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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE MANAGEMENT OF DIABETES MELLITUS

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force

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AMERICAN ASSOCIATION OF CLINCAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE MANAGEMENT OF DIABETES MELLITUS

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **CI** = confidence interval; **GDM** = gestational diabetes mellitus; **HbA_{1c}** = hemoglobin A_{1c}; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **LOE** = level-of-evidence; **NPH** = neutral protamine Hagedorn; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus; **VLDL-C** = very low-density lipoprotein cholesterol

1. INTRODUCTION

1.1. Forward

In 2001, the American College of Endocrinology (ACE) launched the first in a series of conferences to address the important and growing epidemic of diabetes mellitus in the United States and worldwide. The position statements and recommendations resulting from these conferences have articulated the need and laid the groundwork for more intensive inpatient and outpatient management of diabetes mellitus (1,2). Other consensus conferences have addressed the need for improved patient safety and early identification and treatment of the insulin resistance syndrome, a precursor for diabetes mellitus and cardiovascular disease (3,4).

1.2. Specific Mission and Methods

Given the complex and diverse nature of diabetes management, evidence-based clinical practice guidelines are vital to a clinician's ability to effectively treat this disease. The purpose of the recommendations herein is to provide clinicians with clear and accessible guidelines to care for patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). To facilitate ease of use and to enhance clinical utility, this clinical practice guideline is organized by topic; each topic section contains: (a) a general overview of information necessary to interpret the specific recommendations; (b) a succinct executive summary of graded recommendations based on clinical evidence and various subjective factors; and (c) evidence base and clinical considerations that include detailed discussion of the supportive clinical evidence and specific subjective factors (5). Ratings of the clinical evidence derived from each reference are noted next to the citations at the end of each topic section. Target audiences for this clinical practice guideline include: (a) endocrinologists; (b) cardiologists; (c) physicians who specialize in caring for patients with diabetes mellitus or who encounter patients with diabetes mellitus in their practice; and (d) other health care practitioners who wish to learn about diabetes care in the context of endocrinology, metabolism, and nutrition.

The American Association of Clinical Endocrinologists (AACE) Diabetes Mellitus Clinical Practice Guidelines Task Force is composed of endocrinologists who are experts and practitioners in the field of diabetes. The task force members spend more than 50% of their practice in the area of diabetes, and they are active members of AACE. Each contributor has published in the field of diabetes and is active in one or more of the main medical societies committed to diabetes care in the United States and internationally.

Task force members reviewed selected reports and studies and rated the clinical evidence from these sources. A summary of the methods used to prepare these guidelines is presented in Figure 1.1. A separate panel composed of AACE members with expertise in diabetes reviewed the compiled report. Final recommendations included in this clinical practice guideline represent a consensus among the task force members and have been approved by reviewers, the AACE Publications and Executive Committees, and the AACE Board of Directors. Comments and recommendations regarding physician-patient communication are based on expert judgment of task force members.

The available scientific literature cited in these guidelines was reviewed and evaluated for strength of evidence based on 4 level-of-evidence (LOE) categories described in Table 1.1. The evidence categories were adapted from the American Association of Clinical Endocrinologists Protocol for the Standardized Production of Clinical Practice Guidelines (5). References with clinical evidence are accompanied by a LOE assignment following citation in the reference list. References were obtained by performing a computerized search of the literature using PubMed and other search engines; scanning incoming

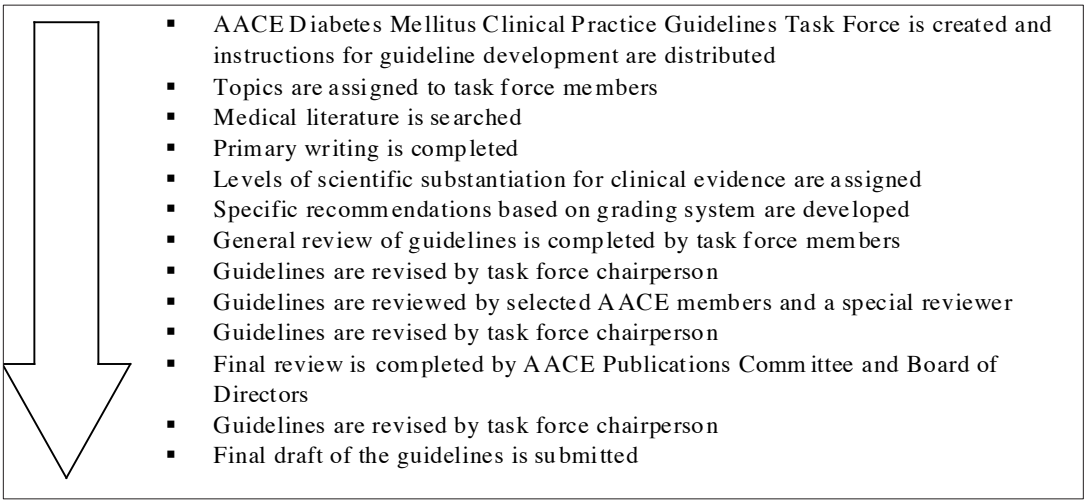

Figure 1.1. Methods used to prepare the American Association of Clinical Endocrinologists (AACE) Medical Guidelines for the Management of Diabetes Mellitus.

journals in the medical library; and reviewing references in publications relevant to diabetes including review articles, leading textbooks, and syllabi from national and international meetings.

LOE 1 data are defined as conclusive results from prospective, randomized controlled trials that have large subject populations representative of the target population and results that are easily generalized to the target population (5). LOE 1 data also include results from meta-analyses of randomized controlled trials, results from multicenter trials, and "all or none" evidence. *LOE 2* data include conclusive results from individual randomized controlled trials that have limited subject numbers or target population representation. *LOE 3* data include all other conclusive clinical findings from nonrandomized studies, studies without controls, and nonexperimental or observational studies (eg, well-documented case reports). Although LOE 3 data may be predicated on sound theory, these data require interpretation and, by themselves, are not compelling. *LOE 4* data are defined as information based solely on experience or expert opinion and are not necessarily substantiated by any conclusive scientific data. Frequently, only LOE 4 data are available.

When possible, clinical recommendations put forth in this clinical practice guideline have been assigned a letter grade (A-D) based on the level of scientific substantiation (Table 1.2). However, when task force members determined that clinical judgment regarding a recommendation outweighed study findings or a recommendation lacked supporting studies, they assigned the final grade based on their extensive clinical experience and expertise in diabetes management. An *A* grade is the strongest recommendation, and a *D* grade is the weakest recommendation. These recommendations include subjective components such as: (a) judgment regarding whether results from a particular study are conclusive; (b) the relative weighing of positive and negative conclusive study results; (c) assignment of evidence rating when certain study methodologies are controversial; (d) the impact of risk-benefit analysis; (e) the impact of cost-effectiveness; (f) assessment of geographical differences in practice standards and availability of certain technologies; (g) assessment of ethnic, racial, and genetic differences in pathophysiology; (h) incorporation of patient preferences; and (i) incorporation of physician preferences.

Criticism that purely evidence-based clinical practice guidelines do not reflect real life because subjective input is stifled or precluded is addressed to some extent by the AACE methodology for developing the guidelines. When the task force members judged that subjective factors influenced the grade of a recommendation to an extent that outweighed the available best evidence, this logic was explicitly described in the detailed discussion that follows each topic section's executive summary. Thus, the process of developing evidence-based recommendations and the incorporation of subjective components are transparent to the reader.

These methods, nevertheless, have the following shortcomings: (a) reliance on some subjective measures, which compromises reproducibility; (b) dependence on the best available evidence, even if only one study is used to formulate a recommendation grade; and (c) dependence on task force primary authors to perform a comprehensive literature search. Multiple levels of review by both AACE-credentialed and non–AACE-credentialed experts from academia and clinical practice backgrounds serve to address these predicted shortcomings.

Table 1.1. Levels of Substantiation in Evidence-Based Medicine[a]

Level-of-Evidence Category[b]	Study Design or Information Type	Comments
1	Randomized controlled trials Multicenter trials Large meta-analyses with quality ratings	Well-conducted, well-controlled trials at 1 or more medical centers Data derived from a substantial number of trials with adequate power; substantial number of subjects and outcome data Consistent pattern of findings in the population for which the recommendation is made—generalizable results Compelling nonexperimental, clinically obvious evidence (eg, use of insulin in diabetic ketoacidosis); "all or none" evidence
2	Randomized controlled trials Prospective cohort studies Meta-analyses of cohort studies Case-control studies	Limited number of trials, small number of subjects Well-conducted studies Inconsistent findings or results not representative for the target population
3	Methodologically flawed randomized controlled trials Nonrandomized controlled trials Observational studies Case series or case reports	Trials with 1 or more major or 3 or more minor methodologic flaws Uncontrolled or poorly controlled trials Retrospective or observational data Conflicting data with weight of evidence unable to support a final recommendation
4	Expert consensus Expert opinion based on experience Theory-driven conclusions Unproven claims Experience-based information	Inadequate data for inclusion in level-of-evidence categories 1, 2, or 3; data necessitates an expert panel's synthesis of the literature and a consensus

[a]Adapted from the American Association of Clinical Endocrinologists Protocol for the Standardized Production of Clinical Practice Guidelines (5).
[b]Level-of-evidence categories 1 through 3 indicate scientific substantiation or proof; level-of-evidence category 4 indicates unproven claims.

1.3. Background

1.3.1. Rationale for Aggressive Diabetes Management

Diabetes mellitus is a worldwide epidemic that has created a crisis for the health care system and society. Recent findings from large randomized controlled trials provide clear and compelling evidence that intensive treatment of diabetes mellitus and conditions known to be risk factors can significantly decrease the development and/or progression of chronic complications (6-10). Nathan and colleagues (11) report that early and aggressive glycemic control in patients with T1DM lowers the risk for cardiovascular disease by 50%. There is no glycemic threshold for the reduction of complications; the better the control, the lower the risk (9). Results from numerous studies have demonstrated the importance of maintaining normoglycemia during severe infections, cerebral ischemia, and perioperative periods, thus indicating a clear need to

Table 1.2. Recommendation Grades in Evidence-Based Medicine[a]

Grade	Description
A	Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power ≥1 conclusive level-of-evidence category 1 publications demonstrating benefit>>risk
B	Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis No conclusive level-of-evidence category 1 publication; ≥1 conclusive level-of-evidence category 2 publications demonstrating benefit>>risk
C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive level-of-evidence category 1 or 2 publication; ≥1 conclusive level-of-evidence category 3 publications demonstrating benefit>>risk No conclusive risk at all and no conclusive benefit demonstrated by evidence
D	Not rated No conclusive level-of-evidence category 1, 2, or 3 publication demonstrating benefit>>risk Conclusive level-of-evidence category 1, 2, or 3 publication demonstrating risk>>benefit

[a]Adapted from the American Association of Clinical Endocrinologists Protocol for the Standardized Production of Clinical Practice Guidelines (5). See Table 1.1 for descriptions of level-of-evidence categories.

initiate better management of diabetes and hyperglycemia in patients who are hospitalized (12-20).

New pharmacologic therapies and treatment technologies safely and effectively lower glycemia to near-normal levels. In addition to new rapid-acting and long-acting insulin analogs, new medications have been introduced to address recently identified pancreatic-hormone and incretin-hormone deficiencies. These new medications, and similar therapies in development, effectively lower hemoglobin A_{1c} (HbA_{1c}) levels, thereby reducing intraday glycemic variability and reducing weight (21,22). Advances in blood glucose monitoring and continuous monitoring of interstitial glucose, along with the introduction of "smart" insulin pumps, provide clinicians and patients with powerful tools to monitor and adjust treatment regimens (23-26).

Despite these new treatments and a broader understanding of the importance of effective disease management, diabetes control in US patients has deteriorated over the past decade. Koro et al (27) report that the percentage of patients with T2DM with HbA_{1c} levels of less than 7% decreased by approximately 20% from 1988 to 2000. In academic-based health care settings, only 7% of patients with T1DM or T2DM achieve the 3 recommended goals for glycemia, lipids, and blood pressure (28). Clearly, earlier and more aggressive application of available treatments and technologies is needed.

1.3.2. Epidemiology of Diabetes Mellitus

An estimated 20.8 million Americans (7% of the US population) have diabetes mellitus (29). Approximately 14.6 million people have been diagnosed with the disease, and 6.2 million remain undiagnosed. Approximately 41 million Americans have prediabetes mellitus, a condition that may progress to clinical diabetes if not detected and treated early (29). The age-adjusted prevalence of diagnosed diabetes mellitus increased among both sexes and all racial groups examined from 1980 through 2004

(29). For individuals born in the year 2000, the estimated lifetime risk for developing diabetes (T1DM or T2DM) is 33% for males and 39% for females (29). The risk for death among individuals with diabetes mellitus is almost twice that of individuals without diabetes of similar age (29). For patients diagnosed before age 40 years, the average reduction in life expectancy is 12 years for men and 19 years for women (30).

Adults aged 65 to 74 years have the highest prevalence of diabetes mellitus—approximately 12 times the prevalence of that seen in adults younger than 45 years (29). Of individuals 60 years or older in the United States, 10.3 million (20.9% of this age group) have diabetes mellitus. Of all individuals 20 years or older, 10.9 million men (10.5%) and 9.7 million women (8.8%) have diabetes mellitus (29). Findings from recent reports indicate that up to 45% of newly diagnosed cases of diabetes among US children and adolescents are classified as T2DM (31). The prevalence of T2DM among American children is expected to continue to increase and exceed that of T1DM over the next 10 years (32).

The latest data (2005) from the Centers for Disease Control and Prevention show a dramatic increase in the prevalence of diabetes mellitus in the United States; it is much higher in certain ethnic populations (29). For example, non–Hispanic black individuals and Mexican American individuals are 1.8 times and 1.7 times, respectively, more likely to have diabetes than non–Hispanic white individuals (29). Sufficient data are not yet available to calculate more precise estimates of the total prevalence of diabetes (both diagnosed and undiagnosed) for Hispanic and Latino populations other than Mexican American. American Indian and Alaska Native individuals are 2.2 times more likely to have diabetes than non–Hispanic white individuals (29). Based on available data, individuals of Asian, Native Hawaiian, and other Pacific Islander ancestry who are 20 years or older are more than twice as likely as non–Hispanic white individuals to have diagnosed diabetes (29). Diabetes mellitus prevalence data for individuals 20 years or older from selected US ethnic populations are listed in the following tabulation (29):

Ethnicity	No. (%) With Diabetes Mellitus
Non–white Hispanic	13 100 000 (8.7)
Non–Hispanic black	3 200 000 (13.3)
Hispanic/Latino American	2 500 000 (9.5)
American Indian and Alaskan Native	118 000 (15.1)

Although the age-adjusted prevalence of diagnosed diabetes mellitus increased among both sexes and all racial groups examined from 1980 through 2004, data show that minority populations are disproportionately affected by diabetes (29). During this time period, age-adjusted prevalence of diagnosed diabetes was higher among black individuals than white individuals and was the highest among black women (29). Age-adjusted prevalence increased 76% for white men, 65% for white women, 68% for black men, and 37% for black women (29). Among Hispanic individuals, the age-adjusted prevalence among men and women was higher in 2004 than in 1997 (29).

The prevalence of obesity among adults has risen notably in the United States during the past 20 years. The latest data from the National Center for Health Statistics show that more than 60 million Americans (30%) 20 years or older are obese (29). The percentage of young Americans who are overweight has more than tripled since 1980; approximately 9 million (16%) children, adolescents, and young adults 6 to 19 years of age are considered overweight (29). Among individuals with known diabetes, unfavorable upward trends in age-adjusted rates of being overweight or obese were observed between 1994 and 2003 (29). During that time, age-adjusted rates of obesity increased 15.2% (from 34.9% to 50.1%); the state of being overweight or obese increased 10.9% (from 69.7% to 80.6%) (29). The prevalence of obesity was greater among black individuals than among white and Hispanic individuals (29).

The association of schizophrenia and diabetes mellitus has been recognized since the turn of the last century (33). Although the reason for this association remains unclear, the etiology of diabetes in patients with schizophrenia is probably multifactorial; contributing factors may include weight gain, impaired lifestyle, and the medication used to treat schizophrenia. Increased visceral adiposity and hyperinsulinemia in the presence of elevated serum cortisol levels have been noted in a small group of treatment-naïve patients with schizophrenia (34). Until recently, patients with schizophrenia were not routinely screened for diabetes. Because they were not always able to obtain routine medical care, the diagnosis of diabetes was frequently delayed. Ongoing epidemiologic and pathophysiologic studies may help delineate the causes for this relationship and for the reported association of antipsychotic therapy and diabetes mellitus.

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2. SCREENING AND DIAGNOSIS

2.1. Executive Summary

- Annually screen all individuals 30 years or older who are at risk for having or developing T2DM (*grade B*) (See Table 2.1 for a list of risk factors and Table 2.2 for clinical interpretations of plasma glucose concentrations)
- Use 1 of the 3 diagnostic criteria presented in Table 2.3 to diagnose diabetes mellitus (*grade B*)
- ACE/AACE does *not* recommend using HbA_{1c} measurement to diagnose diabetes mellitus (*grade C*)
- Screen all pregnant women for gestational diabetes mellitus (GDM) (*grade A*); women at low risk should be screened at 24 to 28 weeks' gestation; women at high risk should be screened at 20 weeks' gestation (*grade B*) (See Table 2.4 for GDM risk factors and Table 2.5 for diagnostic criteria using a 75-g oral glucose tolerance test)

2.2. Evidence Base

Given the large number of Americans with undiagnosed diabetes mellitus and prediabetes mellitus, early detection and treatment is imperative to addressing the diabetes epidemic. ACE/AACE endorses the diagnostic criteria for diabetes mellitus and GDM as established by the World Health Organization (3). ACE/AACE endorses the diagnostic criteria for prediabetes mellitus as established by the American Diabetes Association (2). Table 2.6 lists diabetes mellitus classifications.

Table 2.1. Risk Factors for Prediabetes and Diabetes Mellitus (1)

Risk Factors
Family history of diabetes
Cardiovascular disease
Overweight or obese state
Sedentary lifestyle
Latino/Hispanic, Non–Hispanic black, Asian American, Native American, or Pacific Islander ethnicity
Previously identified impaired glucose tolerance or impaired fasting glucose
Hypertension
Increased levels of triglycerides, low concentrations of high-density lipoprotein cholesterol, or both
History of gestational diabetes
History of delivery of an infant with a birth weight >9 pounds
Polycystic ovary syndrome
Psychiatric illness

Table 2.2. Clinical Interpretations of Plasma Glucose Concentrations (2)

Glucose Concentration, mg/dL	Clinical Interpretation
Fasting	
<100	Within the reference range
100-125	Impaired fasting glucose/prediabetes mellitus
≥126	Overt diabetes mellitus
2-hour postchallenge load (75-g oral glucose tolerance test)	
<140	Within the reference range
140-199	Impaired glucose tolerance/prediabetes mellitus
≥200	Overt diabetes mellitus

Table 2.3. Diagnostic Criteria for Diabetes Mellitus[a] (3)

Diagnostic Criteria
Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) plus casual plasma glucose concentration ≥200 mg/dL
or
Fasting plasma glucose concentration ≥126 mg/dL
or
2-hour postchallenge glucose concentration ≥200 mg/dL during a 75-g oral glucose tolerance test

[a]One of the 3 criteria listed is sufficient to establish the diagnosis of diabetes mellitus. These assessments should be confirmed by repeated testing on a subsequent day in the absence of unequivocal hyperglycemia.

Table 2.4. Risk Factors for Gestational Diabetes Mellitus

Risk Factors
>25 years of age
Overweight or obese state
Family history of diabetes mellitus (ie, in a first-degree relative)
History of abnormal glucose metabolism
History of poor obstetric outcome
History of delivery of an infant with a birth weight >9 pounds
History of polycystic ovary syndrome
Latino/Hispanic, non–Hispanic black, Asian American, Native American, or Pacific Islander ethnicity
Fasting (no energy intake for at least 8 hours) plasma glucose concentration >85 mg/dL or 2-hour postprandial glucose concentration >140 mg/dL (indicates need to perform a 75-g oral glucose tolerance test) (4,5)

Table 2.5. Diagnostic Criteria for Gestational Diabetes Mellitus Using a 75-g Oral Glucose Tolerance Test[a] (2)

State at Plasma Glucose Measurement	Plasma Glucose Concentration, mg/dL
Fasting	>95
1-hour postglucose administration	>180
2-hour postglucose administration	>155

[a]Two or more of the listed venous plasma glucose concentrations must be met or exceeded for a positive diagnosis. The test should be performed after an overnight fast of 8 to 14 hours and after at least 3 days of unrestricted diet (ie, ≥150 g carbohydrate per day) and unlimited physical activity.

Table 2.6. Summary of Diabetes Mellitus Classifications (2)

Type 1 Diabetes Mellitus

- Accounts for only 5% to 10% of all diabetes mellitus cases
- Caused by an absolute deficiency of insulin secretion due to a cellular-mediated autoimmune destruction of the pancreatic β-cells
- Viruses associated with initiation of β-cell destruction include congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus, and mumps
- Markers of β-cell destruction include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β
- Rate of β-cell destruction varies—infants and children often experience rapid β-cell destruction; rate of destruction is usually slower in adults
- Individuals at increased risk can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islet cells and by genetic markers

Type 2 Diabetes Mellitus

- Accounts for 90% to 95% of all diabetes mellitus cases
- Caused by a combination of complex metabolic disorders that result from coexisting defects of multiple organ sites such as insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production, and other hormonal deficiencies
- Before the appearance of clinical symptoms, a degree of hyperglycemia may be present, causing pathologic and functional changes in various target tissues
- Most affected individuals are obese and, therefore, have variable degrees of insulin resistance; affected individuals who are not obese may have an increased percentage of visceral fat, which can cause insulin resistance
- Other risk factors include increasing age and sedentary lifestyle
- Occurs more frequently in women with previous gestational diabetes and in individuals with hypertension or dyslipidemia
- Associated with a strong genetic predisposition

Gestational Diabetes Mellitus

- Defined as any degree of glucose intolerance identified during pregnancy; definition applies regardless of the therapy used to treat the condition

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3. PREVENTION OF TYPE 2 DIABETES MELLITUS

3.1. Executive Summary

- Perform screening with either the 2-hour oral glucose tolerance test or fasting plasma glucose test to establish a diagnosis of diabetes mellitus or to identify prediabetes mellitus (*grade A*) (See Table 2.1 for risk factors indicating who should be screened)
- Initiate interventions that include lifestyle modifications (*grade C*):
    - Refer patients to a registered dietitian or credible weight loss program/service for counseling in energy intake reduction and nutritional strategies; goals include:
        - Weight reduction goal: 5% to10% of total body weight (*grade A*)
        - Nutrition goals: reduce fat intake to less than 30% of total energy intake; reduce saturated fat intake to less than 10% of total energy intake; and increase fiber intake to 15 g/1000 kcal or more (*grade A*)
- Prescribe regular physical activity (approximately 150 minutes per week) (*grade A*)
- Counsel patients with prediabetes mellitus about cardiovascular risk factors such as tobacco use, hypertension, and dyslipidemia (*grade A*)
- Treat hypertension and dyslipidemia aggressively; these conditions are responsive to lifestyle modification and to pharmacologic therapy (*grade A*)

3.2. Evidence Base

3.2.1. Overview

Prediabetes is the term that describes those metabolic states that occur when blood glucose levels are elevated but remain below levels that are established for the clinical diagnosis of diabetes mellitus. Prediabetes includes states of impaired fasting glucose or impaired glucose tolerance. In the absence of intervention, prediabetes often progresses to T2DM (1,2). Ethnic minorities in the United States are disproportionately affected by diabetes mellitus; however, once impaired glucose tolerance develops, ethnic background does not contribute further to the progression of diabetes (1).

Results from epidemiologic studies show that hyperglycemia is strongly associated with the subsequent development of cardiovascular disease and that patients with impaired glucose tolerance frequently have increased cardiovascular risk factors (3-5). Results from epidemiologic studies also show that postprandial hyperglycemia is a strong independent risk factor for cardiovascular disease (3). Clinically significant cardiovascular disease may develop years before the clinical onset of diabetes mellitus (3-5). When current glycemic goals are achieved early in the progression of the disease, β-cell function is preserved (6), and the patient gains residual long-term benefits in reducing vascular complications (7).

The 2-hour oral glucose tolerance test is more sensitive for diagnosing prediabetes than the fasting plasma glucose test (8), and it is the recommended screening method for this condition (9). However, because performing the oral glucose tolerance test is not always practical in an ambulatory care setting, the fasting plasma glucose test may be used to identify patients with impaired fasting glucose. Some patients with glucose intolerance will be missed by the fasting plasma glucose test because it is less sensitive than the 2-hour oral glucose tolerance test.

Results from large randomized controlled trials demonstrate the effectiveness of lifestyle interventions (with and without pharmacologic therapy) in preventing the progression of impaired glucose tolerance to T2DM (1,2). The development of T2DM can be delayed or prevented by modest weight loss (5% to 7% of total body weight) and regular physical activity (eg, 30 minutes of walking, 5 days a week) (1,2).

Results from clinical trials also show several pharmacologic agents to effectively reduce progression from impaired glucose tolerance to T2DM (1,6,10-16). Some of these agents include metformin (1), orlistat (12), acarbose (11), and troglitazone (6). Although troglitazone is no longer available, other thiazolidinediones with similar properties, such as rosiglitazone, have been studied (10). ACE/AACE does not advocate initiation of nonapproved pharmacologic therapy in patients with impaired glucose tolerance. However, study results suggest that reducing postprandial blood glucose concentrations may decrease cardiovascular events in patients with both impaired glucose tolerance and diabetes mellitus (7). Age-related differences in response to therapy are important factors to consider because weight loss in elderly patients, for example, may be deleterious.

3.2.2. Supporting Studies

Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medications Trial

The aim of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) trial (10) was to prospectively assess the ability of rosiglitazone to prevent T2DM in high-risk individuals. This randomized, placebo-controlled, multicenter study included 5269 adults 30 years or older who had impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease. Subjects were followed up for a median of 3 years. The primary outcome was a composite of the development of diabetes mellitus or the occurrence of death. At the end of the study, 59 subjects had dropped out from the rosiglitazone treatment group, and 46 subjects had dropped

out from the placebo group. The primary composite outcome developed in 306 (11.6%) of the 2635 subjects given rosiglitazone and in 686 (26%) of the 2634 subjects given placebo. Regression to normoglycemia occurred in 1330 (50.5%) of the 2635 subjects given rosiglitazone and in 798 (30.3%) of the 2634 subjects given placebo. The rate of cardiovascular events was similar in both subject groups; 14 (0.5%) of 2635 participants in the rosiglitazone treatment group and 2 (0.1%) of 2634 participants in the placebo group developed heart failure.

Diabetes Prevention Program Study

In the Diabetes Prevention Program (DPP) study (1), 3234 subjects with impaired glucose tolerance were randomly assigned to 1 of 3 groups: (a) lifestyle group—intensive nutritional and exercise counseling; (b) metformin treatment group—medication and standard diet and exercise; or (c) control group—placebo and standard diet and exercise. Compared with the control group after an average follow-up of 2.8 years, a 58% relative reduction in the progression to diabetes mellitus was observed in the lifestyle group, and a 31% relative reduction was observed in the metformin treatment group. Approximately 50% of subjects in the lifestyle group achieved a 7% or greater weight reduction in the first year and sustained a 5% total weight loss for the study's duration. Moderately intense activity of 150 minutes per week was maintained in 74% of subjects in the lifestyle group. Lifestyle modifications were most effective in subjects 60 years and older, and the development of diabetes mellitus was reduced by 71% in these participants. The effect of metformin treatment in reducing the risk for diabetes was most pronounced in younger, heavier subjects—those participants aged 25 to 40 years with a body mass index of 36 kg/m^2 or higher. The ethnicity of participants had no influence on the efficacy of the interventions.

Finnish Diabetes Prevention Study

In the large-scale Finnish Diabetes Prevention study of lifestyle intervention (2), 522 middle-aged obese subjects with impaired glucose tolerance were randomly assigned to receive either brief diet and exercise counseling (control group) or intensive personalized instruction on weight reduction and food intake and guidance on increasing physical activity (intervention group). After a mean follow-up of 3.2 years, a 58% relative reduction in the incidence of diabetes mellitus was observed in the intervention group compared with the control group. The ability to stop the progression to diabetes was strongly correlated with the degree to which subjects were able to achieve 1 or more of the following goals: (a) weight loss of more than 5% total body weight, (b) less than 30% of energy intake from fat; (c) less than 10% of energy intake from saturated fat; (d) fiber intake of 15 g/1000 kcal or more; and (e) more than 150 minutes of exercise per week.

Da Qing Impaired Glucose Tolerance and Diabetes Study

In the Da Qing Impaired Glucose Tolerance and Diabetes trial (17), 577 men and women with impaired glucose tolerance were randomly assigned to a control group or to 1 of 3 active treatment groups: (a) diet only, (b) exercise only, or (c) diet plus exercise. The cumulative incidence of diabetes mellitus after 6 years of follow-up was 67.7% in the control group compared with 43.8% in the diet-only group, 41.1% in the exercise-only group, and 46% in the diet-plus-exercise group ($P<.05$). The relative decrease in the rate of diabetes development in the active treatment groups was similar when subjects were stratified as lean (body mass index <25 kg/m^2) or as overweight (body mass index ≥25 kg/m^2). After adjusting for differences in baseline body mass index and fasting glucose concentration, the diet-only, exercise-only, and diet-plus-exercise interventions were associated with 31% ($P<.03$), 46% ($P<.0005$), and 42% ($P<.005$) reductions in risk of developing diabetes, respectively.

Study to Prevent Non–Insulin-Dependent Diabetes Mellitus

In the double-blind Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial (11), 1429 overweight and obese participants with impaired glucose tolerance were randomly assigned to receive either acarbose or placebo. After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes mellitus—based on results of a single oral glucose tolerance test—was observed in the acarbose treatment group compared with the placebo group. When the diabetes diagnosis was confirmed by results of a second oral glucose tolerance test, a 36% relative risk reduction was seen in the acarbose treatment group. The effect of acarbose treatment was consistent among all age groups, all ranges of body mass index values, and both sexes. A secondary analysis of the STOP-NIDDM data was performed to assess reductions in cardiovascular disease outcomes. After adjusting for the main cardiovascular disease risk factors, a 53% relative risk reduction in cardiovascular events was observed in subjects treated with acarbose. The findings from this trial demonstrate the importance of improving postprandial hyperglycemia.

Troglitazone in Prevention of Diabetes Study

The efficacy of troglitazone, a thiazolidinedione, in preventing T2DM was demonstrated by the findings of the Troglitazone in Prevention of Diabetes Study (TRIPOD) (6). A population of 235 Hispanic women with previous GDM was randomly assigned to receive placebo or troglitazone, 400 mg/daily. After a median follow-up of 30 months, the annual incidence of T2DM was 5.4% in the troglitazone treatment group and 12.1% in the placebo group. This translated to a 56% relative reduction in progression to diabetes mellitus in subjects treated with

troglitazone. Troglitazone improved insulin sensitivity and pancreatic β-cell function. After a washout period of more than 8 months, the preventive effects of the drug were still present. Although troglitazone was subsequently withdrawn from the market, 2 additional drugs in this class (pioglitazone and rosiglitazone) are available. The findings from the TRIPOD study suggest that thiazolidinediones may prevent diabetes mellitus rather than delay its onset.

XENical in the Prevention of Diabetes in Obese Subjects Study

The purpose of the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study (12) was to determine whether adding a weight-reducing agent to lifestyle modifications may lead to even greater weight loss, and thus further decrease the incidence of T2DM in obese patients. Participants had a body mass index of 30 kg/m^2 or higher; 79% had blood glucose concentrations in the reference range, and 21% had impaired glucose tolerance. In this 4-year, double-blind, prospective study, 3305 subjects were randomly assigned to 1 of 2 groups: (a) lifestyle changes plus orlistat treatment, 120 mg/daily or (b) lifestyle changes plus placebo, three times daily. Primary end points were time to T2DM onset and change in body weight. After 4 years of follow-up, the cumulative incidence of diabetes mellitus was 9% in the placebo group and 6.2% in the orlistat treatment group, which corresponds to a relative risk reduction of 37.3% (P = .0032). Results from analyses indicated that the preventive effect was demonstrated only in the subjects with impaired glucose tolerance.

Other Studies

Other studies of antihypertensive and lipid therapies in which the development of diabetes mellitus was a secondary end point have been conducted. Results from the Captopril Prevention Project (CAPPP Trial) (13) showed an average 14% (P = .034) reduction in the development of diabetes mellitus in subjects treated with captopril, an angiotensin-converting enzyme inhibitor, compared with subjects treated with a thiazide diuretic or a β_1-adrenoceptor antagonist. Findings from the Heart Outcomes Prevention Evaluation (HOPE) trial (14) showed a 34% (P<.001) reduction in the development of diabetes mellitus in subjects treated with ramipril, an angiotensin-converting enzyme inhibitor, compared with subjects given a placebo. In this study, assessing for diabetes development was a post hoc analysis. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (15) showed a 30% (P<.001) reduction in the development of diabetes mellitus in subjects treated with lisinopril, an angiotensin-converting enzyme inhibitor, compared with subjects treated with chlorthalidone, a monosulfamyl diuretic. The Losartan Intervention for End point Reduction in Hypertension study (LIFE) (16) showed a 25% (P<.001) reduction in the development of diabetes mellitus in subjects treated with losartan, an angiotensin receptor blocker, compared with subjects treated with atenolol, a β-adrenergic blocker. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, a large prospective randomized controlled trial with prevention of T2DM as the primary outcome, is in progress. Clearly, the development of new therapies that preserve β-cell function is desirable. The incretin mimetics and dipeptidyl-peptidase 4 inhibitors, new classes of drugs, may eventually prove to be effective in this capacity (18).

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4. GLYCEMIC MANAGEMENT

4.1. Executive Summary

4.1.1. All Patients With Diabetes Mellitus

- Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia (*grade A*); glycemic targets include:
    - HbA_{1c} ≤6.5% (*grade B*)
    - Fasting plasma glucose concentration <110 mg/dL (*grade B*)
    - 2-hour postprandial glucose concentration <140 mg/dL (*grade B*)
- Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy (*grade A*); education should:
    - Be provided by a qualified health care professional
    - Focus on all aspects of diabetes self-management relevant to each patient's treatment plan
    - Promote behavioral changes to support effective and consistent application of the prescribed diabetes treatment plan and an overall healthy lifestyle
    - Be continued as an ongoing intervention to accommodate changes in the treatment plan and patient status
- Initiate self-monitoring of blood glucose levels (*grade A*)

4.1.2. Patients With Type 1 Diabetes Mellitus

- Initiate intensive insulin therapy (*grade A*) (Table 4.1 describes the pharmacokinetics of available insulin preparations); regimen options include:
    - Basal-bolus therapy, using a long-acting insulin analog in combination with a rapid-acting insulin analog or inhaled insulin at meals
    - Continuous subcutaneous insulin infusion with an insulin pump; insulin pump therapy is indicated for:
        - Patients who are unable to achieve acceptable control using a regimen of multiple daily injections
        - Patients with histories of frequent hypoglycemia and/or hypoglycemia unawareness
        - Patients who are pregnant
        - Patients with extreme insulin sensitivity (pump therapy facilitates better precision than subcutaneous injections)
        - Patients with a history of dawn phenomenon (these patients can program a higher basal rate for the early morning hours to counteract the rise in blood glucose concentration)
        - Patients who require more intensive diabetes management because of complications including neuropathy, nephropathy, and retinopathy
        - Patients taking multiple daily injections who have demonstrated willingness and ability to comply with prescribed diabetes self-care behavior including frequent glucose monitoring, carbohydrate counting, and insulin adjustment
- Consider adding pramlintide to intensive insulin therapy to enhance glycemic control and to assist with weight management (*grade D*)

Table 4.1. Pharmacokinetics of Available Insulin Preparations (1)

Insulin, Generic Name (Brand)	Onset	Peak	Effective Duration
Rapid-acting			
Insulin aspart injection (NovoLog)	5-15 min	30-90 min	<5 h
Insulin lispro injection (Humalog)	5-15 min	30-90 min	<5 h
Insulin glulisine injection (Apidra)	5-15 min	30-90 min	<5 h
Insulin human (rDNA origin) Inhalation Powder (Exubera) (2)	5-15 min	30-90 min	5-8 h
Short-acting			
Regular	30-60 min	2-3 h	5-8 h
Intermediate, basal			
NPH	2-4 h	4-10 h	10-16 h
Long-acting, basal			
Insulin glargine injection (Lantus)[ab]	2-4 h[c]	No peak	20-24 h
Insulin detemir injection (Levemir)[ab] (3)	3-8 h	No peak	5.7-23.2 h
Premixed			
75% insulin lispro protamine suspension/25% insulin lispro injection (Humalog Mix 75/25)	5-15 min	Dual	10-16 h
50% insulin lispro protamine suspension/50% insulin lispro injection (Humalog Mix 50/50) (4)	5-15 min	Dual	10-16 h
70% insulin aspart protamine suspension/30% insulin aspart injection (NovoLog Mix 70/30)	5-15 min	Dual	10-16 h
70% NPH/30% regular	30-60 min	Dual	10-16 h

Abbreviation: NPH, neutral protamine Hagedorn
[a]May require 2 daily injections in patients with type 1 diabetes mellitus.
[b]Assumes 0.1-0.2 U/kg per injection. Onset and duration may vary significantly greatly by injection site.
[c]Time to steady state.

- Consider adding an insulin sensitizer to address insulin resistance as needed (*grade C*); exercise caution because of the potential for increased fluid retention when thiazolidinediones are used with insulin
- Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least 3 times daily (*grade A*)
- Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently; monitoring should include both preprandial and 2-hour postprandial glucose levels and occasional 2:00 AM to 3:00 AM glucose levels (*grade C*)
- Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump (*grade A*)
- Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving (*grade A*)
- Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is greater than 250 mg/dL (*grade C*)

4.1.3. Patients With Type 2 Diabetes Mellitus

- Aggressively implement all appropriate components of care (medical nutrition therapy, physical activity, weight management regimen, pharmacologic interventions, diabetes self-management education) at the time of diagnosis (*grade A*)

- Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved (*grade A*)
    - o First assess the patient's current HbA_{1c} level, fasting/preprandial glycemic profile, and 2-hour postprandial glycemic profile to evaluate the level of control and to identify patterns; this will require the patient to obtain comprehensive fasting, preprandial, and postprandial glucose readings over a 7-day period (*grade A*)
    - o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next 2 to 3 months until all ACE/AACE glycemic goals are achieved (*grade A*) (Table 4.2 shows examples of pharmacologic regimens that are intended to serve as starting points for selecting appropriate therapies. Tables 4.3, 4.4, 4.5, and 4.6 present information about new medications and currently available oral therapies.)
    - o If glycemic goals are not achieved at the end of 2 to 3 months of therapy, initiate a more intensive regimen and persistently monitor and titrate therapy over the next 2 to 3 months until all ACE/AACE glycemic goals are achieved (*grade A*)
    - o Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of their current medications or the addition of a second or third medication (*grade A*)
    - o Consider insulin therapy in patients with HbA_{1c} levels greater than 8% and symptomatic hyperglycemia and in patients with elevated fasting blood glucose levels or exaggerated postprandial glucose excursions regardless of HbA_{1c} levels (*grade A*)
    - o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when the HbA_{1c} level is greater than 10%; insulin treatment can then be modified or discontinued once glucose toxicity is reversed (*grade A*)
    - o Consider use of continuous subcutaneous insulin infusion in insulin-treated patients (*grade C*)
- Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least 3 times daily (*grade B*); although monitoring glucose levels at least 3 times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy
- Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump (*grade B*)
- Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least 2 times daily (*grade C*); there is no supporting evidence regarding optimal frequency of glucose monitoring in these patients
- Instruct patients who are meeting target glycemic levels (including those treated nonpharmacologically) to monitor glucose levels at least once daily (*grade D*)
- Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently; monitoring should include both preprandial and 2-hour postprandial glucose levels and occasional 2:00 AM to 3:00 AM glucose levels (*grade B*)
- Instruct patients to obtain comprehensive preprandial and 2-hour postprandial glucose measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect postprandial hyperglycemia, and to prevent hypoglycemia (*grade B*)
- Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving (*grade A*)
- Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is greater than 250 mg/dL (*grade C*)

4.2. Evidence Base

4.2.1. Overview

T1DM is characterized by an absolute deficiency in insulin secretion (61). T2DM is a progressive, complex metabolic disorder characterized by coexisting defects of multiple organ sites including insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production, and other hormonal deficiencies (62,63,67). Patients often develop T2DM 9 to 12 years before the disease is diagnosed (64). Findings from the United Kingdom Prospective Diabetes Study (UKPDS) show that affected individuals have already lost 50% of β-cell function at the time T2DM is diagnosed (65). Effective management of T2DM requires persistent monitoring and adjustment of therapy (66).

Table 4.2. Examples of Pharmacologic Regimens for Treating Type 2 Diabetes Mellitus[a]

Patients With Type 2 Diabetes Mellitus Naïve to Pharmacologic Therapy
Initiate monotherapy when HbA_{1c} levels are 6%-7%
Options include:
Metformin (5,6)
Thiazolidinediones (7,8)
Secretagogues (9-12)
Dipeptidyl-peptidase 4 inhibitors (13)
α-Glucosidase inhibitors (14,15)
Monitor and titrate medication for 2-3 months
Consider combination therapy if glycemic goals are not met at the end of 2-3 months
Initiate combination therapy when HbA_{1c} levels are 7%-8%
Options include:
Secretagogue + metformin (16,17)
Secretagogue + thiazolidinedione (18,19)
Secretagogue + α-glucosidase inhibitor (20)
Thiazolidinedione + metformin (21,22)
Dipeptidyl-peptidase 4 inhibitor + metformin (23)
Dipeptidyl-peptidase 4 inhibitor + thiazolidinedione (23)
Secretagogue + metformin + thiazolidinedione (24,25)
Fixed-dose (single pill) therapy
Thiazolidinedione (pioglitazone) + metformin (26)
Thiazolidinedione (rosiglitazone) + metformin (27)
Thiazolidinedione (rosiglitazone) + secretagogue (glimepiride) (28)
Thiazolidinedione (pioglitazone) + secretagogue (glimepiride) (29)
Secretagogue (glyburide) + metformin (30)
Rapid-acting insulin analogs or premixed insulin analogs may be used in special situations (31)
Inhaled insulin may be used as monotherapy or in combination with oral agents and long-acting insulin analogs
Insulin-oral medications; all oral medications may be used in combination with insulin; therapy combinations should be selected based on the patient's self-monitoring of blood glucose profiles
Initiate/intensify combination therapy using options listed above when HbA_{1c} levels are 8%-10% to address fasting and postprandial glucose levels
Initiate/intensify insulin therapy when HbA_{1c} levels are >10%
Options include:
Rapid-acting insulin analog or inhaled insulin with long-acting insulin analog or NPH (32,33)
Premixed insulin analogs (31,34)
Patients with Type 2 Diabetes Mellitus Currently Treated Pharmacologically
The therapeutic options for combination therapy listed for patients naïve to therapy are appropriate for patients being treated pharmacologically
Exenatide may be combined with oral therapy in patients who have not achieved glycemic goals
Approved exenatide + oral combinations:
Exenatide + secretagogue (sulfonylurea) (36)
Exenatide + metformin (37)
Exenatide + secretagogue (sulfonylurea) + metformin (38)
Exenatide + thiazolidinedione
Pramlintide may be used in combination with prandial insulin
Add insulin therapy in patients on maximum combination therapy (oral-oral, oral-exenatide) whose HbA_{1c} levels are 6.5%-8.5% (35)
Consider initiating basal-bolus insulin therapy for patients with HbA_{1c} levels >8.5%

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; NPH, neutral protamine Hagedorn.
[a]The options listed are in no order of preference.

Postprandial hyperglycemia, independent of HbA_{1c} levels, has been linked to the development of macrovascular disease (68,69). A strong association has also been shown between postmeal and postchallenge glycemia and cardiovascular risk and outcomes in individuals with normal glucose tolerance, impaired glucose tolerance, and diabetes mellitus (70-73). Causal relationships between postmeal hyperglycemia and known markers of cardiovascular disease (eg, oxidative stress, inflammation, intima-media thickness, endothelial dysfunction) have also been demonstrated (68,74-78). Conversely, effective management of postprandial glucose levels can reduce the risk of macrovascular disease (79-81), improve endothelial function (82), and reduce levels of methylglyoxal and 3-deoxyglucosone (83).

The therapeutic cornerstones to treat T1DM and T2DM are proper nutrition, exercise, education, and appropriate pharmacologic therapy (84). Early and aggressive management of glycemia by addressing mean glucose levels and glucose level variability, is vital to preventing or delaying the development of diabetic complications (79,85-88). Near-normalization of blood glucose concentrations in patients with T1DM can be achieved safely by intensive insulin therapy (89). Patients using insulin analogs (eg, lispro, aspart, glargine) in physiologic regimens, including patients with hypoglycemia unawareness, have fewer hypoglycemic episodes than patients using traditional insulins (eg, regular and neutral protamine Hagedorn [NPH]) (32,90). Intensive insulin therapy may reverse hypoglycemia unawareness in patients with T1DM (89) and can substantially prevent hypoglycemia and maintain target glycemic levels (89,91,92).

Insulin pump therapy is an effective alternative to multiple insulin injections in patients with diabetes mellitus (91). Results from studies have demonstrated that pump therapy can improve overall glucose control, reduce hypoglycemia, reduce hypoglycemia unawareness, reduce morning hyperglycemia due to the dawn phenomenon, and increase lifestyle flexibility (91-93). Children and adolescents have been successfully treated with insulin pump therapy (94).

Therapy should be tailored to the individual to maximize the likelihood of attaining and maintaining appropriate glycemic goals and to reduce the frequency of adverse effects (84). Near-normalization of blood glucose levels in patients with T2DM can be achieved safely by intensive combination therapy—either dual-oral or triple-oral combinations and/or oral-insulin combinations (95-98). The efficacy and safety of continuous subcutaneous insulin infusion with an insulin pump are comparable to multiple daily injection insulin therapy for patients with T2DM. Patients with T2DM can be taught as outpatients to use continuous subcutaneous insulin infusion and prefer this treatment modality over injections (99).

The rationale for the proposed use of the treatment regimens presented in Table 4.2 is derived from a new understanding of the variable relationship between fasting and postprandial glucose levels based on HbA_{1c} levels. As demonstrated by Monnier and colleagues (100), the relative contribution of fasting glucose levels to overall glycemia is approximately 70% in patients with HbA_{1c} levels greater than 10.2%. The contribution of fasting glucose to overall glycemia decreases to approximately 30% when HbA_{1c} levels are less than 7.3%. The contributions of fasting and postprandial glucose levels are approximately equal when HbA_{1c} levels are between 7.3% and 8.4% (100). Findings from a more recent study by Monnier and colleagues (101) show that postbreakfast glucose levels tend to be negatively affected first during the course of diabetes, thus suggesting that treatment efforts should initially target fasting glucose concentrations and then focus on reducing postmeal glucose concentrations. Given the emerging relationship between postprandial hyperglycemia and the development of macrovascular disease, it may be more prudent to address both fasting and postprandial abnormalities simultaneously with the understanding that therapies targeting postmeal glucose concentrations will become more effective as HbA_{1c} levels are reduced.

Results from several studies demonstrate the value of self-monitoring of blood glucose levels in the management of T1DM, T2DM, and GDM (85,102-108). Therapeutic management programs that include structured self-monitoring of blood glucose levels result in greater HbA_{1c} reduction in non–insulin-requiring patients with T2DM compared with programs that do not include self-monitoring of blood glucose levels (109-112). For example, findings from a recent meta-analysis show that interventions that include self-monitoring of blood glucose levels result in an HbA_{1c} level reduction of 0.40% compared with interventions that do not include self-monitoring of blood glucose levels; the HbA_{1c} reduction more than doubles when regular feedback is provided to patients (112). However, self-monitoring of urine glucose levels has not been as closely linked to improved outcomes (112). Therefore, urine glucose monitoring is not an appropriate method to assess glycemic control. The recommendations for how frequently patients should perform self-monitoring of blood glucose levels are adopted from the consensus statements created by an international panel of diabetes experts who conducted a conference to address the use of this management tool (113).

Managing diabetes mellitus requires a team approach to patient care. However, because diabetes is primarily a self-managed disease, education in self-management skills is essential in implementing interventions (84). Initial and ongoing self-management education must be made available to all patients with diabetes mellitus (114,115). Self-management education improves HbA_{1c} levels, and increased contact time with educators enhances the positive

Table 4.3. New Drugs to Treat Diabetes Mellitus

Drug Name, Generic (Brand)	Dosage	Comments
Pramlintide (Symlin) (39)	Type 1 Diabetes Mellitus Initiated at 15 μg and titrated at 15 μg increments to a maintenance dosage of 30 μg or 60 μg as tolerated Reduce preprandial, rapid-acting, or short-acting insulins, including fixed-mix insulins, by 50% Type 2 Diabetes Mellitus Initiated at 60 μg and increased to a dosage of 120 μg as tolerated Reduce preprandial, rapid-acting or short-acting insulin, including fixed-mix insulins, by 50%	Indicated as an adjunct treatment in patients taking prandial insulin who have not achieved desired glucose control Frequent monitoring of blood glucose levels is required to titrate dosage Contraindicated in patients with hypoglycemia unawareness or a diagnosis of gastroparesis
Exenatide (Byetta) (40)	Indicated as adjunct treatment to improve glycemic control in patients with type 2 diabetes mellitus who take metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, but who have not achieved adequate glycemic control Initiated at 5 μg per dose administered twice daily any time within 60 minutes before morning and evening meals Dosage can be increased to 10 μg twice daily after 1 month of therapy	Not a substitute for insulin in insulin-requiring patients Should not be used in patients with type 1 diabetes mellitus or to treat diabetic ketoacidosis Not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min/1.73m^2)
Sitagliptin (Januvia) (23)	Initial dosage: 100 mg once daily in the morning If creatinine clearance is 30 to 50 mL/min/1.73m^2, reduce dosage to 50 mg daily If creatinine clearance is <30 mL/min/1.73m^2, reduce dosage to 25 mg daily Maximum dosage: 100 mg once daily in the morning	Administer with or without food
Sitagliptin plus Metformin (Janumet)	Initial dosage: 50 mg/500 mg twice daily Maximum dosage: 50 mg/1000 mg twice daily	Administer with meals Not recommended for patients with severe renal disease

effect (116). Group-based teaching of patients with T2DM for self-management strategies improves fasting glucose and HbA_{1c} levels and increases knowledge of the disease; these improvements reduce the requirement for glucose-lowering medication (117-120).

4.2.2. Pathophysiology of Type 2 Diabetes Mellitus

T2DM is a complex metabolic disorder that results from coexisting defects at multiple organ sites including insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production, inappropriate glucagon secretion, diminished production of gastrointestinal incretins, and other hormonal deficiencies (62-64).

Insulin resistance initially occurs in skeletal muscle where greater concentrations of insulin are needed to transport glucose into cells. Insulin resistance in normoglycemic individuals predicts the development of T2DM (64,121) and is influenced by both genetic factors (122,123) and environmental factors such as obesity

and sedentary lifestyle. As insulin resistance increases, a compensatory increase in pancreatic insulin secretion allows the body to maintain normal glucose concentrations for a period of time. However, as the disease progresses, pancreatic β-cell function gradually diminishes.

In addition to decreasing β-cell function, other hormonal deficiencies occur as T2DM progresses. With the discovery of the incretin hormones in the 1970s and the pancreatic hormone amylin in the 1980s, it is now understood that several hormones have roles in maintaining glucose homeostasis. Amylin and incretin hormones (ie, glucagon-like peptide 1, glucose-dependant insulinotropic polypeptide) are now recognized as influential factors in maintaining glucose homeostasis (62,124,125).

Glucose abnormalities are first demonstrated by postprandial hyperglycemia, which is caused by the loss of first-phase insulin secretion and reduced suppression of hepatic glucose output after meals due to insulin deficiency and glucagon excess (126). When hepatic glucose output exceeds glucose use, fasting hyperglycemia results (126).

Adipose tissue also has an important role in the pathogenesis of T2DM. Insulin resistance at the adipocyte level leads to unrestrained lipolysis and elevation of circulating free fatty acids. This increase in free fatty acids, in turn, further diminishes the skeletal muscle insulin response (127,128) and β-cell function while prompting increased hepatic glucose production (129). The ensuing glucose toxicity that results from unrestrained hyperglycemia further reduces insulin sensitivity and pancreatic insulin secretion.

4.2.3. Medications

The following text describes the oral medications currently available. Table 4.6 presents information about the effect of oral medications on HbA_{1c} levels when used as monotherapy and in various combinations.

Secretagogues

Sulfonylureas

Sulfonylureas lower blood glucose levels by increasing insulin secretion from the pancreatic β-cells. By binding to sulfonylurea receptors on the surface of pancreatic β-cells, these agents cause the voltage-dependent potassium adenosine triphosphate channels to close, which facilitates cell-membrane depolarization, calcium entry into the cell, and insulin secretion (130). Sulfonylurea therapy reduces HbA_{1c} levels by 1% to 2% (9,10).

Although optimal dosing of sulfonylureas varies by agent, the glucose-lowering effect usually plateaus at approximately one half of the maximum recommended dose (10,54). Because most sulfonylurea agents are metabolized by the liver and cleared by the kidney, they should be used cautiously in patients with hepatic or renal impairment. Sulfonylureas are approved for use as monotherapy and in combination with most other oral drug classes and insulin; they are not approved for use in combination with glinides.

Glinides

Glinides employ a mechanism of action similar to sulfonylureas to facilitate glycemic control; however, they have a much shorter metabolic half-life. Glinides stimulate a rapid but short-lived release of insulin from pancreatic β-cells that lasts 1 to 2 hours (75). When taken at meals, these agents attenuate postprandial glucose excursions and decrease the risk of hypoglycemia during the late postprandial phase because less insulin is secreted several hours after the meal (11,132). Therefore, use of glinides should target postprandial blood glucose levels rather than fasting blood glucose levels.

Two glinides are commercially available: nateglinide and repaglinide. Results from studies show the efficacy of repaglinide to be similar to that of sulfonylureas (11,12); nateglinide appears to be somewhat less potent (133,134). Glinides are metabolized by the liver and cleared by the kidney and should be used with caution in patients with hepatic or renal impairment. However, repaglinide is only minimally cleared by the kidney and can, therefore, be used safely in patients with even severe renal impairment.

Biguanides

Metformin

The precise mode of action of metformin is not fully understood; however, its primary effect is to reduce hepatic glucose production in the presence of insulin (5,135). Metformin has been shown to lower HbA_{1c} levels by 1% to 2% (16,55-57,136,137). Monotherapy with metformin is associated with weight loss (or no weight gain) and much less hypoglycemia than sulfonylurea therapy (5,6). Metformin confers other nonglycemic benefits such as decreasing low-density lipoprotein cholesterol (LDL-C) levels, triglyceride levels, and the antifibrinolytic factor plasminogen activator inhibitor 1 levels (16,129,138). Data from the United Kingdom Prospective Diabetes Study (UKPDS) show that patients treated with metformin experience less hypoglycemia and weight gain than those treated with sulfonylureas (137).

Adverse effects of metformin include gastrointestinal distress such as abdominal pain, nausea, and diarrhea. These effects occur in up to 50% of patients; however, their frequency can be minimized with slow titration of therapy and food consumption (139). Metformin should not be used in patients who are at increased risk for lactic acidosis because of renal impairment. Metformin use should also be avoided in patients with hepatic dysfunction, congestive heart failure, metabolic acidosis, dehydration, and alcoholism. In addition, metformin should be temporarily withheld in patients with acute illness or those undergoing radiocontrast studies or surgery. Metformin is approved for use as a monotherapy and in combination with

Table 4.4. Oral Hypoglycemic Agents

Drug Name, Generic (Brand)	Initial Dosage	Maximum Dosage	Comments
Thiazolidinediones[a]			
Pioglitazone (Actos) (41)	15 or 30 mg once daily	45 mg once daily	Administer with or without food
Pioglitazone + Metformin (ActoPlus Met) (26)	If inadequately controlled on metformin monotherapy: Either 15 mg/500 mg or 15 mg/850 mg once daily or twice daily If initially responsive to pioglitazone monotherapy or switching from combination therapy of pioglitazone + metformin as separate tablets: Either 15 mg/500 mg twice daily or 15 mg/850 mg once daily or twice daily		Indicated for patients: (a) with type 2 diabetes mellitus treated with combination pioglitazone + metformin, (b) with glycemia not adequately controlled with metformin alone, (c) initially responsive to pioglitazone alone but require additional glycemic control Dosage schedule based on current dose of each component Consider administering in divided daily doses with meals to reduce the gastrointestinal adverse effects associated with metformin
Rosiglitazone (Avandia) (42)	4 mg once daily or 2 mg twice daily	8 mg once daily or 4 mg twice daily	Administer with or without food
Rosiglitazone + Metformin (Avandamet) (27)	2 mg/500 mg twice daily	4 mg/1000 mg twice daily	Dosage schedule based on current dose of each component Administer with meals
Rosiglitazone + glimepiride (Avandaryl) (28)	4 mg/1 mg or 4 mg/2 mg once daily	8 mg rosiglitazone and 4 mg glimepiride	Administer with first meal of the day
Biguanides[b]			
Metformin (Glucophage) (43)	500 mg twice daily or 850 mg once daily in the morning	2550 mg in 3 divided doses	Administer with meals Maximum effective dose is 2000 mg/d
Metformin extended release (Glucophage XR) (44)	500 mg once daily in the evening	2000 mg once daily	Increase dosage by 500 mg/d weekly If glycemic control not tightened, switch to twice daily regimen May have better gastrointestinal tolerance than immediate-release metformin
Glyburide + Metformin (Glucovance) (30)	1.25 mg/250 mg once daily or twice daily	20 mg/2000 mg divided daily	Starting doses should not exceed daily doses of glyburide or metformin already taken; dose increases can be made at 2-week intervals
Second Generation Sulfonylureas[c]			
Glyburide (DiaBeta) (45) (Micronase) (46)	1.25 to 5 mg once daily	20 mg in 1 or 2 divided doses once daily or twice daily	Administer once daily doses with breakfast or first main meal Doses >10 mg/d should be divided and given twice daily
Glipizide (Glucotrol) (47)	5 mg once daily; 2.5 mg once daily in elderly patients	40 mg in 2 divided doses	Administer once daily doses 30 min before breakfast or after first main meal Doses >15 mg/d should be divided and given twice daily
Glimepiride (Amaryl) (48)	1 to 2 mg once daily	8 mg once daily	Administer with breakfast or first main meal
Glinides (Short-Acting Secretagogues)			
Repaglinide (Prandin) (49)	Elderly patients and patients not previously treated with hypoglycemic agents or patients with hemoglobin A_{1c} <8%: Give 0.5 mg three times daily Patients previously treated with hypoglycemic agents or those with hemoglobin A_{1c} >8%: Give 1 to 2 mg three times daily	16 mg/d	Administer 15 to 30 min before each meal.
Nateglinide (Starlix) (50)	120 mg three times daily; 60 mg three times daily in elderly patients	120 mg three times daily	Administer 15 to 30 min before each meal
α-Glucosidase Inhibitors[d]			
Acarbose (Precose) (51)	25 mg three times daily	100 mg three times daily	Administer with first bite of each main meal Dosage should be gradually increased as tolerated over several weeks
Miglitol (Glyset) (52)	25 mg three times daily	100 mg three times daily	Administer with first bite of each main meal Dosage may be gradually increased as tolerated over several weeks

[a]Perform liver function tests at baseline followed by periodic monitoring; contraindicated in patients with New York Heart Association class III or IV cardiac disease and functional capacity; monitor for edema.
[b]Start with initial dose and titrate up slowly.
[c]Half maximum dose typically provides most of the benefit.
[d]Start with low dose and titrate up slowly.

sulfonylureas and other secretagogues, thiazolidinediones, and insulin. The combination of glyburide and metformin is more effective than either glyburide or metformin alone (16). Similarly, adding repaglinide to metformin therapy produces additional lowering of fasting plasma glucose levels by 40 mg/dL and HbA_{1c} levels by 1.4% (17).

Thiazolidinediones

The mechanism of action of thiazolidinediones is not fully understood. However, these drugs are known to exert direct effects on the liver and peripheral tissues, which are integrally involved in glucose production and uptake. Thiazolidinediones are pharmacological ligands for a nuclear receptor known as peroxisome proliferator-activated receptor γ. When activated, this receptor binds to response elements on DNA and alters transcription of various genes that regulate carbohydrate and lipid metabolism (140). Through this process, thiazolidinediones increase insulin-stimulated glucose uptake in skeletal muscle cells (141-143). Thiazolidinediones generally lower HbA_{1c} levels the same degree as metformin and sulfonylureas, and to a greater degree than α-glucosidase inhibitors (7,137,144).

The 2 thiazolidinediones currently available, rosiglitazone and pioglitazone, seem to have similar efficacy on glycemic control (7,8). In addition to lowering glycemia, these agents modestly reduce blood pressure (145,146), enhance fibrinolysis (147), and improve endothelial function. Both medications also confer benefits in increasing high-density lipoprotein cholesterol (HDL-C) concentrations and decreasing triglyceride concentrations (7,145). In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study (148), pioglitazone demonstrated modest improvement in the composite outcome of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with T2DM. However, this intervention did not show a significant relative risk reduction in the primary end point, which was a composite of all-cause mortality, nonfatal myocardial infarction, stroke, major leg amputation, acute coronary syndrome, cardiac intervention, and leg revascularization. Findings from the Carotid Intimal-Medial Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial (149) show that carotid artery intima-media thickness was significantly reduced in pioglitazone-treated patients compared with glimepiride-treated patients. Preliminary data from high-risk patient studies and in vitro rodent studies also suggest that thiazolidinediones may prevent β-cell apoptosis (150,151). Findings from the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) trial (152) demonstrate a significant (62%) reduction in the progression to diabetes mellitus in high-risk patients treated with rosiglitazone. Most recently, results from the A Diabetes Outcome Progression Trial (ADOPT) (153) show that treatment with rosiglitazone slows the rate of loss of β-cell function and improves insulin sensitivity to a greater extent than either metformin or glyburide.

Adverse effects of thiazolidinediones include weight gain, edema, anemia, and peripheral fractures in women. Weight gain and edema are more commonly seen in patients treated with thiazolidinediones and insulin. The Food and Drug Administration still recommends periodic measurement of hepatic function in patients treated with thiazolidinediones. Thiazolidinediones should not be used in patients with congestive heart failure (New York Heart Association class III or IV cardiac disease and functional capacity) or hepatic impairment.

Thiazolidinediones are indicated as monotherapy and in combination with metformin, sulfonylureas, and insulin (154). Additionally, combining 2 sensitizers from different drug classes (pioglitazone and metformin or rosiglitazone and metformin) produces an additive effect (21).

In a recent meta-analysis of 42 studies, Nissen and Wolski (155) report an increased risk for myocardial infarction in patients taking rosiglitazone compared with control patients (odds ratio, 1.43; 95% CI [confidence interval] 1.03-1.98; $P<.03$). The odds ratio for cardiovascular death was 1.64 (95% CI, 0.98-2.74; $P = .06$). Nissen and Wolski note several important limitations to their meta-analysis (155). An accompanying editorial in the *New England Journal of Medicine* implies that thiazolidinediones should not be used (156), while an editorial in the *Lancet* (157) recommends a balanced perspective until results from more studies become available. Definitive resolution regarding the magnitude and statistical and clinical significance of these findings will require a more sensitive "time-to-event" (life-table) analysis and the final results of the ongoing phase 3 trial (RECORD) to evaluate cardiovascular outcomes in patients receiving rosiglitazone; the latter is expected in 2009 (158). Interim analysis of the results of the RECORD trial with 4447 patients after 3.75 years of follow-up shows no statistically significant increased risk of myocardial infarction, cardiac death, or all-cause mortality in individuals receiving rosiglitazone (159). This has been called an inconclusive study due to the limited number of cardiac events observed to date (159). It also remains to be seen whether other thiazolidinediones are associated with increased cardiovascular risks.

α-Glucosidase Inhibitors

α-Glucosidase inhibitors provide postprandial glucose control by decreasing the absorption of carbohydrates from the gastrointestinal tract. These agents work by inhibiting α-glucosidase, an enzyme located in the proximal small-intestinal epithelium that breaks down disaccharides and more complex carbohydrates. Through competitive inhibition of this enzyme, α-glucosidase inhibitors delay intestinal carbohydrate absorption, thus attenuating postprandial glucose excursions (8,160). α-Glucosidase inhibitor therapy reduces HbA_{1c} levels by approximately 0.5% to 1.0% compared with HbA_{1c} levels of placebo-treated patients; the drugs' greatest effect is on postprandial glucose excursions (14,15). Adverse effects of

α-glucosidase inhibitors include flatulence, diarrhea, and abdominal discomfort; slow titration may attenuate these gastrointestinal adverse effects over time. α-Glucosidase inhibitors are approved for use as monotherapy and in combination with sulfonylureas.

Amylin Analog

Pramlintide

Pramlintide is a synthetic analog of human amylin, a naturally occurring hormone that is cosecreted with insulin by the pancreatic β-cells (124). Pramlintide is an antihyperglycemic drug used as an adjunct therapy in patients with diabetes mellitus who use prandial insulin and who have failed to achieve desired glycemic control. Amylin has neuroendocrine actions that regulate glucose influx including suppression of glucagon, slowing of gastric emptying, and a potential effect on feeding behavior and weight control (161). Findings from clinical studies demonstrate that pramlintide, a self-administered injection given before meals, helps patients achieve lower blood glucose levels after meals, which leads to less glycemic fluctuations during the day, improved weight control, and better long-term glucose control (HbA_{1c} levels) compared with patients taking insulin alone (162-165). On average, patients in these studies required less prandial insulin and also had a reduction in body weight compared with patients taking insulin alone (161,166). Patients treated with pramlintide should reduce rapid-acting or short-acting insulin dosages (including fixed-mix insulins) by 50%. Frequent monitoring of blood glucose levels is needed, and the dosage must be titrated. Pramlintide is contraindicated in patients with hypoglycemia unawareness or a diagnosis of gastroparesis.

Incretin Mimetics

Exenatide

Exenatide is the first in a new class of drugs, incretin mimetics, for the treatment of T2DM, and it exhibits many of the same effects as the human incretin hormone glucagon-like peptide 1 (167). Glucagon-like peptide 1, secreted in response to food intake, has multiple effects on the stomach, liver, pancreas, and brain that work in concert to regulate blood glucose (125). Exenatide was approved by the Food and Drug Administration for the treatment of T2DM in patients who have not achieved glycemic goals using metformin, a sulfonylurea, or both (168). Exenatide is indicated for combination therapy with a secretagogue (sulfonylurea) (36), metformin (37), a secretagogue (sulfonylurea) plus metformin (38), and a thiazolidinedione with or without metformin.

Incretin mimetics mimic the antidiabetic or glucose-lowering actions of naturally occurring human hormones called incretins. These actions include stimulating insulin production and response to elevated levels of blood glucose, inhibiting the release of glucagon after meals, slowing the rate at which nutrients are absorbed, and increasing satiety (167).

In vitro and in vivo animal models suggest that glucagon-like peptide 1 promotes proliferation and neogenesis from precursor β-cells (167,169); however, this has not yet been demonstrated in humans treated with glucagon-like peptide 1 or exenatide.

Dipeptidyl-Peptidase 4 Inhibitors

Dipeptidyl-peptidase 4 inhibitors exert their action in part by slowing the inactivation of incretin hormones glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide by dipeptidyl-peptidase 4, which increases the concentrations of these intestinally produced hormones that are decreased in patients with T2DM (170). Incretin hormones increase insulin synthesis, stimulate glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and increase satiety (171). Dipeptidyl-peptidase 4 inhibitors preferentially target postprandial glucose excursions, but have also been shown to decrease fasting plasma glucose levels.

Sitagliptin

Sitagliptin has been approved for use as monotherapy (13) and in combination with metformin (171) or a thiazolidinedione (173). Dipeptidyl-peptidase 4 inhibitors have few adverse reactions (23). Results from a randomized, multicenter study of 1172 patients who had failed to achieve satisfactory glycemic control being treated with metformin alone show that sitagliptin is comparable to glipizide in reducing HbA_{1c} levels over 52 weeks of follow-up (174). Sitagliptin treatment results in significant weight loss, in contrast to the weight gain associated with glipizide treatment. The occurence of hypoglycemia in subjects treated with sitagliptin plus metformin is less than one sixth as frequent as that in subjects treated with glipizide plus metformin (174). Another dipeptidyl-peptidase 4 inhibitor, vildagliptin, is currently under review by the Food and Drug Administration (175).

Inhaled Insulin

The first commercial preparation of inhaled insulin was introduced in 2006 as an alternative to traditional insulin injection and continuous subcutaneous insulin infusion. This preparation consists of human insulin inhalation power, which is administered using an inhaler.

The inhaled insulin preparation has an onset of action similar to rapid-acting insulin analogs with a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin (176). Inhaled insulin can be used in combination with long-acting analogs to treat hyperglycemia in patients with T1DM and can be used as monotherapy or in combination with oral agents and long-acting insulin analogs to treat patients with T2DM. Inhaled insulin is contraindicated in patients who

Table 4.5. Considerations for Oral Therapy in Patients With Type 2 Diabetes Mellitus (53)

Drug Class	Primary Mechanism	Possible Adverse Effects	Monitoring[a]	Comments
Sulfonylureas	Stimulates insulin release	Hypoglycemia Weight gain	Fasting plasma glucose at 2 weeks HbA_{1c} at 3 months	Response plateaus after half maximum dose Glipizide and glimepiride may be preferred in elderly patients
Biguanides	Inhibits hepatic glucose output	Dose-related diarrhea (usually self-limiting in 7-10 days) Lactic acidosis in patients with renal compromise	Serum creatinine at initiation Fasting plasma glucose at 2 weeks HbA_{1c} at 3 months	Less associated weight gain than with sulfonylureas and thiazolidinediones; weight loss may occur; helps limit weight gain in combination therapy Maximum effective dosage is 2 g/d Contraindications: Serum creatinine >1.5 mg/dL (men), >1.4 mg/dL (women) Congestive heart failure drug therapy Hepatic disease Alcohol abuse
α-Glucosidase Inhibitors	Delays carbohydrate absorption to decrease postprandial hyperglycemia	Dose-related diarrhea, abdominal pain, flatulence	PPG at initiation HbA_{1c} at 3 months	Administer with first bite of each meal Use slow titration to avoid gastrointestinal adverse effects (eg, 25 mg once daily for 2 weeks; then 25 twice daily for 2 weeks; then 25 mg three times daily for 8 weeks; maximum dosage is 100 mg three times daily) Must use glucose if hypoglycemia occurs
Thiazolidine-diones	Enhances insulin sensitivity	Edema Weight gain Congestive heart failure	AST and ALT at baseline Monitor for signs of fluid overload	Decrease in glucose may not be apparent for 4 weeks Maximum efficacy of dose may not be observed for 4-6 months Contraindications: ALT >2.5 times the upper limit of normal Hepatic disease Alcohol abuse NYHA class III or IV
Glinides	Stimulates insulin secretion	Hypoglycemia	Fasting plasma glucose at 2 weeks HbA_{1c} at 3 months PPG at initiation	Commonly used for basal-bolus dosing schedules
DPP-4 Inhibitors	Restores GLP-1 and GIP levels	Not clinically significant	PPG at initiation Fasting plasma glucose at 2 weeks HbA_{1c} at 3 months	Reduce dosage in patients with renal insufficiency No weight gain or markedly reduced incidence of hypoglycemia

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DPP-4 inhibitors, dipeptidyl-peptidase 4 inhibitors; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; HbA_{1c}, hemoglobin A_{1c}; PPG, postprandial glucose; NYHA, New York Heart Association cardiac disease and functional capacity.

[a]All measurements should be performed at the time noted after initiation of therapy and thereafter as directed by the patient's physician.

Table 4.6. Effect of Oral Therapies on Hemoglobin A_{1c} Levels in Patients With Diabetes Mellitus

Drug Therapy	Hemoglobin A_{1c} Reduction, %
Monotherapy	
Sulfonylureas	0.9 to 2.5 (10,54)
Biguanide (metformin)	1.1 to 3.0 (16,55-58)
Thiazolidinediones	1.5 to 1.6 (7,8,59)
α-Glucosidase inhibitors	0.6 to 1.3 (57,14,60)
Dipeptidyl-peptidase 4 inhibitors	0.8 (23)
Noninsulin Injectables	
Pramlintide	0.43 to 0.56 (39)
Exenatide	0.8 to 0.9 (40)
Combination Therapy	
Sulfonylurea + metformin	1.7 (16)
Sulfonylurea + rosiglitazone	1.4 (18)
Sulfonylurea + pioglitazone	1.2 (19)
Sulfonylurea + acarbose	1.3 (20)
Repaglinide + metformin	1.4 (17)
Pioglitazone + metformin	0.7 (21)
Rosiglitazone + metformin	0.8 (22)
Dipeptidyl-peptidase 4 inhibitor + metformin	0.7 (23)
Dipeptidyl-peptidase 4 inhibitor + pioglitazone	0.7 (23)

have smoked within the previous 6 months or who have unstable or poorly controlled pulmonary disease. Although hypoglycemia is the most common adverse event reported in all insulin therapy, the most common respiratory event experienced by patients in clinical trials of inhaled insulin was cough, which was predominantly mild in severity and decreased with continued use of the inhaled insulin preparation. The Food and Drug Administration mandates pulmonary function testing before initiation of therapy, 6 months after initiation of therapy, and on an annual basis thereafter.

4.3. Clinical Support

The following information is intended as assist clinicians in developing and implementing treatment strategies. The information is based on clinical experience and is not necessarily supported by the literature.

4.3.1. Initiating Insulin Therapy in Patients With Type 2 Diabetes Mellitus

A basal-bolus regimen (long-acting insulin analog with rapid-acting insulin analog or inhaled insulin at meals) is the most physiologic insulin regimen; however, many patients are reluctant to begin insulin therapy with this intensive approach (177). Instead, clinicians may consider starting with less intensive regimens and then adjust as needed. Common initial insulin regimens include:

- Long-acting insulin analog
- Long-acting insulin analog with rapid-acting insulin analog or inhaled insulin at largest meal of the day
- Once daily premixed insulin analog (intermediate-acting/rapid-acting insulin analog) at largest meal of the day
- Long-acting insulin analog with rapid-acting insulin analog or inhaled insulin twice daily (breakfast and supper)
- Premixed insulin analog or inhaled insulin twice daily (breakfast and supper)

An initial dose of 10 units per injection is a safe starting dose for once daily and twice daily subcutaneously administered insulin regimens. Clinicians should refer to prescribing information for inhaled insulin starting doses and titration. More than 90% of patients with T2DM are insulin resistant (178); therefore, much higher doses are often required to achieve glycemic targets (97).

When initiating insulin therapy, patients should measure blood glucose levels at least twice daily and provide self-monitoring of blood glucose data to the clinician weekly (more frequently, if needed); stepwise adjustments can then be made in response to glucose values. For intermediate-acting insulins:

- Adjustments in prebreakfast dosages are based on presupper glucose levels
- Adjustments in presupper dosage adjustments are based on prebreakfast glucose levels

Two-hour postprandial glucose should be measured and addressed if the HbA_{1c} level is elevated but premeal glucose levels are at target. Patients should also assess postprandial glucose levels periodically—even with favorable HbA_{1c} levels—to detect unrecognized exaggerated postprandial glucose excursions.

If a patient has not achieved glycemic goals after 2 to 3 months of therapy, or if recurrent hypoglycemia limits titration, the clinician should consider changing the regimen. The following recommendations are intended as guidelines for transitioning from less intensive to more intensive insulin regimens (177):

- Transition from a long-acting insulin analog to a premixed insulin analog twice daily:
    - Divide the total daily dose in half by giving one half before breakfast, the other half before supper; this new regimen should be started 18 to 24 hours after the last basal dose was given
    - Titrate to goal based on self-monitoring of blood glucose data and diet history; the largest meal will require a larger proportion of insulin
    - Reduce the total dose by 20% if the patient experiences recurrent hypoglycemia
- Transition from a once daily premixed insulin analog to a premixed insulin analog twice daily:
    - Divide the total daily dose in half by giving one half before breakfast, the other half before supper
    - Titrate to goal based on self-monitoring of blood glucose data and diet history; the largest meal will require a larger proportion of insulin
    - Reduce the total dose by 20% if the patient experiences recurrent hypoglycemia
- Transition from a long-acting insulin analog to addition of a rapid-acting insulin analog at largest meal:
    - Give 10% of the total daily dose as a rapid-acting analog at largest meal
    - Reduce the basal dose by 10%
- Transition from a premixed insulin analog twice daily to basal-bolus therapy (a long-acting insulin analog with a rapid-acting insulin analog at meals):
    - Divide the total daily dose in half
    - Initial basal insulin dose = (total daily dose / 2) × 80%
    - Initial prandial insulin dose = (total daily dose / 2) × percentage of estimated carbohydrates for each meal

4.3.2. Clinical Considerations

Type 1 Diabetes Mellitus

- Instruct patients to administer preprandial rapid-acting analog insulin 20 to 30 minutes before the meal when the premeal blood glucose level is high and after the meal has begun when the premeal blood glucose level is below the reference range
- Measure 2:00 AM to 3:00 AM blood glucose periodically in all patients with diabetes to assess for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated
- Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of postprandial and premeal glucose levels in patients with gastroparesis; insulin pump therapy may also be advantageous in these patients
- Some patients with T1DM treated with basal insulin may require 2, not 1, daily injections of basal insulin for greater stability
- Carefully assess postprandial glucose levels when the HbA_{1c} level is elevated and premeal glucose measurements are at target levels
- Instruct patients to assess postprandial glucose levels periodically to detect unrecognized exaggerated postprandial glucose excursions even when the HbA_{1c} level is at or near target
- Arrange for continuous glucose monitoring for patients with T1DM with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level; continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and postprandial hyperglycemia
- Some patients using pramlintide may achieve better postprandial and premeal glucose control by combining it with regular insulin rather than rapid-acting analogs
- Individualize insulin regimens to accommodate patient exercise patterns
- Treat hypoglycemic reactions with simple carbohydrates

Type 2 Diabetes Mellitus

- Combining therapeutic agents with different modes of action may be advantageous
- Use insulin sensitizers such as metformin and/or thiazolidinediones as part of the therapeutic regimen in most patients unless contraindicated or intolerance to these agents has been demonstrated

- Insulin is the therapy of choice in patients with advanced chronic kidney disease
- Metformin, thiazolidinediones, and incretin mimetics do not cause hypoglycemia; when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline
- The weight gain associated with thiazolidinediones in some patients may be partly offset by combination therapy with metformin
- Carefully assess postprandial glucose levels if the HbA_{1c} level is elevated and preprandial blood glucose measurements are at target levels
- Instruct patients to assess postprandial glucose levels periodically to detect unrecognized exaggerated postprandial glucose excursions even when the HbA_{1c} level is at or near target
- Individualize treatment regimens to accommodate patient exercise patterns
- Administer basal insulin in the evening if fasting glucose is elevated
- Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin

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5. HYPERTENSION MANAGEMENT

5.1. Executive Summary

- Aim for target blood pressure goals less than 130/80 mm Hg for management of hypertension in patients with diabetes mellitus (*grade A*)
- Use the following as first-line therapy for patients with diabetes mellitus: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in combination with a low-dose diuretic, calcium channel blocker, and/or third generation β-adrenergic blocker in addition to lifestyle modification (*grade A*)
- Individualize hypertension therapy for patients with diabetes mellitus according to the specific comorbidities and individual needs of the patient in consultation with the patient's physician (*grade A*)

5.2. Evidence Base

5.2.1. Overview

Hypertension represents a serious risk for developing the complications of diabetes mellitus because it amplifies the effects of hyperglycemia in producing microvascular complications. Hypertension is possibly a more clinically significant risk factor for macrovascular complications than hyperglycemia itself (1). Approximately 25% of individuals with T1DM and more than 50% of individuals with T2DM have hypertension. In the African American population, up to 14% of adults have T2DM associated with hypertension (2). Cardiovascular disease is the main cause of morbidity and mortality in patients with diabetes mellitus (2). The results of multiple large randomized controlled trials indicate that blood pressure control reduces morbidity and mortality (1). Therefore, controlling hypertension is critical in preventing myocardial infarction, stroke, and renal failure. ACE/AACE concurs with the target blood pressure goals of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (3) and the National Kidney Foundation (4). The literature is rich with large randomized controlled trials that assess outcomes of different pharmacologic interventions for treating hypertension. Summaries of clinical trial findings are presented in Tables 5.1 and 5.2.

5.2.2. Pathophysiology

In people with diabetes mellitus, hypertension is associated with insulin resistance and abnormalities in both the renin-angiotensin system and sympathetic tone, which result in vascular and metabolic consequences that contribute to morbidity. Metabolic abnormalities associated with diabetes mellitus contribute to endothelial dysfunction. Endothelial cells synthesize several potent bioactive substances that regulate blood vessel structure and function. These substances include nitric oxide, other reactive species, prostaglandins, endothelin, and angiotensin II (21). In individuals without diabetes, nitric oxide helps to inhibit atherogenesis and to protect blood vessels. However, the bioavailability of endothelium-derived nitric oxide is reduced in individuals with diabetes mellitus (22). Hyperglycemia inhibits production of endothelium-derived nitric oxide synthase activation and increases the production of superoxide anion, a reactive oxygen species that impairs nitric oxide formation (23). Nitric-oxide production is further impeded by insulin resistance, which causes excess release of free fatty acids from adipose tissue (24). Free fatty acids, in turn, activate protein kinase C, inhibit phosphatidylinositol-3, and increase reactive oxygen species production; all of these mechanisms directly affect nitric oxide production or decrease its bioavailability (25).

5.2.3. Pharmacology and Mechanisms of Action of Antihypertensive Agents

The use of specific antihypertensive agents may benefit patients with diabetes mellitus by providing renal protection as well as stabilizing the endothelium and reducing the risk of coronary artery disease. Comorbidities, such as congestive heart failure, and certain characteristics, such as ethnicity and drug tolerance, may influence the choice of antihypertensive agents. Study findings consistently indicate that combination therapy is generally required to achieve adequate blood pressure control and to improve clinical outcomes (7). Angiotensin-converting enzyme inhibitors and, in some cases, angiotensin receptor blockers improve cardiovascular and renal outcomes via an effect that is independent of blood pressure reduction (7,19,26).

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors suppress the biosynthesis of angiotensin II from its precursor, angiotensin I. The deleterious effects caused by excessive activation of the renin-angiotensin system at the molecular level and the benefit of regulating this system to reduce insulin resistance and to improve renal and cardiovascular outcomes is well demonstrated (7,14). Because angiotensin-converting enzyme inhibitors reduce the aldosterone response to sodium loss, they have an excellent synergistic effect with diuretics and are also effective as monotherapy. Hyperkalemia and a decline in renal function in patients with renal artery stenosis are concerns. Treating all middle-aged patients with T2DM who are able to tolerate angiotensin-converting enzyme inhibitors has been proposed to be cost effective (27). These agents in combination with diuretics may be required in some patients, particularly in elderly African American patients, to adequately control blood pressure (28).

Table 5.1. Primary Trials of Drug Efficacy in Hypertension Control in Patients With Diabetes Mellitus

Trial	Intervention and Primary Agents	Analysis Type	Relative Risk Reduction of Total Cardiovascular Events, %	Relative Risk Reduction of Total Mortality, %	Relative Risk Reduction of Microvascular End Points, %
SHEP (5)	Thiazide diuretic vs usual care	Subgroup	34	26	Not reported
Syst-Eur (6)	Calcium channel blocker vs placebo	Subgroup	62	41	Not reported
HOPE (7)	Angiotensin-converting enzyme inhibitor vs placebo	Subgroup	25	24	16
RENAAL (8)	Angiotensin II receptor blocker vs placebo	Primary	10[a]	-2[b]	21[c]
IPDM (9)	Angiotensin II receptor blocker vs placebo	Primary	Not reported	Not reported	70[d]
HOT (10)	Target diastolic blood pressure: <80 mm Hg or <90 mm Hg Agents: felodipine, then angiotensin-converting enzyme inhibitor or β-adrenergic blocker	Subgroup	51	44	Not reported
UKPDS (11)	Target blood pressure: <180/105 mm Hg vs <150/85 mm Hg Agent: captopril or atenolol	Primary	34[e]	18	37
ABCD (12)	Target diastolic blood pressure: 75 mm Hg vs 80 to 89 mm Hg Agent: nisoldipine or enalapril	Primary	No difference	49	No difference[f]

Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; HOPE, Heart Outcomes and Prevention Evaluation study; HOT, Hypertension Optimal Treatment; IPDM, Irbesartan in Patients with Type 2 Diabetes Mellitus and Microalbuminuria; RENAAL, Reduction of End Points in Non–Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; UKPDS, United Kingdom Prospective Diabetes Study.

[a]*P*>.2.

[b]Not significant.

[c]Renal outcomes (doubling of serum creatinine concentration and risk for end-stage renal disease).

[d]Comparison for 300-mg dose of irbesartan; 150-mg dose did not significantly reduce risk; risk is for progression of nephropathy.

[e]*P* =0.019.

[f]No combined end point reported. Relative risks for individual end points comparing intensive blood pressure control with moderate blood pressure control: progression from normoalbuminuria to microalbuminuria, 1.38 (95% confidence interval [CI], 0.84-2.27); progression from microalbuminuria to overt albuminuria, 0.70 (95% CI, 0.36-1.36); retinopathy progression, 0.88 (95% CI, 0.68-1.15); and neuropathy progression, 1.30 (95% CI, 1.01-1.66).

Table 5.2. Effects of Different Drug Classes in Patients With Diabetes Mellitus Treated for Hypertension

Trial	Intervention and Primary Agents	Analysis Type	Relative Risk Reduction of Total Cardiovascular Events, %	Relative Risk Reduction of Total Mortality, %	Relative Risk Reduction of Microvascular End Points, %
ABCD (12)	Enalapril vs nisoldipine	Primary	67	33	Not reported
FACET (13)	Fosinopril vs amlodipine	Primary	51	19	Not reported
CAPPP (14)	Captopril vs thiazide diuretic or β-adrenergic blocker	Subgroup	41	46	Not reported
UKPDS (11)	Captopril vs atenolol	Primary	-29[a]	-14[a]	-29[a]
NORDIL (15)	Diltiazem vs β-adrenergic blocker or diuretics	Subgroup	-1[a]	-7[a]	Not reported
INSIGHT (16)	Nifedipine GITS vs coamilozide	Subgroup	1	0.75	Not reported
STOP-2 (17)	Calcium channel blocker vs diuretics or β-adrenergic blocker	Subgroup	9	21	Not reported
	Angiotensin-converting enzyme inhibitor vs diuretics or β-adrenergic blocker		15	12	Not reported
	Angiotensin-converting enzyme inhibitor vs calcium channel blocker		6[b]	-14[a]	Not reported
IDNT (18)	Irbesartan vs placebo	Primary	9	8	20[c]
	Amlodipine vs placebo		12	12	-1[c]
	Irbesartan vs amlodipine		-3[a]	-4[a]	23[c]
LIFE (19)	Losartan vs atenolol	Secondary	24	0.61	Risk for microalbuminuria lower in the losartan group, (P = .002)
ALLHAT (20)	Lisinopril vs chlorthalidone	Secondary	-8[a]	-2[a]	Not reported
	Amlodipine vs chlorthalidone		-6[a]	4	Not reported

Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CAPPP, Captopril Prevention Project; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; GITS, gastrointestinal therapeutic system; IDNT, Irbesartan Diabetic Nephropathy Trial; INSIGHT, International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; LIFE, Losartan Intervention for End Point Reduction in hypertension study; NORDIL, Nordic Diltiazem study; STOP-2, Swedish Trial in Old Patients with Hypertension-2; UKPDS, United Kingdom Prospective Diabetes Study.

[a]Not significant.

[b]The risk for myocardial infarction in the angiotensin-converting enzyme inhibitor treatment group was 0.51 (95% confidence interval, 0.28-0.92) compared with the calcium channel blocker treatment group.

[c]Composite microvascular end point, doubling of serum creatinine concentration plus development of end-stage renal disease equals all-cause mortality; when assessed individually, only doubling of the serum creatinine concentration was significantly lower with irbesartan treatment compared with either placebo or amlodipine treatment.

Angiotensin Receptor Blockers

By blocking the effects of angiotensin II, angiotensin receptor blockers promote smooth-muscle relaxation, vasodilatation, renal salt and water loss, reduction in plasma volume, and decreased cellular hypertrophy (29). Other deleterious actions of angiotensin II, such as insulin resistance, endothelial dysfunction, and increased oxidative stress, are prevented by blockade of its receptor (30). Renal and cardiovascular outcomes are significantly improved by angiotensin receptor blockers as monotherapy (8) and in combination with angiotensin-converting enzyme inhibitors (31).

β-Adrenergic Blockers

β-Adrenergic blockers reduce myocardial contractility, cardiac output, and renin output. At higher doses, the reduction in blood pressure is effected via control of the central sympathetic nervous system, control of peripheral adrenergic neuron function, a change in baroreceptor sensitivity, and an increase in prostacyclin biosynthesis (29). β-Adrenergic blockers decrease myocardial oxygen consumption and myocardial use of free fatty acids (32). These agents also interfere with the recognition of and recovery from hypoglycemia, decrease pancreatic insulin release, and increase insulin resistance. However, the benefits of β-adrenergic blockers in reducing cardiac mortality in patients with diabetes mellitus usually outweigh their potential limitations (33). In the United Kingdom Prospective Diabetes Study (UKPDS), the use of β-adrenergic blockers conferred a level of protection comparable to that of angiotensin-converting enzyme inhibitors (34); however, accumulating literature strongly argues against using β-adrenergic blockers as first-line antihypertensive therapy.

Diuretics

Thiazide diuretics more effectively lower blood pressure than loop diuretics in patients with normal renal function. Peripheral vascular resistance is reduced by these agents because they reduce interstitial fluid volume and smooth-muscle sodium concentration (29). Although worsening hyperglycemia, increased insulin resistance, and elevations of LDL-C may occur, diuretics may be particularly useful in patients with congestive heart failure. Historically, diuretics have been considered superior first-line agents in African American patients; however, this concept has recently been challenged by an extensive review of the literature (35).

α-Adrenergic Blockers

Arteriolar resistance and venous capacitance are reduced with the vasodilatation produced by α-adrenergic blockers. Patients taking α-adrenergic blockers have a marked risk of orthostatic hypotension and an increased risk of congestive heart failure (24). Favorable effects on lipids include reduced total and LDL-C levels, reduced triglyceride levels, and increased HDL-C levels. α-Adrenergic blockers are generally reserved for combination therapy when other forms of treatment have failed (16).

Carvedilol

Carvedilol has nonselective β-blocking and α_1-blocking activity. It improves insulin resistance and lowers blood glucose concentrations. This agent is also beneficial in reducing the risk of microalbuminuria in the presence of renin-angiotensin system blockade. Deterioration of lipid parameters has not been reported with use of carvedilol (37). Results from long-term, randomized clinical outcome studies of carvedilol treatment in patients with hypertension and diabetes mellitus are not yet available.

Calcium Channel Blockers

Calcium channel blockers decrease peripheral resistance by inhibiting transmembrane movement of calcium ions. Reflex sympathetically mediated tachycardia may occur in patients treated with calcium channel blockers, but this finding is absent with verapamil and diltiazem because of their direct negative chronotropic effects. Dihydropyridine agents increase proteinuria; nondihydropyridines are less likely to have this effect (29). However, the nondihydropyridine verapamil confers no protection in patients with diabetes mellitus, hypertension, and no previous history of microalbuminuria when compared with an angiotensin-converting enzyme inhibitor (38).

Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers

Combination therapy with angiotensin-converting enzyme inhibitors and calcium channel blockers is superior in efficacy compared with β-adrenergic blockers and diuretics. Findings from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) (39), which followed 19 257 patients, show that patients treated with an angiotensin-converting enzyme inhibitor (perindopril) and a calcium channel blocker (amlodipine) experience significant reductions in cardiovascular mortality, all-cause mortality, myocardial infarction, and stroke compared with patients treated with a β-adrenergic blocker and a diuretic. The significant reduction in cardiovascular mortality and morbidity prompted an early discontinuation of the trial (39).

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6. LIPID MANAGEMENT

6.1. Executive Summary

- Aggressive management of dyslipidemia in patients with diabetes mellitus is critical; treat patients to achieve the following goals (*grade A*):
    - LDL-C <100 mg/dL (<70 mg/dL is recommended for patients with diabetes mellitus and coronary artery disease)
    - HDL-C >40 mg/dL in men and >50 mg/dL in women
    - Triglycerides <150 mg/dL
- Lifestyle modifications are essential (*grade D*)
- Statins are the pharmacologic treatment of choice (*grade A*)
- Use ezetimibe in patients who are intolerant of statins or in combination with statin therapy and other lipid-modifying agents (*grade B*)
- Combination therapy is indicated in patients who have not achieved the desired goals with monotherapy (*grade C*)
- Multiple options are available for combination therapy including statin plus fibrate, statin plus niacin, statin plus ezetimibe, statin plus bile-acid sequestrant, and statin plus omega-3 fatty acids (*grade C*)
- Use fibrates as primary therapy for patients with triglyceride levels greater than 400 mg/dL (*grade C*)
- Use fibrates cautiously in combination with statins because of the risk of rhabdomyolysis; this risk is markedly lower for fenofibrate than for gemfibrozil (*grade C*)
- Niacin may be a useful adjuvant when the primary abnormality is a low HDL-C level (*grade D*)
- Use low-dose aspirin prophylaxis routinely unless a specific contraindication is present; note that benefits may differ between women and men (*grade A*)

6.2. Evidence Base

6.2.1. Overview

Diabetes mellitus is a cardiovascular risk equivalent (1). In patients with T1DM and T2DM, the condition increases the occurrence of and accelerates the progression of coronary events, strokes, and peripheral arterial disease (2). Atherosclerosis occurs earlier in life, is more diffuse, and is associated with higher mortality rates in individuals with T1DM compared with the general population. Women with T1DM are more likely to die of coronary artery disease than women without diabetes (3). A primary goal is to reduce the LDL-C level to less than 100 mg/dL; however, ACE/AACE also endorses the more aggressive option of the National Cholesterol Education Program Adult Treatment Program III update—targeting the LDL-C goal of less than 70 mg/dL in high-risk individuals (4). In the Heart Protection Study (5), patients with diabetes mellitus older than 40 years who were treated with simvastatin (with the goal of reducing the LDL-C level by 30% from a baseline measurement) showed a 25% reduction in the first-event rate for major coronary artery events, independent of the baseline LDL-C levels.

The lipoprotein pattern in patients with diabetes mellitus is typically characterized by moderate elevation of triglyceride levels, low HDL-C levels, and small, dense LDL-C particles. These small, dense LDL-C particles are highly atherogenic because of their enhanced susceptibility to oxidation and increased uptake by the arterial wall (6).

Aggressive lipid management is critical to reduce morbidity and mortality. Preventive pharmacologic interventions have proved beneficial (eg, lipid-modifying agents, aspirin), and findings from randomized controlled

trials support the therapeutic recommendations as discussed in the following section. Certain lipid-modifying agents may be preferred in patients with diabetes mellitus because of the underlying pathophysiology and comorbidities. Lifestyle modifications including diet, weight management, exercise (7), and tobacco avoidance are of utmost importance.

Compared with individuals without diabetes, the long-term and short-term prognoses following a coronary event are worse in patients with diabetes mellitus. The rates of reinfarction, congestive heart failure, and death are increased compared with the general population, and risk of coronary disease is directly related to duration of diabetes (8,9). Revascularization procedures are less successful in patients with diabetes mellitus than in patients without diabetes (9). Diabetes blunts the beneficial effects of female sex, and the prognosis following an acute cardiovascular event is worse in women than in men (7). Ethnic differences in the risk of clinical coronary artery disease may exist in individuals with diabetes mellitus (10). Cardiovascular markers such as C-reactive protein and lipoprotein-associated phospholipase A_2 may potentially assist in identifying high-risk patients and in instituting preventive measures (11-13).

6.2.2. Rationale for Therapy

The characteristic dyslipidemia of T2DM includes elevated triglyceride levels, decreased HDL-C levels, and a preponderance of small, dense LDL-C particles that are highly atherogenic (6,9).

Cardiovascular fitness is associated with a lower risk for cardiovascular disease mortality in overweight and obese people with diabetes mellitus. Prospective observational data was obtained from the Aerobics Center Longitudinal Study, which evaluated 2316 men with diabetes mellitus who had no history of cardiovascular disease (14). The main outcome measure was cardiovascular disease mortality across levels of fitness with stratification by body mass index. A significantly higher mortality rate was observed in men with a low fitness level, regardless of weight.

6.2.3. Pathophysiology

Cardiovascular disease is the leading cause of morbidity and mortality in individuals with diabetes mellitus, and it accounts for approximately 80% of deaths in this population (15,16). Types of cardiovascular disease include coronary, cerebrovascular, and peripheral arterial disease. Diabetes is associated with an accelerated and diffuse process of atherosclerosis. Compared with individuals without diabetes, individuals with T2DM have a 2-fold to 4-fold higher incidence of coronary artery disease (16) and a 3-fold higher incidence of stroke (16-18). After sustaining a cardiovascular event, patients with diabetes have worse short-term and long-term prognoses compared with patients without diabetes (19-21). In addition, revascularization procedures and particularly percutaneous coronary intervention are less effective in patients with diabetes than in the nondiabetic population (22).

Atherosclerosis is an inflammatory disease (23,24). Endothelial dysfunction is an early manifestation of atherosclerosis, and it is eventually associated with plaque instability leading to cardiovascular events. Plaque morphology has an important role in diabetic atherothrombosis (25-27).

Hyperglycemia results in generation of reactive oxygen species that lead to increased oxidative stress and subsequent decreased nitric oxide bioavailability, activation of vascular angiotensin-converting enzyme, and vasoconstriction (28). Increased monocyte adhesion and migration into the vessel walls occurs by increasing endothelial expression of monocyte chemoattractant protein-1, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1. Hyperglycemia has been associated with increased oxidative stress, leading to the formation of advanced glycation end-products (29). These end-products bind to their receptors, leading to the activation of the transcription factor designated as nuclear factor–κB. Data suggest that large variability in glucose excursions causes oxidative stress (30,31).

6.2.4. Markers

The management of patients with diabetes mellitus involves estimating the risk of coronary artery disease and implementing appropriate risk reduction strategies. Use of biochemical markers associated with increased cardiovascular disease risk has been advocated (11,32).

C-Reactive Protein

C-reactive protein is considered an independent predictor of cardiovascular events; it is the most widely studied inflammatory marker (33,34). In patients taking statins, there is a relationship between the LDL-C level and the risk of cardiovascular events (11). There is also a relationship between higher C-reactive protein levels and increased risk of a cardiovascular event—this relationship is present regardless of the LDL-C level, and it is as strong as the relationship observed between LDL-C levels and risk of cardiovascular events (11).

Homocysteine

The mechanisms by which homocysteine potentially contributes to cardiovascular risk include increased oxidative stress, vascular smooth muscle proliferation, enhanced platelet aggregation, and activation of nuclear factor–κB. Findings from a meta-analysis of 27 studies indicate that elevated levels of homocysteine are associated with an increased risk of coronary artery disease, peripheral arterial disease, stroke, and venous thromboembolism (35). Mild to moderate elevation of homocysteine may contribute to the atherosclerotic process (36). However, increases in homocysteine levels have also been noted with

aging, menopause, hypothyroidism, low levels of vitamin B_6 and B_{12}, folate deficiency, and chronic kidney disease. Administration of supplements containing folic acid and vitamins B_6 and B_{12} is not cardioprotective (37,38).

Lipoprotein-Associated Phospholipase A_2.

Lipoprotein-associated phospholipase A_2 is an emerging independent specific risk marker for cardiovascular disease. This enzyme is secreted by inflammatory cells (eg, monocytes, macrophages, T lymphocytes) and may play a role in the progression of atherosclerosis (12,13,39). Lipoprotein-associated phospholipase A_2 is bound primarily to LDL-C and preferentially cleaves oxidized LDL-C, resulting in the formation of 2 inflammatory products—lysophosphatidylcholine and free oxidized fatty acids. These products exert an atherogenic effect by attracting monocytes and T lymphocytes to the atherosclerotic plaque and enhancing the expression of vascular cell adhesion molecules (12,13,39).

Fibrinogen

Fibrinogen is an important component of the coagulation pathway. Plasma levels of fibrinogen typically increase in patients with diabetes mellitus or adiposity, during advancing age or menopause, and in patients who smoke. Fibrinogen levels have been associated with several risk factors for coronary heart disease and peripheral arterial disease (40,41). Elevated plasma fibrinogen levels are predictive of stroke and myocardial infarctions (42).

Lipoprotein(a)

Lipoprotein(a) is associated with impaired fibrinolysis (43), vascular smooth muscle cell proliferation (44), and increased expression of intercellular adhesion molecule 1 in endothelial cells (45). Lipoprotein(a) is also associated with increased risk of cardiovascular events when plasma levels exceed 20 to 30 mg/dL (46).

Other Markers

Other potential markers include E selectin, vascular cell adhesion molecule, and tumor necrosis factor α. Elevated levels of cell adhesion molecules have been associated with diabetes mellitus and noted in people at increased risk for diabetes.

6.2.5. Cholesterol-Lowering Agents

Statins

Statins act as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase and thereby interfere with the hepatic biosynthesis of mevalonate, a precursor of cholesterol, which then reduces very low-density lipoprotein cholesterol (VLDL-C) secretion. An up-regulation of low-density lipoprotein receptors increases the clearance of LDL-C. Statins are associated with a low incidence of myopathy and elevation of liver enzymes. Concomitant use of certain drugs are contraindicated (eg, cyclosporins, erythromycin) because of increased risk of myopathy. Fibrates and niacin can be used with caution in combination therapy (47). Table 6.1 summarizes the findings from major clinical trials with statins.

Recently, Nicholls and colleagues (48) conducted a meta-analysis of 4 studies using the intravascular ultrasound technique to examine the relationship between changes in lipoprotein levels and coronary artery atheroma volume. They found that statins result in favorable changes in both LDL-C and HDL-C levels, and that both effects are independent predictors of the reduction in atheroma volume if the LDL-C level is reduced below 87.5 mg/dL and the HDL-C level is increased by more than 7.5%.

Fibric Acids

Fibric acids (fibrates) accelerate the degradation of lipoproteins by activating lipoprotein lipase and reducing hepatic apoprotein synthesis. They decrease endothelial cell activation by proinflammatory cytokines and reduce tissue factor production by human macrophages (49). Adverse effects from fibrates may include dyspepsia, gallstones, and myopathy. Table 6.2 summarizes the findings from major clinical trials with fibrates.

Ezetimibe

Ezetimibe selectively inhibits the absorption of dietary cholesterol from the gastrointestinal tract by action at the brush border of the small intestine. This reduces hepatic cholesterol stores and increases clearance of cholesterol from plasma.

Nicotinic Acid

Nicotinic acid (niacin) inhibits the hepatic synthesis of triglycerides and the secretion of VLDL-C by hindering the mobilization of free fatty acids. Niacin increases HDL-C levels and reduces cardiovascular morbidity and mortality (50). Adverse effects of niacin therapy include flushing, mild hyperglycemia, hyperuricemia, upper-gastrointestinal distress, and hepatotoxicity. Although use of niacin in patients with diabetes mellitus has been limited because of associated increased hyperglycemia, niacin therapy is safe and effective in this patient population (51).

Bile-Acid Sequestrants

Bile-acid sequestrants lower cholesterol levels by forming complexes with the cholesterol-containing bile acids in the gastrointestinal tract, interrupting the enterohepatic circulation of bile acids, and increasing hepatic conversion of cholesterol into bile acids. These agents are contraindicated in patients with hypertriglyceridemia, a common condition in people with diabetes mellitus.

Table 6.1. Major Clinical Trials Using Statins in Patients with Diabetes Mellitus

Trial	Medication (Dosage)	Mean Baseline LDL-C, mg/dL	No. Subjects	Outcome (Relative Risk Reduction)
4S (60)	Simvastatin (10-40 mg once daily by mouth)	186	202	Total mortality (43%) Major coronary heart disease event (55%)
CARE (5)	Pravastatin (40 mg once daily by mouth)	136	586	Major coronary heart disease event (13%) Expanded end point (25%)
HPS (61)	Simvastatin (40 mg once daily by mouth)	124	5963	Major coronary heart disease event (27%) Any major cardiovascular event (22%)
CARDS (62)	Atorvastatin (10 mg once daily by mouth)	117	2838	Acute coronary heart disease event (36%) Any major cardiovascular event (48%)
ASCOT-LLA (63)	Atorvastatin (10 mg once daily by mouth)	128	2532	Major coronary heart disease event (16%) Total cardiovascular events and procedures (23%)
PROVE-IT (64)	Pravastatin (40 mg once daily by mouth) vs atorvastatin (80 mg once daily by mouth)	…	4162 (diabetic and nondiabetic subjects)	Primary end point: death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke (16%) Secondary end point: death due to coronary heart disease, myocardial infarction, revascularization (25%)
TNT (65)	Atorvastatin (10 mg once daily by mouth vs 80 mg once daily by mouth)	<130	10 001 (diabetic and nondiabetic subjects)	First major cardiovascular event, defined as death from coronary heart disease, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke (22%, diabetic and nondiabetic subjects)
IDEAL (66)	Atorvastatin (80 mg once daily by mouth) vs simvastatin (20 mg once daily by mouth)	121	1069 diabetic subjects (8888 total)	Coronary death, acute myocardial infarction, cardiac arrest with resuscitation (11%, diabetic and nondiabetic subjects)
REVERSAL (67)	Atorvastatin (80 mg once daily by mouth) vs pravastatin (40 mg once daily by mouth)	150	654 (diabetic and nondiabetic subjects)	Intensively treated patients had no change in atheroma burden, whereas moderately treated patients showed progression
ASTEROID (68)	Rosuvastatin (40 mg once daily by mouth)	130	28 diabetic subjects (191 total)	Regression of coronary atherosclerosis determined by intravascular ultrasound (6.8%, median reduction)

Abbreviations: 4S, Scandinavian Simvastatin Survival Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events Trial; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; LDL-C, low-density lipoprotein cholesterol; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid Lowering; TNT, Treating to New Targets.

Table 6.2. Major Clinical Trials Using Fibrates in Patients with Diabetes Mellitus

Trial	Medication (Dosage)	No. Subjects	Outcome (Relative Risk Reduction)
VA-HIT (69)	Gemfibrozil (600 mg twice daily by mouth)	633 diabetic subjects (2531 total)	Acute coronary heart disease events (22%) Stroke (31%)
DAIS (70)	Fenofibrate (200 mg/d)	713	Acute coronary heart disease events (23%)
FIELD (71)	Fenofibrate (200 mg once daily by mouth)	9795	Acute coronary heart disease events (19%) Nonfatal myocardial infarction (24%)

Abbreviations: DAIS, Diabetes Atherosclerosis Intervention Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; VA-HIT, Veterans Affairs HDL Intervention Trial.

Plant Sterols and Stanols

Plant sterols and stanols displace cholesterol from bile-salt micelles, thereby reducing intestinal cholesterol absorption (52).

Omega-3 Fatty Acids

In high doses, omega-3 fatty acids reduce triglyceride levels. In addition, some evidence suggests that these fatty acids have direct cardioprotective effects. A meta-analysis of 97 studies involving more than 100 000 subjects found that cardiac mortality was reduced by 32% in subjects treated with omega-3 fatty acids (53).

Thiazolidinediones

Thiazolidinediones may decrease the concentration of small, dense LDL-C and increase the resistance of LDL-C to oxidation (54). This drug class is discussed in greater detail in Section 4**.**

6.2.6. Combination Therapy

Using combination therapy to lower cholesterol is logical for several reasons: (a) the various lipid-lowering medications have different mechanisms of action and differentially affect the lipid classes (ie, VLDL-C; LDL-C; HDL-C; triglycerides; small, dense LDL); (b) statins appear to have pleiotropic effects; and (c) patients often still have significant residual risks of atherogenesis and cardiovascular morbidity and mortality despite maximal dosage and effect of any one agent.

Statin + Fibrate

The combination of a statin and a fibrate reduces LDL-C and triglyceride levels and achieves a greater increase in HDL-C levels than either agent alone. The fibrates beneficially affect inflammation and thrombotic processes. Fenofibrate is associated with lower risk of myopathy than gemfibrozil, particularly when used in combination with statins. Gemfibrozil interferes with the glucuronidation of statins, leading to increased serum levels of the agent and hence increased risk of myopathy and hepatotoxicity. Simvastatin has been evaluated in combination with fenofibrate, and it shows greater reduction of triglyceride levels and greater increase in HDL-C levels than either agent alone (55).

Statin + Niacin

The combination of a statin and niacin has additive effects on increasing the HDL-C level, and it consistently reduces LDL-C and triglyceride levels. Findings from the High Density Lipoprotein Atherosclerosis Treatment Study (56) show a 90% reduction in composite cardiovascular end points for statin and niacin combination therapy compared with placebo.

The clinician must titrate niacin gradually to minimize the undesirable effects of flushing and to monitor blood glucose levels to ensure that the niacin does not deteriorate glycemic control. Myopathy occurring with the use of lovastatin and high doses of niacin (≥2.5 g/d) has been reported. Hepatotoxicity from high-dose niacin may cause decreased clearance of the statin, leading to increased risk of myopathy.

Statin + Ezetimibe

The combination of a statin and ezetimibe is convenient because a combination pill is available. Ezetimibe is effective when used alone, and findings from clinical trials

suggest a synergistic effect with simvastatin or atorvastatin. This observation allows the clinician to use a lower statin dosage to maintain the same level of LDL-C, while also achieving further gains in increasing HDL-C levels and possibly decreasing triglyceride levels (57).

The combination of a statin and ezetimibe has an excellent safety profile. Ezetimibe is also effective when combined with a bile-acid sequestrant (57). Coadministration of ezetimibe with statins is well tolerated and effective in lowering LDL-C levels in patients with diabetes mellitus (58). Specifically, combination therapy with ezetimibe and simvastatin is well tolerated and more effectively lowers LDL-C levels than increasing the simvastatin dosage in patients with T2DM who are also taking thiazolidinediones (59).

Statin + Omega-3 Fatty Acids

The combination of a statin and omega-3 fatty acids is an important option, especially in patients with hypertriglyceridemia. Omega-3 polyunsaturated fatty acids favorably affect platelet function, reduce platelet aggregation, exhibit antithrombotic and fibrinolytic activities, reduce blood viscosity, exhibit antiinflammatory action, and have other potentially beneficial effects. The recommended dosage of omega-3 fatty acids is 3 to 4 g/d. This treatment reduces the concentration of small, dense LDL-C and increases the HDL-C level; triglyceride levels are essentially unchanged (57).

6.2.7. Conclusions

We have witnessed tremendous advances in the ability to reduce cardiovascular morbidity and mortality in patients with diabetes mellitus. However, the average risk reduction is approximately 25% to 35%, and patients still have notable residual risk for cardiovascular disease. To achieve still greater risk reduction, more aggressive intervention at earlier stages in the disease process is necessary. The cornerstone of treatment is lifestyle modification including diet, weight reduction, exercise, and smoking cessation. Pharmacologic treatment should include statins that are effective in both primary and secondary prevention of cardiovascular events and in decreasing mortality in patients with diabetes mellitus. Fibrates also have beneficial effects, particularly by lowering triglyceride levels and increasing HDL-C levels. Niacin is indicated for increasing HDL-C levels, although it has been associated with a modest deterioration of glycemic control, which does not preclude its use. Intensive control of hypertension and glycemia is essential as addressed in other sections of this guideline. Aspirin should be included in the therapeutic regimen.

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7. NUTRITION AND DIABETES

7.1. Executive Summary

- Medical nutrition therapy is an essential component of any comprehensive diabetes mellitus management program (*grade A*)
- Meal composition affects glycemic control and cardiovascular risk (*grade A*)
- Tailor a diet for individual patients based on current weight, medication regimen, food preferences, lifestyle, and lipid profile (*grade A*)

- No specific diet is endorsed by ACE/AACE for people with diabetes mellitus (*grade D*)
- Total dietary carbohydrates should represent 45% to 65% of daily energy intake unless otherwise indicated (*grade D*)
- Protein intake should be the same as for patients who do not have diabetes mellitus: 15% to 20% of daily energy intake (*grade D*)
- Fiber should be consumed in amounts of 25 to 50 g/d or 15 to 25 g/1000 kcal ingested (*grade A*)
- Total dietary fat should generally comprise less than 30% of daily energy intake (*grade D*):
    - Dietary monounsaturated fatty acids and n-3 polyunsaturated fatty acids have beneficial effects on the lipid profile and should comprise most fat intake (*grade B*)
    - Dietary saturated fat should be limited to less than 10% of daily energy intake with less than 300 mg/d of cholesterol (*grade A*)
    - If the patient's LDL-C level is greater that 100 mg/dL, consumption of saturated fat should be limited to less than 7% of daily energy intake, and cholesterol should be limited to less than 200 mg/d (*grade A*)
    - *Trans*-fat intake should be minimized, or preferably, eliminated (*grade D*)
- Basal-bolus insulin therapy using insulin analogs or continuous subcutaneous insulin infusion in conjunction with carbohydrate counting is the most physiologic treatment and provides the greatest flexibility in terms of food choices and timing of meals (*grade B*)
- Basal-bolus therapy using a consistent carbohydrate meal plan can be equally effective for patients unable or unwilling to count carbohydrates (*grade D*)
- Instruct patients who choose to consume alcohol to limit intake to 1 drink per day for women and 2 drinks per day for men (*grade D*)
- Secondary prevention strategies for T2DM in individuals with impaired glucose regulation include a controlled-energy diet, exercise, and weight loss (*grade A*)
- Dietary modification to achieve target ranges for glucose, lipids, and blood pressure is a tertiary preventive strategy for the complications of diabetes mellitus (*grade A*)
- Restrict the following in patients with chronic kidney disease: sodium, 1.5 to 2.4 g/d; phosphate, 800 to 1000 mg/d (stages 3-5); potassium, 2 to 3 g/d (stage 5 on hemodialysis) and 3 to 4 g/d (stage 5 on peritoneal dialysis); and protein, 0.8 g/d (stages 1-2), 0.6 g/d (stages 3-4), 1.2 g/d (stage 5 on hemodialysis), and 1.3 g/d (stage 5 on peritoneal dialysis) (*grade A*)
- For optimal nitrogen retention, prescribe 1 daily multivitamin and a diet with adequate protein for patients with diabetes mellitus who have nonhealing wounds; consider additional micronutrients such as zinc and oral vitamins C and A depending on the severity of the wounds and the nutritional status of the patient (*grade D*)

7.2. Evidence Base

7.2.1. Overview

Fiber should be consumed in amounts of 25 to 50 g/d or 15 to 25 g/1000 kcal ingested (1). Dietary saturated fat contributes to cardiovascular risk (2). Dietary monounsaturated fatty acids and n-3 polyunsaturated fatty acids have beneficial effects on the lipid profile and should comprise most fat intake (3-6). Dietary saturated fat should be limited to less than 10% of total daily energy intake with fewer than 300 mg/d of cholesterol (2,6). If the patient's LDL-C level is greater than 100 mg/dL, saturated fat should be limited to less than 7% of total energy intake, and cholesterol should be limited to less than 200 mg/d (2). Currently, no nutraceuticals are supported by strong enough evidence to be recommended as first-line treatment for diabetes mellitus or its related complications (7).

7.2.2. Clinical Considerations

<u>All Patients With Diabetes Mellitus</u>

Carbohydrate absorption may be altered by other foods in a mixed meal. For example, fat (8,9) and fiber (10,11) delay the absorption of carbohydrates and blunt the glycemic response. Terms such as *simple sugars* and *complex carbohydrates* have recently been abandoned since it is now recognized that their effects on blood glucose are similar (12). Sucrose does not need to be avoided by patients with diabetes mellitus, but when it is consumed, it should replace other carbohydrates in the diet (12).

<u>Patients With Type 1 Diabetes Mellitus</u>

The key to successful medical nutrition therapy is synchronizing carbohydrate intake with insulin therapy. The use of basal-bolus insulin therapy using insulin analogs or continuous subcutaneous insulin infusion in conjunction with carbohydrate counting is the most physiologic treatment and provides the greatest flexibility in terms of food choices and timing of meals (11,13,14). For patients unable or unwilling to count carbohydrates, basal-bolus therapy using a consistent carbohydrate meal plan can be equally effective (15). Considering the glycemic index and the glycemic load of foods is another tool that can be used to optimally time the mealtime insulin injection (12). Restricting cow's milk during the first year of life (16) and avoiding vitamin D deficiency (17,18) in early life are associated with decreased risk of developing T1DM. Early exposure to wheat gluten (19) as well as nitrates and nitrites (20) may increase the risk for T1DM.

Patients With Type 2 Diabetes Mellitus

Weight control and a controlled-energy diet are essential components of diabetes mellitus management to lower glucose levels and to reduce the risk for cardiovascular disease (21); cardiovascular risk is lowest when the body mass index is less than 25 kg/m^2 (22). Physical activity of 30 to 90 minutes per day lowers glucose levels and assists with weight loss or weight maintenance (23). Salt restriction to less than 1.5 g/d, in association with increased intake of fresh fruits and vegetables, is helpful in managing hypertension (24). If patients choose to consume alcohol, intake should be limited to 1 drink per day for women and 2 drinks per day for men.

Increased intake of dietary saturated fat is associated with an increased risk for T2DM (25). Obesity is associated with decreased insulin sensitivity and increased risk for developing cardiovascular disease (22). Secondary prevention strategies for T2DM in individuals with impaired glucose regulation include a controlled-energy diet, exercise, and weight loss (26,27). Dietary modification to achieve target ranges for glucose, lipids, and blood pressure is a tertiary preventive strategy for the complications of diabetes mellitus (28).

Special Populations

Patients with chronic kidney disease require special attention to diet, including restrictions of sodium (29), phosphate (renal failure stages 3-5) (30), potassium (29), and protein (29). Patients with diabetes mellitus who have nonhealing wounds should take 1 daily multivitamin and adequate protein for optimal nitrogen retention; additional micronutrients, such as zinc and oral vitamins C and A, can be considered depending on the severity of the wounds and the nutritional status of the patient.

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8. MICROVASCULAR COMPLICATIONS

8.1. Executive Summary

8.1.1. All Patients With Diabetes Mellitus

- Encourage all patients to strive to achieve glycemic goals (*grade A*)
- Use results from postprandial glucose monitoring and the calculated standard deviation of downloaded meter results of self-monitoring of blood glucose when considering glycemic management strategies (*grade B*); evidence demonstrates that glycemic variability is an independent risk factor for microvascular disease (*grade B*)
- Consider preprandial and postprandial self-monitoring of blood glucose readings separately; adjust therapy if 25% of measurements exceed glycemic targets (*grade C*)
- Control other risk factors including (*grade A*):
    - Hypertension—treat blood pressure to the target of less than 130/80 mm Hg
    - Dyslipidemia—strive to achieve all lipid level goals
    - Smoking—refer patients to smoking cessation program as needed
    - Lifestyle—initiate weight reduction/control and individualized exercise regimen
- Select drug therapy with attention to cardiovascular risk (*grade A*)

8.1.2. Nephropathy

- Screen all patients with diabetes mellitus for chronic kidney disease annually; screening should begin 5 years after diagnosis in patients with T1DM and at the time of diagnosis in patients with T2DM (*grade A*). Testing includes:
    - Measurement of albumin-to-creatinine ratio in a spot urine specimen and measurement of the estimated glomerular filtration rate derived from serum creatinine
    - The following are diagnostic criteria for chronic kidney disease:
        - Estimated glomerular filtration rate <60 mL/min/1.73 m^2 or albumin-to-creatinine ratio ≥30 mg albumin/g creatinine
        - Microalbuminuria ≥30 mg albumin/g creatinine
        - Macroalbuminuria ≥300 mg albumin/g creatinine
- Prescribe an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker in the antihypertensive regimen in the absence of contraindications (*grade A*)
- Consider prescribing non–dihydropyridine calcium channel blockers, β-adrenergic blockers, or diuretics to manage blood pressure in the setting of albuminuria or nephropathy in patients unable to tolerate angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers; taking non–dihydropyridine calcium channel blockers may reduce albuminuria in patients with diabetes mellitus, including those patients who are pregnant (*grade C*)
- Reduce protein intake to 0.8 to 1.0 g/kg per day in patients who are in the earlier stages of chronic kidney disease and to 0.8 g/kg per day in patients who are in the later stages of chronic kidney disease (*grade B*)
- The diagnosis of anemia is established if the hemoglobin level is less than 13.5 g/dL in adult men and less than 12 g/dL in adult women (*grade B*)
- When the estimated glomerular filtration rate is less than 30 mL/min/1.73 m^2, refer patients for consultation and evaluation for renal replacement therapy by

a nephrologist (*grade B*); kidney transplantation, in-center hemodialysis, home hemodialysis, and peritoneal dialysis should be considered (*grade B*).
- Monitor diuretic and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy with periodic electrolyte measurement and estimation of glomerular filtration rate (*grade C*)
- Monitor intact parathyroid hormone levels for secondary hyperparathyroidism if the glomerular filtration rate is less than 60 mL/min/1.73 m^2 (*grade D*); consider treatment with paricalcitol (*grade D*)
- Monitor for anemia associated with chronic kidney disease (*grade B*)
- Use perioperative intravenous insulin infusion for glycemic control at the time of renal transplantation (*grade B*)
- ACE/AACE does not recommend pancreas-only transplantation for the isolated indications of retinopathy or neuropathy in patients without life-threatening or disabling metabolic complications of diabetes mellitus who do not require renal replacement therapy (*grade C*)

8.1.3. Retinopathy
- Refer the patient to a trained examiner (ophthalmologist and/or retinal specialist) for annual dilated retinal examination at the time T2DM is diagnosed, or 5 years after T1DM is diagnosed; annual examinations should be performed thereafter (*grade A*)
- Alternatively, the results from 7-field stereo color fundus photography or digital retinal imaging may be read by a qualified reading center, as long as the center operates under the direction of a medical director who is a retinal specialist (*grade B*)
- Promptly refer the patient to a retinal specialist if there is evidence that early retinopathy is progressing or if advanced retinopathy exists (*grade A*)

8.1.4. Neuropathy
- All patients with T2DM should be assessed for neuropathy at the time of diagnosis, and all patients with T1DM should be assessed 5 years after diagnosis (*grade A*); annual examinations should be performed thereafter in all patients. Screening may include:
    - History and examination eliciting signs of autonomic dysfunction
    - Testing for heart rate variability, if indicated, which may include expiration-to-inspiration ratio and response to the Valsalva maneuver and standing.
- Inspect the patient's feet at every visit; evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene (*grade B*)
- Perform an annual comprehensive foot examination (*grade B*); assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament
- Refer the patient to a qualified podiatrist, orthopedist, or neurologist if there is a lack sensation or mechanical foot changes (*grade C*)
- Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy (*grade C*)
- When treating patients with cardiac autonomic neuropathy, choose strategies appropriate for protection against cardiovascular disease (*grade A*)
- Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities (*grade C*)
- Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms (*grade C*)
- Maintain a referral network for podiatric and peripheral vascular studies and care (*grade C*)

8.2. Evidence Base

8.2.1. Overview

Control of hyperglycemia and nonglycemic risk factors for microvascular disease are essential for preventing and treating nephropathy, retinopathy, and neuropathy. Manifestations of microvascular disease may be demonstrable to the examiner before the patient experiences any symptoms. Therefore, a program of periodic preventive monitoring is necessary. Some prevention and treatment strategies are general for all microvascular disease, and other strategies are specific to each affected organ.

Kidney (1,2), retina (2,3), and nerve (4-6) are 3 tissues that exhibit microvascular complications (microangiopathy) of diabetes mellitus. Although these disorders are encompassed under a term that implies the presence of microvasculopathy, tissues affected by microvascular disease contain not only endothelium, pericytes, and capillary basement membranes, but also nonvascular cells at risk, such as the glial or neural elements of the retina and the axons or myelin sheath of nerve. The rationale for a screening program is based on the need to detect unsuspected asymptomatic disease that would be potentially responsive to specific therapy; the treatment goal is to interrupt progression or achieve reversal of the abnormality (7-9).

8.2.2 Glycemic Control

Tight glycemic control prevents the onset and progression of diabetic nephropathy, retinopathy, and neuropathy (10-14). To achieve the benefit of normoglycemia, there is no

threshold above a normal HbA_{1c} level (15). As a normal HbA_{1c} level is approached, postprandial glucose control becomes an increasingly dominant determinant of further improvement of the HbA_{1c} level (16).

Diabetic neuropathy can be classified in 2 categories: (a) generalized symmetric polyneuropathies including acute sensory, chronic sensorimotor, or autonomic; and (b) focal and multifocal neuropathies including cranial, truncal, focal limb, proximal motor, and coexisting chronic inflammatory demyelinating polyneuropathy (17). Painful neuropathy may occur in patients with impaired glucose tolerance, suggesting that postprandial hyperglycemia may be a pathogenetic mechanism of injury even in prediabetes mellitus (5,18). Therefore, postprandial glucose excursions should be considered a target of therapy. Duloxetine or pregabalin are safe and effective for treating diabetic neuropathic pain (3,4).

The extent of glycemic variability may be discerned not only by reviewing the patient's logbook data, but also by analyzing the downloaded meter readings at the time of office or clinic visits (19). The clinician can then calculate the standard deviation of glucose levels and compare it with normal values based on a larger patient population. See Section 4 for details regarding therapies for glycemic control.

Simultaneous pancreas and kidney transplant, pancreas-after-kidney transplant, and pancreas-alone transplant may help prevent progression of microangiopathy (20-22). Observationally, there is a narrow window of time in the immediate hours after kidney transplantation during which adequacy of glycemic control may determine the future risk for acute rejection and postoperative infection (23). If confirmed, this observation would create a strong argument for perioperative use of insulin infusion at the time of kidney transplant.

8.2.3. Interception of Downstream Metabolic Consequences of Hyperglycemia

Pharmacologic interruption of downstream biochemical pathways in conjunction with tight glycemic control may hold promise for the future of preventing and treating microangiopathy (24,25). Specific interventions may be envisioned to combat organ-specific pathogenetic mechanisms or vulnerabilities, such as the use of antagonists to vascular endothelial growth factor for retinopathy (26). Ruboxistaurin is an investigational protein kinase C inhibitor that is currently undergoing evaluation in clinical trials for retinopathy, nephropathy, and symptomatic neuropathy; however it has not yet received Food and Drug Administration approval (24,27,28).

8.2.4. Targeting Organ-Specific Nonglycemic Pathogenetic Mechanisms

Organ-specific pathogenetic mechanisms and vulnerabilities to nonglycemic abnormalities can amplify the risk of developing or experiencing progression of microvascular disease (29). These mechanisms include heritable variation in the angiotensin-converting enzyme gene, systemic hypertension, intraglomerular capillary pressure, glomerular hyperfiltration, smoking, dyslipidemia, and high-protein diet. All of these mechanisms may increase the risk of developing nephropathy (30,31). Vascular endothelial growth factors promote protein kinase C–β signaling in the retina (32). Hypertension and dyslipidemia may exacerbate diabetic retinopathy (33). Conventional macrovascular risk factors may increase the risk for neuropathy (34).

When hypertension is present in patients with T2DM, including an angiotensin-converting enzyme inhibitor in the antihypertensive treatment regimen is helpful for preventing or delaying the onset of nephropathy (35). Modifiable risk factors associated with regression of microalbuminuria include treatment of dyslipidemia and glycemic exposure (36). It is the standard of care to use angiotensin-converting enzyme inhibitors or angiotensin receptor blockers not only for hypertensive patients, but also for normotensive patients with early stage nephropathy (8,37-39). The potential indications for and complications of combination angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy deserve attention (40-42). Angiotensin-converting enzyme inhibitors delay the progression of nephropathy in patients with T1DM who have hypertension and any degree of albuminuria (8,43,44). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers slow the progression of microalbuminuria in patients with T2DM, hypertension, microalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL) (29,38,39,45). The analysis of a spot urine sample to assess the albumin-to-creatinine ratio is strongly recommended by most authorities (46,47). Protein restriction helps slow the progression of albuminuria, glomerular filtration rate decline, and occurrence of end-stage renal disease (48-50), particularly in patients whose nephropathy appears to be progressing despite optimal glucose and blood pressure control with use of an angiotensin-converting enzyme inhibitor and/or an angiotensin receptor blocker (51).

Anemia due to erythropoietin deficiency may occur early in the course of diabetic nephropathy. Anemia has been associated with myocardial infarction or fatal cardiovascular heart disease, stroke, and all-cause mortality (1,52-55). Treatment to achieve a hemoglobin concentration of 11 g/dL has been advocated for individuals with demonstrable deficiency of erythropoietin. Orthostatic hypotension sometimes is benefited by treatment (53). Caution must be exercised to select patients who show a need for replacement, to evaluate need for iron therapy, and to avoid exacerbation of hypertension or development of other therapeutic complications. The outcomes of erythropoietin treatment are presently being studied in the Anaemia CORrection in Diabetes (ACORD) trial (56).

Secondary hyperparathyroidism can be associated with chronic kidney disease in stage 3 and stage 4; paricalcitol decreases parathyroid hormone levels with no effect on

calcium and phosphorous levels (57). In the predialytic stage of chronic kidney disease, some patients with metabolic bone disease require treatment with vitamin D or its analogs. Some patients have frank deficiency of vitamin D and should first receive ergocalciferol replacement (57). For other patients, the comparative safety of replacement regimens with vitamin D analogs is unknown; however, analogs of vitamin D_2, such as paricalcitol, may exhibit superior safety compared with calcitriol when used in stage 3 and stage 4 of chronic kidney disease with respect to hypercalcemic episodes (58). Precautions of therapy include elevation of the calcium x phosphorus product, accelerated progression of renal failure, and the possibility of exacerbated vascular calcifications. Therapy is administered with consideration for the possible need for calcium supplementation and phosphate binder therapy. For patients receiving dialysis, treatment of secondary hyperparathyroidism and metabolic bone disease may require introduction of calcium, vitamin D analogs, and/or cinacalcet (59). Results from one published retrospective study in patients receiving dialysis suggest superiority of paricalcitol compared with calcitriol with respect to mortality and risk for hypercalcemia (60).

Treating retinopathy entails using laser and vitrectomy for specific indications (61-63). Digital retinal imaging system and 7-field stereo color fundus photography may be useful screening tools for diabetic retinopathy (64).

Symptomatic relief of neuropathic pain may be achieved by using tricyclic antidepressants and antiepileptics (27,65). Other treatment modalities have been reviewed (17). Drugs must be prescribed with knowledge of potential toxicities (17). Botanical preparations and dietary supplements have not been proved to confer benefit in treating neuropathic symptoms (66). Neuropathic foot ulcers are associated with increased morbidity and mortality (67). The presence of neuropathy predicts the occurrence of foot ulcers; the care of a podiatrist may reduce recurrent ulcers, and in collaboration with a vascular surgeon, reduce amputation risk (68-70). A multifaceted intervention for prevention may include the following: (a) requesting that patients remove their footwear at the time of examinations; (b) performing foot examinations; and (c) providing foot-care education (71,72).

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9. DIABETES AND PREGNANCY

9.1. Executive Summary

9.1.1. Provide Prepregnancy Counseling

- Identify the possibility of pregnancy annually by directly questioning all fertile women of childbearing age with diabetes mellitus; provide contraceptive advice when appropriate (*grade A*)
- Offer prepregnancy counseling to all women with diabetes mellitus who are considering pregnancy (*grade A*); counseling should address:
    - Information and skills relevant to the management of pregnancy in a woman with diabetes mellitus (*grade B*)
    - The need for optimal control of the HbA_{1c} level (<6%), if safely achievable, (*grade A*) and blood glucose concentration between 60 mg/dL (fasting) and 120 mg/dL (1 hour after a meal) (*grade A*)
    - The need for optimal blood pressure control (<130/80 mm Hg) (*grade A*)
    - The importance of a healthy lifestyle, including advice on nutrition, exercise, smoking cessation, and alcohol use (*grade B*)
- Discontinue oral glucose-lowering drugs and start insulin if needed (*grade A*)
- Discontinue angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; use methyldopa, hydralazine, nifedipine extended release, or labetalol (*grade A*)

- Discontinue statins and fibrates (*grade A*)
- Assess the patient for retinopathy, nephropathy, and thyroid function (*grade A*)
- Initiate folic acid supplementation to reduce the risk of neural tube defects (*grade A*)

9.1.2. Screen for Undiagnosed or New (Gestational) Diabetes During Pregnancy

- In all pregnant women, measure fasting glucose at the first prenatal visit (no later than week 20). Perform a 75-g oral glucose tolerance test if the fasting glucose concentration is greater than 85 mg/dL (*grade A*)
    - Initiate medical nutritional therapy immediately if the diagnosis of gestational diabetes is established (*grade B*)
    - Initiate insulin therapy if the patient is following an optimal diet but the self-monitored glucose levels reveal fasting glucose concentrations greater than 90 mg/dL and/or if postprandial glucose concentrations are greater than 120 mg/dL 1 hour after the first bite of food at each meal (*grade A*)

9.1.3. Diabetes Management Throughout Pregnancy

- Frequently assess the status of diabetes control, risk for and presence of diabetic complications, and the presence of other medical conditions (including weight gain) (*grade B*)
    - Strive for a HbA_{1c} level less than 6%; blood glucose concentrations should remain between 60 to 90 mg/dL (fasting) and less than 120 mg/dL (1 hour after the first bite of food at each meal) (*grade A*)
    - Monitor weight gain and blood pressure and advise and treat the patient accordingly; blood pressure should be maintained at less than 130/80 mm Hg, avoid using renin-angiotensin system blocking drugs (*grade A*)
- Persistently monitor and adjust insulin therapy to achieve all glucose targets (*grade A*)
    - Initiate a basal-bolus insulin regimen if a patient cannot maintain glucose targets with diet alone; this regimen may include either NPH insulin (basal) and rapid-acting insulin at meals or subcutaneous insulin infusion with an insulin pump (*grade B*)
    - Patients should intensively monitor blood glucose levels (*grade A*):
        - Diet only—instruct patients to assess blood glucose concentration 4 times daily, prebreakfast and 1 hour after the first bite of food at each meal (*grade A*)
        - Insulin therapy—instruct patients to assess blood glucose concentrations 6 times daily, before each meal to determine insulin dosage correction and 1 hour after the first bite of food at each meal (*grade A*)
    - Accurate timing of glucose testing at meals is critical to accurately assess glucose control (*grade B*)
    - Expect insulin requirements to rise as pregnancy progresses; insulin requirements may be decreased by hyperemesis; steroid therapy increases insulin requirements (*grade B*)
- Offer medical nutrition therapy and education; if the patient is overweight, advise a diet suitable for someone of optimal weight and encourage moderate exercise such as armchair exercises (*grade A*)
    - Management by a health care team is needed to assess and reinforce patient understanding of diabetes management including dietary needs and considerations, knowledge of glucose targets, current pharmacologic therapy, and use of self-monitoring of blood glucose (timing and interpretation of test results and appropriate response) (*grade B*)

9.1.4. Labor and Delivery

- Maternal hyperglycemia is the main cause of neonatal hypoglycemia; therefore, intrapartum maintenance of maternal euglycemia is essential (*grade B*)
- Insulin is still required before active labor and can be given subcutaneously or by intravenous infusion with a goal of maintaining blood glucose concentrations between 70 to 90 mg/dL (*grade B*)
- As the mother enters active labor, insulin resistance rapidly decreases because of the energy expenditure of labor as a form of strenuous exercise; as a result, insulin requirements drop to zero (Tables 9.1 and 9.2 present protocols for adjusting intrapartum intravenous solutions and insulin administration during labor and the postpartum period in women with insulin-requiring diabetes mellitus; Table 9.3 lists sample glucose infusion rates in active labor) (*grade B*)
- To prevent hypoglycemia:
    - Infuse glucose at a rate of 2.5 mg/kg per min (*grade C*)
    - Measure the capillary blood glucose concentration hourly (*grade C*)
    - Double the glucose infusion for the next hour if the blood glucose value is less than 60 mg/dL (*grade C*)
    - Glucose values greater or equal to 120 mg/dL require the administration of regular insulin subcutaneously or intravenously until the blood glucose value falls to 70 to 90 mg/dL; now, the insulin dose is titrated to maintain normoglycemia while glucose is infused at a rate of 2.5 mg/kg per min (*grade C*)

Table 9.1. Protocol for Adjusting Intrapartum Intravenous Solutions and Insulin Administration During Labor and the Postpartum Period in Women With Insulin-Requiring Diabetes Mellitus Treated With Insulin Pump Therapy[a]

Blood Glucose Concentration, mg/dL	Adjustment
≤70	D_{10} normal saline[b], 100 mL/h for 10 to 15 min
71-100	D_5 normal saline[c], 100 mL/h
101-120	Normal saline, 100 mL/h
>121	Normal saline plus regular insulin intravenously or bolus analog subcutaneously as percent of TDIR
121-140	Normal saline, 100 mL/h plus 3% of TDIR
>141	Normal saline, 100 mL/h plus 6% of TDIR

Abbreviation: TDIR, total daily insulin requirement.
[a]Basal insulin infusion rate to be reduced in half. At term, the insulin requirement is 1.0 units/kg/d; thus, 3% of this dose would be 3 units in a woman weighing 100 kg at term.
[b]D_{10} normal saline is 10% dextrose in normal (isotonic saline).
[c]D_5 normal saline is 5% dextrose in normal (isotonic) saline.

  - Do not give bolus doses of glucose because they can raise maternal blood glucose concentrations and increase the risk of neonatal hypoglycemia, fetal hypoxia, and fetal or neonatal acidosis (*grade A*)
  - Anticipate changed insulin requirements, and thus the need for more frequent glucose monitoring, if the patient is continuing insulin therapy postpartum and during lactation (*grade C*)
- Provide appropriate care and facilities for the newborn (*grade B*)
- At 45 to 60 days after delivery, screen for diabetes in women who developed new diabetes in pregnancy; if there is no evidence of diabetes, advise the patient of the high risk of future diabetes and educate the patient about preventative lifestyle measures; advise the patient to be examined for diabetes annually because women with GDM have a 50% risk of developing T2DM within 5 years (10% conversion per year) (*grade A*)

9.2. Evidence Base

Approximately 8% of all pregnancies in the United States are complicated by hyperglycemia (1). Hyperglycemia at conception (when the woman may not know she is pregnant) and during the first trimester increases the risk of fetal malformations; later in pregnancy, it increases the risk of macrosomia and metabolic complications at birth (2). Therefore, prepregnancy counseling and planning are essential in women of childbearing age who have diabetes mellitus.

Women with T2DM are less likely than women with T1DM to have preconception care and counseling—often because the diagnosis of diabetes mellitus has not yet been made—and thus, they are at even greater risk of bearing child with a birth defect than women with T1DM (3,4). Assessing fasting plasma glucose is a useful test for screening both subcategories of women with GDM (5).

Higher HbA_{1c} values early in pregnancy are correlated with higher rates of spontaneous abortion and major congenital malformations (6-8). Although most studies have been performed in women with T1DM, the same risks resulting from hyperglycemia apply to those with T2DM (9). Normalizing blood glucose concentrations before pregnancy or early in gestation can reduce the risks of spontaneous abortion and congenital malformations nearly to that of the general population (10). The importance of normalizing the postprandial glucose levels to decrease macrosomia was first reported in 1991 (11), and this observation has subsequently been confirmed in several studies (12,13). Self-monitoring of blood glucose during pregnancy is essential, and both preprandial and postprandial glucose measurements are recommended to guide therapy (14,15).

The rationale for the recommended blood pressure target of less than 130/80 mm Hg stems from the increased risk of retinopathy; even mild background retinopathy

Table 9.2. Protocol for Adjusting Intrapartum Intravenous Solutions and Insulin Administration in Women With Insulin-Requiring Diabetes Mellitus Based on Hourly Blood Glucose Measurement[a]

Blood Glucose Concentration, mg/dL	Adjustment
≤60	Twice the target rate[b]
61-100	Target rate[b] or D_5 normal saline[c]
101-120	Normal saline, 100 mL/h
121-140	Normal saline, 100 mL/h plus 3% TDIR
≥141	Normal saline, 100 mL/h plus 6% TDIR

Abbreviation: TDIR, total daily insulin requirement.
[a]Discontinue neutral protamine Hagedorn (NPH) insulin administration.
[b]Glucose infusion rate is 2.55 mg/kg of pregnant weight/min.
[c]D_5 normal saline is 5% dextrose in normal (isotonic) saline.

can rapidly progress during pregnancy (16). Because mild degrees of retinopathy can be missed in women with undiagnosed T2DM the blood pressure criteria is a safety feature to prevent progression of retinopathy in all pregnant women with diabetes mellitus.

Although a consistent hallmark of the diabetic pregnancy is an increased insulin requirement in late gestation (17), there is a decline in the insulin requirement in patients with T1DM who are treated early in the first trimester of pregnancy (18). The rise and fall in insulin requirement is most notable in patients with initially poorly controlled diabetes and in overweight and obese patients, but can also be seen in pregnant women with very well-controlled diabetes who do not otherwise have pregnancy complications. Particularly for women with good glycemic control, even a modest decrease in insulin requirement could increase the risk of hypoglycemia. Thus, all insulin-requiring women with diabetes mellitus and their caregivers should be taught to anticipate the possibility of a decrease in insulin requirement in the mid-late first trimester. From the physiologic point of view, these clinical observations are consistent with the underlying pattern of declining glucose concentrations in the first trimester of normal pregnancy (19). This decline appears to reflect a transient increase in

Table 9.3. Sample Glucose Infusion Rates for Women With Insulin-Requiring Diabetes Mellitus in Active Labor[a]

Weight, kg	Glucose, mg/min	D_5 Normal Saline[b], mL/min
50	127.5	2.55
60	153.0	3.06
70	178.5	3.56
80	204.0	4.08
90	229.5	4.58
100	255.0	5.10
110	280.5	5.60
120	306.0	6.12

[a]The rate of infusion is equal to dextrose 2.55 mg/kg/min.
[b]D_5 normal saline is 5% dextrose in normal (isotonic) saline.

insulin sensitivity in the latter half of the first trimester, which in turn is rooted in the underlying maternal endocrine adaptations to pregnancy. This trend is the opposite of the better known late rise in insulin requirement, which reflects a rise in maternal contra-insulin hormones in late pregnancy. These data provide a basis to anticipate a sometimes sudden and dramatic decrease in insulin requirement in the mid-late first trimester of the diabetic pregnancy.

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10. DIABETES MANAGEMENT IN THE HOSPITAL SETTING

10.1. Executive Summary

10.1.1. Hospital Preadmission Planning

- For elective hospital admissions, develop a glycemic management plan with the patient before admission and share the plan with colleagues who will be involved in the patient's care (*grade C*)

10.1.2. Data Collection and Record Keeping

- Measure the blood glucose concentration at hospital admission (*grade A*)
- Record "diabetes mellitus" on the medical chart, if the diagnosis of diabetes mellitus is known (*grade C*)
- Measure the HbA_{1c} level at hospital admission if hyperglycemia is present, if a history of diabetes mellitus exists, or if a HbA_{1c} value (within the past 3 months) is not available for review (*grade B*)
- Order point-of-care glucose monitoring in a pattern appropriate to the patient's diagnoses and carbohydrate exposure if hyperglycemia is present at hospital admission or if conditions present high risk for developing hyperglycemia (*grade A*)

10.1.3. Meal Plan

- For hyperglycemic patients who are eating, either: (a) order a consistent carbohydrate diet or (b) for knowledgeable nurses or insulin-requiring patients, permit the use of advanced carbohydrate counting and nurse-determination or patient self-determination of prandial insulin doses (*grade C*)

10.1.4. Target Blood Glucose Levels

- Preprandial, less than 110 mg/dL (*grade C*)
- Peak postprandial, less than 180 mg/dL (*grade B*)
- Critically ill patients, between 80 to 110 mg/dL (*grade A*)

10.1.5. Insulin Management Plan

- If appropriate for the patient, use intravenous insulin infusion (*grade A*)
- If hyperglycemia is reproducibly present and intravenous insulin infusion is not necessary, order scheduled subcutaneous insulin (*grade B*)
- For subcutaneous management, order amounts of insulin sufficient to cover basal and nutritional needs (*grade B*)
- Plan the patterns of glucose monitoring and delivery of insulin to match carbohydrate exposure (*grade B*)
- Revise the amounts of scheduled insulin daily or more frequently based on patient response (*grade B*)
- For patients receiving scheduled insulin, order an as needed correction dose of subcutaneous insulin with dosing that is: (a) proportionate to blood glucose elevation and insulin sensitivity of the patient and (b) appropriate to time of day; specify the times or mealtimes to which the order applies (*grade B*)

10.1.6. Hypoglycemia Prevention

- Modify insulin therapy preventively if a downward trend in blood glucose concentrations is observed or there are other conditions that predispose to hypoglycemia (*grade A*)
- For abrupt interruption of carbohydrate exposure within the time frame of action of previously administered nutritional insulin, treat the patient preemptively with intravenous concentrated dextrose before hypoglycemia occurs (*grade B*)

10.1.7. Comanagement

- Work collaboratively with diabetes care professionals from the disciplines of nursing, nutrition, pharmacy, quality assurance, hospital administration, and others (*grade B*)

10.1.8. Hospital Discharge Planning

- Offer inpatient education to patients regarding medication administration (including subcutaneous insulin injections if appropriate), glucose monitoring, nutrition, physical activity, and other lifestyle factors (*grade B*)
- At hospital discharge, offer appropriate intensification of the patient's preadmission management plan (*grade B*)
- At hospital discharge, provide an explanation of circumstances that should prompt the patient to call the clinician for guidance (*grade B*)
- Plan follow-up visits to be conducted after hospital discharge to discuss glycemic control and to continue patient education (*grade B*)

10.2. Evidence Base

10.2.1. Overview

In the hospital setting, patient mortality, morbidity, and length of stay have been linked to failure of glycemic control. Standards have been developed for blood glucose targets and for the use of intravenous insulin and subcutaneous insulin as part of a comprehensive glycemic management plan. Findings from observational studies and ongoing clinical trials comparing intensified regimens with historical controls show correlation between poor glycemic control and unfavorable outcomes. The outcomes studied include hospital or critical care unit mortality (1-8) and the outcome of strokes (9-15), trauma (16), renal transplantation (17), duration of remission after induction chemotherapy for acute lymphocytic leukemia (18), myocardial infarction (11,19-22), mortality related to endocarditis (23), nosocomial infections (24-28), pneumococcal sepsis (29), cardiac surgery (30-34), labor and delivery (35), and length of stay or costs (36-40).

Using intravenous insulin infusion in appropriately selected patients is cost-effective (40,41). Results from randomized controlled trials using glucose-insulin-potassium infusions show benefit in the setting of myocardial infarction or cardiac surgery when blood glucose concentrations are lowered (42-44). In one randomized controlled trial, the maintenance of normoglycemia using intravenous insulin infusion in patients being cared for in the surgical intensive care unit reduced the duration of ventilatory assistance, transfusion requirements, progression to renal failure, the occurrence of sepsis, and the development of neuropathy (7).

With study results demonstrating that glycemic control reduces mortality, international attention has now focused on intensive insulin management. Standards for blood glucose monitoring and record keeping are necessary for clinicians to effectively prescribe and administer insulin therapy. The usefulness of measuring HbA_{1c} levels has been supported by its predictive value for outcomes (45). Standards for intensive insulin management have been articulated by consensus (46-48), and criteria and strategies for using intravenous insulin infusion have been established (49-51). Sliding-scale insulin regimens used

alone are ineffective and potentially harmful (52,53); when using subcutaneous insulin injection therapy, scheduled or "standing" insulin regimens should be the standard of care (54-56). Hypoglycemia is usually predictable and therefore preventable (57,58). Patient self-management in the hospital is feasible and desirable for experienced patients when they are competent to continue self-management under the conditions of the hospital admission (59,60).

Endocrinologists should participate as members of the health care team managing individual patient care and as agents promoting institutional changes by developing hospital order sets completed by check marks and numbers; protocols activated by a single signature; computerized order entry systems that guide and teach; and various guidelines, procedures, and policies (50,54,61-67).

10.2.2. Clinical Considerations

The following considerations are relevant for clinician involvement unless the need already is covered under policies of the hospital, the ward, or other service entity.

All Patients With Diabetes Mellitus

Using rapid-acting insulin analogs should be restricted to prandial and correction dose therapy. In patients whose conditions are clinically unstable, the use of long-acting insulin analogs should be restricted to basal requirements. Nutritional insulin orders should be tagged with directions that nurses can follow in case the patient has delayed or reduced carbohydrate exposure. Correction dose insulin orders should be tagged with additional directions to *not withhold*, to *withhold*, or to *reduce* the insulin dose in the event that the patient has delayed or reduced carbohydrate exposure or point-of-care test results are obtained at an irregular time. Call parameters should be ordered, which describe when the clinician should be alerted to revise scheduled insulin therapy, adjust carbohydrate exposure, or respond to other factors resulting in destabilization based on blood glucose concentration thresholds. A call order should be included to alert the clinician if the patient experiences a sudden change in carbohydrate exposure.

Patients With Type 1 Diabetes Mellitus

For patients with T1DM, the basal insulin requirement should be identified in units per day, and basal insulin should be ordered separately from nutritional coverage. Basal insulin orders should be tagged with the specification *do not withhold insulin*.

Patients With Type 2 Diabetes Mellitus

For patients with T2DM, basal insulin orders should be tagged with additional directions to *not withhold*, to *withhold*, or to *reduce* the insulin dose in the event that the patient has reduced carbohydrate exposure.

Patients Without Confirmed Diabetes Mellitus Who Have Hyperglycemia While Hospitalized

For patients without confirmed diabetes mellitus who experience hyperglycemia while hospitalized, the presence or absence of diabetes should be established in outpatient follow-up using venous blood and plasma glucose concentration criteria.

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11. PATIENT SAFETY IN DIABETES CARE

11.1 Executive Summary

11.1.1 Systems Issues

- Medical errors are common and adversely affect important outcomes in diabetes care (*grade A*)
- Most medical errors are not injurious because they are discovered and corrected by the health care team before they cause harm (*grade A*)
- A high level of patient safety is not a predictable outcome of complex medical systems and is usually achievable only with considerable and continuous effort (*grade C*)
- Create a nonpunitive environment to encourage learning from mistakes and involve all members of the health care team who are responsible for the care of the diabetic patient in the clinical setting (*grade B*)
- Schedule regular health care team meetings to address patient safety as a priority and insert a line item into the annual budget to pay for needed changes (*grade B*)
- Encourage voluntary sharing of error data and address them using an analytic method to improve the system of care and to reduce the frequency of injurious medical errors (*grade B*)
- As part of diabetes care coordination, develop *a culture of safety*, a group of health care workers who function as a team to protect the patient from injurious medical errors (*grade B*)
- Use algorithms to address complex medical procedures and provide ample time for relevant staff to learn and practice how to use the algorithms (*grade B*)
- Always balance profitability with safety concerns (*grade A*)
- Implement and use an electronic health record or information sharing system; a well-designed system may significantly reduce the frequency of medical errors (*grade A*)
- Implement and use well-designed computerized physician order entry systems to reduce medication errors (*grade A*)

- Although comorbid conditions, economic conditions, and patient preferences often cause necessary and appropriate variations in care practice, wherever possible, reduce variations in care that are not evidence-based to decrease the occurrence of errors; allow others (peers, allied health professionals, patients, and families of patients) to facilitate best practices. Also, monitoring of desired clinical performance standards becomes easier (*grade A*)

11.1.2. Patient Issues

- Give explicit, clear insulin orders to anticipate each of the common or important situations that patients must confront (*grade A*)
- Use written algorithms for insulin therapy; if possible, they should be typed or printed (*grade A*)
- Provide frequent glucose monitoring according to the medical needs of the patient (*grade A*)
- Routinely recheck patient understanding of basic concepts of self-care at appropriate intervals (*grade A*)
- Assess for coronary heart disease in patients with diabetes mellitus (*grade A*)
- Evaluate all patients for their relative risk of hypoglycemia (*grade A*)
- Use diabetes education programs that are evidence-based and focused on issues of patient safety (*grade C*)
- Encourage all patients who drive motor vehicles, who have high-risk occupations, or whose leisure time involves high-risk activities to participate in an education program with emphasis on hypoglycemia recognition, prevention, and treatment (*grade A*)

11.2. Evidence Base

11.2.1. Overview

Although abundant evidence is available regarding proven strategies in patient safety efforts, most data are not derived from randomized controlled trials. Because of ethical concerns, a randomized controlled trial is more conducive to assessing quality than safety. For example, it is unethical to put subjects in harm's way to prove that injurious medical errors are more common in the control group.

Health care professionals are understandably reluctant to voluntarily disclose injurious errors they have made. As a result, Bates and others report that underreporting of errors is common even in hospitals known to provide outstanding medical care (1). Fortunately, an abundance of studies, many of them cohort or observational studies, have provided excellent outcome information and evidence that support the recommendations for methods to improve patient safety (2). Results from several randomized controlled trials document the validity of recommendations related to safety (3-8). The most compelling data in the safety arena are from outcome studies that use clear clinical end points such as mortality or infection data. Because the health care systems**,** such as hospitals**,** studied in the field of patient safety are complex, the architecture of such clinical research involves multiple simultaneous, linked interventions, often iterated over a period of time (2,9). Findings from some outcome studies show striking reductions in infectious complications and death rates (10). Some system data are also based on studies in other systems, but the organizational behavior is the focus (11).

11.2.2. Rationale

Medical errors are common and adversely affect clinically important outcomes in diabetes care (12,13). Evidence shows that a high prevalence of injurious medical errors in diabetes care increases the frequency of not only death, but of morbidity, complications, and disability (13,14). Most errors are not injurious and are discovered and corrected by the health care team. It is necessary to adopt a nonpunitive approach when discussing medical errors; without such an approach, improvement in safety is often difficult to achieve (15).

A systems approach to medical error reduction has a much greater chance of successfully improving patient safety because factors at the so-called blunt end of care—parts of the health care system that are not in direct contact with patients, but which affect personnel and equipment—are much more powerful influences than factors at the so-called sharp end of care—parts of the health care system that care for patients directly (16). Modern patient safety programs focus on improving the system of care because the blunt end of care has a much greater effect on patient safety. In an unsafe system of care, even excellent physicians usually will be unable to notably improve overall care, despite their best efforts (16).

Nearly all medical errors are inadvertent or systematic. Almost always, the error is inadvertent; for example, when physicians order tests or medications, the patient medical information they have access to is often incomplete (13). An error may be outside of a physician's ability to correct because it was both unanticipated and unobserved. Therefore, coordination of care should include development of *a culture of safety* in the clinical diabetes care setting. A culture of safety can be defined as a group of health care workers who work together to protect the patient from preventable, injurious medical errors. A culture of safety is designed to provide a system of care that will assist health care providers anticipate and prevent such events. For example, in a hospital setting, a common injury to a patient with diabetes mellitus is hypoglycemia that occurs when a patient is taken to radiology by a transportation worker after an insulin injection, but before the patient eats. Such system

problems are best solved by effective communication among all members of the team who care for the patient (13). The size and complexity of the group can be extremely varied. The common methods of resolution include backup checks and timely communication of medical information (14,15).

Abundant data show the importance of taking a nonpunitive approach when discussing medical errors. Data from the Federal Aviation Administration and from the US Nuclear Regulatory Commission—high-safety level organizations with exemplary performance—show the necessity of providing safe harbor for those who report medical errors, particularly errors with which they were involved (13). In contrast, the modern medical tort system encourages hiding errors, which, if not exposed, are often repeated inadvertently by others (17).

Implementing an electronic medical record or information-sharing system would reduce errors in medical care (9). An electronic medical record can provide critically important clinical information to physicians when they most need it. With a few keystrokes, the ability to quickly review years of clinical data, aggregate and display data before making a clinical decision, and check for contraindications or for drug interactions make an electronic medical record a powerful tool to improve patient safety.

Medication errors can be markedly reduced with the use of a well-designed computerized physician order entry system, which is currently available mostly in inpatient settings (1,18). In hospitals, 14 to 60 steps—or more—may occur before a medication order is fulfilled and the medication is given to the patient. Computerized physician order entry systems greatly reduce the possibility of error or ambiguity. For example, with prescriptions submitted using computerized physician order entry systems, pharmacy staff do not need to decipher physicians' handwritten scripts (1,19). Some computer systems have decision aids or clinical reminders that can enhance performance (20).

Evidence-based patient education programs can potentially enhance the safety of the patient with diabetes mellitus. Such programs should be a part of the ongoing care of the patient. The optimal form or content of such programs are not yet established but should be designed to aid in communication with the health care team and to increase the level of safety for the patient with diabetes mellitus (13).

Profitability must always be balanced by safety concerns. In diabetes care settings, it is important to preserve the capability of the system to provide safe medical care. Providing the resources to ensure that patient education is effective, nursing care is sufficient, and proper technology is available when needed may cost more initially. However, budgeting for safety is a valid short-term and long-term strategy that ultimately leads to better outcomes and more value for patients, systems of care, and society (16,21).

11.2.3. Clinical Considerations

All Patients With Diabetes Mellitus

Insulin is a potent and invaluable medication, but it is a source of many serious medical errors of commission or omission by health care providers, patients, and other caregivers such as family members; these errors can be lethal (13). Explicit, clear insulin orders should be given to anticipate each of the common or important situations that patients encounter (13,22). Written algorithms, preferably typed or printed, should be used to guide insulin therapy. When many different people use only a few selected algorithms, training the entire group is easier (13).

Frequent glucose monitoring should be conducted according to the medical needs of the patient. Generally, it is safest to assess the patient's glucose level each time insulin is administered. This information will allow the dose to be matched more closely to the patient's needs (13).

Many patients forget what they once were taught, and clinicians should not assume that patients under long-term care understand instructions regarding their treatment regimen. Rechecking patients' understanding of basic self-care concepts should be done routinely at appropriate intervals (13).

Inadequate screening for cardiac complications of diabetes mellitus is common because patients with neuropathy frequently have atypical chest pain or no chest pain; silent ischemia is common in this population (23). A high index of suspicion for coronary heart disease in diabetic patients will reduce the risk of sudden death (24-26).

The complications of diabetes mellitus often affect the patient's risk of injury. Both the patient and the physician may be uniformed about the other's knowledge regarding changes in the status of diabetes complications and the related increased risk for injury (27). For example, a patient may be unaware of the new risks to the feet that result from neuropathy or peripheral vascular disease (14), or a physician may be unaware of how much a patient's visual loss has affected usual self-care activities such as drawing up insulin. To help reduce the risk of accidents, the clinician should periodically check in with the patient and strive for better communication.

Patients With Type 1 Diabetes Mellitus

Hypoglycemia is a common problem that causes accidents and serious injury. An assessment of the frequency, severity, and any recent exacerbation of hypoglycemia should be done when the patient presents for evaluation of hypoglycemia. The presence of autonomic neuropathy, chronic kidney disease, diminished oral intake, use of β-adrenergic blockers, and many other factors should be noted as well as the frequency of glucose monitoring (27-29). The enlistment of the patient's family or other support system may be needed to protect the patient from hypoglycemic

episodes. Frequent glucose monitoring is useful in nearly all circumstances, but by itself, it may not be sufficient to prevent hypoglycemia.

Patients who drive motor vehicles and become hypoglycemic are at particularly high risk of serious morbidity and death. Patients are often unaware that they may be impaired even 45 minutes after the onset of severe hypoglycemia. An education program for all patients with T1DM who drive motor vehicles may be lifesaving (30,31). The same strategy should be used for patients with high-risk occupations or for patients whose leisure time involves activities such as climbing ladders or scuba diving, during which hypoglycemia could cause serious accidents.

Cognitive impairment is not limited to hypoglycemic episodes (32). Medications and other comorbid conditions may affect cognitive function in patients with diabetes mellitus. A patient recovering from mild ketosis or marked hyperglycemia (33) may also be temporarily impaired in their memory or judgment.

Patients With Type 2 Diabetes Mellitus

The most common error that leads to preventable complications is delayed diagnostic screening (25), which is most often a system-derived problem because of the pressures to limit screening, even in high-risk populations. More than 50% of patients diagnosed with T2DM have at least 1 complication at the time of diagnosis, which would probably have been preventable with earlier diagnosis.

Elderly and frail patients, particularly those who are institutionalized, are particularly prone to delayed diagnosis and delayed treatment (28,29). Hyperglycemia, if sufficiently severe, may present with central nervous system findings of coma or focal weakness. These patients often experience cognitive impairment, and their sensory apparatus may also be severely impaired. Their care should be customized to fit their needs.

Adverse drug interactions are problematic, particularly in patients with T2DM who have multiple comorbidities that confer an added risk for mortality (10). A systems solution is required to monitor for potential drug interactions and to improve patient safety (13). The most commonly used tools to assess for drug interactions in real time are computers and PDAs.

Recent data show that as many as 30% of patients with health coverage by Medicare will not take at least 1 of their medications because of financial constraints (34). Patients may not realize how important medications are for promoting their health and safety. Patient compliance with a prescribed medication regimen should not be assumed. Patients who repeatedly miss medical appointments may be at increased risk for medication noncompliance and may require diligent follow-up measures to resolve underlying issues.

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