ketoacidosis (DKA) (2,3). Attention to family dynamics, developmental stages, and physiological differences related to sexual maturity are all essential in developing and implementing an optimal diabetes treatment plan (4). Due to the paucity of clinical research in children, the recommendations for children and adolescents are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the American Diabetes Association (ADA) position statement "Care of Children and Adolescents With Type 1 Diabetes" (5) and have been updated in the ADA position statement "Type 1 Diabetes Through the Life Span" (6).

A multidisciplinary team of specialists trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes and their families should provide care for this population. It is essential that diabetes self-management education (DSME) and support (DSMS), medical nutrition therapy, and psychosocial support be provided at diagnosis and regularly thereafter in a developmentally appropriate format that builds on prior knowledge by individuals experienced with the educational, nutritional, behavioral, and emotional needs of the growing child and family. The appropriate balance between adult supervision and independent self-care should be defined at the first interaction and reevaluated at subsequent visits. The balance between adult supervision and independent self-care will evolve as the adolescent gradually becomes an emerging young adult.

Diabetes Self-management Education and Support

Recommendation

- Youth with type 1 diabetes and parents/caregivers (for patients aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support according to national standards at diagnosis and routinely thereafter. **B**

No matter how sound the medical regimen, it can only be effective if the family and/or affected individuals are able to implement it. Family involvement is a vital component of optimal diabetes management throughout childhood and adolescence. Health care providers (the diabetes care team) who care for children and adolescents must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact implementation of a treatment plan and must work with the individual and family to overcome barriers or redefine goals as appropriate. DSME and DSMS require periodic reassessment, especially as the youth grows, develops, and acquires the need for greater independent self-care skills. In addition, it is necessary to assess the educational needs and skills of day care providers, school nurses, or other school personnel who participate in the care of the young child with diabetes (7).

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School and Child Care

As a large portion of a child's day is spent in school, close communication with and the cooperation of school or day care personnel are essential for optimal diabetes management, safety, and maximal academic opportunities. Refer to the ADA position statements "Diabetes Care in the School Setting" (8) and "Care of Young Children With Diabetes in the Child Care Setting" (9) for additional details.

Psychosocial Issues

Recommendations

- At diagnosis and during routine follow-up care, assess psychosocial issues and family stresses that could impact adherence to diabetes management and provide appropriate referrals to trained mental health professionals, preferably experienced in childhood diabetes. **E**
- Mental health professionals should be considered integral members of the pediatric diabetes multidisciplinary team. **E**
- Encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognizing that premature transfer of diabetes care to the child can result in nonadherence and deterioration in glycemic control. **B**
- Providers should assess children's and adolescents' diabetes distress, social adjustment (peer relationships), and school performance to determine whether further intervention is needed. **B**
- In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, or significant distress, consider referral to a mental health provider for evaluation and treatment. **E**
- Adolescents should have time by themselves with their care provider(s) starting at age 12 years. **E**
- Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of childbearing potential. **A**

Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Diabetes management during childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial status and diabetes distress during routine diabetes visits (10–12). Early detection of depression, anxiety, eating disorders, and learning disabilities can facilitate effective treatment options and help minimize adverse effects on diabetes management and disease outcomes (13). Furthermore, the complexities of diabetes management require ongoing parental involvement in care throughout childhood with developmentally appropriate family teamwork between the growing child/teen and parent in order to maintain adherence and to prevent deterioration in glycemic control (14,15). As diabetes-specific family conflict is related to poorer adherence and glycemic control, it is appropriate to inquire about such conflict during visits and to either help to negotiate a plan for resolution or refer to an appropriate mental health specialist (16). Monitoring of social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement. Suboptimal glycemic control is a risk factor for below average school performance and increased absenteeism (17).

Shared decision-making with youth regarding the adoption of regimen components and self-management behaviors can improve diabetes self-efficacy, adherence, and metabolic outcomes (18). Although cognitive abilities vary, the ethical position often adopted is the "mature minor rule," whereby children after age 12 or 13 years who appear to be "mature" have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health (19).

Beginning at the onset of puberty or at diagnosis of diabetes, all adolescent girls and women with childbearing potential should receive education about the risks of malformations associated with unplanned pregnancies and poor metabolic control and the use of effective contraception to prevent unplanned pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (20). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (21).

Screening

Screening for psychosocial distress and mental health problems is an important component of ongoing care. It is important to consider the impact of diabetes on quality of life as well as the development of mental health problems related to diabetes distress, fear of hypoglycemia (and hyperglycemia), symptoms of anxiety, disordered eating behaviors as well as eating disorders, and symptoms of depression (22). Consider assessing youth for diabetes distress, generally starting at 7 or 8 years of age (13). Consider screening for depression and disordered eating behaviors using available screening tools (10,23). With respect to disordered eating, it is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight control in type 1 diabetes (24). The presence of a mental health professional on pediatric multidisciplinary teams highlights the importance of attending to the psychosocial issues of diabetes. These psychosocial factors are significantly related to nonadherence, suboptimal glycemic control, reduced quality of life, and higher rates of acute and chronic diabetes complications.

Glycemic Control

Recommendation

- An A1C goal of <7.5% (58 mmol/mol) is recommended across all pediatric age-groups. **E**

Current standards for diabetes management reflect the need to lower glucose as safely as possible. This should be done with stepwise goals. When establishing individualized glycemic targets, special consideration should be given to the risk of hypoglycemia in young children (aged <6 years) who are often unable to recognize, articulate, and/or manage hypoglycemia.

Type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence. Factors that contribute to adverse effects on brain development and function include young age or DKA at onset of type 1 diabetes, severe hypoglycemia <6 years of age, and chronic hyperglycemia (25,26). However, meticulous use of new therapeutic modalities, such as rapid- and long-acting insulin analogs, technological advances (e.g., continuous glucose monitors, low glucose suspend insulin pumps), and intensive self-management education now make it more feasible to achieve excellent glycemic control while reducing the incidence of severe hypoglycemia (27,28).

The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus regimens, insulin pumps, frequent blood glucose monitoring, goal setting, and improved patient education in youth from infancy through adolescence have been associated with more children reaching the blood glucose targets recommended by the ADA (29–32), particularly in those families in which both the parents and the child with diabetes participate jointly to perform the required diabetes-related tasks. Furthermore, studies documenting neurocognitive imaging differences related to hyperglycemia in children provide another motivation for lowering glycemic targets (2).

In selecting glycemic goals, the long-term health benefits of achieving a lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens of intensive regimens in children and youth. In addition, achieving lower A1C levels is more likely to be related to setting lower A1C targets (33,34). A1C goals are presented in **Table 12.1**.

Autoimmune Conditions

Recommendation

- Assess for the presence of autoimmune conditions associated with type 1 diabetes soon after the diagnosis and if symptoms develop. E

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction and celiac disease should be considered. Periodic screening in asymptomatic individuals has been recommended, but the optimal frequency and benefit of screening are unclear.

Although much less common than thyroid dysfunction and celiac disease, other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population and should be assessed and monitored as clinically indicated.

Thyroid Disease

Recommendations

- Consider testing individuals with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after the diagnosis. E
- Measure thyroid-stimulating hormone concentrations soon after the diagnosis of type 1 diabetes and after glucose control has been established. If normal, consider rechecking every 1–2 years or sooner if the patient develops symptoms suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or an unexplained glycemic variation. E

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes (35). At the time of diagnosis, about 25% of children with type 1 diabetes have thyroid autoantibodies (36); their presence is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of patients with type 1 diabetes (37,38). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, thyroid function tests should be performed soon after a period of metabolic stability and good glycemic control. Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia (39) and reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemic control.

Celiac Disease

Recommendations

- Consider screening individuals with type 1 diabetes for celiac disease by measuring either tissue transglutaminase or deamidated gliadin antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes. E
- Consider screening individuals who have a first-degree relative with celiac disease, growth failure, weight loss, failure to gain weight, diarrhea, flatulence, abdominal pain, or signs of malabsorption or in individuals with frequent unexplained hypoglycemia or deterioration in glycemic control. E
- Individuals with biopsy-confirmed celiac disease should be placed on a gluten-free diet and have a consultation with a dietitian experienced in managing both diabetes and celiac disease. B

Table 12.1—Blood glucose and A1C goals for children and adolescents with type 1 diabetes

Blood glucose goal range			
Before meals	**Bedtime/overnight**	**A1C**	**Rationale**
90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<7.5% (58 mmol/mol)	A lower goal (<7.0% [53 mmol/mol]) is reasonable if it can be achieved without excessive hypoglycemia

Key concepts in setting glycemic goals:

- Goals should be *individualized*, and lower goals may be reasonable based on a benefit-risk assessment.
- Blood glucose goals should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to assess preprandial insulin doses in those on basal-bolus or pump regimens.

Celiac disease is an immune-mediated disorder that occurs with increased frequency in patients with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population) (40–42).

Screening. Screening for celiac disease includes measuring serum levels of IgA and anti–tissue transglutaminase antibodies, or, with IgA deficiency, screening can include measuring IgG tissue transglutaminase antibodies or IgG deamidated gliadin peptide antibodies. Because most cases of celiac disease are diagnosed within the first 5 years after the diagnosis of type 1 diabetes, screening should be considered at the time of diagnosis and repeated 2 and 5 years thereafter.

Although celiac disease can be diagnosed more than 10 years after diabetes diagnosis, there are insufficient data after 5 years to determine the optimal screening frequency. Measurement of anti–tissue transglutaminase antibody should be considered at other times in patients with symptoms suggestive of celiac disease (42). A small-bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (43). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggest that biopsy may not be necessary in symptomatic children with high antibody titers (i.e., greater than 10 times the upper limit of normal) provided that further testing is performed (verification of endomysial antibody positivity on a separate blood sample). It is also advisable to check for HLA types in patients who are diagnosed without a small intestinal biopsy. Asymptomatic at-risk children should have an intestinal biopsy (44).

In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (45). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, a biopsy to confirm the diagnosis of celiac disease is recommended, especially in asymptomatic children, before endorsing significant dietary changes.

Management of Cardiovascular Risk Factors

Hypertension

Recommendations

Screening

- Blood pressure should be measured at each routine visit. Children found to have high-normal blood pressure (systolic blood pressure or diastolic blood pressure ≥90th percentile for age, sex, and height) or hypertension (systolic blood pressure or diastolic blood pressure ≥95th percentile for age, sex, and height) should have elevated blood pressure confirmed on 3 separate days. **B**

Treatment

- Initial treatment of high-normal blood pressure (systolic blood pressure or diastolic blood pressure consistently ≥90th percentile for age, sex, and height) includes dietary modification and increased exercise, if appropriate, aimed at weight control. If target blood pressure is not reached within 3–6 months of initiating lifestyle intervention, pharmacologic treatment should be considered. **E**
- In addition to lifestyle modification, pharmacologic treatment of hypertension (systolic blood pressure or diastolic blood pressure consistently ≥95th percentile for age, sex, and height) should be considered as soon as hypertension is confirmed. **E**
- ACE inhibitors or angiotensin receptor blockers should be considered for the initial pharmacologic treatment of hypertension, following reproductive counseling and implementation of effective birth control due to the potential teratogenic effects of both drug classes. **E**
- The goal of treatment is blood pressure consistently <90th percentile for age, sex, and height. **E**

Blood pressure measurements should be performed using the appropriate size cuff with the child seated and relaxed. Hypertension should be confirmed on at least 3 separate days. Evaluation should proceed as clinically indicated. Treatment is generally initiated with an ACE inhibitor, but an angiotensin receptor blocker can be used if the ACE inhibitor is not tolerated (e.g., due to cough) (46). Normal blood pressure levels for age, sex, and height and appropriate methods for measurement are available online at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

Dyslipidemia

Recommendations

Testing

- Obtain a fasting lipid profile in children ≥10 years of age soon after the diagnosis (after glucose control has been established). **E**
- If lipids are abnormal, annual monitoring is reasonable. If LDL cholesterol values are within the accepted risk level (<100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 3–5 years is reasonable. **E**

Treatment

- Initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet to decrease the amount of saturated fat in the diet. **B**
- After the age of 10 years, addition of a statin is suggested in patients who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dL (4.1 mmol/L) or LDL cholesterol >130 mg/dL (3.4 mmol/L) and one or more cardiovascular disease risk factors, following reproductive counseling and implementation of effective birth control due to the potential teratogenic effects of statins. **E**
- The goal of therapy is an LDL cholesterol value <100 mg/dL (2.6 mmol/L). **E**

Population-based studies estimate that 14–45% of children with type 1 diabetes have two or more cardiovascular disease (CVD) risk factors (47–49), and the prevalence of CVD risk factors increases with age (49), with girls having a higher risk burden than boys (48).

Pathophysiology. The atherosclerotic process begins in childhood, and although CVD events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis (50–52). Studies of carotid intima-media thickness have yielded inconsistent results (46).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes (53–55); however, there are few studies on modifying lipid levels in children with type 1 diabetes. A 6-month trial of dietary counseling produced a significant improvement in lipid levels (56); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (57).

Although intervention data are sparse, the American Heart Association (AHA) categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (55,58). Initial therapy should be with a Step 2 AHA diet, which restricts saturated fat to 7% of total calories and restricts dietary cholesterol to 200 mg/day. Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (59).

For children with a significant family history of CVD, the National Heart, Lung, and Blood Institute recommends obtaining a fasting lipid panel beginning at 2 years of age (53). Abnormal results from a random lipid panel should be confirmed with a fasting lipid panel. Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose control over a 2-year period is associated with a more favorable lipid profile; however, improved glycemic control alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia (60).

Neither long-term safety nor cardiovascular outcome efficacy of statin therapy has been established for children; however, studies have shown short-term safety equivalent to that seen in adults and efficacy in lowering LDL cholesterol levels in familial hypercholesterolemia or severe hyperlipidemia, improving endothelial function and causing regression of carotid intimal thickening (61,62). Statins are not approved for patients aged <10 years, and statin treatment should generally not be used in children with type 1 diabetes before this age. Statins are category X in pregnancy; therefore, prevention of unplanned pregnancies is of paramount importance for postpubertal girls (see Section 13 "Management of Diabetes in Pregnancy" for more information).

Smoking

Recommendation

- Elicit a smoking history at initial and follow-up diabetes visits. Discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke. **B**

The adverse health effects of smoking are well recognized with respect to future cancer and CVD risk. Despite this, smoking rates are significantly higher among youth with diabetes than among youth without diabetes (63,64). In youth with diabetes, it is important to avoid additional CVD risk factors. Smoking increases the risk of onset of albuminuria; therefore, smoking avoidance is important to prevent both microvascular and macrovascular complications (53,65). Discouraging cigarette smoking, including e-cigarettes, is an important part of routine diabetes care. In younger children, it is important to assess exposure to cigarette smoke in the home due to the adverse effects of secondhand smoke and to discourage youth from ever smoking if exposed to smokers in childhood.

Microvascular Complications

Nephropathy

Recommendations

Screening

- Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered once the child has had type 1 diabetes for 5 years. **B**
- Estimate glomerular filtration rate at initial evaluation and then based on age, diabetes duration, and treatment. **E**

Treatment

- When persistently elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented with at least two of three urine samples, treatment with an ACE inhibitor should be considered and the dose titrated to maintain blood pressure within the age-appropriate normal range. The urine samples should be obtained over a 6-month interval following efforts to improve glycemic control and normalize blood pressure. **C**

Data from 7,549 participants <20 years of age in the T1D Exchange clinic registry emphasize the importance of good glycemic and blood pressure control, particularly as diabetes duration increases, in order to reduce the risk of nephropathy. The data also underscore the importance of routine screening to ensure early diagnosis and timely treatment of albuminuria (66). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (67), should be determined at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. Estimated GFR is calculated from a serum creatinine measurement using an estimating equation. There are ongoing clinical trials assessing the efficacy of early treatment of persistent albuminuria with ACE inhibitors (68).

Retinopathy

Recommendations

- An initial dilated and comprehensive eye examination is recommended at age ≥10 years or after puberty has started, whichever is earlier, once the youth has had type 1 diabetes for 3–5 years. **B**
- After the initial examination, annual routine follow-up is generally recommended. Less frequent examinations, every 2 years, may be acceptable on the advice of an eye care professional. **E**

Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (69). Referrals should be made to eye care professionals with expertise in diabetic retinopathy and experience in counseling the pediatric patient and family on the importance of early prevention and intervention.

Neuropathy

Recommendation

- Consider an annual comprehensive foot exam for the child at the start of puberty or at age ≥10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. **E**

Diabetic neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (69). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior tibial pulses, assessment of the patellar and Achilles reflexes, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with an assessment of symptoms of neuropathic pain. Foot inspection can be performed at each visit to educate youth regarding the importance of foot care (see Section 10 "Microvascular Complications and Foot Care").

TYPE 2 DIABETES

For information on testing for type 2 diabetes and prediabetes in children and adolescents, please refer to Section 2 "Classification and Diagnosis of Diabetes."

Type 2 diabetes in youth has increased over the past 20 years and recent estimates suggest an incidence of ~5,000 new cases per year in the U.S. (70). The Centers for Disease Control and Prevention published projections for type 2 diabetes prevalence using the SEARCH database: assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years (71,72).

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications (73,74). Type 2 diabetes disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviors. Additional risk factors associated with type 2 diabetes in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status (74).

As with type 1 diabetes, youth with type 2 diabetes spend much of the day in school. Therefore, close communication with and the cooperation of school personnel are essential for optimal diabetes management, safety, and maximal academic opportunities.

Diagnostic Challenges

Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Overweight and obesity are common in children with type 1 diabetes (75), and diabetes-associated autoantibodies and ketosis may be present in pediatric patients with features of type 2 diabetes (including obesity and acanthosis nigricans) (76). At onset, DKA occurs in ~6% of youth aged 10–19 years with type 2 diabetes (77). Accurate diagnosis is critical as treatment regimens, educational approaches, dietary advice, and outcomes differ markedly between patients with the two diagnoses.

Treatment

The general treatment goals for youth with type 2 diabetes are the same as those for youth with type 1 diabetes. A multidisciplinary diabetes team, including a physician, diabetes nurse educator, registered dietitian, and psychologist or social worker, is essential. In addition to blood glucose control, initial treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and microvascular complications.

Current treatment options for youth-onset type 2 diabetes are limited to two approved drugs—insulin and metformin (73). Presentation with ketosis or ketoacidosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal levels. Metformin therapy may be used as an adjunct after resolution of ketosis/ketoacidosis. Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in patients who have random blood glucose concentrations ≥250 mg/dL (13.9 mmol/L) and/or A1C >9% (75 mmol/mol) (78).

Patients and their families must prioritize lifestyle modifications such as eating a balanced diet, achieving and maintaining a healthy weight, and exercising regularly. A family-centered approach to nutrition and lifestyle modification is essential in children with type 2 diabetes, and nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 4 "Lifestyle Management"). Given the complex social and environmental context surrounding youth with type 2 diabetes, individual-level lifestyle interventions may not be sufficient to target the complex interplay of family dynamics, mental health, community readiness, and the broader environmental system (73).

When insulin treatment is not required, initiation of metformin is recommended. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study found that metformin alone provided durable glycemic control (A1C ≤8% [64 mmol/mol] for 6 months) in approximately half of the subjects (79). To date, the TODAY study is the only trial combining lifestyle and metformin therapy in youth with type 2 diabetes; the combination did not perform better than metformin alone in achieving durable glycemic control (79).

Small retrospective analyses and a recent prospective multicenter nonrandomized study suggest that bariatric or metabolic surgery may have similar benefits in obese adolescents with type 2 diabetes compared with those observed in adults. Teenagers experience similar degrees of weight loss, diabetes remission, and improvement of cardiometabolic risk factors for at least 3 years after surgery (80). No randomized trials, however, have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents (81).

Comorbidities

Comorbidities may already be present at the time of diagnosis of type 2 diabetes in youth (74,82). Therefore, blood pressure measurement, a fasting lipid panel, assessment of random urine albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis. Thereafter, screening guidelines and treatment recommendations for hypertension, dyslipidemia, urine albumin excretion, and retinopathy are similar to those for youth with type 1 diabetes. Additional problems that may need to be addressed include polycystic ovary disease and other comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA consensus report "Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities" (73) and an American Academy of Pediatrics clinical practice guideline (83) provide guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in children and adolescents.

TRANSITION FROM PEDIATRIC TO ADULT CARE

Recommendations

- Health care providers and families should begin to prepare youth with diabetes in early to midadolescence and, at the latest, at least 1 year before the transition to adult health care. **E**
- Both pediatricians and adult health care providers should assist in providing support and links to resources for the teen and emerging adult. **B**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or type 2 diabetes throughout childhood and adolescence. The shift from pediatric to adult health care providers, however, often occurs abruptly as the older teen enters the next developmental stage referred to as emerging adulthood (84), which is a critical period for young people who have diabetes. During this period of major life transitions, youth begin to move out of their parents' homes and must become fully responsible for their diabetes care. Their new responsibilities include self-management of their diabetes, making medical appointments, and financing health care, once they are no longer covered by their parents' health insurance plans (ongoing coverage until age 26 years is now available under provisions of the Affordable Care Act). In addition to lapses in health care, this is also a period associated with deterioration in glycemic control; increased occurrence of acute complications; psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications (85–88).

Although scientific evidence is limited, it is clear that comprehensive and coordinated planning that begins in early adolescence, or at least 1 year before the date of transition, is necessary to facilitate a seamless transition from pediatric to adult health care (85,86). A comprehensive discussion regarding the challenges faced during this period, including specific recommendations, is found in the ADA position statement "Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems" (86).

The National Diabetes Education Program (NDEP) has materials available to facilitate the transition process (http://ndep.nih.gov/transitions), and the Endocrine Society in collaboration with the ADA and other organizations has developed transition tools for clinicians and youth and families (http://www.endo-society.org/clinicalpractice/transition_of_care.cfm).

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For guidelines related to the diagnosis of gestational diabetes mellitus, please refer to Section 2 "Classification and Diagnosis of Diabetes."

Recommendations

Preexisting Diabetes

- Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of childbearing potential. A
- Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. A
- Preconception counseling should address the importance of glycemic control as close to normal as is safely possible, ideally A1C <6.5% (48 mmol/mol), to reduce the risk of congenital anomalies. B
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1 year postpartum as indicated by degree of retinopathy and as recommended by the eye care provider. B

Gestational Diabetes Mellitus

- Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for the treatment for many women. Medications should be added if needed to achieve glycemic targets. A
- Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus, as it does not cross the placenta to a measurable extent. Metformin and glyburide may be used, but both cross the placenta to the fetus, with metformin likely crossing to a greater extent than glyburide. All oral agents lack long-term safety data. A
- Metformin, when used to treat polycystic ovary syndrome and induce ovulation, need not be continued once pregnancy has been confirmed. A

General Principles for Management of Diabetes in Pregnancy

- Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. B
- Fasting and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve glycemic control. Some women with preexisting diabetes should also test blood glucose preprandially. B
- Due to increased red blood cell turnover, A1C is lower in normal pregnancy than in normal nonpregnant women. The A1C target in pregnancy is 6–6.5% (42–48 mmol/mol); <6% (42 mmol/mol) may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% (53 mmol/mol) if necessary to prevent hypoglycemia. B
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. E

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DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. The majority is gestational diabetes mellitus (GDM) with the remainder primarily preexisting type 1 diabetes and type 2 diabetes. The rise in GDM and type 2 diabetes in parallel with obesity both in the U.S. and worldwide is of particular concern. Both type 1 diabetes and type 2 diabetes confer significantly greater maternal and fetal risk than GDM, with some differences according to type of diabetes as outlined below. In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others. In addition, diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life (1,2).

PRECONCEPTION COUNSELING

All women of childbearing age with diabetes should be counseled about the importance of tight glycemic control prior to conception. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, and caudal regression directly proportional to elevations in A1C during the first 10 weeks of pregnancy. Although observational studies are confounded by the association between elevated periconceptional A1C and other poor self-care behaviors, the quantity and consistency of data are convincing and support the recommendation to optimize glycemic control prior to conception, with A1C <6.5% (48 mmol/mol) associated with the lowest risk of congenital anomalies (3,4).

There are opportunities to educate all women and adolescents of reproductive age with diabetes about the risks of unplanned pregnancies and the opportunities for improved maternal and fetal outcomes with pregnancy planning (5). Effective preconception counseling could avert substantial health and associated cost burden in offspring (6). Family planning should be discussed, and effective contraception should be prescribed and used, until a woman is prepared and ready to become pregnant.

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all women with diabetes of childbearing potential should receive education about *1*) the risks of malformations associated with unplanned pregnancies and poor metabolic control and *2*) the use of effective contraception at all times when preventing a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (5). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (7).

Preconception Testing

Preconception counseling visits should include rubella, syphilis, hepatitis B virus, and HIV testing, as well as Pap smear, cervical cultures, blood typing, prescription of prenatal vitamins (with at least 400 μg of folic acid), and smoking cessation counseling if indicated. Diabetes-specific testing should include A1C, thyroid-stimulating hormone, creatinine, and urinary albumin–to–creatinine ratio; review of the medication list for potentially teratogenic drugs, i.e., ACE inhibitors (8), angiotensin receptor blockers (8), and statins (9,10); and referral for a comprehensive eye exam. Women with preexisting diabetic retinopathy will need close monitoring during pregnancy to ensure that retinopathy does not progress.

GLYCEMIC TARGETS IN PREGNANCY

Pregnancy in women with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones.

Insulin Physiology

Early pregnancy is a time of insulin sensitivity, lower glucose levels, and lower insulin requirements in women with type 1 diabetes. The situation rapidly reverses as insulin resistance increases exponentially during the second and early third trimesters and levels off toward the end of the third trimester. In women with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in women with GDM and preexisting diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial monitoring of blood glucose is recommended to achieve metabolic control in pregnant women with diabetes. Preprandial testing is also recommended for women with preexisting diabetes using insulin pumps or basal-bolus therapy, so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia (11–13). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Similar to the targets recommended by the American College of Obstetricians and Gynecologists (14), the ADA-recommended targets for women with type 1 or type 2 diabetes (the same as for GDM; described below) are as follows:

- Fasting ≤95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)

These values represent optimal control if they can be achieved safely. In practice, it may be challenging for women with type 1 diabetes to achieve these targets without hypoglycemia, particularly women with a history of recurrent hypoglycemia or hypoglycemia unawareness.

If women cannot achieve these targets without significant hypoglycemia, the ADA suggests less stringent targets based on clinical experience and individualization of care.

A1C in Pregnancy

Observational studies show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation (4,15–17). Clinical trials have not evaluated the risks and benefits of achieving these targets, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized target of <6% (42 mmol/mol) to <7% (53 mmol/mol). Due to physiological increases in red

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blood cell turnover, A1C levels fall during normal pregnancy (18,19). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic control, after self-monitoring of blood glucose.

In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants, whereas other adverse outcomes increase with A1C ≥6.5% (48 mmol/mol). *Taking all of this into account, a target of 6–6.5% (42–48 mmol/mol) is recommended but <6% (42 mmol/mol) may be optimal as pregnancy progresses. These levels should be achieved without hypoglycemia*, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight. Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

GDM is characterized by increased risk of macrosomia and birth complications and an increased risk of maternal type 2 diabetes after pregnancy. The association of macrosomia and birth complications with oral glucose tolerance test (OGTT) results is continuous, with no clear inflection points (20). In other words, risks increase with progressive hyperglycemia. Therefore, all women should be tested as outlined in Section 2 "Classification and Diagnosis of Diabetes." Although there is some heterogeneity, many randomized controlled trials suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling (21,22).

Lifestyle Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management depending on pregestational weight, as outlined in the section below on preexisting type 2 diabetes, and glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (23):

- Fasting ≤95 mg/dL (5.3 mmol/L) and either
  - One-hour postprandial ≤140 mg/dL (7.8 mmol/L) or
  - Two-hour postprandial ≤120 mg/dL (6.7 mmol/L)

Depending on the population, studies suggest that 70–85% of women diagnosed with GDM under Carpenter-Coustan or National Diabetes Data Group (NDDG) criteria can control GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (24) diagnostic thresholds are used.

Pharmacologic Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacologic therapy. Treatment has been demonstrated to improve perinatal outcomes in two large randomized studies as summarized in a U.S. Preventive Services Task Force review (25). Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual randomized controlled trials support the efficacy and short-term safety of metformin (26,27) and glyburide (28) for the treatment of GDM, both agents cross the placenta. Long-term safety data are not available for any oral agent (29).

Sulfonylureas

Concentrations of glyburide in umbilical cord plasma are approximately 70% of maternal levels (30). Glyburide may be associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin (31).

Metformin

Metformin may be associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin (31–33); however, metformin may slightly increase the risk of prematurity. Furthermore, nearly half of patients with GDM who were initially treated with metformin in a randomized trial needed insulin in order to achieve acceptable glucose control (26). Umbilical cord blood levels of metformin are higher than simultaneous maternal levels (34,35). None of these studies or meta-analyses evaluated long-term outcomes in the offspring. Patients treated with oral agents should be informed that they cross the placenta, and although no adverse effects on the fetus have been demonstrated, long-term studies are lacking.

Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in women with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (36), and there is no evidence-based need to continue metformin in such patients once pregnancy has been confirmed (37–39).

Insulin

Insulin may be required to treat hyperglycemia, and its use should follow the guidelines below.

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Insulin Use

Insulin is the preferred agent for management of both type 1 diabetes and type 2 diabetes in pregnancy.

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent self-monitoring of blood glucose. In the first trimester, there is often a decrease in total daily insulin requirements, and women, particularly those with type 1 diabetes, may experience increased hypoglycemia. In the second trimester, rapidly increasing insulin resistance requires weekly or biweekly increases in insulin dose to achieve glycemic targets. In general, a smaller proportion of the total daily dose should be given as basal insulin (<50%) and a greater proportion (>50%) as prandial insulin. In the late third trimester, there is often a leveling off or small decrease in insulin requirements. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including high-risk obstetrician, endocrinologist or other provider experienced in managing pregnancy in women with preexisting diabetes, dietitian, nurse, and social worker, as needed) is recommended if this resource is available.

None of the currently available insulin preparations have been demonstrated to cross the placenta.

Type 1 Diabetes

Women with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all women, have altered counterregulatory response in pregnancy that may decrease hypoglycemia awareness. Education for patients and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help to prevent and manage the risks of hypoglycemia. Insulin resistance drops rapidly with delivery of the placenta. Women become very insulin sensitive immediately following delivery and may initially require much less insulin than in the prepartum period.

Pregnancy is a ketogenic state, and women with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis at lower blood glucose levels than in the nonpregnant state. Women with preexisting diabetes, especially type 1 diabetes, need ketone strips at home and education on diabetic ketoacidosis prevention and detection. In addition, rapid implementation of tight glycemic control in the setting of retinopathy is associated with worsening of retinopathy (40).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for overweight women is 15–25 lb and for obese women is 10–20 lb (41). Glycemic control is often easier to achieve in women with type 2 diabetes than in those with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. As in type 1 diabetes, insulin requirements drop dramatically after delivery. The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as with type 1 diabetes, even if diabetes is better controlled and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in women with type 2 diabetes compared with the first trimester in women with type 1 diabetes (42,43).

POSTPARTUM CARE

Postpartum care should include psychosocial assessment and support for self-care.

Lactation

In light of the immediate nutritional and immunological benefits of breastfeeding for the baby, all women including those with diabetes should be supported in attempts to breastfeed. Breastfeeding may also confer longer-term metabolic benefits to both mother (44) and offspring (45).

Gestational Diabetes Mellitus

Initial Testing

Because GDM may represent preexisting undiagnosed type 2 or even type 1 diabetes, women with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks' postpartum with a 75-g OGTT using nonpregnancy criteria as outlined in Section 2 "Classification and Diagnosis of Diabetes."

Postpartum Follow-up

The OGTT is recommended over A1C at the time of the 4- to 12-week postpartum visit because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy or blood loss at delivery and because the OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. Reproductive-aged women with prediabetes may develop type 2 diabetes by the time of their next pregnancy and will need preconception evaluation. Because GDM is associated with increased maternal risk for diabetes, women should also be tested every 1–3 years thereafter if the 4- to 12-week 75-g OGTT is normal, with frequency of testing depending on other risk factors including family history, prepregnancy BMI, and need for insulin or oral glucose-lowering medication during pregnancy. Ongoing evaluation may be performed with any recommended glycemic test (e.g., hemoglobin A1C, fasting plasma glucose, or 75-g OGTT using nonpregnant thresholds).

Gestational Diabetes Mellitus and Type 2 Diabetes

Women with a history of GDM have a greatly increased risk of conversion to type 2 diabetes over time and not solely within the 4- to 12-week postpartum time frame (46). In the prospective Nurses' Health Study II, subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating patterns (47). Adjusting for BMI moderately, but not completely, attenuated this association. Interpregnancy or postpartum weight gain is associated with increased risk of adverse pregnancy outcomes in subsequent pregnancies (48) and earlier progression to type 2 diabetes.

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in women with prediabetes and a history of GDM. Of women with a history of GDM and prediabetes, only 5–6 women need to be treated with either intervention to prevent one case of diabetes over 3 years (49). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (50). If the pregnancy has motivated the adoption of a healthier diet, building on these gains to support weight loss is recommended in the postpartum period.

Preexisting Type 1 and Type 2 Diabetes

Insulin sensitivity increases with delivery of the placenta and then returns to prepregnancy levels over the following 1–2 weeks. In women taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in women with preexisting diabetes due to the need for preconception glycemic control and preventive health services. Therefore, all women with diabetes of childbearing potential should have family planning options reviewed at regular intervals. This applies to women in the immediate postpartum period. Women with diabetes have the same contraception options and recommendations as those without diabetes. The risk of an unplanned pregnancy outweighs the risk of any given contraception option.

PREGNANCY AND DRUG CONSIDERATIONS

In normal pregnancy, blood pressure is lower than in the nonpregnant state. In a pregnancy complicated by diabetes and chronic hypertension, target goals for systolic blood pressure 120–160 mmHg and diastolic blood pressure 80–105 mmHg are reasonable (51). Lower blood pressure levels may be associated with impaired fetal growth. In a 2015 study targeting diastolic blood pressure of 100 mmHg versus 85 mmHg in pregnant women, only 6% of whom had GDM at enrollment, there was no difference in pregnancy loss, neonatal care, or other neonatal outcomes, although women in the less intensive treatment group had a higher rate of uncontrolled hypertension (52).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, and intrauterine growth restriction (8). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (53). On the basis of available evidence, statins should also be avoided in pregnancy (54).

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14. Diabetes Care in the Hospital

American Diabetes Association

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Recommendations

- Perform an A1C for all patients with diabetes or hyperglycemia admitted to the hospital if not performed in the prior 3 months. **B**
- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill patients **A** and noncritically ill patients. **C**
- More stringent goals, such as <140 mg/dL (<7.8 mmol/L), may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. **C**
- Intravenous insulin infusions should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and insulin dose. **E**
- Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill patients with poor oral intake or those who are taking nothing by mouth. An insulin regimen with basal, nutritional, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake. **A**
- Sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged. **A**
- A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. **E**
- The treatment regimen should be reviewed and changed as necessary to prevent further hypoglycemia when a blood glucose value is <70 mg/dL (3.9 mmol/L). **C**
- There should be a structured discharge plan tailored to the individual patient with diabetes. **B**

In the hospital, both hyperglycemia and hypoglycemia are associated with adverse outcomes including death (1,2). Therefore, inpatient goals should include the prevention of both hyperglycemia and hypoglycemia. Hospitals should promote the shortest, safe hospital stay and provide an effective transition out of the hospital that prevents acute complications and readmission.

For in-depth review of inpatient hospital practice, consult recent reviews that focus on hospital care for diabetes (3,4).

HOSPITAL CARE DELIVERY STANDARDS

High-quality hospital care for diabetes requires both hospital care delivery standards, often assured by structured order sets, and quality assurance standards for process improvement. "Best practice" protocols, reviews, and guidelines (2) are inconsistently implemented within hospitals. To correct this, hospitals have established protocols for structured patient care and structured order sets, which include computerized physician order entry (CPOE).

Considerations on Admission

Initial orders should state the type of diabetes (i.e., type 1 or type 2 diabetes) or no previous history of diabetes. Because inpatient insulin use (5) and discharge orders (6) can be more effective if based on an A1C level on admission (7), perform an A1C test on all patients with diabetes or hyperglycemia admitted to the hospital if the

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test has not been performed in the prior 3 months. In addition, diabetes self-management knowledge and behaviors should be assessed on admission and diabetes self-management education (DSME) should be provided, if appropriate. DSME should include appropriate skills needed after discharge, such as taking antihyperglycemic medications, monitoring glucose, and recognizing and treating hypoglycemia (2).

Computerized Physician Order Entry

The Institute of Medicine recommends CPOE to prevent medication-related errors and to increase efficiency in medication administration (8). A Cochrane review of randomized controlled trials using computerized advice to improve glucose control in the hospital found significant improvement in the percentage of time patients spent in the target glucose range, lower mean blood glucose levels, and no increase in hypoglycemia (9). Thus, where feasible, there should be structured order sets that provide computerized advice for glucose control. Electronic insulin order templates also improve mean glucose levels without increasing hypoglycemia in patients with type 2 diabetes, so structured insulin order sets should be incorporated into the CPOE (10).

Diabetes Care Providers in the Hospital

Appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes, but studies are few. A call to action outlined the studies needed to evaluate these outcomes (11). Details of team formation are available from the Society of Hospital Medicine and the Joint Commission standards for programs.

Quality Assurance Standards

Even the best orders may not be carried out in a way that improves quality, nor are they automatically updated when new evidence arises. To this end, the Joint Commission has an accreditation program for the hospital care of diabetes (12), and the Society of Hospital Medicine has a workbook for program development (13).

GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

Standard Definition of Glucose Abnormalities

Hyperglycemia in hospitalized patients is defined as blood glucose levels >140 mg/dL (7.8 mmol/L). Blood glucose levels that are persistently above this level may require alterations in diet or a change in medications that cause hyperglycemia. An admission A1C value ≥6.5% (48 mmol/mol) suggests that diabetes preceded hospitalization (see Section 2 “Classification and Diagnosis of Diabetes”). Previously, hypoglycemia in hospitalized patients has been defined as blood glucose <70 mg/dL (3.9 mmol/L) and severe hypoglycemia as <40 mg/dL (2.2 mmol/L) (14). However, the American Diabetes Association (ADA) now defines clinically significant hypoglycemia as glucose values <54 mg/dL (3.0 mmol/L), while severe hypoglycemia is defined as that associated with severe cognitive impairment regardless of blood glucose level (see Section 6 “Glycemic Targets” for additional detail on the new hypoglycemia criteria) (15). A blood glucose level of ≤70 mg/dL is considered an alert value and may be used as a threshold for further titration of insulin regimens.

Moderate Versus Tight Glycemic Control

A meta-analysis of over 26 studies, including the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, showed increased rates of severe hypoglycemia (blood glucose <40 mg/dL) and mortality in tightly versus moderately controlled cohorts (16). This evidence established new standards: insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients (2). More stringent goals, such as <140 mg/dL (<7.8 mmol/L), may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. Conversely, higher glucose ranges may be acceptable in terminally ill patients, in patients with severe comorbidities, and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible.

Clinical judgment combined with ongoing assessment of the patient’s clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), should be incorporated into the day-to-day decisions regarding insulin doses (2).

BEDSIDE BLOOD GLUCOSE MONITORING

Indications

In the patient who is eating meals, glucose monitoring should be performed before meals. In the patient who is not eating, glucose monitoring is advised every 4–6 h (2). More frequent blood glucose testing ranging from every 30 min to every 2 h is required for patients receiving intravenous insulin. Safety standards should be established for blood glucose monitoring that prohibit the sharing of fingerstick lancing devices, lancets, and needles (17).

Point-of-Care Meters

Point-of-care (POC) meters have limitations for measuring blood glucose. Although the U.S. Food and Drug Administration (FDA) has standards for blood glucose meters used by lay persons, there have been questions about the appropriateness of these criteria, especially in the hospital and for lower blood glucose readings (18). Significant discrepancies between capillary, venous, and arterial plasma samples have been observed in patients with low or high hemoglobin concentrations and with hypoperfusion. Any glucose result that does not correlate with the patient’s clinical status should be confirmed through conventional laboratory glucose tests. The FDA established a separate category for POC glucose meters for use in health care settings and has released a guidance on in-hospital use with stricter standards (19). Before choosing a device for in-hospital use, consider the device’s approval status and accuracy.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) provides frequent measurements of interstitial glucose levels, as well as direction and magnitude of glucose trends, which may have an advantage over POC glucose testing in detecting and reducing the incidence of hypoglycemia. Several inpatient studies have shown that CGM use did not improve glucose control but detected a greater number of hypoglycemic events than POC testing. However, a recent review has recommended against using CGM in adults in a hospital setting until more safety and efficacy data become available (20).

ANTIHYPERGLYCEMIC AGENTS IN HOSPITALIZED PATIENTS

In most instances in the hospital setting, insulin is the preferred treatment for glycemic control (2). However, in certain circumstances, it may be appropriate to continue home regimens including oral antihyperglycemic medications (21). If oral medications are held in the hospital, there should be a protocol for resuming them 1–2 days before discharge. Insulin pens are the subject of an FDA warning due to potential blood-borne diseases, and care should be taken to follow the label insert "For single patient use only."

Insulin Therapy

Critical Care Setting

In the critical care setting, continuous intravenous insulin infusion has been shown to be the best method for achieving glycemic targets. Intravenous insulin infusions should be administered based on validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose (2).

Noncritical Care Setting

Outside of critical care units, scheduled insulin regimens are recommended to manage hyperglycemia in patients with diabetes. Regimens using insulin analogs and human insulin result in similar glycemic control in the hospital setting (22).

The use of subcutaneous rapid- or short-acting insulin before meals or every 4–6 h if no meals are given or if the patient is receiving continuous enteral/parenteral nutrition is indicated to correct hyperglycemia (2). Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill patients with poor oral intake or those who are taking nothing by mouth (NPO). An insulin regimen with basal, nutritional, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake.

If the patient is eating, insulin injections should align with meals. In such instances, POC glucose testing should be performed immediately before meals. If oral intake is poor, a safer procedure is to administer the rapid-acting insulin immediately after the patient eats or to count the carbohydrates and cover the amount ingested (22).

A randomized controlled trial has shown that basal-bolus treatment improved glycemic control and reduced hospital complications compared with sliding scale insulin in general surgery patients with type 2 diabetes (23). Prolonged sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged (2,11).

While there is evidence for using premixed insulin formulations in the outpatient setting (24), a recent inpatient study of 70/30 NPH/regular versus basal-bolus therapy showed comparable glycemic control but signifcantly increased hypoglycemia in the group receiving premixed insulin. Therefore, premixed insulin regimens are not routinely recommended for in hospital use.

Type 1 Diabetes

For patients with type 1 diabetes, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or caloric intake, increasing both hypoglycemia and hyperglycemia risks and potentially leading to diabetic ketoacidosis (DKA). Typically basal insulin dosing schemes are based on body weight, with some evidence that patients with renal insufficiency should be treated with lower doses (25).

Transitioning Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is associated with less morbidity and lower costs of care (26) and is therefore recommended. A patient with type 1 or type 2 diabetes being transitioned to outpatient subcutaneous insulin should receive subcutaneous basal insulin 1–2 h before the intravenous insulin is discontinued. Converting to basal insulin at 60–80% of the daily infusion dose has been shown to be effective (2,26,27). For patients continuing regimens with concentrated insulin in the inpatient setting, it is important to ensure the correct dosing by utilizing an individual pen and cartrige for each patient, meticulous pharmacist supervision of the dose administered, or other means (28,29).

Noninsulin Therapies

The safety and efficacy of noninsulin antihyperglycemic therapies in the hospital setting is an area of active research. A recent randomized pilot trial in general medicine and surgery patients reported that a dipeptidyl peptidase 4 inhibitor alone or in combination with basal insulin was well tolerated and resulted in similar glucose control and frequency of hypoglycemia compared with a basal-bolus regimen (30). However, a recent FDA bulletin states that providers should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (31). A review of antihyperglycemic medications concluded that glucagon-like peptide 1 receptor agonists show promise in the inpatient setting (32); however, proof of safety and efficacy await the results of randomized controlled trials (33). Moreover, the gastrointestinal symptoms associated with the glucagon-like peptide 1 receptor agonists may be problematic in the inpatinet setting.

Regarding the sodium–glucose transporter 2 (SGLT2) inhibitors, the FDA includes warnings about DKA and urosepsis (34), urinary tract infections, and kidney injury (35) on the drug labels. A recent review suggested SGLT2 inhibitors be avoided in severe illness, when ketone bodies are present, and during prolonged fasting and surgical procedures (3). Until safety and effectivenss are established, SGLT2 inhibitors cannot be recommended for routine in-hospital use.

HYPOGLYCEMIA

Patients with or without diabetes may experience hypoglycemia in the hospital setting. While hypoglycemia is associated with increased mortality, hypoglycemia may be a marker of underlying disease rather than the cause of increased mortality. However, until it is proven not to be causal, it is prudent to avoid hypoglycemia. Despite the preventable nature of many inpatient episodes of hypoglycemia, institutions are more likely to have nursing protocols for hypoglycemia treatment than for its prevention when both are needed.

A hypoglycemia prevention and management protocol should be adopted and implemented by each hospital or hospital system. There should be a standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol to immediately address blood glucose levels of $\leq$70 mg/dL [3.9 mmol/L], as well as individualized plans for preventing and treating hypoglycemia for each patient. An ADA consensus report suggested that a patient's overall treatment regimen be reviewed when a blood glucose value of $<$70 mg/dL (3.9 mmol/L) is identified because such readings often predict imminent severe hypoglycemia (2).

Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked (2).

Triggering Events

Iatrogenic hypoglycemia triggers may include sudden reduction of corticosteroid dose, reduced oral intake, emesis, new NPO status, inappropriate timing of short-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of oral, enteral, or parenteral feedings, and altered ability of the patient to report symptoms.

Predictors of Hypoglycemia

In one study, 84% of patients with an episode of severe hypoglycemia (<40 mg/dL [2.2 mmol/L]) had a prior episode of hypoglycemia (<70 mg/dL [3.9 mmol/L]) during the same admission (36). In another study of hypoglycemic episodes (<50 mg/dL [2.8 mmol/L]), 78% of patients were using basal insulin, with the incidence of hypoglycemia peaking between midnight and 6 A.M. Despite recognition of hypoglycemia, 75% of patients did not have their dose of basal insulin changed before the next insulin administration (37).

Prevention

Common preventable sources of iatrogenic hypoglycemia are improper prescribing of hypoglycemic medications, inappropriate management of the first episode of hypoglycemia, and nutrition–insulin mismatch, often related to an unexpected interruption of nutrition. Studies of "bundled" preventative therapies including proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management showed that hypoglycemic episodes in the hospital could be prevented. Compared with baseline, two such studies found that hypoglycemic events fell by 56% to 80% (38,39). The Joint Commission recommends that all hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues.

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy in the hospital are to provide adequate calories to meet metabolic demands, optimize glycemic control, address personal food preferences, and facilitate creation of a discharge plan. The ADA does not endorse any single meal plan or specified percentages of macronutrients, and the term "ADA diet" should no longer be used. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Consistent carbohydrate meal plans are preferred by many hospitals as they facilitate matching the prandial insulin dose to the amount of carbohydrate consumed (40). Regarding enteral nutritional therapy, diabetes-specific formulas appear to be superior to standard formulas in controlling postprandial glucose, A1C and the insulin response (41).

When the nutritional issues in the hospital are complex, a registered dietitian, knowledgeable and skilled in medical nutrition therapy, can serve as an individual inpatient team member. That person should be responsible for integrating information about the patient's clinical condition, meal planning, and lifestyle habits and for establishing realistic treatment goals after discharge. Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events.

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for select youth and adult patients. Candidates include patients who successfully conduct self-management of diabetes at home, have the cognitive and physical skills needed to successfully self-administer insulin, and perform self-monitoring of blood glucose. In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, use multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII) pump therapy, have stable insulin requirements, and understand sick-day management. If self-management is to be used, a protocol should include a requirement that the patient, nursing staff, and physician agree that patient self-management is appropriate. If CSII is to be used, hospital policy and procedures delineating guidelines for CSII therapy including the changing of infusion sites are advised (42).

STANDARDS FOR SPECIAL SITUATIONS

Enteral/Parenteral Feedings

For patients receiving enteral or parenteral feedings who require insulin, insulin should be divided into basal, nutritional, and correctional components. This is particularly important for people with type 1 diabetes to ensure that they continue to receive basal insulin even if the feedings are discontinued. One may use the patient's preadmission basal insulin dose or a percentage of the total daily dose of insulin when the patient is being fed (usually 30 to 50% of the total daily dose of insulin) to estimate basal insulin requirements. However, if no basal insulin was used, consider using 5 units of NPH/detemir insulin subcutaneously every 12 h or 10 units of insulin glargine every 24 h (43). For patients receiving continuous tube feedings, the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g carbohydrate per day or as a percentage of the total daily dose of insulin when the patient is being fed (usually 50 to 70% of the total daily dose of insulin) Correctional insulin should also be administered subcutaneously every 6 h using human regular insulin or every 4 h using a rapid-acting insulin such as lispro, aspart, or glulisine. For patients receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin should be given per 10–15 g carbohydrate subcutaneously before each feeding. Correctional insulin coverage should be added as needed before each feeding. For patients receiving continuous peripheral or central parenteral nutrition, regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required in the past 24 h. A starting dose of 1 unit of human regular insulin for every 10 g dextrose has been recommended (44), to be adjusted daily in the solution. Correctional insulin should be administered subcutaneously. For full enteral/parenteral feeding guidance, the reader is encouraged to consult review articles (2,45) and see **Table 14.1**.

Glucocorticoid Therapy

Glucocorticoid type and duration of action must be considered in determining insulin treatment regimens. Once-a-day, short-acting glucocorticoids such as prednisone peak in about 4 to 8 h

Table 14.1—Insulin dosing for enteral/parenteral feedings

Situation	Basal/nutritional	Correctional
Continuous enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine daily Nutritional: regular insulin every 6 h or rapid-acting insulin every 4 h, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia
Bolus enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine daily Nutritional: give regular insulin or rapid-acting insulin SQ before each feeding, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia
Parenteral feedings	Add regular insulin to TPN IV solution, starting with 1 unit per 10 g of carbohydrate; adjust daily	SQ regular insulin every 6 h or rapid-acting insulin every 4 h for hyperglycemia

IV, intravenous; SQ, subcutaneous; TDD, total daily dose; TPN, total parenteral nutrition.

(46), so coverage with intermediate-acting insulin (NPH) may be sufficient. For long-acting glucocorticoids such as dexamethasone or multidose or continuous glucocorticoid use, long-acting insulin may be used (21,45). For higher doses of glucocorticoids, increasing doses of prandial and supplemental insulin may be needed in addition to basal insulin (47). Whatever orders are started, adjustments based on anticipated changes in glucocorticoid dosing and POC glucose test results are critical.

Perioperative Care

Many standards for perioperative care lack a robust evidence base. However, the following approach (48) may be considered:

1. Target glucose range for the perioperative period should be 80–180 mg/dL (4.4–10.0 mmol/L).
2. Perform a preoperative risk assessment for patients at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
3. Withold metformin 24 h before surgery.
4. Withhold any other oral hypoglycemic agents the morning of surgery or procedure and give half of NPH dose or 60–80% doses of a long-acting analog or pump basal insulin.
5. Monitor blood glucose at least every 4–6 h while NPO and dose with short-acting insulin as needed.

A review found that perioperative glycemic control tighter than 80–180 mg/dL (4.4–10.0 mmol/L) did not improve outcomes and was associated with more hypoglycemia (49); therefore, in general, tighter glycemic targets are not advised. In noncardiac general surgery patients, basal insulin plus premeal regular or short-acting insulin (basal-bolus) coverage has been associated with improved glycemic control and lower rates of perioperative complications compared with the traditional sliding scale regimen (regular or short-acting insulin coverage only with no basal dosing) (23,50).

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

There is considerable variability in the presentation of DKA and hyperosmolar hyperglycemic state, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma; therefore, treatment individualization based on a careful clinical and laboratory assessment is needed (51).

Management goals include restoration of circulatory volume and tissue perfusion, resolution of hyperglycemia, and correction of electrolyte imbalance and ketosis. It is also important to treat any correctable underlying cause of DKA such as sepsis.

In critically ill and mentally obtunded patients with DKA or hyperosmolar hyperglycemic state, continuous intravenous insulin is the standard of care. However, there is no significant difference in outcomes for intravenous regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA (52). Patients with uncomplicated DKA may sometimes be treated with subcutanous insulin in the emergency department or step-down units (53), an approach that may be safer and more cost-effective than treatment with intravenous insulin (54). If subcutaneous administration is used, it is important to provide adequate fluid replacement, nurse training, frequent bedside testing, infection treatment if warranted, and appropriate follow-up to avoid recurrant DKA. Several studies have shown that the use of bicarbonate in patients with DKA made no difference in resolution of acidosis or time to discharge, and its use is generally not recommended (55). For further information, regarding treatment, refer to recent in-depth reviews (3,56).

TRANSITION FROM THE ACUTE CARE SETTING

A structured discharge plan tailored to the individual patient may reduce length of hospital stay, readmission rates, and increase patient satisfaction (57). Therefore, there should be a structured discharge plan tailored to each patient. Discharge planning should begin at admission and be updated as patient needs change.

Transition from the acute care setting is a risky time for all patients. Inpatients may be discharged to varied settings including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. For the patient who is discharged to home or to assisted living, the optimal program will need to consider diabetes type and severity, effects of the patient's illness on blood glucose levels, and the patient's capacities and desires.

An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes educator within 1 month of discharge is advised for all patients having hyperglycemia in the hospital. If glycemic medications are changed or glucose control is not optimal at discharge, an earlier appointment (in 1–2 weeks) is preferred, and frequent contact may be needed to avoid hyperglycemia and hypoglycemia. A recent discharge algorithm for glycemic medication adjustment based on admission A1C found that the average A1C in patients with diabetes after discharge was significantly improved (6). Therefore, if an A1C from the prior 3 months is unavailable, measuring the A1C in all patients with diabetes or hyperglycemia admitted to the hospital is recommended.

Clear communication with outpatient providers either directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the cause of hyperglycemia (or the plan for determining the cause), related complications and comorbidities, and recommended treatments can assist outpatient providers as they assume ongoing care.

The Agency for Healthcare Research and Quality (AHRQ) recommends that at a minimum, discharge plans include the following (58):

Medication Reconciliation

- The patient's medications must be cross-checked to ensure that no chronic medications were stopped and to ensure the safety of new prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the patient and family at or before discharge.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient physicians.
- Discharge summaries should be transmitted to the primary physician as soon as possible after discharge.
- Appointment-keeping behavior is enhanced when the inpatient team schedules outpatient medical follow-up prior to discharge.

It is recommended that the following areas of knowledge be reviewed and addressed prior to hospital discharge:

- Identify the health care provider who will provide diabetes care after discharge.
- Level of understanding related to the diabetes diagnosis, self-monitoring of blood glucose, explanation of home blood glucose goals, and when to call the provider.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Information on consistent nutrition habits.
- If relevant, when and how to take blood glucose–lowering medications, including insulin administration.
- Sick-day management.
- Proper use and disposal of needles and syringes.

It is important that patients be provided with appropriate durable medical equipment, medications, supplies (e.g., insulin pens), and prescriptions along with appropriate education at the time of discharge in order to avoid a potentially dangerous hiatus in care.

PREVENTING ADMISSIONS AND READMISSIONS

Preventing Hypoglycemic Admissions in Older Adults

Insulin-treated patients 80 years of age or older are more than twice as likely to visit the emergency department and nearly five times as likely to be admitted for insulin-related hypoglycemia than those 45–64 years of age (59). However, older adults with type 2 diabetes in long-term care facilities taking either oral antihyperglycemic agents or basal insulin have similar glycemic control (60), suggesting that oral therapy may be used in place of insulin to lower the risk of hypoglycemia for some patients. In addition, many older adults with diabetes are overtreated (61), with half of those maintaining an A1C $<$7% being treated with insulin or a sulfonlyurea, which are associated with hypoglycemia. To further lower the risk of hypoglycemia-related admissions in older adults, providers may, on an individual basis, relax A1C targets to $<$8% or $<$8.5% in patients with shortened life expectancies and significant comorbidities (refer to Section 11 "Older Adults" for detailed criteria).

Preventing Readmissions

In patients with diabetes, the readmission rate is between 14% and 20% (62). Risk factors for readmission include lower socioeconomic status, certain racial/ethnic minority groups, comorbidities, urgent admission, and recent prior hospitalization (62). Of interest, 30% of patients with two or more hospital stays account for over 50% of hospitalizations and their accompanying hospital costs (63). While there is no standard to prevent readmissions, several successful strategies have been reported, including an intervention program targeting ketosis-prone patients with type 1 diabetes (64), initiating insulin treatment in patients with admission A1C $>$9% (65), and a transitional care model (66). For people with diabetic kidney disease, patient-centered medical home collaboratives may decrease risk-adjusted readmission rates (67).

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15. Diabetes Advocacy

American Diabetes Association

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Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face additional discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the American Diabetes Association (ADA) can help to ensure that they live a healthy and productive life. A strategic goal of the ADA is that more children and adults with diabetes live free from the burden of discrimination.

One tactic for achieving this goal is to implement the ADA's Standards of Care through advocacy-oriented position statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, and diabetes management in certain settings such as schools, child care programs, and correctional institutions. In addition to the ADA's clinical position statements, these advocacy position statements are important tools in educating schools, employers, licensing agencies, policymakers, and others about the intersection of diabetes medicine and the law.

ADVOCACY POSITION STATEMENTS

Partial list, with most recent publications appearing first

Diabetes Care in the School Setting (1)
First publication: 1998 (revised 2015)
A sizeable portion of a child's day is spent in school, so close communication with and cooperation of school personnel are essential to optimize diabetes management, safety, and academic opportunities. See the ADA position statement "Diabetes Care in the School Setting" (http://care.diabetesjournals.org/content/38/10/1958.full).

Care of Young Children With Diabetes in the Child Care Setting (2)
First publication: 2014
Very young children (aged <6 years) with diabetes have legal protections and can be safely cared for by child care providers with appropriate training, access to resources, and a system of communication with parents and the child's diabetes provider. See the ADA position statement "Care of Young Children With Diabetes in the Child Care Setting" (http://care.diabetesjournals.org/content/37/10/2834).

Diabetes and Driving (3)
First publication: 2012
People with diabetes who wish to operate motor vehicles are subject to a great variety of licensing requirements applied by both state and federal jurisdictions, which may lead to loss of employment or significant restrictions on a person's license. Presence of a medical condition that can lead to significantly impaired consciousness or cognition may lead to drivers being evaluated for fitness to drive. People with diabetes should be individually assessed by a health care professional knowledgeable in diabetes if license restrictions are being considered, and patients should be counseled about detecting and avoiding hypoglycemia while driving. See the ADA position statement "Diabetes and Driving" (http://care.diabetesjournals.org/content/37/Supplement_1/S97).

Diabetes and Employment (4)
First publication: 1984 (revised 2009)
Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which he or she is otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. When questions arise about the medical fitness of a person with diabetes for a particular job, a health care professional with expertise in treating diabetes should perform

Suggested citation: American Diabetes Association. Diabetes advocacy. Sec. 15. In Standards of Medical Care in Diabetes—2016*. Diabetes Care 2017;40(Suppl. 1):S128–S129*

an individualized assessment. See the ADA position statement “Diabetes and Employment” (http://care.diabetesjournals.org/content/37/Supplement_1/S112).

Diabetes Management in Correctional Institutions (5)

First publication: 1989 (revised 2008)

People with diabetes in correctional facilities should receive care that meets national standards. Because it is estimated that nearly 80,000 inmates have diabetes, correctional institutions should have written policies and procedures for the management of diabetes and for training of medical and correctional staff in diabetes care practices. See the ADA position statement “Diabetes Management in Correctional Institutions” (http://care.diabetesjournals.org/content/37/Supplement_1/S104).

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4. American Diabetes Association. Diabetes and employment. Diabetes Care 2014;37(Suppl. 1):S112–S117
5. American Diabetes Association. Diabetes management in correctional institutions. Diabetes Care 2014;37(Suppl. 1):S104–S111

Professional Practice Committee Disclosures

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ADA, American Diabetes Association; DSMB, Data and Safety Monitoring Board; MEDCAC, Medicare Evidence Development & Coverage Advisory Committee. *≥$10,000 per year from company to individual.

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W.H.H.	None	None	Merck Sharp & Dohme (Chair, DSMB),* Lexicon Pharmaceuticals (Chair, DSMB, Travel), RTI International (Member, Ad Board, Travel)	National Committee for Quality Assurance (Chair, Diabetes Panel), Centers for Medicare & Medicaid Services (member, MEDCAC), *Diabetic Medicine* (former Editor for the Americas), *Diabetes Care* (ad hoc Editor in Chief)
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S.U.	None	None	None	None
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