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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" 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 Medical Care in Diabetes," position statements, and scientific statements undergo a formal review process by ADA's Professional Practice Committee (PPC) and the Executive Committee of the Board of Directors. The Standards and all ADA position statements, scientific statements, and consensus reports are available on the Association's Web site at http://professional.diabetes.org/adastatements.

"Standards of Medical Care in Diabetes"

Standards of Care: ADA position statement that provides key clinical practice recommendations. The PPC performs an extensive literature search and updates the Standards 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 for the first time having the majority of bulleted recommendations supported by **A**- or **B**-level evidence

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

(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 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 2016;39(Suppl. 1):S3 | DOI: 10.2337/dc16-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 revisions 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 for the *Standards of Medical Care in Diabetes—2016*" table (see p. S107).

For the current revision, PPC members systematically searched MEDLINE for human studies related to each section and published since 1 January 2015. 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 reviewed and 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 2016 revision of the Standards of Care. Readers who wish to comment on the *Standards of Medical Care in Diabetes—2016* 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: *Lloyd Paul Aiello, MD, PhD; Sheri Colberg-Ochs, PhD; Jo Ellen Condon, RD, CDE; Donald R. Coustan, MD; Silvio E. Inzucchi, MD; George L. King, MD; Shihchen Kuo, RPh, PhD; Ira B. Lamster, DDS, MMSc; Greg Maynard, MD, MSc, SFHM; Emma Morton-Eggleston, MD, MPH; Margaret A. Powers, PhD, RD, CDE; Robert E. Ratner, MD; Erinn Rhodes, MD, MPH; Amy Rothberg, MD; Sharon D. Solomon, MD; Guillermo E. Umpierrez, MD; Willy Valencia, MD; and Kristina F. Zdanys, MD.*

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Standards of Medical Care in Diabetes—2016: Summary of Revisions

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GENERAL CHANGES

In alignment with the American Diabetes Association's (ADA's) position that diabetes does not define people, the word "diabetic" will no longer be used when referring to individuals with diabetes in the "Standards of Medical Care in Diabetes." The ADA will continue to use the term "diabetic" as an adjective for complications related to diabetes (e.g., diabetic retinopathy).

*Although levels of evidence for several recommendations have been updated, these changes are not included below as the clinical recommendations have remained the same. Changes in evidence level from, for example, **C** to **E** are not noted below. The "Standards of Medical Care in Diabetes—2016" contains, in addition to many minor changes that clarify recommendations or reflect new evidence, the following more substantive revisions.*

SECTION CHANGES

Section 1. Strategies for Improving Care

This section was revised to include recommendations on tailoring treatment to vulnerable populations with diabetes, including recommendations for those with food insecurity, cognitive dysfunction and/or mental illness, and HIV, and a discussion on disparities related to ethnicity, culture, sex, socioeconomic differences, and disparities.

Section 2. Classification and Diagnosis of Diabetes

The order and discussion of diagnostic tests (fasting plasma glucose, 2-h plasma glucose after a 75-g oral glucose tolerance test, and A1C criteria) were revised to make it clear that no one test is preferred over another for diagnosis.

To clarify the relationship between age, BMI, and risk for type 2 diabetes and prediabetes, the ADA revised the screening recommendations. The recommendation is now to test all adults beginning at age 45 years, regardless of weight.

Testing is also recommended for asymptomatic adults of *any age* who are overweight or obese and who have one or more additional risk factors for diabetes. Please refer to Section 2 for testing recommendations for gestational diabetes mellitus.

For monogenic diabetes syndromes, there is specific guidance and text on testing, diagnosing, and evaluating individuals and their family members.

Section 3. Foundations of Care and Comprehensive Medical Evaluation

Section 3 "Initial Evaluation and Diabetes Management Planning" and Section 4 "Foundations of Care: Education, Nutrition, Physical Activity, Smoking Cessation, Psychosocial Care, and Immunization" from the 2015 Standards were combined into one section for 2016 to reflect the importance of integrating medical evaluation, patient engagement, and ongoing care that highlight the importance of lifestyle and behavioral modification. The nutrition and vaccination recommendations were streamlined to focus on those aspects of care most important and most relevant to people with diabetes.

Section 4. Prevention or Delay of Type 2 Diabetes

To reflect the changing role of technology in the prevention of type 2 diabetes, a recommendation was added encouraging the use of new technology such as apps and text messaging to affect lifestyle modification to prevent diabetes.

Section 5. Glycemic Targets

Because of the growing number of older adults with insulin-dependent diabetes, the ADA added the recommendation that people who use continuous glucose monitoring and insulin pumps should have continued access after they turn 65 years of age.

Section 6. Obesity Management for the Treatment of Type 2 Diabetes

This new section, which incorporates prior recommendations related to bariatric surgery, has new recommendations related to the comprehensive assessment of weight in diabetes and to the treatment of overweight/obesity with behavior modification and pharmacotherapy.

This section also includes a new table of currently approved medications for the long-term treatment of obesity.

Section 7. Approaches to Glycemic Treatment

Bariatric surgery was removed from this section and placed in a new section entitled "Obesity Management for the Treatment of Type 2 Diabetes."

Section 8. Cardiovascular Disease and Risk Management

"Atherosclerotic cardiovascular disease" (ASCVD) has replaced the former term "cardiovascular disease" (CVD), as ASCVD is a more specific term.

A new recommendation for pharmacological treatment of older adults was added.

To reflect new evidence on ASCVD risk among women, the recommendation to consider aspirin therapy in women aged >60 years has been changed to include women aged ≥50 years. A recommendation was also added to address antiplatelet use in patients aged <50 years with multiple risk factors.

A recommendation was made to reflect new evidence that adding ezetimibe

to moderate-intensity statin provides additional cardiovascular benefits for select individuals with diabetes and should be considered.

A new table provides efficacy and dose details on high- and moderate-intensity statin therapy.

Section 9. Microvascular Complications and Foot Care

"Nephropathy" was changed to "diabetic kidney disease" to emphasize that, while nephropathy may stem from a variety of causes, attention is placed on kidney disease that is directly related to diabetes. There are several minor edits to this section. The significant ones, based on new evidence, are as follows:

Diabetic kidney disease: guidance was added on when to refer for renal replacement treatment and when to refer to physicians experienced in the care of diabetic kidney disease.

Diabetic retinopathy: guidance was added on the use of intravitreal anti-VEGF agents for the treatment of center-involved diabetic macular edema, as they were more effective than monotherapy or combination therapy with laser.

Section 10. Older Adults

The scope of this section is more comprehensive, capturing the nuances of diabetes care in the older adult population. This includes neurocognitive function, hypoglycemia, treatment goals, care in skilled nursing facilities/nursing homes, and end-of-life considerations.

Section 11. Children and Adolescents

The scope of this section is more comprehensive, capturing the nuances of diabetes care in the pediatric population. This includes new recommendations addressing diabetes self-management education and support, psychosocial issues, and treatment guidelines for type 2 diabetes in youth.

The recommendation to obtain a fasting lipid profile in children starting at age 2 years has been changed to age 10 years, based on a scientific statement on type 1 diabetes and cardiovascular disease from the American Heart Association and the ADA.

Section 12. Management of Diabetes in Pregnancy

The scope of this section is more comprehensive, providing new recommendations on pregestational diabetes, gestational diabetes mellitus, and general principles for diabetes management in pregnancy.

A new recommendation was added to highlight the importance of discussing family planning and effective contraception with women with preexisting diabetes.

A1C recommendations for pregnant women with diabetes were changed, from a recommendation of $<$6% (42 mmol/mol) to a target of 6–6.5% (42–48 mmol/mol), although depending on hypoglycemia risk the target may be tightened or relaxed.

Glyburide in gestational diabetes mellitus was deemphasized based on new data suggesting that it may be inferior to insulin and metformin.

Section 13. Diabetes Care in the Hospital

This section was revised to focus solely on diabetes care in the hospital setting. This comprehensive section addresses hospital care delivery standards, more detailed information on glycemic targets and antihyperglycemic agents, standards for special situations, and transitions from the acute care setting.

This section also includes a new table on basal and bolus dosing recommendations for continuous enteral, bolus enteral, and parenteral feedings.

Section 14. Diabetes Advocacy

"Diabetes Care in the School Setting: A Position Statement of the American Diabetes Association" was revised in 2015. This position statement was previously called "Diabetes Care in the School and Day Care Setting." The ADA intentionally separated these two populations because of the significant differences in diabetes care between the two cohorts.

1. Strategies for Improving Care

American Diabetes Association

Diabetes Care 2016;39(Suppl. 1):S6–S12 | DOI: 10.2337/dc16-S004

Recommendations

- A patient-centered communication style that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care should be used. **B**
- Treatment decisions should be timely and based on evidence-based guidelines that are tailored to individual patient preferences, prognoses, and comorbidities. **B**
- Care should be aligned with components of the Chronic Care Model to ensure 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 CARE CONCEPTS

In the following sections, different components of the clinical management of patients with (or at risk for) diabetes are reviewed. Clinical practice guidelines are key to improving population health; however, for optimal outcomes, diabetes care must be individualized for each patient. The American Diabetes Association highlights the following three themes that clinicians, policymakers, and advocates should keep in mind:

1. **Patient-Centeredness:** 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 would not have met eligibility criteria for the studies on which guidelines were based. Recognizing that one size does not fit all, these Standards provide guidance for when and how to adapt recommendations. Because patients with diabetes have greatly increased risk for cardiovascular disease, a patient-centered approach should include a comprehensive plan to reduce cardiovascular risk by addressing blood pressure and lipid control, smoking prevention and cessation, weight management, physical activity, and healthy lifestyle choices.
2. **Diabetes Across the Life Span:** An increasing proportion of patients with type 1 diabetes are adults. For less salutary reasons, the incidence of type 2 diabetes is increasing in children and young adults. Patients with type 1 diabetes and those with type 2 diabetes are living well into older age, a stage of life for which there is little evidence from clinical trials to guide therapy. All these demographic changes highlight another challenge to high-quality diabetes care, which is the need to improve coordination between clinical teams as patients transition through different stages of the life span.
3. **Advocacy for Patients With Diabetes:** Advocacy can be defined as active support and engagement to advance a cause or policy. Advocacy is needed to improve the lives of patients with (or at risk for) diabetes. Given the tremendous toll that obesity, physical inactivity, and smoking have on the health of patients with diabetes, efforts are needed to address and change the societal determinants at the root of these problems. Within the narrower domain of clinical practice guidelines, the application of evidence level grading to practice recommendations can help to identify areas that require more research (1). Refer to Section 14 "Diabetes Advocacy."

Suggested citation: American Diabetes Association. Strategies for improving care. Sec. 1. In Standards of Medical Care in Diabetes—2016. *Diabetes Care 2016;39(Suppl. 1):S6–S12*

CARE DELIVERY SYSTEMS

There has been steady improvement in the proportion of patients with diabetes treated with statins and achieving recommended levels of A1C, blood pressure, and LDL cholesterol in the last 10 years (2). The mean A1C nationally 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 compared with 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 and nonsmoking status (2). Evidence also suggests that progress in cardiovascular risk factor control (particularly tobacco use) may be slowing (2,3). Certain patient groups, such as young adults and patients with complex comorbidities, financial or other social hardships, and/or limited English proficiency, may present particular challenges to goal-based care (4–6). Even after adjusting for patient factors, the persistent variation in quality of diabetes care across providers and practice settings indicates that there is potential for substantial system-level improvements.

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 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) has been shown to be an effective framework for improving the quality of diabetes care (7).

Six Core Elements

The CCM includes six core elements for the provision of optimal 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 promoting self-management on the part of the patient 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).

Key Objectives

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 should prioritize timely and appropriate intensification of lifestyle and/or pharmacological therapy for patients who have not achieved beneficial levels of glucose, blood pressure, or lipid control (12). Strategies such as explicit goal setting with patients (13); identifying and addressing language, numeracy, or cultural barriers to care (14–17); integrating evidence-based guidelines and clinical information tools into the process of care (18–20); and incorporating care management teams including nurses, pharmacists, and other providers (21,22) have each been shown to optimize provider and team behavior and thereby catalyze reductions in A1C, blood pressure, and LDL cholesterol.

Objective 2: Support Patient Behavior Change

Successful diabetes care requires a systematic approach to supporting patients' behavior change efforts, including

1. Healthy lifestyle choices (physical activity, healthy eating, tobacco cessation, weight management, and effective coping)
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)

High-quality diabetes self-management education (DSME) has been shown to improve patient self-management, satisfaction, and glucose control. 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 (23).

Objective 3: Change the Care System

An institutional priority in most successful care systems is providing high quality of care (24). Changes that have been shown to increase quality of diabetes care include basing care on evidence-based guidelines (18); expanding the role of teams to implement more intensive disease management strategies (6,21,25); redesigning the care process (26); implementing electronic health record tools (27,28); activating and educating patients (29,30); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, self-monitoring of blood glucose, and necessary medications (6); and identifying/developing/engaging community resources and public policy that support healthy lifestyles (31).

Initiatives such as the Patient-Centered Medical Home show promise for improving outcomes through coordinated primary care and offer new opportunities for team-based chronic disease care (32). 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 (33), and incentives that accommodate personalized care goals (6,34).

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).

WHEN TREATMENT GOALS ARE NOT MET

In general, providers should seek evidence-based approaches that improve the clinical outcomes and quality of life of patients with diabetes. Recent reviews of quality improvement strategies in diabetes care (24,35,36) have not identified a particular approach that is more effective than others. However, the Translating Research Into Action for Diabetes (TRIAD) study provided objective data from large managed care systems demonstrating effective tools for specific targets (6). TRIAD found it useful to divide interventions into those that affected **processes of care** and **intermediate outcomes.**

Processes of Care

Processes of care included periodic testing of A1C, lipids, and urinary albumin; examining the retina and feet; advising on aspirin use; and smoking cessation. TRIAD results suggest that providers control these activities. Performance feedback, reminders, and structured care (e.g., guidelines, formal case management, and patient education resources) may influence providers to improve processes of care (6).

Intermediate Outcomes and Treatment Intensification

For intermediate outcomes, such as A1C, blood pressure, and lipid goals, tools that improved processes of care did not perform as well in addressing barriers to treatment intensification and adherence (6). In 35% of cases, uncontrolled A1C, blood pressure, or lipids were associated with a lack of treatment intensification, defined as a failure to either increase a drug dose or change a drug class (37). Treatment intensification was associated with improvement in A1C, hypertension, and hyperlipidemia control (38). A large multicenter study confirmed the strong association between treatment intensification and improved A1C (39).

Intermediate Outcomes and Adherence

In 23% of cases, poor adherence was associated with uncontrolled A1C, blood pressure, or lipids (40). Although there are many ways to measure adherence (40), Medicare uses percent of days covered (PDC), which is a measure of the number of pills prescribed divided by the days between first and last prescriptions. "Adequate" adherence is defined as 80% (40). This metric can be used to find and track poor adherence and help to guide system improvement efforts to overcome the barriers to adherence. Barriers to adherence may include patient factors (remembering to obtain or take medications, fears, depression, or health beliefs), medication factors (complexity, multiple daily dosing, cost, or side effects), and system factors (inadequate follow-up or support).

Improving Adherence

Simplifying a complex treatment regimen may improve adherence. Nurse-directed interventions, home aides, diabetes education, and pharmacy-derived interventions improved adherence but had a very small effect on outcomes, including metabolic control (41). Success in overcoming barriers may be achieved if the patient and provider agree on a targeted treatment for a specific barrier. For example, one study found that when depression was identified as a barrier, agreement on antidepressant treatment subsequently allowed for improvements in A1C, blood pressure, and lipid control (10). Thus, to improve adherence, systems should continually monitor and prevent or treat poor adherence by identifying barriers and implementing treatments that are barrier specific and effective.

A systematic approach to achieving intermediate outcomes involves three steps:

1. **Assess adherence.** Adherence should be addressed as the first priority. If adherence is 80% or above, then treatment intensification should be considered (e.g., up-titration). If medication up-titration is not a viable option, then consider initiating or changing to a different medication class.
2. **Explore barriers** to adherence with the patient/caregiver and find a mutually agreeable approach to overcoming the barriers.
3. **Establish a follow-up plan** that confirms the planned treatment change and assess progress in reaching the target.

TAILORING TREATMENT TO VULNERABLE POPULATIONS

Health Disparities

The causes of health disparities are complex and include societal issues such as institutional racism, discrimination, socioeconomic status, poor access to health care, and lack of health insurance. Disparities are particularly well documented for cardiovascular disease.

Ethnic/Cultural/Sex/Socioeconomic Differences

Ethnic, cultural, religious, and sex differences and socioeconomic status may affect diabetes prevalence and outcomes. Type 2 diabetes develops more frequently in women with prior gestational diabetes mellitus (42), in individuals with hypertension or dyslipidemia, and in certain racial/ethnic groups (African American, Native American, Hispanic/Latino, and Asian American) (43).

Access to Health Care

Ethnic, cultural, religious, sex, and socioeconomic differences affect health care access and complication risk in people with diabetes. Recent studies have recommended lowering the BMI cut point for testing for Asian Americans to $\geq$23 kg/m^2 (44). Women with diabetes, compared with men with diabetes, have a 40% greater risk of incident coronary heart disease (45). Socioeconomic and ethnic inequalities exist in the provision of health care to individuals with diabetes (46). As a result, children with type 1 diabetes from racial/ethnic 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).

Addressing Disparities

Therefore, diabetes management requires individualized, patient-centered, and culturally appropriate strategies. To overcome disparities, community health workers (49), peers (50,51), and lay leaders (52) may assist in the delivery of DSME and diabetes self-management support services (53). Strong social support leads to improved clinical outcomes, reduced psychosocial symptomatology, and adoption of healthier lifestyles (54). Structured interventions, tailored to ethnic populations that integrate culture, language, religion, and literacy skills, positively influence patient outcomes (55).

To decrease disparities, all providers and groups are encouraged to use the National Quality Forum's National Voluntary Consensus Standards for Ambulatory Care—Measuring Healthcare Disparities (56).

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 (57). The affordable care act has improved access to health care; however, many remain without coverage. In a recent study of predominantly African American or Hispanic uninsured patients with diabetes, 50–60% were hypertensive, but only 22–37% had systolic blood pressure controlled by treatments to under 130 mmHg (58).

Food Insecurity

Recommendations

- Providers should evaluate hyperglycemia and hypoglycemia in the context of food insecurity and propose solutions accordingly. **A**
- Providers should recognize that homelessness, poor literacy, and poor numeracy often occur with food insecurity, and appropriate resources should be made available for patients with diabetes. **A**

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 out 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 nutritious food for inexpensive and more energy- and carbohydrate-dense processed foods.

In people with FI, interventions should focus on preventing diabetes and, in those with diabetes, limiting hyperglycemia and preventing hypoglycemia. The risk for type 2 diabetes is increased twofold in those with FI. The risks of uncontrolled hyperglycemia and severe hypoglycemia are increased in those with diabetes who are also food insecure.

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 (59).

Food Insecurity and Hyperglycemia. Hyperglycemia is more common in those with diabetes and FI. Reasons for this include the steady consumption of carbohydrate-rich processed foods, binge eating, not filling antidiabetes medication prescriptions owing to financial constraint, and anxiety/depression that lead to poor diabetes self-care behaviors. Providers should be well versed in these risk factors for hyperglycemia and take practical steps to alleviate them in order to improve glucose control.

Food Insecurity and Hypoglycemia

Type 1 Diabetes. Individuals with type 1 diabetes and FI may develop hypoglycemia as a result of inadequate or erratic carbohydrate consumption following insulin administration. Long-acting insulin, as opposed to shorter-acting insulin that may peak when food is not available, may lower the risk for hypoglycemia in those with FI. Short-acting insulin analogs, preferably delivered by a pen, may be used immediately after consumption of a meal, whenever food becomes available. Unfortunately, the greater cost of insulin analogs should be weighed against their potential advantages. Caring for those with type 1 diabetes in the setting of FI may mirror "sick day" management protocols.

Type 2 Diabetes. Those with type 2 diabetes and FI can develop hypoglycemia for similar reasons after taking certain oral hypoglycemic agents. If using a sulfonylurea, glipizide is the preferred choice due to the shorter half-life. Glipizide can be taken immediately before meal consumption, thus limiting its tendency to produce hypoglycemia as compared with longer-acting sulfonylureas (e.g., glyburide).

Homelessness. Homelessness often accompanies the most severe form of FI. Therefore, providers who care for those with FI who are uninsured and homeless and individuals with poor literacy and numeracy 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, homeless patients with diabetes need secure places to keep their diabetes supplies and refrigerator access to properly store their insulin.

Literacy and Numeracy Deficiencies. FI and diabetes are more common among non-English speaking individuals and those with poor literacy and numeracy skills. Therefore, it is important to consider screening for FI, proper housing, and diabetes in this population. Programs that see such patients should work to develop services in multiple languages with the specific goal of preventing diabetes and building diabetes awareness in people who cannot easily read or write in English.

Cognitive Dysfunction

Recommendations

- Intensive glucose control is not advised for the improvement of poor cognitive function in hyperglycemic individuals with type 2 diabetes. **B**
- In individuals with poor cognitive function or severe hypoglycemia, glycemic therapy should be tailored to avoid significant hypoglycemia. **C**
- In individuals with diabetes at high cardiovascular risk, the cardiovascular benefits of statin therapy outweigh the risk of cognitive dysfunction. **A**
- If a second-generation antipsychotic medication is prescribed, changes in weight, glycemic control, and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed. **C**

Dementia

The most severe form of cognitive dysfunction is dementia. 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 (60). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia.

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 (61). 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 (62). However, the ACCORD study found no difference in cognitive outcomes between 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 (63).

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 (64). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (65). 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 (66). However, a recent Cochrane review found insufficient evidence to recommend any dietary change for the prevention or treatment of cognitive dysfunction (67).

Statins. Given the controversy over a potential link between statins and dementia, it is worth noting that a Cochrane systematic review has reported that data do not support an adverse effect of statins on cognition. 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 (68). Therefore individuals with diabetes and a high risk for cardiovascular disease should be placed on statin therapy regardless of cognitive status.

Mental Illness

Severe mental disorder that includes schizophrenia, bipolar disorder, and depression is increased 1.7-fold in people with diabetes (69). The prevalence of type 2 diabetes is two–three times higher in people with schizophrenia, bipolar disorder, and schizoaffective disorder than in the general population (70). A meta-analysis showed a significantly increased risk of incident depression (relative risk [RR] = 1.15), and, in turn, depression was associated with a significantly increased risk of diabetes (RR = 1.6) (71). Depression and psychosocial issues are discussed more extensively in Section 3 "Foundations of Care and Comprehensive Medical Evaluation."

Medications

Diabetes medications are effective, regardless of mental health status. Treatments for depression are effective in patients with diabetes, and treating depression may improve short-term glycemic control (72). If a second-generation antipsychotic medication is prescribed, changes in weight, glycemic control, and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed if significant changes are noted (73). Awareness of an individual's medication profile, especially if an individual takes psychotropic medications, is key to effective management.

Diabetes Care in Patients With HIV

Recommendation

- Patients with HIV should be screened for diabetes and prediabetes with a fasting glucose level before starting antiretroviral therapy and 3 months after starting or changing it. If initial screening results are normal, checking fasting glucose each year is advised. If prediabetes is detected, continue to measure 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 HIV-infected patients on PIs, whereas more than 15% may have prediabetes (74). 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 proper screening protocol is recommended (75). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among HIV patients with 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 (76). 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, antidiabetes agents may still be necessary.

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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 β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of insulin secretion on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
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). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and approximately one-third with DKA (2). 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.

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on the **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 the **A1C criteria** (1,3) (**Table 2.1**).

The same tests are 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 2.1**). 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 cut points and A1C, 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

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Table 2.1—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.

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.

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) (4).

It is important to take age, race/ethnicity, and anemia/hemoglobinopathies into consideration when using the A1C to diagnose diabetes.

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 (4,5).

Race/Ethnicity

A1C levels may vary with patients' race/ethnicity (6,7). For example, African Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and postglucose load glucose levels. African Americans 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 (8). Moreover, the association of A1C with risk for complications is similar in African Americans and non-Hispanic whites (9).

Hemoglobinopathies/Anemias

Interpreting A1C levels in the presence of certain hemoglobinopathies and anemia 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.

Red Blood Cell Turnover

In conditions associated with increased red blood cell turnover, such as pregnancy (second and third trimesters), recent blood loss or transfusion, erythropoietin therapy, or hemolysis, 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 least likely for A1C, more likely for FPG, and most likely for the 2-h PG, especially if the glucose samples remain at room temperature and are not centrifuged promptly. Barring laboratory error, such patients will likely 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

- Testing to assess 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 patients, 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 to detect 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 (10,11) 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 impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and indicates an increased risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes (**Table 2.2**) and cardiovascular disease (CVD). IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

In 1997 and 2003, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (10,11) defined IFG as FPG levels 100–125 mg/dL (5.6–6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels 140–199 mg/dL (7.8–11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous 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 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 an A1C between 5.5–6.0% (37–42 mmol/mol) 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 an A1C of 5.0% (31 mmol/mol) (12). 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 (13). Other analyses suggest that an A1C of 5.7% (39 mmol/mol) is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (14), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (15).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–46 mmol/mol) as identifying individuals with prediabetes. As with those with IFG and/or IGT, individuals with an A1C of 5.7–6.4% (39–46 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 4 "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 (12). 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 2.3 summarizes the categories of prediabetes and **Table 2.2** the criteria for prediabetes testing. For recommendations regarding risk factors and screening for prediabetes, see pp. S17–S18 ("Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults" 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 acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia. **E**
- Inform the relatives of patients with type 1 diabetes of the opportunity to be tested for type 1 diabetes risk, but only in the setting of a clinical research study. **E**

Diagnosis

In a patient with acute symptoms, measurement of blood glucose is part of the definition of diabetes (classic 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, this 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 insulin, GAD (GAD65), the tyrosine phosphatases IA-2 and IA-2β, and ZnT8. Type 1 diabetes is defined by 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 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. These patients are also prone to other autoimmune disorders such as Hashimoto thyroiditis, celiac disease, Graves disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

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

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - 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
   - A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
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.

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 (16). 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 (2). 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 (17). Such testing, coupled with education about diabetes symptoms and close follow-up in an observational clinical study, may enable earlier identification of type 1 diabetes onset (18). There is evidence to suggest that early diagnosis may limit acute complications (19).

A recent 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 (19,20). 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.

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://www2.diabetestrialnet.org). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. Higher-risk individuals may be tested, but only in the context of a clinical research setting. 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).

Table 2.3—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% (39–46 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.

TYPE 2 DIABETES

Recommendations

- Testing to detect type 2 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 patients, 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, if appropriate, treat other cardiovascular disease risk factors. **B**
- Testing to detect 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 "non–insulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes. This form encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. 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.

Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults

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 4 "Prevention or Delay of Type 2 Diabetes") and reduce the risk of diabetes complications (see Section 8 "Cardiovascular Disease and Risk Management" and Section 9 "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 (21). 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 (22). General practice patients between the ages of 40–69 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 (22). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to prove that screening and early intensive treatment impact outcomes. Mathematical modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of glycemia and cardiovascular risk factors in type 2 diabetes (23); 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) (24).

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

Age

Testing recommendations for diabetes in asymptomatic adults are listed in **Table 2.2**. Age is a major risk factor for diabetes. Testing should begin at age 45 years for all patients.

BMI and Ethnicity

Testing should be considered in adults of any age with BMI ≥25 kg/m^2 and one or more additional risk factors for diabetes. However, recent data (25) and evidence from the ADA position statement "BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening" (26) suggest that the BMI cut point should be lower for the Asian American population. For diabetes screening purposes, 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 ≥23 kg/m^2 should be used to define increased risk in Asian Americans (27). The finding that half of diabetes in Asian Americans is undiagnosed suggests that testing is not occurring at lower BMI thresholds (21).

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 (28).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (29), are known to increase the risk of diabetes and should be considered when ascertaining a diagnosis.

Diagnostic Tests

FPG, 2-h PG after 75-g OGTT, and A1C are equally appropriate for 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 (30,31) has primarily been demonstrated among individuals with IGT, not for individuals with isolated IFG or for those with prediabetes defined by A1C criteria.

Testing Interval

The appropriate interval between tests is not known (32). 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 (32).

Community Screening

Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment.

Community testing 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.

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 ethnic populations (16). 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 (33). 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 (34). 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 (35,36). The modified recommendations of the ADA consensus report "Type 2 Diabetes in Children and Adolescents" are summarized in **Table 2.4**.

GESTATIONAL DIABETES MELLITUS

Recommendations

- Test for undiagnosed type 2 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**
- Screen women with gestational diabetes mellitus for persistent diabetes at 6–12 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 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 (10), 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 (37). 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 2.2**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.1**). Women with diabetes in the first trimester would be classified as having type 2 diabetes. GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes (see Section 12 "Management of Diabetes in Pregnancy").

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 (38), a large-scale (25,000 pregnant women) multinational cohort study, 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 2.5**) 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 (39), the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (40). The IADPSG defined diagnostic cut points for GDM as the average glucose values (fasting, 1-h, and 2-h PG) in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean glucose 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 significant impact on the costs, medical infrastructure capacity, and potential for increased "medicalization" of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their offspring.

The expected benefits to these pregnancies and offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (41,42). It is important to note that 80–90% of women being treated for mild GDM in two randomized controlled trials (whose glucose values overlapped with the thresholds recommended by the IADPSG) could be managed with lifestyle therapy alone. Data are lacking on how the

Table 2.4—Testing for type 2 diabetes or prediabetes in asymptomatic children*

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.

treatment of lower levels of hyperglycemia affects a mother's risk for the development of type 2 diabetes in the future and her offspring's risk for obesity, diabetes, and other metabolic dysfunction. 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 on diagnosing GDM. The 15-member panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields to consider diagnostic criteria (43). The panel recommended the two-step approach of screening with a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive, a strategy commonly used in the U.S.

Key factors reported in the NIH panel's decision-making process were the lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM, including medicalization of pregnancy with increased interventions 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 (44), and shoulder dystocia, without increasing small-for-gestational-age births. The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines in 2013 and supported the two-step approach (45).

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. 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., cost–benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (46) and may be the preferred approach. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria (47). 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 genetic testing. **B**
- Maturity-onset diabetes of the young should be considered in individuals who have mild stable fasting hyperglycemia and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes. **E**
- Because a diagnosis of maturity-onset diabetes of the young may impact therapy and lead to identification of other affected family members, consider referring individuals with diabetes not typical of type 1 or type 2 diabetes and occuring in successive generations (suggestive of an autosomal dominant pattern of inheritance) to a specialist for further evaluation. **E**

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years).

Neonatal Diabetes

Neonatal diabetes is a monogenic form of diabetes with onset in the first 6 months of life. It can be mistaken for the more common type 1 diabetes, but type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. The most common genetic defect causing transient disease is a defect on ZAC/HYAMI imprinting, whereas permanent neonatal diabetes is most commonly an autosomal dominant defect in the gene encoding the Kir6.2 subunit of the β-cell K_{ATP} channel. Correct diagnosis has important implications, because children with neonatal diabetes due to mutations affecting Kir6.2 should be treated with sulfonylureas rather than insulin.

Maturity-Onset Diabetes of the Young

MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action. It is inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form (MODY 3) is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α and also referred to as transcription factor-1 (TCF-1). The second most common form (MODY 2) is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell. The less common forms of MODY result from mutations in other

Table 2.5—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 ≥140 mg/dL* (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 (55)	or	NDDG (56)
• 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 a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

transcription factors, including HNF-4α, HNF-1β, insulin promoter factor-1 (IPF-1), and NeuroD1.

Diagnosis

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. These individuals should be referred to a specialist for further evaluation. Readily available commercial genetic testing now enables a genetic diagnosis. It is important 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 treatment regimens and delays in diagnosing other family members (48,49).

The diagnosis of monogenic diabetes should be considered in children with the following findings:

- Diabetes diagnosed within the first 6 months of life
- Strong family history of diabetes but without typical features of type 2 diabetes (nonobese, low-risk ethnic group)
- Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and nonobese
- Diabetes with negative diabetes-associated autoantibodies and without typical clinical features of type 2 diabetes

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 who do not have 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**
- In patients with cystic fibrosis and impaired glucose tolerance without confirmed diabetes, prandial insulin therapy should be considered to maintain weight. **B**
- 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. 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, but evidence linking continuous glucose monitoring results to long-term outcomes is lacking and its use is not recommended for screening (50).

CRFD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (51). 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 (52). Insulin remains the most widely used therapy for CFRD (53).

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" (54).

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3. Foundations of Care and Comprehensive Medical Evaluation

American Diabetes Association

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The foundations of care include self-management education, nutrition, counseling, physical activity, smoking cessation, immunizations, psychosocial care, and medications (covered in other sections). The comprehensive medical evaluation includes the initial and ongoing evaluations, assessment of complications, management of comorbid conditions, and engagement of the patient throughout the process.

FOUNDATIONS OF CARE

Optimal diabetes management starts with laying down the foundations of care. The health care provider must take a holistic approach in providing care, accounting for all aspects of the patient's life circumstances. A team approach to diabetes management facilitates a comprehensive assessment and development of a plan that addresses the patient's values and circumstances. The investment of time and collaboration can facilitate, and potentially expedite, care delivery and achieve and maintain outcomes.

The initial clinical evaluation should be as comprehensive as possible as the patient will now have to address behavioral, dietary, lifestyle, and pharmaceutical interventions to effectively manage this newly identified chronic condition. The components for the comprehensive medical evaluation (**Table 3.1**) will provide the health care team with information necessary to optimally support a patient with diabetes. In addition to the medical history and physical examination, laboratory tests, nutrition, and psychosocial assessments should be obtained.

Patient Engagement

As discussed in Section 1 "Strategies for Improving Care," the Chronic Care Model (CCM) has been shown to be an effective framework for improving the quality of diabetes care (1–3). This is a patient-centered approach to care that requires a close working relationship between the patient and clinicians involved in care planning and delivery. The foundation of successful diabetes management includes ongoing individual lifestyle and behavioral changes, engagement of the patient, and assessment of the patient's level of understanding about the disease and level of preparedness for self-management.

BASIS FOR INITIAL CARE

Diabetes self-management education (DSME), diabetes self-management support (DSMS), medical nutrition therapy (MNT), counseling on smoking cessation, education on physical activity, guidance on routine immunizations, and psychosocial care are the cornerstone of diabetes management. Patients should be referred for such services if not readily available in the clinical care setting, i.e., referral for DSME, DSMS, MNT, and emotional health concerns. Additionally, specialty and lifestyle change services and programs may be beneficial (**Table 3.2**). Patients should also receive recommended preventive care services (e.g., cancer screening and immunizations); referral for smoking cessation, if needed; and podiatric, ophthalmological, and dental referrals. Clinicians should ensure that individuals with diabetes are screened for complications and comorbidities. Identifying and implementing the initial approach to glycemic control with the patient is one part, not the sole aspect, of the comprehensive care strategy.

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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, and physical activity habits; nutrition education and behavioral support history and needs
- Presence of common comorbidities, psychosocial problems, and dental disease
- Screen for depression using PHQ-2 (PHQ-9 if PHQ-2 is positive) or Edinburgh Postnatal Depression Scale (EPDS)
- Screen for diabetes distress using DDS or PAID-1
- History of smoking, 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)
- 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, increased lipids, and tobacco use
- 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

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 or dyslipidemia or women aged >50 years

ONGOING CARE MANAGEMENT

People with diabetes should receive medical care from a collaborative, integrated team with diabetes expertise. This team 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, physician, and other members of the health care team should formulate the management plan. Integral components of the management plan include the foundations of care (DSME, DSMS, MNT, smoking cessation, physical activity, immunizations, and psychosocial care). Various strategies and techniques should be used to enable patients to self-manage diabetes, including providing education on problem-solving skills for all aspects of diabetes management. Treatment goals and plans should be individualized and take patient preferences into account. In developing the plan, health care providers should consider the patient's age, school/work schedule and conditions, physical activity, eating patterns, social situation, cultural factors, diabetes complications, health priorities, other medical conditions, preferences for care and self-management, and life expectancy.

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

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations
- In accordance with the national standards for diabetes self-management education (DSME) and support (DSMS), all people with diabetes should participate in DSME to facilitate the knowledge, skills, and ability necessary for diabetes self-care and in DSMS 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, improved clinical outcomes, health status, and quality of life are key outcomes of DSME and DSMS and should be measured and monitored as part of care. **C**
- DSME and DSMS should be patient centered, respectful, and responsive to individual patient preferences, needs, and values, which should guide clinical decisions. **A**
- DSME and DSMS programs should have the necessary elements in their curricula that are needed to prevent the onset of diabetes. DSME and DSMS programs should therefore tailor their content specifically when prevention of diabetes is the desired goal. **B**
- Because DSME and DSMS can result in cost savings and improved outcomes **B**, DSME and DSMS should be adequately reimbursed by third-party payers. **E**

DSME and DSMS are the ongoing processes of facilitating the knowledge,

skills, and ability necessary for diabetes self-care. These processes 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 (4).

DSME and DSMS are essential elements of diabetes care (5,6), and the current national standards for DSME and DSMS (4) are based on the evidence of their benefits. Education helps people with diabetes to initiate effective self-management and cope with diabetes when they are first diagnosed. Ongoing DSMS helps people with diabetes to maintain effective self-management throughout a lifetime of diabetes as they face new challenges and as treatment advances become available.

The DSME and DSMS algorithm defines four critical time points for DSME and DSMS delivery (7):

1. At diagnosis
2. Annually for assessment of education, nutrition, and emotional needs
3. When new complicating factors arise that influence self-management
4. When transitions in care occur

Current best practice of DSME is a skill-based approach that focuses on helping those with diabetes to make informed self-management choices (4,5). DSME has changed from a didactic approach that focused on providing information to empowerment models that focus on helping those with diabetes to make informed self-management decisions (5). 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 (8).

Evidence for the Benefits

Studies have found that DSME is associated with improved diabetes knowledge, improved self-care behaviors (4), lower A1C (6,9,10), lower self-reported weight (11,12), improved quality of life (10,13), healthy coping (14,15), and lower costs (16,17). Better outcomes were reported for DSME interventions that were longer (>10 h) and included follow-up support (DSMS) (18,19), were culturally (20,21) and age appropriate (22,23), were tailored to individual needs and preferences, and addressed psychosocial issues and incorporated behavioral strategies (5,14,24,25). Both individual and group approaches have been found effective (12,26). 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 increased primary and preventive service use (16,31,32) and lower acute, inpatient hospital service use (11). 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 (17,31).

Reimbursement

DSME and DSMS, when provided by a program that meets the national standards (4) and is recognized by the American Diabetes Association (ADA) or other approval bodies, are reimbursed as part of the Medicare program as overseen by the Centers for Medicare & Medicaid Services. DSME is also covered by most health insurance plans. Although DSMS has been shown to be instrumental for improving outcomes and can be provided via phone calls and telehealth, it currently has limited reimbursement as compared with in-person follow-up to DSME.

MEDICAL NUTRITION THERAPY

For many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat. It is the position of the ADA that there is not a one-size-fits-all eating pattern for individuals with diabetes. The ADA recognizes the integral role of MNT in overall diabetes management and recommends that each person with diabetes be actively engaged in self-management, education, and treatment planning with his or her health care team, including the collaborative development of an individualized eating plan (33,34). Therefore, 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. See **Table 3.3** for specific nutrition recommendations.

Goals of Medical 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 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 with practical tools for developing healthful eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

MNT is an integral component of diabetes prevention, management, and self-management education. All individuals with diabetes should receive individualized MNT, preferably provided by a registered dietitian who is knowledgeable and skilled in providing diabetes-specific MNT. MNT delivered by a registered dietitian shows A1C decreases of 0.3–1% for people with type 1 diabetes (35–37) and 0.5–2% for people with type 2 diabetes (38–41).

Weight Management

Intensive lifestyle programs with frequent follow-up are required to achieve significant reductions in excess body weight and improve clinical indicators. There is strong and consistent evidence that obesity management can delay progression from prediabetes to type 2 diabetes (42,43) and benefits type 2 diabetes treatment.

In overweight and obese patients with type 2 diabetes, modest weight loss, defined as sustained reduction of 5% of initial body weight, has been shown to improve glycemic control

Table 3.3—Nutrition therapy 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 or those with type 2 diabetes who are prescribed a flexible insulin therapy program, education on how to use carbohydrate counting or 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 healthy food choices and portion control 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.	**C**
	• 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 lifestyle modification and the reduction of energy intake benefits overweight or obese adults with type 2 diabetes and also those at risk for diabetes. Interventional 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**
	• 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 sucrose-containing foods 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 omega-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 omega-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 diabetes, 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 delayed 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**

and to reduce the need for glucose-lowering medications (44–46). 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. 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 (47–50). 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 (51,52). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex. Although in some studies lowering the glycemic load of consumed carbohydrates has demonstrated A1C reductions of −0.2% to −0.5% (53,54), a systematic review (53) 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 (55). 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 "low-fat" or "nonfat" products with high amounts of refined grains and added sugars should be discouraged (56).

Individuals with type 1 or type 2 diabetes taking insulin at mealtimes should be offered intensive education on coupling insulin administration with carbohydrate intake. For people whose meal schedules or carbohydrate consumption is variable, regular counseling to help them to understand the complex relationship between carbohydrate intake and insulin needs, as well as the carbohydrate-counting approach to meal planning, can assist them with effectively modifying insulin dosing from meal to meal and improving glycemic control (36,51,57,58). 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 (34). 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 (34–36,38,51,57).

Protein

For individuals without evidence of diabetic kidney disease, the evidence is inconclusive about recommending an ideal amount of protein for optimizing glycemic control or for improving one or more CVD risk measures (53). Therefore, these goals should be individualized. For those with diabetic kidney disease (with albuminuria, reduced estimated glomerular filtration rate), dietary protein should be maintained at the recommended daily allowance of 0.8 g/kg body weight per 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 (59,60). In individuals with type 2 diabetes, ingested protein may enhance the insulin response to dietary carbohydrates (61). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. The effects of protein intake on blood glucose levels in type 1 diabetes are less clear.

Fats

Limited research exists concerning the ideal amount of fat for individuals with diabetes. The Institute of Medicine has defined an acceptable macronutrient distribution range for all adults for total fat of 20–35% of energy with no tolerable upper intake level defined (62). The type of fatty acids consumed is more important than total amount of fat when looking at metabolic goals and CVD risk (63–65). Multiple randomized controlled trials including patients with type 2 diabetes have reported that a Mediterranean-style eating pattern (63,66–68), rich in monounsaturated fats, can improve both glycemic control and blood lipids. However, a systematic review concluded that dietary supplements with omega-3 fatty acids did not improve glycemic control in individuals with type 2 diabetes (53). Randomized controlled trials also do not support recommending omega-3 supplements for primary or secondary prevention of CVD (69–73). 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 (74). The American Heart Association recommends 1,500 mg/day for African Americans; people diagnosed with hypertension, diabetes, or chronic kidney disease; and people over 51 years of age (75). However, other studies (76,77) have recommended caution for universal sodium restriction to 1,500 mg in this population. Sodium intake recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet (78).

For complete discussion and references of all recommendations, see the ADA position statement "Nutrition Therapy Recommendations for the Management of Adults With Diabetes" (34).

PHYSICAL ACTIVITY

Recommendations

- Children with diabetes or prediabetes should be encouraged to engage in at least 60 min of physical activity each day. **B**
- Adults with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise. **A**
- All individuals, including those with diabetes, should be encouraged to reduce sedentary time, particularly by breaking up extended amounts of time (>90 min) spent sitting. **B**
- In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week. **A**

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. Although both 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 preventing diabetes complications and controlling blood glucose is not as clear as it is for those with type 2 diabetes.

Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals (43,79,80) (see Section 4 "Prevention or Delay of 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 with no significant change in BMI (80). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, muscle strength, improved insulin sensitivity, etc.) of regular exercise for those with type 1 diabetes (81). Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness (82). Other benefits include slowing the decline in mobility among overweight patients with diabetes (83). "Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint Position Statement" (84) reviews the evidence for the benefits of exercise in people with type 2 diabetes.

Exercise and Children

As is recommended for all children, children with diabetes or prediabetes should be encouraged to engage in at least 60 min of physical activity each day. Included in the 60 min each day, children should engage in vigorous-intensity aerobic activity, muscle-strengthening activities, and bone-strengthening activities at least 3 of those days (85).

Frequency and Type of Physical Activity

The U.S. Department of Health and Human Services' physical activity guidelines for Americans (86) suggest that adults over age 18 years do 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 or those with disabilities follow the adult guidelines if possible or, if this is 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), particularly, by breaking up extended amounts of time (>90 min) spent sitting by briefly standing or walking (87).

Physical Activity and Glycemic Control

On the basis of physical activity studies that include people with diabetes, it is reasonable to recommend that people with diabetes will specifically benefit from following the U.S. Department of Health and Human Services' physical activity guidelines. For example, studies included in the meta-analysis of the effects of exercise interventions on glycemic control (80) reported a mean of 3.4 sessions/week, with a mean of 49 min/session.

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (84) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (88,89). 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 of five or more different resistance exercises involving the large muscle groups (84).

Pre-exercise Evaluation

As discussed more fully in Section 8 "Cardiovascular Disease and Risk Management," the best protocol for screening asymptomatic patients with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (90) concluded that routine testing is not recommended. Providers should perform a careful history being aware of the atypical presentation of coronary artery disease in patients with diabetes and assess other cardiovascular risk factors. 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, autonomic neuropathy, peripheral neuropathy, a history of foot lesions, and untreated proliferative retinopathy. 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 (81).

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. Hypoglycemia is less common in patients with diabetes who are not treated with insulin or insulin secretagogues, and no preventive measures for hypoglycemia are usually advised in these cases. Intense activities may actually raise blood glucose levels instead of lowering them (91).

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 (92).

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. 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 (93). In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with milder forms of neuropathy (94). 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 (95). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (96). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Albuminuria and Nephropathy

Physical activity can acutely increase urinary protein 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 (92).

SMOKING CESSATION: TOBACCO AND e-CIGARETTES

Recommendations

- Advise all patients not to use cigarettes, other tobacco products, or e-cigarettes. **A**
- 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 (97). 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 (98). 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 (99).

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 (100). 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 (101). 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 (102–104).

IMMUNIZATION

Recommendations

- Provide routine vaccinations for children and adults with diabetes as for the general population according to age-related recommendations. **C**
- Administer hepatitis B vaccine to unvaccinated adults with diabetes who are aged 19–59 years. **C**
- Consider administering hepatitis B vaccine to unvaccinated adults with diabetes who are aged ≥60 years. **C**

As for the general population, all children and adults with diabetes should receive routine vaccinations (105,106) according to age-specific recommendations (see the **adult vaccination schedule** available from http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html and the **child and adolescent vaccination schedule** available from http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html).

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommends influenza and pneumococcal vaccines for all 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, such as the young and the elderly and people with chronic diseases. Regardless of sex, race, and socioeconomic status, adults with diabetes 25–64 years of age who died are four times more likely to have pneumonia and influenza recorded on their death certificates than adults without diabetes who died at comparable ages (107). In a case-control series, the influenza vaccine was shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics (108).

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% (109). All patients with diabetes 2 years of age and older should receive the pneumococcal polysaccharide vaccine 23 (PPSV23). There is sufficient evidence to support that people with diabetes have appropriate serologic and clinical responses to these

vaccinations. The ADA endorses the CDC advisory panel recommendation that both pneumococcal conjugate vaccine 13 (PCV13) and PPSV23 should be administered routinely in series to all adults aged ≥65 years.

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.

PSYCHOSOCIAL ISSUES

Recommendations

- The patient's psychological and social situation should be addressed in the medical management of diabetes. **B**
- Psychosocial screening and follow-up may include, but are not limited to, attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional), and psychiatric history. **E**
- Routinely screen for psychosocial problems such as depression, diabetes-related distress, anxiety, eating disorders, and cognitive impairment. **B**
- Older adults (aged ≥65 years) with diabetes should be considered for evaluation of cognitive function and depression screening and treatment. **B**
- Patients with comorbid diabetes and depression should receive a stepwise collaborative care approach for the management of depression. **A**

Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (110–112) or family's (113) ability to carry out diabetes care tasks and therefore compromise health status. There are opportunities for the clinician to routinely assess psychosocial status in a timely and efficient manner for referral for 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. However, there was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes (114).

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. 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. Depression affects ~20–25% of people with diabetes (115). Individuals with both diabetes and major depressive disorder have a twofold increased risk for new-onset myocardial infarction compared with either disease state alone (116). There appears to be a bidirectional relationship between both diabetes (117) and metabolic syndrome (118) and depression.

Diabetes Distress

Diabetes-related distress (DD) is distinct from depressive disorders and is very common (119–121) in people with diabetes and their family members (113). 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 (120–122). Its prevalence is reported to be 18–45%, with an incidence of 38–48% over 18 months. High levels of distress are significantly linked to medication nonadherence (122), higher A1C, lower self-efficacy, and poorer dietary and exercise behaviors (15,120). The clinician needs to understand that individuals may fall into one of three categories: those with depression and DD, those with depression without significant DD, and those with DD without significant depression. Understanding the category in which a particular patient belongs facilitates a customized care approach that may include DSME, DSMS, cognitive therapy, or treatment for depression (psychotherapy and/or psychotropic medications). The screening of all patients with diabetes with the Patient Health Questionnaire-2 (PHQ-2) and either the Diabetes Distress Scale (DDS) or Problem Areas in Diabetes (PAID)-1 scale can help to facilitate this (24,123,124).

Other issues known to affect self-management and health outcomes include attitudes about the illness, expectations for medical management and outcomes, anxiety, general and diabetes-related quality of life, resources (financial, social, and emotional) (125), and psychiatric history (126).

Referral to a Mental Health Specialist

Indications for referral to a mental health specialist familiar with diabetes management may include possibility of self-harm, gross disregard for the medical regimen (by self or others) (127), depression, overall stress related to work-life balance, debilitating anxiety (alone or with depression), indications of an eating disorder (128), or cognitive functioning that significantly impairs judgment. It is preferable to incorporate psychological assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status (24,119). 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 team asked them how diabetes affected their life (119).

Although the clinician may not feel qualified to treat psychological problems (129), 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 and depression (130,131). Interventions to enhance self-management and address severe distress have demonstrated efficacy in DD (15).

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**

Besides assessing diabetes-related complications and comorbidities, clinicians and their patients need to be aware of other common conditions that affect people with diabetes. Improved disease prevention and treatment mean that people with diabetes are living longer and developing heart failure, fatty liver disease, obstructive sleep apnea, and arthritis—conditions that affect people with diabetes more often than age-matched people without diabetes and that may complicate diabetes management (132–136).

Adults who develop type 1 diabetes may develop additional autoimmune disorders including thyroid or adrenal dysfunction and celiac disease, although the risk of coexisting autoimmunity is lower in adults than for youth with type 1 diabetes. For additional details on autoimmune conditions, see Section 11 "Children and Adolescents."

COMORBIDITIES

Fatty Liver Disease

Elevations of hepatic transaminase concentrations are significantly 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 (137). 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 (138).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for CVD, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (139). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23% (140). In obese participants enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (141). Sleep apnea treatment significantly improves quality of life and blood pressure control. The evidence for a treatment effect on glycemic control is mixed (142).

Cancer

Diabetes (possibly only type 2 diabetes) is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (143). 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 hyperinsulinemia or hyperglycemia (144). Patients with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (smoking, obesity, and physical inactivity).

Fractures

Age-specific hip fracture risk is significantly increased in both type 1 (relative risk 6.3) and type 2 (relative risk 1.7) diabetes in both sexes (145). 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) (146). 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 (147). 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 (148) and sodium–glucose cotransporter 2 inhibitors should be avoided as their use has been associated with a higher risk of fractures (149).

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 (150). Treatment in asymptomatic men is controversial. The evidence that testosterone replacement affects outcomes is mixed, and recent guidelines do not recommend testing and treating men without symptoms (151).

Periodontal Disease

Periodontal disease is more severe, but not necessarily more prevalent, in patients with diabetes than in those without (152). Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (136).

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 (153).

Cognitive Impairment

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (154,155). In a 15-year prospective study of community-dwelling people aged >60 years, 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 (156). In a substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, there were no differences in cognitive outcomes between the intensive and standard glycemic control

groups, although there was significantly less of a decrement in total brain volume, as measured by MRI, in participants in the intensive arm (157). The effects of hyperglycemia and insulin on the brain are areas of intense research interest.

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4. Prevention or Delay of Type 2 Diabetes

American Diabetes Association

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Recommendations

- Patients with prediabetes should be referred to an intensive diet and physical activity behavioral counseling program adhering to the tenets of the Diabetes Prevention Program (DPP) targeting a loss of 7% of body weight and should increase their moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**
- Follow-up counseling and maintenance programs should be offered for long-term success in preventing diabetes. **B**
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. **B**
- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI $>$35 kg/m^2, those aged $<$60 years, and women with prior gestational diabetes mellitus. **A**
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested. **E**
- Screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. **B**
- Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. **B**
- Technology-assisted tools including Internet-based social networks, distance learning, DVD-based content, and mobile applications can be useful elements of effective lifestyle modification to prevent diabetes. **B**

LIFESTYLE MODIFICATION

Randomized controlled trials have shown that individuals at high risk for developing type 2 diabetes (impaired fasting glucose, impaired glucose tolerance, or both) can significantly decrease the rate of diabetes onset with particular interventions (1–7). These include intensive lifestyle modification programs that have been shown to be very effective (~58% reduction after 3 years). Follow-up of all three large studies of lifestyle intervention has shown sustained reduction in the rate of conversion to type 2 diabetes: 43% reduction at 20 years in the Da Qing study (8), 43% reduction at 7 years in the Finnish Diabetes Prevention Study (DPS) (9), and 34% reduction at 10 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS) (10).

A cost-effectiveness model suggested that lifestyle interventions in the Diabetes Prevention Program (DPP) are cost-effective (11). Actual cost data from the DPP and DPPOS also confirm this (12). Group delivery of DPP content into community settings has the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (13,14). The Centers for Disease Control and Prevention (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).

Given the clinical trial results and the known risks of progression from prediabetes to diabetes, people with an A1C 5.7–6.4% (39–46 mmol/mol), impaired glucose tolerance, or impaired fasting glucose should be counseled on lifestyle changes with goals similar to those of the DPP (7% weight loss and moderate-intensity physical activity of at least 150 min/week).

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Nutrition

As for people with diabetes (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation"), evidence supports the importance of maintaining a healthy diet in order to prevent diabetes onset. Unlike past recommendations that focused on simply reducing total dietary fat and cholesterol consumption, more recent evidence argues against the preventative effects of lowering fat and cholesterol intake across the board and supports instead that the *quality of fats consumed in the diet is more important than the total quantity of dietary fat*. For example, recent work supports the Mediterranean diet, which is relatively rich in monounsaturated fats, as a means to help to prevent type 2 diabetes (15). Studies evaluating glycemic index to guide carbohydrate recommendations have been inconsistent (16,17); however, data suggest that consumption of a diet enriched in whole grains is helpful in preventing type 2 diabetes (18). Finally, increased consumption of nuts (19) and berries (20) in the context of a diet high in vegetables and whole fruits has been correlated with reduced diabetes risk. Individualized medical nutrition therapy (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation" for more detailed information) has been shown to be effective in lowering A1C in individuals diagnosed with prediabetes (7). This indicates that nutritional interventions are potentially effective in staving off the progression toward type 2 diabetes (e.g., individuals showing signs of metabolic syndrome).

Physical Activity and Exercise

Physical activity and exercise are important for those living with diabetes (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation"), but they have also been evaluated for diabetes prevention. Physical activity is a more general term that covers all types of activity, whereas exercise refers to structured or planned activities. Although not well studied in isolation, exercise and physical activity have been validated to prevent or delay diabetes development as part of a comprehensive approach to lifestyle modification (21). These studies suggest that while exercise treatment programs may not reduce body weight, programs of sufficient intensity have been shown to decrease diabetes risk (21). Therefore, health care providers should inform at-risk patients of these benefits in order to motivate them to engage in regular moderate-intensity physical activity.

Moderate exercise, such as brisk walking or other activities of equivalent intensity, has been also observed to improve insulin sensitivity and reduce abdominal fat content in children and young adults (22,23). The DPP included 150 min/week of moderate-intensity exercise and showed beneficial effect on glycemia in those with prediabetes (1). Both resistance training and endurance exercise appear to have beneficial effects on waist circumference, insulin sensitivity, and thus diabetes risk (24,25). The preventative effects of exercise appear to extend to the prevention of gestational diabetes mellitus (GDM) as well (26).

Prevention of Cardiovascular Disease

People with prediabetes often have other cardiovascular risk factors, such as obesity, hypertension, and dyslipidemia and are at increased risk for cardiovascular disease events. While 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 risk factors (e.g., smoking).

Technology Assistance to Deliver Lifestyle Modification

Technology may be an effective means to deliver the core components of the DPP (27,28). Initial studies have validated DVD-based content delivery (29). This has been corroborated in a primary care patient population (30). Recent studies support content delivery through virtual small groups (31), Internet-driven social networks (32,33), 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 (33). The CDC's 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-style prevention content that may be considered alongside more traditional face-to-face and coach-driven programs.

PHARMACOLOGICAL INTERVENTIONS

Pharmacological agents, such as metformin, α-glucosidase inhibitors, orlistat, and thiazolidinediones, have each been shown to decrease incident diabetes to various degrees. Metformin has the strongest evidence base and demonstrated long-term safety as pharmacological therapy for diabetes prevention (34). 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 (12). 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 (1). In the DPP, for women with a history of GDM, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (35), and both interventions remained highly effective during a 10-year follow-up period (36). Metformin may be recommended for high-risk individuals (e.g., those with a history of GDM, those who are very obese, and/or those with more severe or progressive hyperglycemia) and/or those with rising A1C despite lifestyle intervention.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

As for those with established diabetes, the standards for diabetes self-management education and support (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation") can also apply to the education and support of 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 onset of diabetes (7,37).

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5. Glycemic Targets

American Diabetes Association

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ASSESSMENT OF GLYCEMIC CONTROL

Two primary techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control: patient self-monitoring of blood glucose (SMBG) and A1C. Continuous glucose monitoring (CGM) or interstitial glucose may be a useful adjunct to SMBG in selected patients.

Recommendations

- When prescribed as part of a broader educational context, self-monitoring of blood glucose (SMBG) results may help to guide treatment decisions and/or self-management for patients using less frequent insulin injections **B** or non-insulin 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**
- Most patients on intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should consider SMBG prior to meals and snacks, occasionally postprandially, at bedtime, 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 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 supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. **C**
- Given 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 glucose at least once daily, many report taking no action when results are high or

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low. In a yearlong study of insulin-naïve 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 on intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should consider SMBG prior to meals and snacks, occasionally postprandially, at bedtime, 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 an intensive insulin regimen, such as those with type 2 diabetes using oral agents or on basal insulin. For patients on basal insulin, lowering of A1C has been demonstrated for those who adjust their dose to attain a fasting glucose 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 has been shown to be inversely correlated with glycemic control (9).

Several randomized trials have called into question the clinical utility and cost-effectiveness of routine SMBG in noninsulin-treated patients (10–12). A meta-analysis suggested that SMBG reduced A1C by 0.25% at 6 months (13), but the effect was attenuated at 12 months (14). 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

Real-time CGM measures interstitial glucose (which correlates well with plasma glucose) and includes sophisticated alarms for hypo- and hyperglycemic excursions, but the U.S. Food and Drug Administration (FDA) has not approved these devices as a sole agent to monitor glucose. CGMs require calibration with SMBG, with the latter still required for making acute treatment decisions.

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

A registry study of 17,317 participants confirmed that more frequent CGM use is associated with lower A1C (16), whereas another study showed that children with >70% sensor use missed fewer school days (17). Small randomized controlled trials in adults and children with baseline A1C 7.0–7.5% (53–58 mmol/mol) have confirmed favorable outcomes (A1C and hypoglycemia occurrence) in groups using CGM, suggesting that CGM may provide further benefit for individuals with type 1 diabetes who already have tight control (18,19).

A meta-analysis suggests that, compared with SMBG, CGM is associated with short-term A1C lowering of ~0.26% (20). The long-term effectiveness of CGM needs to be determined. This technology may be particularly useful in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not shown consistent reductions in severe hypoglycemia (20–22). 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 showed that sensor-augmented insulin pump therapy with a low glucose suspend significantly reduced nocturnal hypoglycemia, without increasing A1C levels for those over 16 years of age (23). These devices may offer the opportunity to reduce severe hypoglycemia for those with a history of nocturnal hypoglycemia. 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 (16,24). 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 after they turn 65 years of age.

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 several months and has strong predictive value for diabetes complications (25,26). 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. Patients with type 2 diabetes with stable glycemia well within target may do well with testing only twice per year. Unstable or highly intensively managed patients (e.g., pregnant women with type 1 diabetes) may require testing more frequently than every 3 months (27).

Table 5.1—Mean glucose levels for specified A1C levels (24,28)

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	7.0								
<6.5 (48)			122	6.8	118	6.5	144	8.0	136	7.5
6.5–6.99 (48–53)			142	7.9	139	7.7	164	9.1	153	8.5
7 (53)	154	8.6								
>7.0–7.49 (53–58)			152	8.4	152	8.4	176	9.8	177	9.8
7.5–7.99 (58–64)			167	9.3	155	8.6	189	10.5	175	9.7
8 (64)	183	10.2								
>8.0–8.5 (64–69)			178	9.9	179	9.9	206	11.4	222	12.3
9 (75)	212	11.8								
10 (86)	240	13.4								
11 (97)	269	14.9								
12 (108)	298	16.5								

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 (28).

A1C Limitations

The A1C test is subject to certain 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 blood glucose levels. For patients in whom A1C/estimated average glucose (eAG) and measured blood glucose appear discrepant, clinicians should consider the possibilities of hemoglobinopathy or altered red blood cell turnover and the options of more frequent and/or different timing of SMBG or CGM use. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose 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 5.1 shows the correlation between A1C levels and mean glucose levels based on two studies: the international A1C-Derived Average Glucose (ADAG) trial, which based the correlation with A1C on frequent SMBG and CGM in 507 adults (83% non-Hispanic whites) with type 1, type 2, and no diabetes (28), 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 (24). 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. Clinicians should note that the mean plasma glucose numbers in the table are based on ~2,800 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 there was a trend toward a difference between the African/African American and non-Hispanic white cohorts. 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 (29). Whether there are significant differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (30,31). 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.

A1C GOALS

For glycemic goals in children, please refer to Section 11 "Children and Adolescents." For glycemic goals in pregnant women, please refer to Section 12 "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. 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 general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. **B**

A1C and Microvascular Complications

Type 1 Diabetes

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 relatively recently diagnosed type 1 diabetes, showed definitively that improved glycemic control is associated with significantly decreased rates of microvascular (retinopathy [32] and diabetic kidney disease) and neuropathic complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (33) demonstrated persistence of these microvascular benefits in previously intensively treated subjects, even though their glycemic control approximated that of previous standard arm subjects during follow-up.

Type 2 Diabetes

The Kumamoto Study (34) and UK Prospective Diabetes Study (UKPDS) (35,36) confirmed that intensive glycemic control was associated with 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 (37).

Therefore, achieving glycemic control of A1C targets of $<$7% (53 mmol/mol) has been shown to reduce microvascular complications of diabetes and, in patients with type 1 diabetes, mortality. If implemented soon after the diagnosis of diabetes, this target is associated with long-term reduction in macrovascular disease.

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 (38–40).

Epidemiological analyses of the DCCT (1) and UKPDS (41) 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.

The concerning mortality findings in the ACCORD trial (42), 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 study 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 randomly assigned to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death compared with those previously in the standard arm (43). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (44) and to be associated with a modest reduction in all-cause mortality (45).

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 trial, 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 follow-up, those originally randomly assigned 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) (37).

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 participants with more long-standing diabetes (mean duration 8–11 years) and either known 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" (46).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard 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 arm (42).

Longer-term follow-up has shown no evidence of cardiovascular benefit or harm in the ADVANCE trial (47), which is perhaps not unexpected given the narrow

separation in A1C between groups. The end-stage renal disease rate was lower in the intensive group over follow-up. However, 10-year follow-up of the VADT cohort (48) 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 (49).

Mortality findings in ACCORD (42) and subgroup analyses of VADT (50) 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 severe hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (51,52).

Providers should be vigilant in preventing severe 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 5.2**).

Table 5.2—Summary of glycemic recommendations for 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.

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 5.1** is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making (53), both in type 1 and type 2 diabetes.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 5.2**. 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 (54). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiological studies. 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 glycemic control trials 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 (55). 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. Taking postprandial plasma glucose measurements 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.

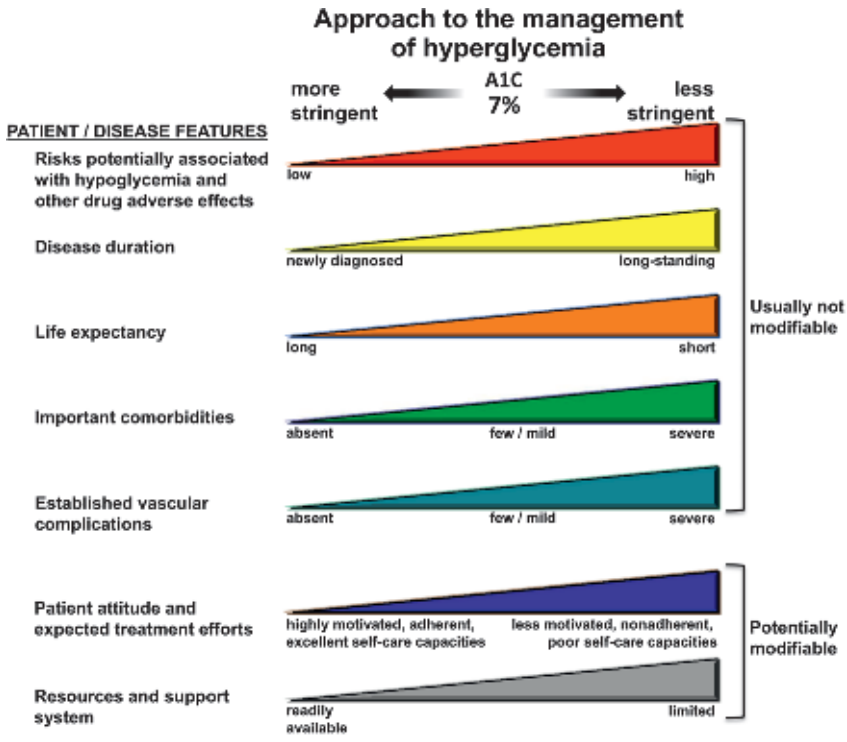

Figure 5.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (53).

An analysis of data from 470 participants of 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 5.1**) (24,28). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data have prompted a revision in the ADA-recommended premeal target to 80–130 mg/dL (4.4–7.2 mmol/L).

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, 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 severe hypoglycemia, defined as hypoglycemia requiring assistance, and caregivers, school personnel, or family members of these individuals should be instructed in its administration. 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 severe hypoglycemia should be advised to raise their glycemic targets to strictly avoid further 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 insulin-treated type 2 diabetes. Mild hypoglycemia may be inconvenient or frightening to patients with diabetes. Severe hypoglycemia is defined as hypoglycemia requiring assistance from another person. It is characterized by cognitive impairment that may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death, and it is reversed by administration of rapid-acting glucose. Severe hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle 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 (56). 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 (57). Evidence from DCCT/EDIC, which involved younger adults and adolescents with type 1 diabetes, found no association between frequency of severe hypoglycemia and cognitive decline (58), as discussed in Section 11 "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 (59). An association between self-reported severe hypoglycemia and 5-year mortality has also been reported in clinical practice (60).

Young children with type 1 diabetes and the elderly are noted as particularly vulnerable to severe hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized 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 (61). Documented symptomatic hypoglycemia and asymptomatic hypoglycemia are defined as occurring at a plasma glucose concentration of $\leq$70 mg/dL (3.9 mmol/L) (61). This level remains a general threshold for defining hypoglycemia.

In 2014, the ADA changed its glycemic *target* 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 (24). 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

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.

Glucagon

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. 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, 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 awareness to some extent in many patients (62). Hence, patients with one or more episodes of severe 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 13 "Diabetes Care in the Hospital."

Stressful events (e.g., illness, trauma, surgery, etc.) frequently aggravate glycemic control and may 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 diabetic ketoacidosis management or hyperglycemic nonketotic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (63).

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6. 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 progression from prediabetes to type 2 diabetes (1,2) and may be beneficial in the treatment of type 2 diabetes. 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 (6,7). 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). 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 (9), it did show the feasibility of achieving and maintaining long-term weight loss in patients with type 2 diabetes.

LOOK AHEAD

In the Look AHEAD intensive lifestyle intervention group, mean weight loss was 4.7% (SE 0.2) at 8 years (10). Approximately 50% of intensive lifestyle intervention participants lost ≥5% and 27% lost ≥10% of their initial body weight at 8 years (10). 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 (11). 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 (**Table 6.1**). In Asian Americans, the BMI cutoff points to define overweight and obesity are lower: normal (<23 kg/m^2), overweight (23.0–27.4 kg/m^2), obese (27.5–37.4 kg/m^2), and extremely obese (≥37.5 kg/m^2) (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 bariatric surgery (**Table 6.1**). The latter two strategies may be prescribed for carefully selected patients as adjuncts to diet, physical activity, and behavioral therapy.

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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 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 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) high-intensity lifestyle 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 (9,10).

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 (13–16). 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 (17).

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 (18).

When provided by trained practitioners in medical care settings with close medical monitoring, short-term (3-month) high-intensity lifestyle 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 high-intensity lifestyle interventions is greater than following intensive behavioral lifestyle interventions unless a long-term comprehensive weight loss maintenance program is provided (19,20).

Table 6.1—Treatment for overweight and obesity in type 2 diabetes

	BMI category (kg/m^2)				
Treatment	23.0* or 25.0–26.9	27.0–29.9	30.0–34.9	35.0–39.9	≥40
Diet, physical activity, and behavioral therapy	†	†	†	†	†
Pharmacotherapy		†	†	†	†
Bariatric surgery				†	†

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

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% 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**

When considering 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, glucagon-like peptide 1 agonists, amylin mimetics, and sodium–glucose cotransporter 2 inhibitors. 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 7 "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. The latter include atypical antipsychotics (clozapine, olanzapine, risperidone, etc.) and antidepressants (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 Medications

The U.S. Food and Drug Administration (FDA) has approved five weight loss medications (or combination medications) for long-term use by patients with BMI $\geq$27 kg/m^2 with one or more obesity-associated comorbid conditions and by patients with BMI $\geq$30 kg/m^2 who are motivated to lose weight (21–23). Medications approved for long-term weight loss and weight loss maintenance and their advantages and disadvantages are summarized in **Table 6.2**. 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. All medications are FDA pregnancy category X. 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 (21).

BARIATRIC SURGERY

Recommendations

- Bariatric surgery may be considered for adults with BMI $>$35 kg/m^2 and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. **B**
- Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and annual medical monitoring, at a minimum. **B**
- Although small trials have shown a glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m^2, there is currently insufficient evidence to generally recommend surgery in patients with BMI $\leq$35 kg/m^2. **E**

Bariatric and metabolic surgeries, either gastric banding or procedures that involve resecting, bypassing, or transposing sections of the stomach and small intestine, can be effective weight loss treatments for severe obesity when performed as part of a comprehensive weight management program with lifelong lifestyle support and medical monitoring. In one meta-analysis, gastric banding resulted in less weight loss than sleeve gastrectomy and Roux-en-Y gastric bypass (1-year excess weight loss ~33% vs. ~70%) (24). National guidelines support consideration of bariatric surgery for people with type 2 diabetes with BMI $>$35 kg/m^2.

Advantages

Treatment with bariatric surgery has been shown to achieve near or complete normalization of glycemia 2 years following surgery in 72% of patients (compared with 16% in a matched control group treated with lifestyle and pharmacological interventions) (25). A study evaluated the effectiveness of surgical intervention (Roux-en-Y gastric bypass or sleeve gastrectomy) and medical therapy compared with medical therapy alone (quarterly visits, pharmacological therapy, self-monitoring of blood glucose, diabetes education, lifestyle counseling, and encouragement to participate in Weight Watchers) in achieving a target A1C $\leq$6% (42 mmol/mol) at 3 years among obese patients with uncontrolled type 2 diabetes (mean A1C 9.3% [78 mmol/mol]). This A1C target was achieved by 38% ($P <$ 0.001) in the gastric bypass group, 24% ($P = 0.01$) in the sleeve gastrectomy group, and 5% in the group that received only medical therapy (26). Diabetes remission rates tend to be higher with procedures that bypass portions of the small intestine and lower with procedures that only restrict the stomach.

Younger age, shorter duration of type 2 diabetes, lower A1C, higher serum insulin levels, and nonuse of insulin have all been associated with higher remission rates after bariatric surgery (27).

Although bariatric surgery has been shown to improve the metabolic profiles of morbidly obese patients with type 1 diabetes, the role of bariatric surgery in such patients will require larger and longer studies (28).

Disadvantages

Bariatric surgery is costly and has associated risks. Morbidity and mortality rates directly related to the surgery have decreased considerably in recent years, with 30-day mortality rates now 0.2% for laparoscopic procedures, similar to those for laparoscopic cholecystectomy, and 2.1% for open procedures (29,30). Outcomes vary depending on the procedure and the experience of the surgeon and center. Longer-term concerns include dumping syndrome (nausea, colic, diarrhea), vitamin and mineral deficiencies, osteoporosis, and, rarely, severe hypoglycemia from insulin hypersecretion. More recent studies also suggest that patients who undergo bariatric surgery may be at increased risk for substance use, including drug and alcohol use and cigarette smoking (31). Cohort studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality (25).

In contrast, a propensity score–adjusted analysis of older, severely obese patients in Veterans Affairs Medical Centers found that bariatric surgery was not associated with decreased mortality compared with usual care (mean follow-up 6.7 years) (32). Retrospective analyses

Table 6.2—Medications approved by the FDA for the long-term 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]		Adverse effects[2,6–12]	
			Average weight loss relative to placebo	% Patients with ≥5% loss of baseline weight	Common[7]	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)	$41–82 (60 mg) $615 (120 mg)	2.5 kg (60 mg) 3.4 kg (120 mg)	35–73%	Abdominal pain/discomfort, oily spotting/stool, fecal urgency, malabsorption of fat-soluble vitamins (A, D, E, K) and medications (e.g., cyclosporine, thyroid hormone replacement, or anticonvulsants), potentiation of the effects of warfarin	Liver failure and oxalate nephropathy
Selective serotonin (5-HT) 5-HT$_{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, 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	$239 (maximum dose)	2.0–4.1 kg (32 mg/360 mg)	36–57%	Nausea, constipation, headache, vomiting	Depression, precipitation of mania
Acylated human glucagon-like peptide 1 receptor agonist						
Liraglutide (Saxenda) 6 mg/mL prefilled pen	Maintenance dose: 3 mg s.c. q.d.	$1,282	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 FDA pregnancy category X; 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. 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.

and modeling studies suggest that bariatric 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 (33,34). Understanding the long-term benefits and risks of bariatric surgery in individuals with type 2 diabetes, especially those who are not severely obese, will require well-designed clinical trials, with optimal medical therapy as the comparator (35). Unfortunately, such studies may not be feasible (36).

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7. Approaches to Glycemic Treatment

American Diabetes Association

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PHARMACOLOGICAL THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple-dose insulin injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. **A**
- Consider educating individuals with type 1 diabetes on matching prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. **E**
- Most individuals with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. **A**
- Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. **E**

Insulin Therapy

Insulin is the mainstay of therapy for individuals with type 1 diabetes. There are excellent reviews to guide the initiation and management of insulin therapy to achieve desired glycemic goals (1). Although most studies of multiple-dose insulin versus pump therapy 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 (2). A large 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 values (3). Intensive management through pump therapy/continuous glucose monitoring and active patient/family participation should be strongly encouraged (4–6). Selected individuals who have mastered carbohydrate counting should be educated that fat increases glucose concentrations and insulin requirements (7).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin therapy (three or more injections per day of insulin) or continuous subcutaneous insulin infusion (CSII) (insulin pump therapy) was a key part of improved glycemia and better outcomes (8,9). The study was carried out with short-acting and intermediate-acting human insulins. Despite better microvascular, macrovascular, and all-cause mortality outcomes, intensive insulin therapy was associated with a high rate of severe hypoglycemia (62 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 (10,11).

Rapid-acting inhaled insulin used before meals in type 1 diabetes leads to inferior A1C lowering when compared with aspart insulin, with less hypoglycemia across all A1C target categories (12).

Postprandial glucose excursions can be better controlled by adjusting the timing of prandial (bolus) insulin dose administration. The optimal time to inject prandial insulin varies, based on the type of insulin injected (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.

Suggested citation: American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In Standards of Medical Care in Diabetes—2016. *Diabetes Care 2016;39(Suppl. 1):S52–S59*

Recommended therapy for type 1 diabetes consists of the following:

1. Multiple-dose insulin injections (three to four injections per day of basal and prandial insulin) or CSII therapy.
2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated physical activity.
3. For most patients (especially those at elevated risk of hypoglycemia), use insulin analogs.
4. For patients with frequent nocturnal hypoglycemia, recurrent severe hypoglycemia, and/or hypoglycemia unawareness, a sensor-augmented low glucose threshold suspend pump may be considered.

Pramlintide

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

Pancreas and Islet Cell Transplantation

Pancreas and islet cell 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 aggressive glycemic management (13). Islet cell transplantation remains investigational. Autoislet transplantation may be considered for patients requiring total pancreatectomy who meet eligibility criteria.

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%, $P = 0.42$) (14).

Incretin-Based Therapies

Therapies approved for the treatment of type 2 diabetes are currently being evaluated in type 1 diabetes. Glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are not currently FDA approved for those with type 1 diabetes but are being studied in this population.

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. There are three FDA-approved agents for use in patients with type 2 diabetes, but there are insufficient data to recommend treatment in type 1 diabetes (15). The FDA recently issued a warning about the risk of ketoacidosis with SGLT2 inhibitors in individuals with type 1 or type 2 diabetes. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and dyspnea. Urinary tract infections leading to urosepsis and pyelonephritis may also occur with SGLT2 inhibitors. Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have symptoms of ketoacidosis (16).

PHARMACOLOGICAL THERAPY FOR TYPE 2 DIABETES

Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. **A**
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C. **E**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, then 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 pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences. **E**
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. **B**

An American Diabetes Association/European Association for the Study of Diabetes position statement (17) evaluated the data and developed recommendations, including advantages and disadvantages, for antihyperglycemic agents for patients with type 2 diabetes. A patient-centered approach is stressed, including patient preferences, cost, and potential side effects of each class, effects on body weight, and hypoglycemia risk. Lifestyle modifications that improve health (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation") should be emphasized along with any pharmacological therapy.

Initial Therapy

Most patients should begin with lifestyle changes, which may include lifestyle counseling, setting a physical activity goal of 150 min/week minimum, and weight loss counseling to lose a minimum of 7% of body weight (for details on lifestyle therapy, see Section 6 "Obesity Management for the Treatment of Type 2 Diabetes"). When lifestyle efforts alone do not achieve or maintain glycemic goals, metformin monotherapy should be added at, or soon after, diagnosis, unless there are contraindications or intolerance. Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events and death (18). Accumulating observational data suggest that metformin may be safely continued down to glomerular filtration rate (GFR) of 45 mL/min/1.73 m^2 or even 30 mL/min/1.73 m^2 (19). If metformin is used in the lower GFR range, the dose should be reduced and patients should be advised to stop the medication for nausea, vomiting, and dehydration. In patients with metformin intolerance or contraindications, consider an initial drug from other classes depicted in **Fig. 7.1** under "Dual therapy" and proceed accordingly.

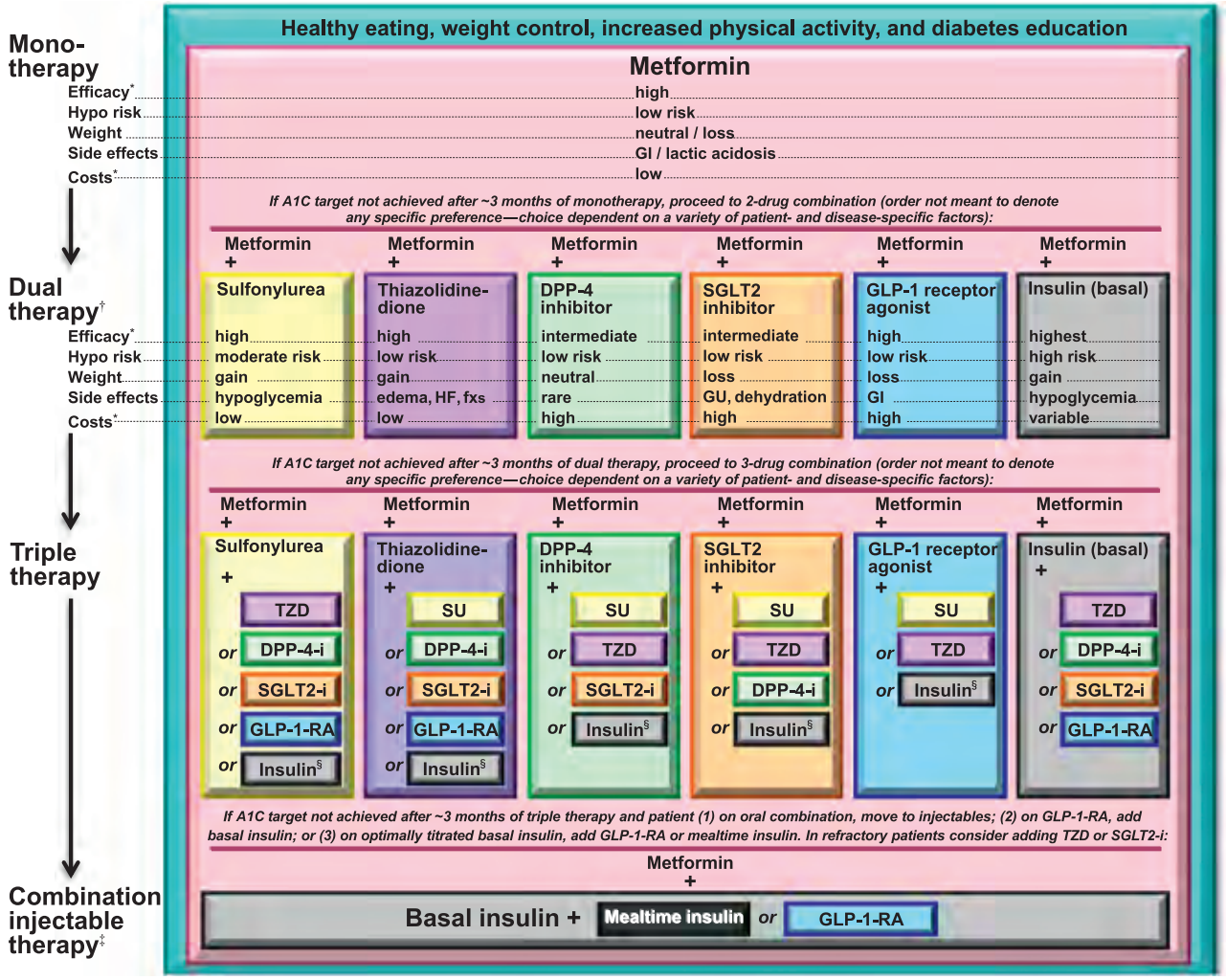

Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (17). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic 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. 17 for description of efficacy categorization. †Consider starting at this stage when A1C is ≥9% (75 mmol/mol). ‡Consider starting at this stage when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12% (86–108 mmol/mol), especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (17).

Combination Therapy

Although there are numerous trials comparing dual therapy with metformin alone, few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis (20) suggests that overall each new class of noninsulin agents added to initial therapy lowers A1C around 0.9–1.1%. A comprehensive listing, including the cost, is available in **Table 7.1.** The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) will compare the effect of four major drug classes (sulfonylurea, DPP-4 inhibitor, GLP-1 analog, and basal insulin) over 4 years on glycemic control and other medical, psychosocial, and health economic outcomes (21).

If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors (22), SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin (**Fig. 7.1**). Drug choice is based on patient preferences (23), as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. **Figure 7.1** emphasizes drugs commonly used in the U.S. and/or Europe. Cost-effectiveness models have suggested that some of the newer agents may be low-value based on high cost and moderate glycemic effect (24).

Rapid-acting secretagogues (meglitinides) may be used instead of sulfonylureas in patients with irregular meal schedules or those who develop late postprandial hypoglycemia on a sulfonylurea. Other drugs not shown in the figure (e.g., α-glucosidase inhibitors, colesevelam, bromocriptine, pramlintide) may be tried in specific situations, but are generally not favored due to modest efficacy, the frequency of administration, and/or side effects.

For all patients, consider initiating therapy with a dual combination when A1C is ≥9% (75 mmol/mol) to more

Table 7.1—Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes (17)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Vitamin B_{12} deficiency • Contraindications: CKD, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd Generation • Glyburide/ glibenclamide • Glipizide • Gliclazide† • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• 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	• No hypoglycemia • Durability • ↑ HDL-C • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin† • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• No hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ? ↑ Heart failure hospitalizations	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High

Continued on p. S56

Table 7.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of type 2 diabetes • Associated with lower CVD event rate and mortality in patients with CVD (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	• No hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors	• 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	• Generally 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 • Basal insulin analogs - Glargine - Detemir - Degludec† • Premixed (several types)	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Mitogenic effects • Training requirements • Patient reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	Moderate to high#

CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (31); GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MI, myocardial infarction; PPAR-γ, peroxisome proliferator–activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (32); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (33); TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study (34,35). Cycloset trial of quick-release bromocriptine (36). *Cost is based on lowest-priced member of the class (see ref. 17). †Not licensed in the U.S. ‡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. (17).

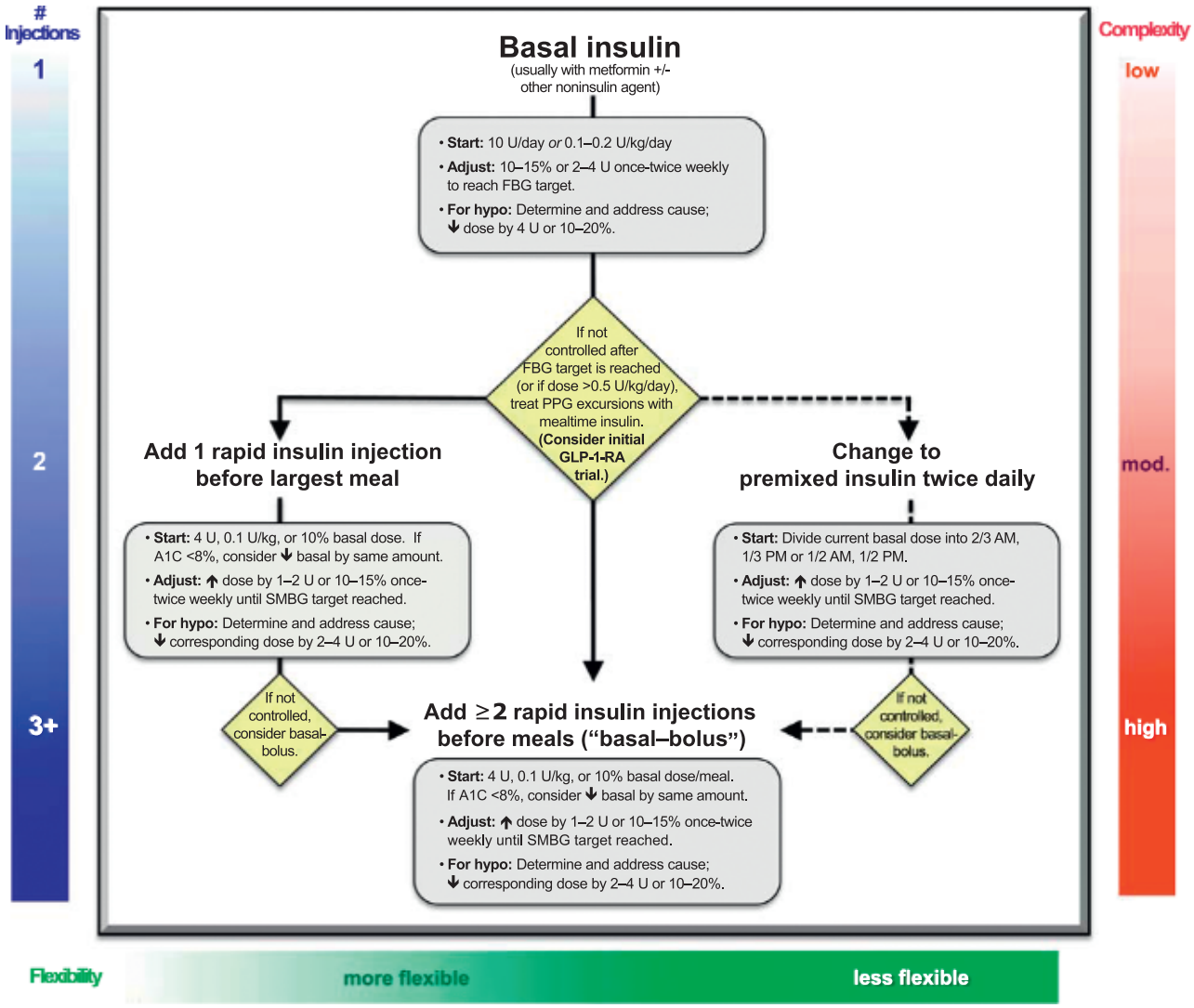

Figure 7.2—Approach to starting and adjusting insulin in type 2 diabetes (17). FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; mod., moderate; PPG, postprandial glucose; #, number. Adapted with permission from Inzucchi et al. (17).

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 when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12% (86–108 mmol/mol). As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

Insulin Therapy

Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C. Many patients with type 2 diabetes eventually require and benefit from insulin therapy. 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 (**Fig. 7.2**). The progressive nature of type 2 diabetes and its therapies should be regularly and objectively explained to patients. For patients with type 2 diabetes who are not achieving glycemic goals, providers should promptly initiate insulin therapy.

Providers should avoid using insulin as a threat or describing it as a 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 (25).

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units or 0.1–0.2 units/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly 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 history of hypoglycemia or severe hypoglycemia may use NPH safely at much lower cost (24,26). Concentrated preparation of basal insulin such as U-500 regular is five times as potent per volume of insulin (i.e.,

0.01 mL ~5 units of U-100 regular) and has a delayed onset and longer duration of action than U-100 regular. U-300 glargine and U-200 degludec are three and two times, respectively, as potent per volume, have a longer duration of action, and may allow higher doses of insulin administration in smaller volumes. These concentrated preparations may be more comfortable for the patient and allow better absorption. However, they are more expensive, and accurate dosing may be more complicated.

If basal insulin has been titrated to an acceptable fasting blood glucose level, but A1C remains above target, consider advancing to combination injectable therapy (**Fig. 7.2**) to cover postprandial glucose excursions. Options include adding a GLP-1 receptor agonist (27) or mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (lispro, aspart, or glulisine) administered just before eating. A less studied alternative, transitioning from basal insulin to twice-daily premixed (or biphasic) insulin analogs (70/30 aspart mix, 75/25 or 50/50 lispro mix), could also be considered; pharmacodynamic profiles make them suboptimal to cover postprandial glucose excursions.

Bolus Insulin

Some individuals with type 2 diabetes may require bolus insulin dosing in addition to basal insulin. Rapid-acting analogs are preferred due to their prompt onset of action after dosing. The FDA recently approved a more concentrated formulation of rapid-acting insulin analog, U-200 (200 units/mL), dosed 15 min or immediately prior to a meal.

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 make them suboptimal to cover postprandial glucose excursions.

Continuous Subcutaneous Insulin Infusion

A less commonly used and more costly alternative to "basal–bolus" therapy with multiple daily injections is CSII (insulin pump) (28,29). In addition to the suggestions provided for determining the starting dose of mealtime insulin under a basal–bolus regimen, another method consists of adding up the total current insulin dose and then providing one-half of this amount as basal and one-half as mealtime insulin, the latter split evenly between three meals. It is critical that individuals who have been successfully using CSII should have continued access after they turn 65 years of age (30).

Inhaled Insulin

Inhaled insulin is now available for prandial use with a more limited dosing range and may require serial lung function testing prior to and after starting therapy.

Treatment Strategies

Figure 7.2 focuses solely on sequential insulin strategies, describing the number of injections and the relative complexity and flexibility of each stage. Once an insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the prevailing blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control).

Noninsulin agents may be continued, although 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 increasing insulin doses, adjunctive use of thiazolidinediones (usually pioglitazone) or SGLT2 inhibitors may be helpful in improving control and reducing the amount of insulin needed. Comprehensive education regarding SMBG, diet, exercise, and the avoidance of and response to hypoglycemia are critically important in any patient using insulin.

BARIATRIC SURGERY

Bariatric surgery also improves glycemic control in type 2 diabetes. Its effects are discussed in Section 6 "Obesity Management for the Treatment of Type 2 Diabetes."

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8. 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 11 "Children and Adolescents."

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

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).

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

Systolic Targets

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. **A**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden. **C**

Diastolic Targets

- Individuals with diabetes should be treated to a diastolic blood pressure goal of <90 mmHg. **A**
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden. **B**

Treatment

- Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes to reduce blood pressure. **B**
- Patients with confirmed office-based blood pressure >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. **A**

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- In older adults, pharmacological therapy to achieve treatment goals of <130/70 mmHg is not recommended; treating to systolic blood pressure <130 mmHg has not been shown to improve cardiovascular outcomes and treating to diastolic blood pressure <70 mmHg has been associated with higher mortality. **C**
- Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. **B**
- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker but not both. **B** If one class is not tolerated, the other should be substituted. **C**
- Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/angiotensin receptor blocker, at maximal doses) is generally required to achieve blood pressure targets. **B**
- If ACE inhibitors, angiotensin receptor blockers, or diuretics are used, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. **E**
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 110–129/65–79 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. **E**

Hypertension is a common diabetes comorbidity that affects many patients, with the prevalence depending on type of diabetes, age, BMI, and 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.

Screening and Diagnosis

Blood pressure measurement should be done 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 (5,6). 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 and that systolic blood pressure (SBP) >120 mmHg predicts long-term end-stage renal disease. 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 (7). There is limited prespecified clinical trial evidence for the benefits of lower SBP or diastolic blood pressure (DBP) targets (8). 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 (9).

ACCORD, ADVANCE, SPRINT, AND HOT

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.

ACCORD. The ACCORD trial examined whether a lower 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 (10). The study did not find a benefit in primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive blood pressure treatment (goal <120 mmHg, average blood pressure achieved = 119/64 mmHg on 3.4 medications) with standard treatment (average blood pressure achieved = 143/70 mmHg on 2.1 medications). In ACCORD, there was no benefit of aggressive blood pressure lowering, despite the extra cost and efforts.

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 (11). 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. Recently published 6-year follow-up of 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 (12).

SPRINT. 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. *Of note, patients with diabetes*

were excluded from participating in this trial, so the results have no direct implications for blood pressure management in this population. The National Institutes of Health halted this study early because intensive therapy with a target SBP of 120 mmHg demonstrated a risk reduction of cardiovascular events by almost a third and the risk of death by almost a quarter compared with a target SBP of 140 mmHg (13).

HOT. The results from the ACCORD and Hypertension Optimal Treatment (HOT) (14) trials support the recommendation to achieve blood pressure levels <140/90 mmHg and underscore the important clinical difference between patients who are able to easily achieve lower blood pressure levels (e.g., as seen in observational epidemiological studies) and patients who require intensive medical management to achieve lower blood pressure goals (e.g., the clinical trials).

Systolic Blood Pressure

There is strong evidence that SBP >140 mmHg is harmful, suggesting that clinicians should promptly initiate and titrate therapy in an ongoing fashion to achieve and maintain SBP <140 mmHg in most patients (see Section 10 "Older Adults"). 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 (15). Therefore, individuals in whom stroke risk is a concern may, as part of shared decision making, have lower systolic targets such as <130 mmHg. This is especially true if lower blood pressure can be achieved with few drugs and without side effects of therapy.

Diastolic Blood Pressure

Similarly, strong evidence from randomized clinical trials supports DBP targets of <90 mmHg. Prior recommendations for lower DBP targets (<80 mmHg) were based primarily on a post hoc analysis of the HOT trial (14). A DBP of <80 mmHg may still be appropriate for patients with long life expectancy, those with chronic kidney disease, elevated urinary albumin excretion, and additional ASCVD risk factors such as dyslipidemia, smoking, or obesity (14). The 2016 American Diabetes Association (ADA) Standards of Care recommendations have been revised to reflect the higher-quality evidence that exists to support a goal of DBP <90 mmHg, although lower targets may be appropriate for certain individuals. These targets are in harmonization with a recent publication by the Eighth Joint National Committee that recommended for individuals over 18 years of age with diabetes a DBP threshold of <90 mmHg and SBP <140 mmHg (8).

Treatment Strategies

Lifestyle Modification

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 pharmacological monotherapy.

Lifestyle therapy consists of reducing excess body weight, 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) (16), and increasing activity levels (17).

These lifestyle (nonpharmacological) 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. Nonpharmacological 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, pharmacological therapy should be initiated along with nonpharmacological therapy (17). To enable long-term adherence, lifestyle therapy should be adapted to suit the needs of the patient and discussed as part of diabetes management.

Pharmacological Interventions

ACE Inhibitors. Lowering of blood pressure with regimens based on a variety of antihypertensive agents, including ACE inhibitors, angiotensin receptor blockers (ARBs), β-blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events. Several studies have suggested that ACE inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events (18–20). However, several studies have also shown no specific advantage to ACE inhibitors as an initial treatment of hypertension in the general hypertensive population, while showing an advantage of initial therapy with low-dose thiazide diuretics on cardiovascular outcomes (17,21,22).

Angiotensin Receptor Blockers. In people with diabetes, inhibitors of the renin-angiotensin system (RAS) 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 (23). In patients with congestive heart failure, including subgroups with diabetes, ARBs have been shown to reduce major ASCVD outcomes (24–27). In patients with type 2 diabetes with significant diabetic kidney disease, ARBs were superior to calcium channel blockers for reducing heart failure (28). Although evidence for distinct advantages of RAS inhibitors on ASCVD outcomes in diabetes remains conflicting (11,22), the high ASCVD risks associated with diabetes and the high prevalence of undiagnosed ASCVD may still favor recommendations for their use as first-line antihypertensive therapy in people with diabetes (17).

However, 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 renal dysfunction (29).

Other Pharmacological Interventions

The blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed combination of the ACE inhibitor perindopril and the 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 (11). Another trial showed a decrease

in morbidity and mortality in those receiving benazepril and amlodipine versus benazepril and hydrochlorothiazide (HCTZ) (30). The compelling benefits of RAS inhibitors in patients with diabetes and albuminuria or renal insufficiency provide additional rationale for the use of these agents (see Section 9 "Microvascular Complications and Foot Care"). If needed to achieve blood pressure targets, amlodipine, HCTZ, or chlorthalidone can be added. If estimated glomerular filtration rate is <30 mL/min/1.73 m^2, a loop diuretic, rather than HCTZ or chlorthalidone, 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 increase in sleep-time blood pressure and incidence of ASCVD events. 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 (31). Consider administering one or more antihypertensive medications at bedtime (32).

Other Considerations

An important caveat is that most patients with diabetes with hypertension require multiple-drug therapy to reach treatment goals (16). 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

In a pregnancy complicated by diabetes and chronic hypertension, target blood pressure goals of SBP 110–129 mmHg and DBP 65–79 mmHg are reasonable, as they contribute to improved long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, as they may cause fetal damage. 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 (33).

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 omega-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 ($\geq$150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol ($<$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 $\geq$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 and may be considered for patients with a recent acute coronary syndrome with LDL cholesterol $\geq$50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high-intensity statin therapy. **A**
- 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 $\geq$204 mg/dL (2.3 mmol/L) and HDL cholesterol level $\leq$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, pharmacological treatment, lipid levels, and medical conditions. Recommendations should focus on reducing saturated fat, cholesterol, and *trans* fat intake and increasing plant stanols/sterols, omega-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus). Glycemic control can 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 pharmacological (statin) therapy on ASCVD outcomes in subjects with and without CHD (34,35). Subgroup analyses of patients with diabetes in larger trials (36–40) and trials in patients with diabetes (41,42) 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 (43).

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 (44,45). 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 (46). In light of this fact, the 2016 ADA Standards of Care position statement was revised to recommend when to initiate and intensify statin therapy (high vs. moderate intensity) based on risk profile (**Table 8.1** and **Table 8.2**).

Table 8.1—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) in patients 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) in patients 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, overweight and obesity, and family history of premature ASCVD.

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

Age ≥40 Years

In all patients with diabetes aged ≥40 years, moderate-intensity statin treatment should be considered in addition to lifestyle therapy. Clinical trials in high-risk patients, such as those with ACS or previous cardiovascular events (47–49), have demonstrated that more aggressive therapy with high doses of statins led to a significant reduction in further events. Therefore, high-dose statins are recommended in 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) or with ASCVD.

Age >75 Years

For adults with diabetes over 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 10 "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

Table 8.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy	Moderate-intensity statin therapy
Lowers LDL cholesterol by ≥50%	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.

similar, although not statistically significant, reduction in risk as patients with type 2 diabetes (37). 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" (50) 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.

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 (51). 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 (52).

Increased frequency of LDL cholesterol monitoring should be considered for patients with new-onset ACS. A recent randomized controlled trial evaluated the addition of ezetimibe to moderate-intensity statin therapy and demonstrated ASCVD risk benefit over statin monotherapy (53). 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 who 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 (53). Therefore, for people meeting IMPROVE-IT eligibility criteria who can only tolerate a moderate-dose statin, the addition of ezetimibe to statin therapy should be considered.

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the novel 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 (54,55). 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 (56). Severe hypertriglyceridemia (>1,000 mg/dL) may warrant immediate pharmacological 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 (57). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (58).

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 (59) (compared with fenofibrate).

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) (60).

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 (61). 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 (62,63), 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 (64). 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) (64). 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 (63).

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 prohibit their use in individuals with diabetes at high risk for ASCVD (65).

ANTIPLATELET AGENTS

Recommendations

- 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 (10-year risk >10%). This includes most men or women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, smoking, dyslipidemia, 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 (10-year atherosclerotic cardiovascular disease risk <5%), such as in men or women with diabetes aged <50 years with no major additional atherosclerotic cardiovascular disease risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. **C**
- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. **E**
- 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. **B**

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 (66,67). 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 (68–71).

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 (66). 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 (72).

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 (10-year risk of ASCVD events over 10%) and who are not at increased risk for bleeding. This previous recommendation included most men over age 50 years and women over age 60 years who also have one or more of the following major risk factors: smoking, hypertension, dyslipidemia, family history of premature ASCVD, and albuminuria (73).

Sex Considerations

Multiple recent well-conducted studies and meta-analyses 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, the recommendations for using aspirin as primary

prevention are now revised to include both men and women aged ≥50 years with diabetes and one or more major risk factors to reflect these more recent findings (74–77). Sex differences in the antiplatelet effect of aspirin have been suggested in the general population (78); 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; 10-year ASCVD risk <5%) as the low benefit is likely to be outweighed by the risks of significant 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; those with 10-year ASCVD risk of 5–10%) until further research is available. Aspirin use in patients aged <21 years is 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 (79). 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 (80). "Aspirin resistance" appears higher in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (78). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (81); 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. 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 (82).

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 renal function is normal 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. Pharmacological 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 pharmacological stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (44), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (83,84). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (85). 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 (86–88). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (89). 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 (90,91). 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

(86,92,93), 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 Pharmacological 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. 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 (94,95). In patients with prior MI, β-blockers should be continued for at least 2 years after the event (96).

Diabetes and Heart Failure

Almost 50% of patients with type 2 diabetes will develop heart failure (97). 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 (98–100). Therefore, thiazolidinedione use should be avoided in patients with symptomatic heart failure.

Recent studies have now examined the relationship between dipeptidyl peptidase 4 (DPP-4) inhibitors and heart failure and have 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) (101). However, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), recent multicenter, randomized, double-blind, noninferiority trials, evaluated heart failure and mortality outcomes in patients with type 2 diabetes taking different DPP-4 inhibitors, alogliptin and sitagliptin, respectively, compared with placebo. 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]) (102). 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]) (102). 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) (103).

EMPA-REG OUTCOME Study

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind, placebo-controlled trial that assessed the effect of empagliflozin, a sodium–glucose cotransporter 2 inhibitor on cardiovascular outcomes (stroke, MI, amputation, or coronary, carotid, or peripheral artery obstruction) in patients with type 2 diabetes at high risk for cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 70% had a history of either stroke or MI. EMPA-REG OUTCOME showed that the therapy reduced the aggregate outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group), due to a 38% reduction in cardiovascular death (absolute rate 3.7% vs. 5.9%) (104). Empagliflozin is the first of the recently approved diabetes treatments associated with a lower risk of cardiovascular disease. Whether empagliflozin or other sodium–glucose cotransporter 2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

Metformin

A systematic review of 34,000 patients showed that metformin is as safe as other glucose-lowering treatments in patients with diabetes and congestive heart failure, even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease; however, metformin should be avoided in hospitalized patients (105).

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9. 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 (<140/90 mmHg) 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 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. **A**
- Either an ACE inhibitor or an angiotensin receptor blocker is recommended for the treatment of nonpregnant patients with diabetes and modestly elevated urinary albumin excretion (30–299 mg/day) **B** and is *strongly* recommended for those with urinary albumin excretion ≥300 mg/day 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), 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 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 Renal Function

Diabetic kidney disease, or kidney disease attributed to diabetes, occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD) (1).

Screening for kidney damage (albuminuria) can be most easily performed by urinary albumin–to–creatinine ratio (UACR) in a random spot urine collection. Timed or 24-h collections are more burdensome and add little to prediction or

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accuracy (2,3). 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 defined as <30 mg/g Cr, and increased urinary albumin excretion is defined as ≥30 mg/g Cr. Because of 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.

Estimated Glomerular Filtration Rate

Serum Cr should be used to estimate glomerular filtration rate (GFR). Estimated GFR (eGFR) is commonly reported by laboratories or can be estimated using formulae such as the Modification of Diet in Renal Disease (MDRD) study equation (4) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The latter is the preferred GFR estimating equation. GFR calculators are available at http://www.nkdep.nih.gov.

Abnormal urinary albumin excretion and eGFR may be used to stage chronic kidney disease (CKD). The National Kidney Foundation classification (**Table 9.1**) is based on both kidney damage (UACR ≥30 mg/g Cr) and eGFR.

Surveillance

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitor or angiotensin receptor blocker (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. Some suggest that reducing UACR to normal (<30 mg/g Cr) or near normal may improve CKD and cardiovascular disease (CVD) prognosis, but this approach has not been formally evaluated in prospective trials, and evidence demonstrates spontaneous remission of albuminuria in up to 40% of patients with type 1 diabetes.

Progression of Diabetic Kidney Disease

Conversely, patients with increasing UACR, declining eGFR, retinopathy, increasing blood pressure, macrovascular disease, elevated lipids and/or uric acid concentrations, or a family history of CKD are more likely to experience a progression of diabetic kidney disease (5).

Complications of kidney disease correlate with level of kidney function. When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 9.2**). Early vaccination against hepatitis B virus is indicated in patients likely to progress to ESRD.

Identifying and monitoring diabetic kidney disease relies on assessments of kidney damage (albuminuria) and kidney function (eGFR). Persistently increased UACR in the range of UACR 30–299 mg/g Cr is an early indicator of diabetic kidney disease in type 1 diabetes and a marker for development of diabetic kidney disease in type 2 diabetes. It is also a well-established marker of increased CVD risk (6–8).

Not all people with diabetes, kidney disease, and reduced eGFR have albuminuria. In addition, there is increasing evidence that up to 40% of patients with type 1 diabetes and UACR levels 30–299 mg/g Cr have spontaneous remissions and approximately 30–40% remain with UACR levels of 30–299 mg/g Cr and do not progress to higher levels over 5–10 years of follow-up (5,9–11). Patients with persistent and severely increased (≥300 mg/g Cr) levels of albuminuria are likely to develop ESRD (12,13).

The presence of diabetic retinopathy in patients with UACR ≥300 mg/g Cr strongly suggests diabetic kidney disease, and its absence in those with reduced eGFR and UACR <300 mg/g Cr suggests nondiabetic CKD. Other causes of CKD should be considered in patients with diabetes and CKD but without diabetic retinopathy and in those with an active urine sediment, with rapidly increasing proteinuria or nephrotic syndrome with low or rapidly decreasing eGFR, with >30% reduction in eGFR within 2–3 months of initiating ACE inhibitor or ARB therapy, with refractory hypertension, or with signs or symptoms of other systemic diseases.

Table 9.1—Stages of CKD

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage* with normal or increased eGFR	≥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 abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (3).

Interventions

Nutrition

For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be 0.8 g/kg body weight per day (the recommended daily allowance). 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

A number of interventions have been demonstrated to reduce the risk and slow the progression of diabetic kidney disease. Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of increased urinary albumin excretion and reduced eGFR in patients with type 1 diabetes (13) and type 2 diabetes (1,14–17).

Despite prior concerns and published case reports, current data indicate that the overall risk of metformin-associated

Table 9.2—Management of CKD in diabetes

GFR (mL/min/1.73 m^2)	Recommended management
All patients	Yearly measurement of Cr, UACR, 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 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

lactic acidosis is low (1). GFR may be a more appropriate measure to assess continued metformin use than serum Cr, considering that the serum Cr level can translate into widely varying eGFR levels depending on age, ethnicity, and muscle mass (18). A review (19) proposed that metformin use should be reevaluated at an eGFR <45 mL/min/1.73 m^2 with a reduction in maximum dose to 1,000 mg/day. Metformin should be discontinued when eGFR is <30 mL/min/1.73 m^2; in clinical situations in which there is an increased risk of lactic acidosis, such as sepsis, hypotension, and hypoxia; or when there is a high risk of acute kidney injury resulting in a worsening of GFR, such as administration of radiocontrast dye in those with eGFR <60 mL/min/1.73 m^2.

Blood Pressure

There are no randomized controlled trials of blood pressure levels in diabetes that have examined CKD events as outcomes. Blood pressure levels below 140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression. In individuals with albuminuria, consider lower blood pressure targets of <130/80 mmHg (20,21). Of note, there is an adverse safety signal in clinical trials of diabetic kidney disease when diastolic blood pressure is treated to below 70 mmHg and especially below 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 below 60–70 mmHg.

The UK Prospective Diabetes Study (UKPDS) provided strong evidence that blood pressure control can reduce the development of diabetic kidney disease (22). Interruption of the renin-angiotensin-aldosterone system with either ACE inhibitors or ARBs contributes to reductions of kidney disease events in hypertensive patients with diabetes and eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g Cr.

ACE inhibitors have been shown to reduce major CVD events in patients with diabetes (23), thus further supporting the use of these agents in patients with albuminuria, a CVD risk factor. In those with diabetic kidney disease, some evidence suggests that ARBs compared with ACE inhibitors are associated with a smaller increase in serum potassium levels (24).

Combination Therapy

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) (25). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Mineralocorticoid receptor blockers (spironolactone) in combination with ACE inhibitors or ARBs remain an area of great interest and have been explored in several short-term studies with a positive effect on albuminuria reduction in diabetic kidney disease. There was, however, an increase in hyperkalemic episodes in those on dual therapy, and larger trials 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 (26) 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 (absence of retinopathy, heavy proteinuria, active urine sediment, or rapid decline in GFR). Other triggers for referral may include difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances) or advanced kidney disease. 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 (27). 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, then exams every 2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations for patients with type 1 or type 2 diabetes 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, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. **E**
- 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 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 and treatment 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 antivascular endothelial growth factor are indicated for center-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 (28), nephropathy (29), hypertension (30), and dyslipidemia (31). 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 (15,32).

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic $<$120 mmHg) do not impart additional benefit (32). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy (NPDR) at baseline (31). 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 (33,34). Laser photocoagulation surgery can minimize the risk of vision loss (34).

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 (35). Examinations will be required more frequently by the ophthalmologist 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 (36). 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 (37). In-person exams are still necessary when the retinal photos are unacceptable and for follow-up if abnormalities are detected. Retinal photos are not a substitute for a comprehensive eye exam, 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 (38).

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 (39,40). 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 tight glycemic control in the setting of retinopathy is associated with worsening of retinopathy

(34). Women who develop gestational diabetes mellitus do not require an eye examination during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (41).

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 (42) 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 risk–benefit ratio in those with 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.

Antivascular Endothelial Growth Factor Treatment

While the ETDRS (43) 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 multiple well-designed clinical trials demonstrate that intravitreal antivascular endothelial growth factor (anti-VEGF) agents provide a more effective treatment regimen for center-involved diabetic macular edema than monotherapy or even combination therapy with laser (44–46).

Historically, laser photocoagulation surgery in both trials was beneficial in reducing the risk of further visual loss in affected patients but generally not beneficial in reversing already diminished acuity. Now, intravitreal therapy with recombinant monoclonal neutralizing antibody to VEGF improves vision and has replaced the need for laser photocoagulation in the vast majority of patients with diabetic macular edema (47). 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 center-involved diabetic macular edema. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacological 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 should include a careful history and 10-g monofilament testing and at least one of the following tests: pinprick, temperature, or vibration sensation. **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**

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 (48,49) and may modestly slow their progression in type 2 diabetes (17) but does not reverse neuronal loss. Therapeutic strategies (pharmacological and nonpharmacological) for the relief of symptoms related to painful DPN or autonomic neuropathy can potentially reduce pain (50) 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 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 B_{12} deficiency, hypothyroidism, renal disease, malignancies (multiple myeloma, bronchogenic carcinoma), infections (HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (51).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic dysfunction 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 independent of other cardiovascular risk factors (52,53). 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 glucose control or with upper gastrointestinal symptoms without another identified cause. Evaluation of gastric emptying using the gastric emptying breath test, a new noninvasive test that does not use radiation-emitting compounds (54), or the double-isotope scintigraphy may be performed if symptoms suggest gastroparesis, but test results are likely to be abnormal in the setting of recent uncontrolled hyperglycemia or diabetic ketoacidosis and often correlate poorly with symptoms. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Genitourinary Disturbances

Diabetic autonomic neuropathy may also cause genitourinary disturbances. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation. 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 (55–58). 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 (59,60) without reversal of neuronal loss. Several observational studies suggest that neuropathic symptoms improve not only with optimization of glycemic control but also with the avoidance of extreme blood glucose fluctuations.

Diabetic Peripheral Neuropathy

DPN symptoms, and especially neuropathic pain, can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (61). Several medications have been demonstrated to be effective for the treatment of pain associated with DPN, but there is limited clinical evidence regarding which medication is most effective for an individual patient (62,63).

The U.S. Food and Drug Administration (FDA) has approved three medications (pregabalin, duloxetine, and tapentadol) for the treatment of pain associated with DPN, but none affords complete relief, even when used in combination. 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. Comparative efficacy 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 pharmacological 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 (50,64,65).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacological measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacological measures. Midodrine is the only drug approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Gastroparesis may improve with a low-fat, low-fiber diet, optimized glycemic control, and prokinetic agents such as metoclopramide or erythromycin. In 2009, the FDA added a boxed warning to the metoclopramide label highlighting the risks of irreversible tardive dyskinesia after long-term use of metoclopramide. The chronic use of metoclopramide should be avoided (66). Metoclopramide should be reserved for patients with the most severe symptoms that are unresponsive to other therapies. The medication should be used at the lowest dose and for the shortest duration possible, generally not to exceed 3 months, and side effects should be closely monitored.

Erectile Dysfunction

Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. Interventions for other manifestations of autonomic neuropathy are described in the American Diabetes Association (ADA) statement on neuropathy (67). 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 each year to identify risk factors for ulcers and amputations. **B**
- 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 including 10-g monofilament testing and pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet. **B**
- Patients with a history of ulcers or amputations, foot deformities, insensate feet, and peripheral arterial disease are at substantially increased risk for ulcers and amputations and should have their feet examined at every visit. **C**
- Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment. **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 foot self-care education to all patients with diabetes. **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:

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

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (67).

Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually to identify high-risk conditions. 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 assessment 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) rule out LOPS.

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history for 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. Due to the high estimated prevalence of PAD in patients with diabetes and the fact that many patients with PAD are asymptomatic, an ADA consensus report on PAD (68) suggested that ankle-brachial index screening be performed in patients 50 years of age and older and be considered in patients under 50 years of age who have other PAD risk factors (e.g., smoking, hypertension, dyslipidemia, or duration of diabetes >10 years).

Patient Education

Patients with diabetes and high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) should be educated about their risk factors and appropriate management. 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 a nonbreakable 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 in 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 extra-wide 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 an 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.

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. *Staphylococci* 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 (69). 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 (69).

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10. Older Adults

American Diabetes Association

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Recommendations

- Consider the assessment of medical, functional, mental, and social geriatric domains for diabetes management in older adults to provide a framework to determine targets and therapeutic approaches. **E**
- 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. **E**
- 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 screened for and managed by adjusting glycemic targets and pharmacological interventions. **B**
- Older adults who are functional and cognitively intact and have significant life expectancy may receive diabetes care with goals similar to those developed for younger adults. **E**
- 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. **E**
- Screening for diabetes complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment. **E**
- Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention 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 a glycemic goal 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**

OVERVIEW

Diabetes is an important health condition for the aging population; ~26% of patients over the age of 65 years have diabetes (1), and this number is expected to grow 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 a greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, urinary incontinence, injurious falls, and persistent pain. Screening for diabetes complications in older adults also should be individualized and periodically revisited, since 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

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(2). Diabetes management may require assessment of medical, functional, mental, 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. Diabetes increases the incidence of all-cause dementia, Alzheimer disease, and vascular dementia when compared with rates in people with normal glucose tolerance (6). The effects of hyperglycemia and hyperinsulinemia on the brain are areas of intense research interest. 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 or 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 (MMSE) and the Montreal Cognitive Assessment (MoCA), 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).

HYPOGLYCEMIA

It is important to prevent hypoglycemia to reduce the risk of cognitive decline and 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 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 deficits have been associated with increased risk of hypoglycemia and with severe hypoglycemia linked to increased dementia. Therefore, it is important to routinely screen older adults for cognitive dysfunction and discuss findings with the caregivers. Hypoglycemic events should be diligently monitored and avoided, whereas glycemic targets and pharmacological 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 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. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning. Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable for this population 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 (**Table 10.1**).

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 for older adults and their caregivers.

Patients With Complications and Reduced Functionality

For patients with advanced diabetes complications, life-limiting comorbid illness, or substantial cognitive or functional impairment, it is reasonable to set less intensive glycemic target 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

Table 10.1—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 (27).
**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.

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 (13,14).

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 the elderly (15,16). There is less evidence for lipid-lowering and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames seen in clinical trials.

PHARMACOLOGICAL THERAPY

Special care is required in prescribing and monitoring pharmacological therapy in older adults (17). Cost may be a significant factor, especially as older adults tend to be on many medications.

Insulin Sensitizers

Metformin is the first-line agent in older adults with type 2 diabetes. However, it is contraindicated in patients with renal insufficiency or significant heart failure. Since serum creatinine levels do not adequately reflect renal function in older people (muscle mass losses are associated with chronic conditions and functional decline), a timed urine collection to assess creatinine clearance has been recommended, particularly in those aged ≥80 years. Metformin may be temporarily discontinued before procedures, during hospitalizations, and when acute illness may compromise renal or liver function. Thiazolidinediones, if used at all, should be used very cautiously in those with, or at risk for, congestive heart failure and have been associated with fractures.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues are associated with hypoglycemia and should be used with caution. Glyburide is contraindicated in older adults (18). Insulin can also cause hypoglycemia, and its use requires that patients or caregivers have good visual and motor skills and cognitive ability.

Incretin-Based Therapies

Glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors have few side effects, 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 (19). Glucagon-like peptide 1 receptor agonists are injectable agents, which require visual, motor, and cognitive skills.

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.

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. The patient's living situation must be considered, as it may affect diabetes management and support.

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. The American Medical Directors Association (AMDA) guidelines offer a 12-step program for staff (20). This training includes diabetes detection and institutional quality assessment. It is also recommended 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. Major organizations such as the ADA, the American Geriatrics Society (AGS), the International Association of Gerontology and Geriatrics (IAGG), and the European Diabetes Working Party for Older People (EDWPOP) concur with the AMDA on the need to individualize treatments for each patient, the need to avoid both hypoglycemia and the metabolic complications of diabetes, and the need to provide adequate diabetes training to LTC staff (3,21).

Nutrition 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 (22).

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 renal function, slowed hormonal regulation and counterregulation, and suboptimal hydration, variable appetite and nutritional intake, polypharmacy, and slowed intestinal absorption (23).

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 hypoglycemia (<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) or when any reading is too high, e) or the patient is sick, with vomiting or other malady that can reflect hyperglycemic crisis, may lead to poor oral intake, and thus requires regimen adjustment.

END-OF-LIFE CARE

The management of the older adult at the end of life receiving palliative medicine or hospice is a unique situation. Overall, palliative medicine promotes comfort, symptom control, and prevention (pain, hypoglycemia and hyperglycemia, dehydration) and preservation of dignity and quality of life in patients with limited life expectancy (21,24). 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 (25). 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 (26). The pharmacological 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 down and discontinued.

Strata have been proposed for diabetes management in those with advanced disease (14).

1. **A stable patient**: continue with the patient's previous regimen, with a focus on the prevention of hypoglycemia and the management of hyperglycemia, 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 handled. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases. 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 pertinent approach, as they 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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11. 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. 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 (1,2). Attention to family dynamics, developmental stages, and physiological differences related to sexual maturity are all essential in developing and implementing an optimal diabetes regimen (3). 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" (4) and have been updated in the ADA position statement "Type 1 Diabetes Through the Life Span" (5).

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 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 clinic 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 (6).

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

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management, safety, and maximal academic opportunities. Refer to the ADA position statements "Diabetes Care in the School Setting" (7) and "Care of Young Children With Diabetes in the Child Care Setting" (8) 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**
- 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**
- Consider mental health professionals as integral members of the pediatric diabetes multidisciplinary team. **E**

Diabetes management throughout childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial issues and distress during routine diabetes visits (9–11). Further, 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 (12,13). 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 (14).

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 (15). Consider screening for depression and disordered eating behaviors using available screening tools (9,16), and, 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 (17). 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. 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 their hypoglycemic symptoms. This "hypoglycemia unawareness" should be considered when establishing individualized glycemic targets.

Although it was previously thought that young children were at risk for cognitive impairment after episodes of severe hypoglycemia, current data have not confirmed this notion (18–20). Furthermore, new therapeutic modalities, such as rapid- and long-acting insulin analogs, technological advances (e.g., continuous glucose monitors, low glucose suspend insulin pumps), and education may mitigate the incidence of severe hypoglycemia (21).

The Diabetes Control and Complications Trial (DCCT) 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 set by the ADA (7,22–25) 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 compelling motivation for lowering glycemic targets (1).

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 (26,27). A1C goals are presented in **Table 11.1**.

Autoimmune Conditions

Recommendation

- Assess for the presence of additional autoimmune conditions 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

Table 11.1—Blood glucose and A1C goals for type 1 diabetes across all pediatric age-groups

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 regimens.

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 celiac disease and thyroid dysfunction, 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 children 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 (28). At the time of diagnosis, about 25% of children with type 1 diabetes have thyroid autoantibodies (29); their presence is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of cases (30,31). 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 (32) and reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of metabolic control.

Celiac Disease

Recommendations

- Consider screening children 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 in children 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 children with frequent unexplained hypoglycemia or deterioration in glycemic control. **E**
- Children 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**

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) (33–35).

Testing. Testing for celiac disease includes measuring serum levels of IgA and antitissue 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 within 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. Testing for antitissue transglutaminase antibody should be considered at other times in patients with symptoms suggestive of celiac disease (35). A small-bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (36). 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 (37).

In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (38). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, we recommend a biopsy to confirm the diagnosis of celiac disease, 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 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 with 3–6 months of initiating lifestyle intervention, pharmacological treatment should be considered. **E**
- In addition to lifestyle modification, pharmacological 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 pharmacological treatment of hypertension, following reproductive counseling 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 determined 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). 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 (39).

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. **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 (40–42), and the prevalence of CVD risk factors increases with age (42), with girls having a higher risk burden than boys (41).

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 abnormalities within the first decade of diagnosis (43–45). Studies of carotid intima-media thickness have yielded inconsistent results (39).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes (46–48); 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 (49); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (50).

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 pharmacological treatment for those with elevated LDL cholesterol levels (48,51). 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 (52).

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 (46). 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 (53).

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 (54,55). 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, pregnancy prevention is of paramount importance for postpubertal girls (see Section 12 "Management of Diabetes in Pregnancy" for more information).

Smoking

Recommendation
- Elicit a smoking history at initial and follow-up diabetes visits and 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. 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 (46,56). 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 diabetes for 5 years. **B**
- Estimate glomerular filtration rate at initial evaluation and then based on age, diabetes duration, and treatment. **E**

Treatment

- Treatment with an ACE inhibitor, titrated to normalization of albumin excretion, should be considered when elevated urinary albumin–to–creatinine ratio (>30 mg/g) is documented with at least two of three urine samples. These should be obtained over a 6-month interval following efforts to improve glycemic control and normalize blood pressure. **B**

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 (57). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (58), 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. This is not a recommendation to perform a measurement of creatinine clearance (involves timed urine collection) every year. There are ongoing clinical trials assessing the efficacy of early treatment of persistent albuminuria with ACE inhibitors (59).

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 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**

Although retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (60), it has been reported in prepubertal children and with diabetes duration of only 1–2 years. 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**

Neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (60). 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 assessment of symptoms of neuropathic pain. Foot inspection can be performed at each visit to educate youth regarding the importance of 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."

The Centers for Disease Control and Prevention recently published projections for type 2 diabetes prevalence using the SEARCH database. Assuming a 2.3% annual increase, the prevalence of type 2 diabetes in those under 20 years of age will quadruple in 40 years (61,62). Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. For example, excessive weight is common in children with type 1 diabetes (63). Furthermore, diabetes-associated autoantibodies and ketosis may be present in patients with features of type 2 diabetes (including obesity and acanthosis nigricans) (64). Nevertheless, accurate diagnosis is critical as treatment regimens, educational approaches, dietary advice, and outcomes differ markedly between the two diagnoses.

Treatment

The general treatment goals for type 2 diabetes are the same as those for type 1 diabetes. A multidisciplinary diabetes team, including a physician, diabetes nurse educator, registered dietitian, and behavioral specialist or social worker, is essential. In addition to blood glucose control, treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and albumin levels from the outset.

Presentation with ketosis or ketoacidosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal. 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) (65).

Patients and their families must prioritize lifestyle modifications such as eating a balanced diet, maintaining a healthy weight, and exercising regularly. A family-centered approach to nutrition and lifestyle modification is essential in children with type 2 diabetes. Nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation").

When insulin treatment is not required, initiation of metformin, currently the only oral hypoglycemic agent specifically approved for use in children with type 2 diabetes, is recommended. However, 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 (66), suggesting that many youth with type 2 diabetes are likely to require combination treatment within a few years of diagnosis.

Comorbidities

Comorbidities may already be present at the time of diagnosis in youth with type 2 diabetes (67). Therefore, blood pressure measurement, a fasting lipid panel, assessment for albumin excretion, and a dilated eye examination should be performed at diagnosis. Thereafter, screening guidelines and treatment recommendations for hypertension, dyslipidemia, 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 "Type 2 Diabetes in Children and Adolescents" (68) and a more recent American Academy of Pediatrics clinical practice guideline (69) 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 in early to mid-adolescence 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 diabetes throughout childhood and adolescence. The shift from pediatrics to adult health care providers, however, often occurs abruptly as the older teen enters the next developmental stage referred to as emerging adulthood (70), 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' home 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 plan (ongoing coverage until age 26 years is possible with recent U.S. health care reform). 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 (71–74).

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 (71,72). 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" (72).

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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12. Management of Diabetes in Pregnancy

American Diabetes Association

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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

Pregestational Diabetes

- Provide preconception counseling that addresses 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**
- Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. **A**
- 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. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for 1 year postpartum as indicated by degree of retinopathy. **B**

Gestational Diabetes Mellitus

- Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. **A**
- Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. **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, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. **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**

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 pregestational type 1 diabetes and type 2 diabetes. The rise in GDM and pregestational type 2 diabetes in parallel with obesity both in the U.S. and worldwide is of particular concern. Both pregestational type 1 diabetes and type 2 diabetes confer significantly greater maternal and fetal risk than GDM, with some differences according to type as outlined below. In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, intrauterine 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).

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PRECONCEPTION COUNSELING

All women of childbearing age with diabetes should be counseled about the importance of near-normal 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.

Preconception Testing

Preconception counseling visits should address rubella, rapid plasma reagin, 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 testing; review of the medication list for potentially teratogenic drugs (i.e., ACE inhibitors, statins); and referral for a comprehensive eye exam.

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 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 pregestational type 2 diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, preprandial and postprandial monitoring of blood glucose is recommended to achieve metabolic control in pregnant women with diabetes. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia (7). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Nevertheless, the American College of Obstetricians and Gynecologists (ACOG) (8) recommends the following targets for women with pregestational type 1 or type 2 diabetes:

- Fasting ≤90 mg/dL (5.0 mmol/L)
- One-hour postprandial ≤130–140 mg/dL (7.2–7.8 mmol/L)
- 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 severe hypoglycemia or hypoglycemia unawareness.

If women cannot achieve these targets without significant hypoglycemia, the American Diabetes Association (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 (4,9–11). 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 blood cell turnover, A1C levels fall during normal pregnancy (12). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, while A1C may be useful, it should be used as a secondary measure, after self-monitoring of blood glucose.

In the second and third trimester, 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 diabetes after pregnancy. The association of macrosomia and birth complications with oral glucose tolerance test (OGTT) results is continuous, with no clear inflection points (13). In other words, risks increase with progressive hyperglycemia. Therefore, all women should be screened 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 (14,15).

Lifestyle Management

After diagnosis, treatment starts with medical nutrition therapy, physical

activity, and weight management depending on pregestational weight, as outlined in the section on pregestational type 2 diabetes below, and glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (16):

- 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 increase using the lower International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (17) diagnostic thresholds.

Pharmacological Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacological 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 (18). Insulin is the first-line agent recommended for treatment of GDM in the U.S. Individual randomized controlled trials support the efficacy and short-term safety of metformin (19,20) (pregnancy category B) and glyburide (21) (pregnancy category B) for the treatment of GDM. However, both agents cross the placenta, and long-term safety data are not available for either agent (22).

Sulfonylureas

More recently, several meta-analyses and large observational studies examining maternal and fetal outcomes have suggested that sulfonylureas, such as glyburide, may be inferior to insulin and metformin due to increased risk of neonatal hypoglycemia and macrosomia with this class.

Metformin

Metformin, which is associated with a lower risk of hypoglycemia and potential lower weight gain, may be preferable to insulin for maternal health if it suffices to control hyperglycemia (23–25); however, metformin may slightly increase the risk of prematurity. None of these studies or meta-analyses evaluated long-term outcomes in the offspring. Thus, patients treated with oral agents should be informed that they cross the placenta and, while no adverse effects on the fetus have been demonstrated, long-term studies are lacking.

Insulin

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

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

Insulin Use

Insulin is the preferred agent for management of pregestational type 1 diabetes and type 2 diabetes that are not adequately controlled with diet, exercise, and metformin.

The physiology of pregnancy requires frequent titration of insulin to match changing requirements. 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, dietitian, nurse, and social worker, as needed) is recommended if this resource is available.

All insulins are pregnancy category B except for glargine, glulisine, and degludec, which are labeled category C.

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. Hypoglycemia education for patients and family members is important before and during early pregnancy and throughout 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. All insulin-deficient women 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 (26).

Type 2 Diabetes

Pregestational 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. Glycemic control is often easier to achieve in type 2 diabetes than in 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. Associated hypertension and other comorbidities often render pregestational type 2 diabetes as high or higher risk than pregestational type 1 diabetes, even if the diabetes is better controlled and of shorter duration, with pregnancy loss appearing to be more prevalent in the third trimester in type 2 diabetes compared with the first trimester in type 1 diabetes (27,28).

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 (29) and offspring (30).

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 6–12 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 6- 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. Because GDM is associated with increased maternal risk for diabetes, women should also be tested every 1–3 years thereafter if 6- to 12-week 75-g OGTT is normal, with frequency of screening depending on other risk factors including family history, prepregnancy BMI, and need for insulin or oral glucose-lowering medication during pregnancy. Ongoing screening 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 6- to 12-week postpartum time frame (31). 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 (32). 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 (33) 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 impaired glucose tolerance, only 5–6 individuals need to be treated with either intervention to prevent one case of diabetes over 3 years (34). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (35).

Pregestational 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 is needed to hypoglycemia prevention in the setting of erratic sleep and eating schedules. 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.

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 pregestational diabetes due to the need for preconception glycemic control and preventive health services. Therefore, all women with diabetes of childbearing age 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 ANTIHYPERTENSIVE DRUGS

In normal pregnancy, blood pressure is lower than in the nonpregnant state. In a pregnancy complicated by diabetes and chronic hypertension, target goals of systolic blood pressure 110–129 mmHg and diastolic blood pressure 65–79 mmHg are reasonable. 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 (36).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated, because they may cause fetal renal dysplasia, oligohydramnios, and intrauterine growth restriction. 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 (37).

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American Diabetes Association

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Recommendations

- Consider performing an A1C on all patients with diabetes or hyperglycemia admitted to the hospital if not performed in the prior 3 months. **C**
- 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 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected critically ill 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**
- 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 patients with good nutritional intake. **A**
- The 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 if 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. **B**

Both hyperglycemia and hypoglycemia are associated with adverse outcomes, including death (1,2). Therefore, hospital goals for the patient with diabetes include preventing both hyperglycemia and hypoglycemia, promoting the shortest safe hospital stay, and providing an effective transition out of the hospital that prevents complications and readmission.

High-quality hospital care requires both hospital care delivery standards, often assured by structured order sets, and quality assurance standards for process improvement.

HOSPITAL CARE DELIVERY STANDARDS

"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).

Computerized Physician Order Entry

In 2009, the federal Health Information Technology for Economic and Clinical Health (HITECH) Act was enacted. A core requirement for stage 1 of the HITECH Act's "meaningful use" included CPOE. The Institute of Medicine also recommends CPOE to prevent medication-related errors and increase efficiency in medication administration (3). A Cochrane review of randomized controlled trials using computerized advice to improve glucose control in the hospital found significant improvement in percentage of time in target glucose range, lower mean blood glucose, and no increase in hypoglycemia (4). As hospitals move to comply with "meaningful

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use," efforts should be made to ensure that all components of structured insulin order sets are incorporated in the orders (5). Thus, where feasible, there should be routine structured order sets that produce computerized advice for glucose control.

CONSIDERATIONS ON ADMISSION

Initial orders should state that the patient has type 1 diabetes or type 2 diabetes or no previous history of diabetes. If the patient has diabetes, an order for an A1C should be placed if none is available within the prior 3 months (2). In addition, diabetes self-management education should be ordered and should include appropriate skills needed after discharge, such as taking glycemic medication, glucose monitoring, and coping with hypoglycemia (2).

GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

Standard Definition of Glucose Abnormalities

Hyperglycemia in hospitalized patients has been defined as blood glucose >140 mg/dL (7.8 mmol/L). Blood glucose levels that are significantly and persistently above this level require reassessing treatment. An admission A1C value ≥6.5% (48 mmol/mol) suggests that diabetes preceded hospitalization (see Section 2 "Classification and Diagnosis of Diabetes"). 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) (6).

Moderate Versus Tight Glycemic Control

Glycemic goals within the hospital setting have changed in the last 14 years. The initial target of 80–110 mg/dL (4.4–6.1 mmol/L) was based on a 42% relative reduction in intensive care unit mortality in critically ill surgical patients (7). However, a meta-analysis of over 26 studies, including the largest, Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR), showed increased rates of severe hypoglycemia and mortality in tightly versus moderately controlled cohorts (8). This evidence established new standards: initiate insulin therapy for persistent hyperglycemia greater than 180 mg/dL (10.0 mmol/L). Once insulin therapy is initiated, a glucose target of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill patients (2). More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for select patients, such as cardiac surgery patients (7), and patients with acute ischemic cardiac (9) or neurological events provided the targets can be achieved without significant hypoglycemia.

A glucose target between 140 and 180 mg/dL (between 7.8 and 10.0 mmol/L) is recommended for most patients in noncritical care units (2). Patients with a prior history of successful tight glycemic control in the outpatient setting who are clinically stable may be maintained with a glucose target below 140 mg/dL (7.8 mmol/L). Conversely, higher glucose ranges may be acceptable in terminally ill patients, in patients with severe comorbidities, and in in-patient 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).

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 (10). If oral medications are held in the hospital, there should be a protocol for resuming them 1–2 days before discharge.

Insulin Therapy

The sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged (2,11).

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 (2,12).

Noncritical Care Setting

Outside of critical care units, scheduled subcutaneous insulin injections should align with meals and bedtime or every 4–6 h if no meals or if continuous enteral/parenteral therapy is used (2). A basal plus correction insulin regimen is the preferred treatment for patients with poor oral intake or those who are taking nothing by mouth (NPO) (13). An insulin regimen with basal, nutritional, and correction components (basal–bolus) is the preferred treatment for patients with good nutritional intake (10). In such instances, point-of-care (POC) glucose testing should be performed immediately before meals.

If oral intake is poor, a safer procedure is to administer the short-acting insulin after the patient eats or to count the carbohydrates and cover the amount ingested. 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 (14).

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 calorie 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 (15).

Transitioning Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is associated with less morbidity and lower costs of care (16) and is therefore recommended. A patient with type 1 or type 2 diabetes being transitioned to outpatient subcutaneous insulin should receive subcutaneous 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 (2,16,17).

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 (18). A report suggested that given the serious consequences of hypoglycemia, incretin agents, which do not cause hypoglycemia, may substitute for insulin, sulfonylureas, or metformin (19). A review of several studies concluded that incretins show promise; however, proof of safety and efficacy compared with standard therapies await the results of further randomized controlled trials (20).

STANDARDS FOR SPECIAL SITUATIONS

Enteral/Parenteral Feedings

For full enteral/parenteral feeding guidance, the reader is encouraged to consult review articles (2,21) and see **Table 13.1**.

Glucocorticoid Therapy

The duration of glucocorticoid action must be considered to prevent hyperglycemia. Once-a-day short-acting steroids such as prednisone peak in about 8 h, so coverage with intermediate-acting insulin (NPH) may be sufficient. For long-acting steroids such as dexamethasone or multidose or continuous steroid use, long-acting insulin may be used (10,21). Whatever orders are started, adjustments based on POC glucose test results are critical.

Perioperative Care

Standards for perioperative care include the following:

1. Target glucose range for the perioperative period should be 80–180 mg/dL (4.4–10.0 mmol/L).
2. Preoperative risk assessment for patients at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
3. The morning of surgery or procedure, hold any oral hypoglycemic agents and give half of NPH dose or full doses of a long-acting analog or pump basal insulin.
4. Monitor blood glucose every 4–6 h while NPO and dose with short-acting insulin as needed.

A review found that tight perioperative glycemic control did not improve outcomes and was associated with more hypoglycemia (22); therefore, in general, tighter glycemic targets than mentioned above are not advised.

Moderate Versus Tight Glycemic Control Targets

In general surgery (noncardiac) 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) (13,14).

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 (23).

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. Low-dose insulin, given intravenously, intramuscularly, or subcutaneously, is safe and effective in treating DKA (23).

Several studies have shown that in uncomplicated mild-to-moderate DKA, subcutaneous lispro (24) or aspart insulin (25) dosed every 1–2 h is as effective and safe as intravenous regular insulin when used in conjunction with standard intravenous fluid and potassium replacement protocols (23). If subcutaneous administration is used, it is important, for safety reasons, to provide adequate nursing training and care and frequent bedside testing. However, in critically ill and mentally obtunded patients, continuous intravenous insulin infusion is required. 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 (26).

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) provides continuous estimates, direction, and magnitude of glucose trends, which may have an advantage over POC glucose testing in detecting and reducing the incidence of hypoglycemia. Several studies have shown that CGM use did not improve glucose control, but detected a greater number of hypoglycemic events than POC testing. A recent review has recommended against using CGM in adults in a hospital setting until more safety and efficacy data become available (27).

TREATING AND PREVENTING HYPOGLYCEMIA

Patients with or without diabetes may experience hypoglycemia in the hospital setting. While increased mortality is associated with hypoglycemia, it 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.

Triggering Events

Iatrogenic hypoglycemia triggers may include sudden reduction of corticosteroid dose, altered ability of the patient to

Table 13.1—Insulin dosing for enteral/parenteral feedings

Situation	Basal	Bolus
Continuous enteral feedings	Glargine q.d. or NPH/detemir b.i.d.	SQ rapid-acting correction every 4 h
Bolus enteral feedings	Continue prior basal; if none, consider 10 units NPH or glargine insulin	SQ rapid-acting insulin with each bolus feeding to cover the bolus feeding and to correct for hyperglycemia
Parenteral feedings	Regular insulin to TPN IV bottle	Rapid-acting insulin SQ every 4 h to correct for hyperglycemia

IV, intravenous; SQ, subcutaneous; TPN, total parenteral nutrition.

report symptoms, reduced oral intake, emesis, new NPO status, inappropriate timing of short-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, and unexpected interruption of oral, enteral, or parenteral feedings.

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 (28). 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 (29).

Hypoglycemia Treatment

There should be a standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol to immediately address hypoglycemia (<70 mg/dL [3.9 mmol/L]) (2).

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. A study 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, the study found that the relative risk of a severe hypoglycemic event was 0.44 (95% CI 0.34–0.58) in the postintervention period (30).

Hospital Hypoglycemia Prevention and Treatment

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. An American Diabetes Association (ADA) hypoglycemia consensus report suggested that the treatment regimen be reviewed when a blood glucose value is <70 mg/dL (3.9 mmol/L), a hypoglycemia protocol be adopted and implemented in each hospital system, and all episodes should be tracked in the medical records (2).

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 are advised (31).

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy are to optimize glycemic control, provide adequate calories to meet metabolic demands, address personal food preferences, and create 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 (32).

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 reflect that the meal delivery and nutritional insulin coverage be matched, as their variability often creates the possibility of hyperglycemic and hypoglycemic events.

TRANSITION FROM THE ACUTE CARE SETTING

A Cochrane systematic review noted that a structured discharge plan tailored to the individual patient may reduce length of hospital stay, readmission rates, and increase patient satisfaction (33). 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 assisted living or to home, 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, continuing 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 decreased from 8.7% (72 mmol/mol) on admission to 7.3% (56 mmol/mol) 3 months after discharge (34). 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 (35):

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, and explanation of home blood glucose goals.
- 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.

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, and the Society of Hospital Medicine has a workbook for program development (36).

DIABETES CARE PROVIDERS IN THE HOSPITAL

Appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes, but the 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.

BEDSIDE BLOOD GLUCOSE MONITORING

Indications

Bedside POC blood glucose monitoring guides insulin dosing. In the patient receiving nutrition, glucose monitoring should be performed before meals to match food ingestion. In the patient not receiving nutrition, 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, needles, and pens to reduce the risk of transmission of blood-borne diseases.

Limitations in the Hospital Setting

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 (37). 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 draft on in-hospital use with stricter standards. Before choosing a device, consider the device's approval status and accuracy.

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14. 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 Medical 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 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.pdf+html).

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

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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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Professional Practice Committee for the *Standards of Medical Care in Diabetes—2016*

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