Standards of Medical Care in Diabetes—2007

AMERICAN DIABETES ASSOCIATION

CONTENTS

I. CLASSIFICATION AND DIAGNOSIS, p. S4
- A. Classification
- B. Diagnosis

II. SCREENING FOR DIABETES, p. S5

III. DETECTION AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS, p. S7

IV. PREVENTION/DELAY OF TYPE 2 DIABETES, p. S7

V. DIABETES CARE, p. S8
- A. Initial evaluation
- B. Management
- C. Glycemic control
  1. Assessment of glycemic control
     - a. Self-monitoring of blood glucose
     - b. A1C
  2. Glycemic goals
  3. Approach to treatment
- D. Medical nutrition therapy
- E. Diabetes self-management education
- F. Physical activity
- G. Psychosocial assessment and care
- H. Referral for diabetes management
- I. Intercurrent illness
- J. Hypoglycemia
- K. Immunization

VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS, p. S15
- A. Cardiovascular disease
  1. Hypertension/blood pressure control
  2. Dyslipidemia/lipid management
  3. Antiplatelet agents
  4. Smoking cessation
  5. Coronary heart disease screening and treatment
- B. Nephropathy screening and treatment
- C. Retinopathy screening and treatment
- D. Neuropathy
- E. Foot care

VII. DIABETES CARE IN SPECIFIC POPULATIONS, p. S24
- A. Children and adolescents
- B. Preconception care
- C. Older individuals

VIII. DIABETES CARE IN SPECIFIC SETTINGS, p. S27
- A. Diabetes care in the hospital
- B. Diabetes care in the school and day care setting
- C. Diabetes care at diabetes camps
- D. Diabetes care at correctional institutions
- E. Emergency and disaster preparedness

IX. HYPOGLYCEMIA AND EMPLOYMENT/LICENSURE, p. S33

X. THIRD-PARTY REIMBURSEMENT FOR DIABETES CARE, SELF-MANAGEMENT EDUCATION, AND SUPPLIES, p. S33

XI. STRATEGIES FOR IMPROVING DIABETES CARE, p. S33

The recommendations in this article are based on the evidence reviewed in the following publication: Standards of care for diabetes (Technical Review). *Diabetes Care* 17:1514–1522, 1994.

Originally approved 1988. Most recent review/revision, October 2006.

Abbreviations: ABI, ankle-brachial index; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CBG, capillary blood glucose; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CMS, Centers for Medicare and Medicaid Services; CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; DCCB, dihydropyridine calcium channel blocker; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; DMMP, diabetes medical management plan; DPN, distal symmetric polyneuropathy; DPP, Diabetes Prevention Program; DRI, dietary reference intake; DRS, Diabetic Retinopathy Study; DSME, diabetes self-management education; DSMT, diabetes self-management training; ECG, electrocardiogram; ESRD, end-stage renal disease; ETDRS, Early Treatment Diabetic Retinopathy Study; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; GFR, glomerular filtration rate; HRC, high-risk characteristic; ICU, intensive care unit; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MNT, medical nutrition therapy; NDEP, National Diabetes Education Program; NPDR, nonproliferative diabetic retinopathy; OGTT, oral glucose tolerance test; PAD, peripheral arterial disease; PDR, proliferative diabetic retinopathy; PPG, postprandial plasma glucose; RDA, recommended dietary allowance; SMBG, self-monitoring of blood glucose; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study.

DOI: 10.2337/dc07-S004

© 2007 by the American Diabetes Association.

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

These standards of care are intended to provide clinicians, patients, researchers, payors, and other interested individuals with the components of diabetes care, treatment goals, and tools to evaluate the quality of care. While individual preferences, comorbidities, and other patient factors may require modification of goals, targets that are desirable for most patients with diabetes are provided. These standards are not intended to preclude more extensive evaluation and management of the patient by other specialists as needed. For more detailed information, refer to refs. 1–3.

The recommendations included are diagnostic and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. A grading system (Table 1), developed by the American Diabetes Association (ADA) and modeled after existing methods, was utilized to clarify and codify the evidence that forms the basis for the recommendations. The level of evidence that supports each recommendation is listed after each recommendation using the letters A, B, C, or E.

I. CLASSIFICATION AND DIAGNOSIS

A. Classification

In 1997, ADA issued new diagnostic and classification criteria (4); in 2003, modifications were made regarding the diagnosis of impaired fasting glucose (IFG) (5). The classification of diabetes includes four clinical classes:

- Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

10/11/24 Ahmann
EXHIBIT 2035
exhibitsticker.com

ABBOTT Exhibit 2235 - Page 1 of 38
Dexcom v. Abbott, IPR2024-00521

Table 1—*ADA evidence grading system for clinical practice recommendations*

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

β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical induced (such as in the treatment of AIDS or after organ transplantation)

- Gestational diabetes mellitus (GDM) (diagnosed during pregnancy)

Some patients cannot be clearly classified as type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients who otherwise have type 2 diabetes may present with ketoacidosis. Similarly, patients with type 1 may have a late onset and slow (but relentless) progression of disease despite having features of autoimmune disease. Such difficulties in diagnosis may occur in children, adolescents, and adults. The true diagnosis may become more obvious over time.

B. Diagnosis

Recommendations

- The FPG is the preferred test to diagnose diabetes in children and nonpregnant adults. (E)
- Use of the A1C for the diagnosis of diabetes is not recommended at this time. (E)

Criteria for the diagnosis of diabetes in nonpregnant adults are shown in Table 2. Three ways to diagnose diabetes are available, and each must be confirmed on a subsequent day unless unequivocal symptoms of hyperglycemia are present. Although the 75-g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than fasting plasma glucose (FPG) to diagnose diabetes, it is poorly reproducible and rarely performed in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG is the preferred diagnostic test. It should be noted that the vast majority of people who meet diagnostic criteria for diabetes by OGTT, but not by FPG, will have an A1C value <7.0%. The use of the A1C for the diagnosis of diabetes is not recommended at this time.

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either IFG or impaired glucose tolerance (IGT), depending on whether it is identified through an FPG or an OGTT:

- IFG = FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)
- IGT = 2-h plasma glucose 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)

Recently, IFG and IGT have been officially termed "pre-diabetes." Both categories, IFG and IGT, are risk factors for future diabetes and cardiovascular disease (CVD).

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use but may be required in the evaluation of patients with IFG (see text) or when diabetes is still suspected despite a normal FPG, as with the postpartum evaluation of women with GDM.

II. SCREENING FOR DIABETES

Recommendations

- Screening to detect pre-diabetes (IFG or IGT) and diabetes should be considered in individuals ≥45 years of age, particularly in those with a BMI ≥25 kg/m^2. Screening should also be considered for people who are <45 years of age and are overweight if they have an-

Table 2—*Criteria for the diagnosis of diabetes*

1.	Symptoms of diabetes and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
	OR
2.	FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
	OR
3.	2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 2 of 38
Dexcom v. Abbott, IPR2024-00521

Table 3—*Criteria for testing for diabetes in asymptomatic adult individuals*

1. Testing for diabetes should be considered in all individuals at age 45 years and above, particularly in those with a BMI ≥25 kg/m^2*, and, if normal, should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI ≥25 kg/m^2*) and have additional risk factors:
   - are habitually physically inactive
   - have a first-degree relative with diabetes
   - are members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - have delivered a baby weighing >9 lb or have been diagnosed with GDM
   - are hypertensive (≥140/90 mmHg)
   - have an HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
   - have PCOS
   - on previous testing, had IGT or IFG
   - have other clinical conditions associated with insulin resistance (e.g., PCOS or acanthosis nigricans)
   - have a history of vascular disease

*May not be correct for all ethnic groups. PCOS, polycystic ovary syndrome.

other risk factor for diabetes (Table 3). Repeat testing should be carried out at 3-year intervals. (E)

- Screen for pre-diabetes and diabetes in high-risk, asymptomatic, undiagnosed adults and children within the health care setting. (E)
- To screen for diabetes/pre-diabetes, either an FPG test or 2-h OGTT (75-g glucose load) or both are appropriate. (B)
- An OGTT may be considered in patients with IFG to better define the risk of diabetes. (E)

There is a major distinction between diagnostic testing and screening. Both utilize the same clinical tests, which should be done within the context of the health care setting. When an individual exhibits symptoms or signs of the disease, diagnostic tests are performed, and such tests do not represent screening. The purpose of screening is to identify asymptomatic individuals who are likely to have diabetes or pre-diabetes. Separate diagnostic tests using standard criteria are required after positive screening tests to establish a definitive diagnosis as described above.

Type 1 diabetes

Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels. Because of the acute onset of symptoms, most cases of type 1 diabetes are detected soon after symptoms develop. Widespread clinical testing of asymptomatic individuals for the presence of autoantibodies related to type 1 diabetes cannot be recommended at this time as a means to identify individuals at risk. Reasons for this include the following: *1*) cutoff values for some of the immune marker assays have not been completely established in clinical settings; *2*) there is no consensus as to what action should be taken when a positive autoantibody test result is obtained; and *3*) because the incidence of type 1 diabetes is low, testing of healthy children will identify only a very small number (<0.5%) who at that moment may be "pre-diabetic." Clinical studies are being conducted to test various methods of preventing type 1 diabetes in high-risk individuals (e.g., siblings of type 1 diabetic patients). These studies may uncover an effective means of preventing type 1 diabetes, in which case targeted screening may be appropriate in the future.

Type 2 diabetes

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Individuals at high risk should be screened for diabetes and pre-diabetes. Criteria for testing for diabetes in asymptomatic, undiagnosed adults are listed in Table 3. The effectiveness of early diagnosis through screening of asymptomatic individuals has not been determined (6).

Screening should be carried out within the health care setting. Either an FPG test or 2-h OGTT (75-g glucose load) is appropriate. The 2-h OGTT identifies people with IGT, and thus, more people are at increased risk for the development of diabetes and CVD. It should be noted that the two tests do not necessarily detect the same individuals (7). It is important to recognize that although the efficacy of interventions for primary prevention of type 2 diabetes have been demonstrated among individuals with IGT (8–10), such data among individuals with IFG (who do not also have IGT) are not available. The FPG test is more convenient to patients, more reproducible, less costly, and easier to administer than the 2-h OGTT (4,5). Therefore, the recommended initial screening test for nonpregnant adults is the FPG. An OGTT may be considered in patients with IFG to better define the risk of diabetes.

The incidence of type 2 diabetes in adolescents has increased dramatically in the last decade. Consistent with screening recommendations for adults, only children and youth at increased risk for the presence or the development of type 2 diabetes should be tested (11) (Table 4).

The effectiveness of screening may also depend on the setting in which it is performed. In general, community screening outside a health care setting may be less effective because of the failure of people with a positive screening test to seek and obtain appropriate follow-up testing and care or, conversely, to ensure appropriate repeat testing for individuals who screen negative. That is, screening outside of clinical settings may yield ab-

Table 4—*Testing for type 2 diabetes in children*

Criteria
- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus any two of the following risk factors:
- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or PCOS)
- Maternal history of diabetes or GDM

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency: every 2 years
Test: FPG preferred

Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria. PCOS, polycystic ovary syndrome.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 3 of 38
Dexcom v. Abbott, IPR2024-00521

normal tests that are never discussed with a primary care provider, low compliance with treatment recommendations, and a very uncertain impact on long-term health. Community screening may also be poorly targeted, i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk (the worried well) or even those already diagnosed (12,13).

On the basis of expert opinion, screening should be considered by health care providers at 3-year intervals beginning at age 45, particularly in those with BMI ≥25 kg/m^2. The rationale for this interval is that false negatives will be repeated before substantial time elapses, and there is little likelihood of an individual developing any of the complications of diabetes to a significant degree within 3 years of a negative screening test result. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight and have one or more of the other risk factors for type 2 diabetes.

III. DETECTION AND DIAGNOSIS OF GDM

Recommendations

- Screen for diabetes in pregnancy using risk factor analysis and, if appropriate, use of an OGTT. (C)
- Women with GDM should be screened for diabetes 6–12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes. (E)

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk for GDM (e.g., those with marked obesity, personal history of GDM or delivery of a previous large-for-gestation-age infant, glycosuria, polycystic ovary syndrome, or a strong family history of diabetes) should undergo glucose testing as soon as possible (14). An FPG ≥126 mg/dl or a casual plasma glucose ≥200 mg/dl meets the threshold for the diagnosis of diabetes and needs to be confirmed on a subsequent day as soon as possible unless unequivocal symptoms of hyperglycemia are present. High-risk women not found to have GDM at the initial screening and average-risk women should be tested between 24 and 28 weeks of gestation. Testing should follow one of two approaches:

- One-step approach: perform a diagnostic 100-g OGTT
- Two-step approach: perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test) and perform a diagnostic 100-g OGTT on that subset of women exceeding the glucose threshold value on the glucose challenge test. When the two-step approach is used, a glucose threshold value ≥140 mg/dl identifies ~80% of women with GDM, and the yield is further increased to 90% by using a cutoff of ≥130 mg/dl.

Diagnostic criteria for the 100-g OGTT are as follows: ≥95 mg/dl fasting, ≥180 mg/dl at 1 h, ≥155 mg/dl at 2 h, and ≥140 mg/dl at 3 h. Two or more of the plasma glucose values must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of 8–14 h. The diagnosis can be made using a 2-h, 75-g glucose tolerance test, but that test is not as well validated for detection of at-risk infants or mothers as the 3-h, 100-g OGTT.

Low-risk status requires no glucose testing, but this category is limited to those women meeting all of the following characteristics:

- Age <25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of diabetes
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

Because women with a history of GDM have an increased subsequent risk for diabetes, they should be screened for diabetes 6–12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes. For information on the National Diabetes Education Program (NDEP) campaign to prevent type 2 diabetes in women with GDM, go to www.ndep.nih.gov/diabetes/pubs/NeverTooEarly_Tipsheet.pdf.

IV. PREVENTION/DELAY OF TYPE 2 DIABETES

Recommendations

- Individuals at high risk for developing diabetes need to become aware of the many benefits of modest weight loss and participating in regular physical activity. (A)
- Patients with IGT should be given counseling on weight loss as well as instruction for increasing physical activity. (A) (Reimbursement for such counseling is encouraged.)
- Patients with IFG should be given counseling on weight loss as well as instruction for increasing physical activity. (E) (Reimbursement for such counseling is encouraged.)
- Follow-up counseling appears to be important for success. (B)
- Monitoring for the development of diabetes in those with pre-diabetes should be performed every 1–2 years. (E)
- Close attention should be given to, and appropriate treatment given for, other CVD risk factors (e.g., tobacco use, hypertension, dyslipidemia). (A)
- Because of possible side effects and cost, there is insufficient evidence to support the use of drug therapy. (E)

Many studies have shown that individuals at high risk for developing diabetes (those with IFG, IGT, or both) can be given a wide variety of interventions that significantly delay, and sometimes prevent, the onset of diabetes (8–10,15–18). An intensive lifestyle modification program has been shown to be very effective (~58% reduction after 3 years). Use of the pharmacologic agents metformin, acarbose, orlistat, and rosiglitazone has also been shown to decrease incident diabetes to various degrees. Of note, however, each of these drugs may cause side effects of varying severity in a small number of individuals.

Lifestyle modification

In well-controlled studies that included a lifestyle intervention arm, substantial efforts were necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to achieve an important reduction in the incidence of diabetes. In the DPP lifestyle group, a low-fat (<25% fat) intake was recommended; if reducing fat did not produce weight loss to goal, calorie restriction was also recommended. Participants weighing 120–174 lb (54–78 kg) at baseline were instructed to follow a 1,200 kcal/day diet (33 g fat), those 175–219 lb (79–99 kg) were instructed to follow a 1,500 kcal/day diet (42 g fat), those 220–249 lb (100–113 kg) were instructed to follow an 1,800 kcal/day diet (50 g fat), and

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 4 of 38
Dexcom v. Abbott, IPR2024-00521

those >250 lb (114 kg) were instructed to follow a 2,000 kcal/day diet (55 g fat). On average, 50% of the lifestyle group achieved the goal of ≥7% weight reduction and 74% maintained at least 150 min/week of moderately intense activity (8). In the Finnish Diabetes Prevention Study, weight loss averaged 9.2 lb at 1 year, 7.7 lb after 2 years, and 4.6 lb after 5 years (9); "moderate exercise," such as brisk walking, for 30 min/day was suggested. In the Finnish study, there was a direct relationship between adherence with the lifestyle intervention and the reduced incidence of diabetes.

Lifestyle or medication?

Many factors must be considered when undertaking the effort to modify the course of glucose intolerance. Lifestyle modification may have other beneficial effects (e.g., reduced CVD), but is often very difficult to sustain, and its cost-effectiveness is questionable if the regimen is similar to what was employed in clinical trials. Even so, lifestyle intervention still may be cost-effective compared with some pharmacologic treatments. Drug therapy can be very costly (except for metformin, which is a generic drug), and side effects can range from mild/moderate discomfort to serious cardiovascular events. Finally, whether diabetes prevention efforts can, over the long term, influence the development of micro- or macrovascular events is unknown. It is possible that at least microvascular complications will be delayed or diminished, since they are more closely related to hyperglycemia.

In light of the above, health care professionals should first actively counsel patients to maintain normal weight and exercise regularly (even before glucose intolerance occurs). Because of potential side effects and cost, there is insufficient evidence to support the use of drug therapy as a substitute for, or routinely used in addition to, lifestyle modification to prevent diabetes. Public health messages, health care professionals, and health care systems should all encourage behavior changes to achieve a healthy lifestyle. Further research is necessary to understand how to better facilitate effective and efficient programs for the primary prevention of type 2 diabetes.

An ADA consensus statement offering more comprehensive guidance on diabetes prevention will be published in 2007.

Table 5—*Components of the comprehensive diabetes evaluation*

- Medical history
  - Age and characteristics of onset of diabetes (e.g., DKA, routine laboratory evaluation)
  - Prior A1C records
  - Eating patterns, nutritional status, and weight history; growth and development in children and adolescents
  - Diabetes education history
  - Review of previous treatment programs
  - Current treatment of diabetes, including medications, meal plan, and results of glucose monitoring and patient's use of data
  - Exercise history
  - DKA frequency, severity, and cause
  - Hypoglycemic episodes
    - Any severe hypoglycemia: frequency, severity, and cause
  - History of diabetes-related complications
    - Microvascular: eye, kidney, nerve
    - Macrovascular: cardiac, CVD, PAD
    - Other: sexual dysfunction, gastroparesis
- Physical examination
  - Blood pressure determination, including orthostatic measurements when indicated
  - Fundoscopic examination
  - Thyroid palpation
  - Skin examination (for acanthosis nigricans and insulin injection sites)
  - Neurological/foot examination examination
  - Inspection
  - Palpation of DP and PT pulses
  - Presence/absence of patellar and Achilles reflexes
  - Determination of proprioception, vibration, and monofilament sensation
- Laboratory evaluation
  - A1C
  - Fasting lipid profile, including total LDL and HDL cholesterol and triglycerides
  - Liver function tests
  - Test for microalbuminuria
  - Serum creatinine and calculated GFR
  - Thyroid-stimulating hormone
  - Screen for celiac disease in type 1 diabetes and as indicated in type 2 diabetes
- Referrals
  - Eye exam, if indicated
  - Family planning for women of reproductive age
  - MNT
  - Diabetes educator if not provided by physician or practice staff

DP, dorsalis pedis; PT, posterior tibial; PAD, peripheral arterial disease.

V. DIABETES CARE

A. Initial evaluation

A complete medical evaluation should be performed to classify the patient, detect the presence or absence of diabetes complications, assist in formulating a management plan, and provide a basis for continuing care. If the diagnosis of diabetes has already been made, the evaluation should review the previous treatment and the past and present degrees of glycemic control. Laboratory tests appropriate to the evaluation of each patient's general medical condition should be performed. A focus on the components of comprehensive care (Table 5) will assist the health care team to ensure optimal management of the patient with diabetes.

B. Management

People with diabetes should receive medical care from a physician-coordinated team. Such teams may include, but are not limited to, physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. It is essential in this collaborative and integrated team approach that individuals with diabetes assume an active role in their care.

The management plan should be formulated as an individualized therapeutic alliance among the patient and family, the

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 5 of 38
Dexcom v. Abbott, IPR2024-00521

physician, and other members of the health care team. Any plan should recognize diabetes self-management education (DSME) as an integral component of care. In developing the plan, consideration should be given to the patient's age, school or work schedule and conditions, physical activity, eating patterns, social situation and personality, cultural factors, and presence of complications of diabetes or other medical conditions. A variety of strategies and techniques should be used to provide adequate education and development of problem-solving skills in the various aspects of diabetes management. Implementation of the management plan requires that each aspect is understood and agreed on by the patient and the care providers and that the goals and treatment plan are reasonable.

C. Glycemic control

1. Assessment of glycemic control. Techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control.

a. *Self-monitoring of blood glucose*

Recommendations

- Clinical trials using insulin that have demonstrated the value of tight glycemic control have used self-monitoring of blood glucose (SMBG) as an integral part of the management strategy. (A)
- SMBG should be carried out three or more times daily for patients using multiple insulin injections. (A)
- For patients using less frequent insulin injections or oral agents or medical nutrition therapy (MNT) alone, SMBG is useful in achieving glycemic goals. (E)
- To achieve postprandial glucose targets, postprandial SMBG may be appropriate. (E)
- Instruct the patient in SMBG and routinely evaluate the patient's technique and ability to use data to adjust therapy. (E)

The ADA's consensus statements on SMBG provide a comprehensive review of the subject (19,20). Major clinical trials assessing the impact of glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications, MNT, and physical activity.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the patients. Daily SMBG is especially important for patients treated with insulin to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is recommended three or more times daily. The optimal frequency and timing of SMBG for patients with type 2 diabetes on oral agent therapy is not known but should be sufficient to facilitate reaching glucose goals. A recent meta-analysis of SMBG in non–insulin-treated patients with type 2 diabetes concluded that some regimen of monitoring was associated with a reduction in A1C of ~0.4%. However, many of the studies in this analysis also included patient education with diet and exercise counseling and, in some cases, pharmacologic intervention, making it very difficult to assess the contribution of SMBG alone to improved control (21). Patients with type 2 diabetes on insulin typically need to perform SMBG more frequently than those not using insulin. When adding to or modifying therapy, type 1 and type 2 diabetic patients should test more often than usual. The role of SMBG in stable diet–treated patients with type 2 diabetes is not known.

Because the accuracy of SMBG is instrument and user dependent (22), it is important for health care providers to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise, or pharmacological therapy to achieve specific glycemic goals. Health professionals should evaluate at regular intervals the patient's ability to use SMBG data to guide treatment.

b. *A1C*

Recommendations

- Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). (E)
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. (E)
- Use of point-of-care testing for A1C allows for timely decisions on therapy changes, when needed. (E)

By performing an A1C test, health providers can measure a patient's average glycemia over the preceding 2–3 months (22) and, thus, assess treatment efficacy. A1C testing should be performed routinely in all patients with diabetes, first to document the degree of glycemic control at initial assessment and then as part of continuing care. Since the A1C test reflects mean glycemia over the preceding 2–3 months, measurement approximately every 3 months is required to determine whether a patient's metabolic control has been reached and maintained within the target range. Thus, regular performance of the A1C test permits detection of departures from the target (Table 6) in a timely fashion. For any individual patient, the frequency of A1C testing should be dependent on the clinical situation, the treatment regimen used, and the judgment of the clinician.

The A1C test is subject to certain limitations. Conditions that affect erythrocyte turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's clinical situation (22). The availability of the A1C result at the time that the patient is seen (point-of-care testing) has been reported to result in the frequency of intensification of therapy and improvement in glycemic control (23,24).

Glycemic control is best judged by the combination of the results of the patient's SMBG testing (as performed) and the current A1C result. The A1C should be used not only to assess the patient's control over the preceding 2–3 months, but also as a check on the accuracy of the meter (or the patient's self-reported results) and the adequacy of the SMBG testing schedule. Table 7 contains the correlation between A1C levels and mean plasma glucose levels based on data from the Diabetes Control and Complications Trial (DCCT) (25).

2. Glycemic goals

Recommendations

- Lowering A1C has been associated with a reduction of microvascular and neuropathic complications of diabetes (A) and possibly macrovascular disease (B).
- The A1C goal *for patients in general* is an A1C goal of <7%. (B)
- The A1C goal *for the individual patient* is

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 6 of 38
Dexcom v. Abbott, IPR2024-00521

Table 6—*Summary of recommendations for adults with diabetes*

Glycemic control	
A1C	<7.0%*
Preprandial capillary plasma glucose	90–130 mg/dl (5.0–7.2 mmol/l)
Peak postprandial capillary plasma glucose†	<180 mg/dl (<10.0 mmol/l)
Blood pressure	<130/80 mmHg
Lipids‡	
LDL	<100 mg/dl (<2.6 mmol/l)
Triglycerides	<150 mg/dl (<1.7 mmol/l)
HDL	>40 mg/dl (>1.0 mmol/l)§
Key concepts in setting glycemic goals:	
• A1C is the primary target for glycemic control	
• Goals should be individualized	
• Certain populations (children, pregnant women, and elderly) require special considerations	
• More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia	
• Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia	
• Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals	

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes. ‡Current NCEP/ATP III guidelines suggest that in patients with triglycerides ≥200 mg/dl, the "non-HDL cholesterol" (total cholesterol minus HDL) be utilized. The goal is ≤130 mg/dl (121). §For women, it has been suggested that the HDL goal be increased by 10 mg/dl.

an A1C as close to normal (<6%) as possible without significant hypoglycemia. (E)

- Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children or older adults, and individuals with comorbid conditions. (E)
- Aggressive glycemic management with insulin may reduce morbidity in patients with severe acute illness, perioperatively, following myocardial infarction, and in pregnancy. (B)

Glycemic control is fundamental to the management of diabetes. The goal of therapy is to achieve an A1C as close to normal as possible (representing normal fasting and postprandial glucose concentrations) in the absence of hypoglycemia. However, this goal is difficult to achieve with present therapies (26). Prospective, randomized, clinical trials in type 1 diabetes such as the DCCT (27,28) have shown that improved glycemic control is associated with sustained decreased rates of microvascular (retinopathy and nephropathy), macrovascular, and neuropathic complications (28–31).

Table 7—*Correlation between A1C level and mean plasma glucose levels on multiple testing over 2–3 months (25)*

	Mean plasma glucose	
A1C (%)	mg/dl	mmol/l
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

In type 2 diabetes, the U.K. Prospective Diabetes Study (UKPDS) demonstrated significant reductions in microvascular and neuropathic complications with intensive therapy (32–34). The potential of intensive glycemic control to reduce CVD in type 2 diabetes is supported by epidemiological studies (32–34) and a recent meta-analysis (35), but this potential benefit on CVD events has not been demonstrated in a randomized clinical trial.

In each of these large randomized prospective clinical trials, treatment regimens that reduced average A1C to ~7% (~1% above the upper limits of normal) were associated with fewer long-term microvascular complications; however, intensive control was found to increase the risk of severe hypoglycemia and weight gain (31,34).

Recommended glycemic goals for nonpregnant individuals are shown in Table 6. A major limitation to the available data is that they do not identify the optimum level of control for particular patients, as there are individual differences in the risks of hypoglycemia, weight gain, and other adverse effects. Furthermore, with multifactorial interventions, it is unclear how different components (e.g., educational interventions, glycemic targets, lifestyle changes, pharmacological agents) contribute to the reduction of complications. There are no clinical trial data available for the effects of glycemic control in patients with advanced complications, the elderly (≥65 years of age), or young children (<13 years of age). Less stringent treatment goals may be appropriate for patients with limited life expectancies, in the very young or older adults, and in individuals with comorbid conditions. Severe or frequent hypoglycemia is an indication for the modification of treatment regimens, including setting higher glycemic goals.

More stringent goals (i.e., a normal A1C, <6%) should be considered in individual patients based on epidemiological analyses suggesting that there is no lower limit of A1C at which further lowering does not reduce the risk of complications, at the risk of increased hypoglycemia (particularly in those with type 1 diabetes). However, the absolute risks and benefits of lower targets are unknown. The risks and benefits of an A1C goal of <6% are currently being tested in an ongoing study (ACCORD [Action to Control Cardiovascular Risk in Diabetes]) of type 2 diabetes.

Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of FPG in some epidemiological studies. Postprandial plasma glucose (PPG) levels >140 mg/dl are unusual in nondiabetic individuals, although large evening meals can be followed by plasma glucose values up to 180 mg/dl. There are now pharmacological agents that primarily modify PPG and thereby reduce A1C in parallel. Thus, in individuals who have premeal glucose values within target but are not meeting A1C targets, monitoring PPG 1–2 h after the start of the meal and treatment aimed at reducing PPG values <180 mg/dl may lower A1C. However, it should be noted that the effect of these approaches on micro- or macrovascular complications has not been studied (36).

As regards goals for glycemic control

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 7 of 38
Dexcom v. Abbott, IPR2024-00521

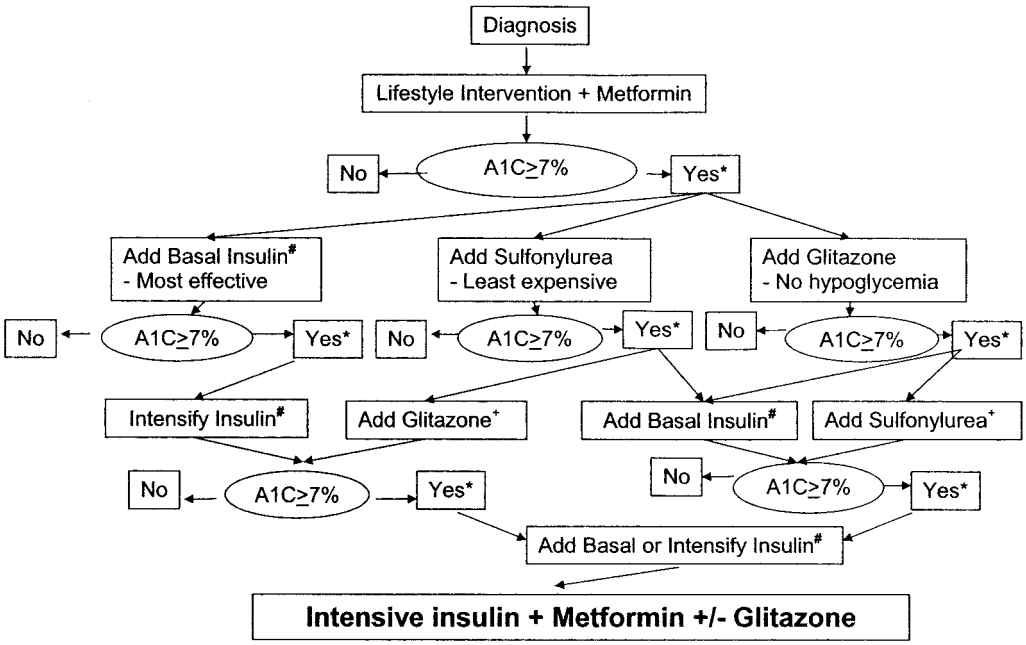

Figure 1—*Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle intervention at every visit. *Check A1C every 3 months until <7% and then at least every 6 months. +Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense. #See Fig. 1 in ref. 39 for initiation and adjustment of insulin.*

for women with GDM, recommendations from the Fourth International Workshop-Conference on Gestational Diabetes suggest lowering maternal capillary blood glucose concentrations to ≤95 mg/dl (5.3 mmol/l) fasting, ≤140 mg/dl (7.8 mmol/l) at 1 h, and/or ≤120 mg/dl (6.7 mmol/l) at 2 h after the meal (37). For further information on GDM, refer to the ADA position statement (14). For information on glycemic control during pregnancy in women with preexisting diabetes, refer to ref. 38.

3. Approach to treatment. A consensus statement from the ADA and the European Association for the Study of Diabetes on the approach to management of hyperglycemia in individuals with type 2 diabetes has recently been published (39). Early intervention with metformin in combination with lifestyle changes (MNT and exercise) with continuing, timely augmentation therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e., A1C <7% for most patients) are highlights of this approach. See Fig. 1 for metabolic management of type 2 diabetes.

Early initiation of insulin would be a safer approach for individuals presenting with weight loss, more severe symptoms, and glucose values >250–300 mg/dl.

Insulin therapy, consisting of intermediate- or long-acting basal insulin in combination with premeal rapid- or short-acting insulin is recommended for all patients with type 1 diabetes. An algorithm for adjusting premeal insulin doses to correct for blood glucose values outside of target ranges is appropriate for most patients with type 1 diabetes and insulin-treated type 2 diabetes. There are excellent reviews available that guide the initiation and management of insulin therapy to achieve desired glycemic goals (40,41).

D. MNT (42)

Recommendations

Diabetes and obesity management

- Individuals who have pre-diabetes or diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT. (B)
- MNT should be covered by insurance and other payors. (E)
- In overweight and obese insulin-resistant individuals, modest weight loss has been shown to reduce insulin resistance. Thus, weight loss is recommended for all overweight or obese individuals who have or are at risk for diabetes. (A)
- Structured programs that emphasize lifestyle changes, including education, reduced energy and fat (~30% of total energy) intake, regular physical activity, and regular participant contact, can produce long-term weight loss on the order of 5–7% of starting weight. Thus, lifestyle change should be the primary approach to weight loss. (A)
- Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintenance of weight loss. (B)

Fat intake

- Saturated fat intake should be <7% of total calories. (A)
- Intake of *trans* fat should be minimized. (E)

Carbohydrate intake

- Monitoring carbohydrate, whether by carbohydrate counting, exchanges, or experience-based estimation, remains a key strategy in achieving glycemic control. (A)
- For individuals with diabetes, the use of the glycemic index and glycemic load may provide a modest additional benefit for glycemic control over that observed when total carbohydrate is considered alone. (B)
- There is not sufficient evidence to recommend use of glycemic index or glycemic load for prevention of diabetes, although foods high in fiber are encouraged. (E)
- Low-carbohydrate diets (restricting total carbohydrate to <130 g/day) are not recommended in the treatment of overweight/obesity. The long-term effects of these diets are unknown, and although such diets produce short-term weight loss, maintenance of weight loss is sim-

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 8 of 38
Dexcom v. Abbott, IPR2024-00521

ilar to that from low-fat diets and the impact on CVD risk profile is uncertain. (B)

Other nutrition recommendations

- Sugar alcohols and nonnutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the Food and Drug Administration (FDA). (A)
- If adults with diabetes choose to use alcohol, daily intake should be limited to a moderate amount (one drink per day or less for adult women and two drinks per day or less for adult men). (E)
- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. (A)
- Benefit from chromium supplementation in people with diabetes or obesity has not been conclusively demonstrated and, therefore, cannot be recommended. (E)

MNT is an integral component of diabetes prevention, management, and self-management education. In addition to its role in preventing and controlling diabetes, ADA recognizes the importance of nutrition as an essential component of an overall healthy lifestyle. These recommendations are based on principles of good nutrition for the overall population from the 2005 Dietary Guidelines (43) and the recommended dietary allowances (RDAs) from the Institute of Medicine of the National Academies of Sciences (44). A review of the evidence regarding nutrition in preventing and controlling diabetes and its complications for the above nutrition recommendations and additional nutrition-related recommendations can be found elsewhere in this document. Achieving nutrition-related goals requires a coordinated team effort that includes the active involvement of the person with pre-diabetes or diabetes. Because of the complexity of nutrition issues, it is recommended that a registered dietitian who is knowledgeable and skilled in implementing nutrition therapy into diabetes management and education be the team member who provides MNT. However, it is essential that all team members are knowledgeable about nutrition therapy and are supportive of the person with diabetes.

For those individuals seeking guidance regarding macronutrient distribution, the DRIs may be helpful. The DRI report recommends that to meet the body's daily nutritional needs while minimizing risk for chronic diseases, adults (in general, not specifically those with diabetes) should consume 45–65% of total energy from carbohydrate, 20–35% from fat, and 10–35% from protein (44). The best mix of carbohydrate, protein, and fat appears to vary depending on individual circumstances.

E. DSME

Recommendations

- People with diabetes should receive DSME according to national standards when their diabetes is diagnosed and as needed thereafter. (B)
- DSME should be provided by health care providers who are qualified to provide that DSME based on their professional training and continuing education. (E)
- DSME should address psychosocial issues, since emotional well-being is strongly associated with positive diabetes outcomes. (C)
- DSME should be reimbursed by third-party payors. (E)

DSME is an essential element of diabetes care (45–51), and National Standards for DSME are based on evidence for its benefits. Education helps people with diabetes initiate effective self-care when they are first diagnosed. Ongoing DSME also helps people with diabetes maintain effective self-management as their diabetes presents new challenges and treatment advances become available. DSME helps patients optimize metabolic control, prevent and manage complications, and maximize quality of life, in a cost-effective manner.

Evidence for the benefits of DSME

Since the 1990s, there has been a shift from a didactic approach with DSME focusing on providing information to a skill-based approach that focuses on helping those with diabetes make informed self-management choices. Several studies have found that DSME is associated with improved diabetes knowledge (46), improved self-care behavior (46), improved clinical outcomes such as lower A1C (47,48,50,51), lower self-reported weight (46), and improved quality of life (49). Better outcomes were reported for DSME that were longer and included follow-up support (46), that were tailored to individual needs and preferences (45), and that addressed psychosocial issues (45,46,50).

The national standards for DSME

ADA-recognized DSME programs have staff that includes at least a registered nurse and a registered dietitian; these staff must be certified diabetes educators or have recent experience in diabetes education and management. The curriculum of ADA-recognized DSME programs must cover all areas of diabetes management, with the assessed needs of the individual determining which areas are addressed. All ADA-recognized DSME programs utilize a process of continuous quality improvement to evaluate the effectiveness of the DSME provided and to identify opportunities for improvement.

Reimbursement for DSME

DSME is reimbursed as part of the Medicare program as overseen by the Centers for Medicare and Medicaid Services (CMS) (www.cms.hhs.gov/DiabetesSelfManagement).

F. Physical activity

Recommendations

- To improve glycemic control, assist with weight maintenance, and reduce risk of CVD, at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (>70% of maximum heart rate) is recommended. The physical activity should be distributed over at least 3 days/week and with no more than two 2 consecutive days without physical activity. (A)
- In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance exercise three times a week, targeting all major muscle groups, progressing to three sets of 8–10 repetitions at a weight that cannot be lifted more than 8–10 times. (A)

Indications for graded exercise test with electrocardiogram monitoring

- A graded exercise test with electrocardiogram (ECG) monitoring should be seriously considered before undertaking aerobic physical activity with intensity exceeding the demands of everyday living (more intense than brisk walking) in previously sedentary diabetic

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 9 of 38
Dexcom v. Abbott, IPR2024-00521

individuals whose 10-year risk of a coronary event is likely to be ≥10%. (E)

ADA technical reviews on exercise in patients with diabetes have summarized the value of exercise in the diabetes management plan (52,53). Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals (8–10).

Definitions

The following definitions are based on those outlined in *Physical Activity and Health*, the 1996 report of the Surgeon General (54). Physical activity is defined as bodily movement produced by the contraction of skeletal muscle that requires energy expenditure in excess of resting energy expenditure. Exercise is a subset of physical activity: planned, structured, and repetitive bodily movement performed to improve or maintain one or more component of physical fitness. Aerobic exercise consists of rhythmic, repeated, and continuous movements of the same large muscle groups for at least 10 min at a time. Examples include walking, bicycling, jogging, swimming, water aerobics, and many sports. Resistance exercise consists of activities that use muscular strength to move a weight or work against a resistive load. Examples include weight lifting and exercises using weight machines.

Effects of structured exercise interventions on glycemic control and body weight in type 2 diabetes

Boulé et al. (55) undertook a systematic review and meta-analysis on the effects of structured exercise interventions in clinical trials of duration ≥8 weeks on A1C and body mass in people with type 2 diabetes. Twelve aerobic training studies and two resistance training studies were included (totaling 504 subjects), and the results were pooled using standard meta-analytic statistical methods. Postintervention A1C was significantly lower in exercise than control groups. Metaregression confirmed that the beneficial effect of exercise on A1C was independent of any effect on body weight. Therefore, structured exercise programs had a statistically and clinically significant beneficial effect on glycemic control, and this effect was not mediated primarily by weight loss.

Boulé et al. (56) later undertook a meta-analysis of the interrelationships among exercise intensity, exercise volume, change in cardiorespiratory fitness, and change in A1C. This meta-analysis provides support for higher-intensity aerobic exercise in people with type 2 diabetes as a means of improving A1C. These results would provide support for encouraging type 2 diabetic individuals who are already exercising at moderate intensity to consider increasing the intensity of their exercise in order to obtain additional benefits in both aerobic fitness and glycemic control.

Frequency of exercise

The U.S. Surgeon General's report (54) recommended that most people accumulate ≥30 min of moderate-intensity activity on most, ideally all, days of the week. The American College of Sports Medicine now recommends including resistance training in fitness programs for adults with type 2 diabetes (57). Resistance exercise improves insulin sensitivity to about the same extent as aerobic exercise (58). Two clinical trials published in 2002 provided strong evidence for the value of resistance training in type 2 diabetes (59,60).

Evaluation of the diabetic patient before recommending an exercise program

Before beginning a program of physical activity more vigorous than brisk walking, people with diabetes should be assessed for conditions that might be associated with increased likelihood of CVD or that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy, and preproliferative or proliferative retinopathy or macular edema. The patient's age and previous physical activity level should be considered.

A recent systematic review for the U.S. Preventive Services Task Force came to the conclusion that stress tests should usually not be recommended to detect ischemia in asymptomatic individuals at low CAD risk (<10% risk of a cardiac event over 10 years) because the risks of subsequent invasive testing triggered by false-positive tests outweighed the expected benefits from detection of previously unsuspected ischemia (61,62).

Exercise in the presence of nonoptimal glycemic control

Hyperglycemia. When people with type 1 diabetes are deprived of insulin for 12–48 h and are ketotic, exercise can worsen hyperglycemia and ketosis (63). Vigorous activity should probably be avoided in the presence of ketosis. However, provided the patient feels well and urine and/or blood ketones are negative, it is not necessary to postpone exercise based simply on hyperglycemia.

Hypoglycemia. In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. Hypoglycemia is rare in diabetic individuals who are not treated with insulin or insulin secretagogues. Added carbohydrate should be ingested if preexercise glucose levels are <100 mg/dl (5.6 mmol/l) (64). Supplementary carbohydrate is generally not necessary for individuals treated only with diet, metformin, α-glucosidase inhibitors, and/or TZDs without insulin or a secretagogue (65).

Exercise in the presence of specific long-term complications of diabetes

Retinopathy. In the presence of proliferative diabetic retinopathy (PDR) or severe non-PDR (NPDR), vigorous aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (66).

Peripheral neuropathy. Decreased pain sensation in the extremities results in increased risk of skin breakdown and infection and of Charcot joint destruction. Therefore, in the presence of severe peripheral neuropathy, it may be best to encourage non–weight-bearing activities such as swimming, bicycling, or arm exercises (67,68).

Autonomic neuropathy. Autonomic neuropathy can increase the risk of exercise-induced injury by decreasing cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation due to impaired skin blood flow and sweating, impaired night vision due to impaired papillary reaction, impaired thirst increasing risk of dehydration, and gastroparesis with unpredictable food delivery (67). Autonomic neuropathy is also strongly associated with CVD in people with diabetes (69,70). People with diabetic autonomic neuropathy should definitely undergo cardiac investigation before beginning physical activity more

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 10 of 38
Dexcom v. Abbott, IPR2024-00521

intense than that to which they are accustomed.

Microalbuminuria and nephropathy. Physical activity can acutely increase urinary protein excretion. There is no evidence from clinical trials or cohort studies demonstrating that vigorous exercise increases the rate of progression of diabetic kidney disease. There may be no need for any specific exercise restrictions for people with diabetic kidney disease (71).

G. Psychosocial assessment and care

Recommendations

- Preliminary assessment of psychological and social status should be included as part of the medical management of diabetes. (E)
- Psychosocial screening should include but is not limited to attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional), and psychiatric history. (E)
- Screening for psychosocial problems such as depression, eating disorders, and cognitive impairment is needed when adherence to the medical regimen is poor. (E)
- It is preferable to incorporate psychological treatment into routine care rather than wait for identification of a specific problem or deterioration in psychological status. (E)

Psychological and social state can impact the patient's ability to carry out diabetes care tasks (72–77). As a result, health status may be compromised. Family conflict around diabetes care tasks is also common and may interfere with treatment outcomes (78). There are opportunities for the clinician to assess psychosocial status in a timely and efficient manner so that referral for appropriate services can be accomplished (79).

Key opportunities for screening of psychosocial status occur at diagnosis, during regularly scheduled management visits, during hospitalizations, at discovery of complications, or at the discretion of the clinician when problems in glucose control, quality of life, or adherence are identified (80). Patients are likely to exhibit psychological vulnerability at diagnosis and when their medical status changes, i.e., the end of the honeymoon period, when the need for intensified treatment is evident, and when complications are discovered (75,77).

Psychosocial screening should include but is not limited to attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional) (76), and psychiatric history (77,80,81). Particular attention needs to be paid to gross noncompliance with medical regimen (due to self or others) (81), depression with the possibility of self-harm (73,74), indications of an eating disorder (82) or a problem that appears to be organic in origin, and cognitive functioning that significantly impairs judgment (74). In these cases, immediate referral for further evaluation by a mental health specialist familiar with diabetes management should occur. Behavioral assessment of management skills is also recommended.

It is preferable to incorporate psychological treatment into routine care rather than waiting for identification of a specific problem or deterioration in psychological status (79). Screening tools can facilitate this goal, and although the clinician may not feel qualified to treat psychological problems, utilizing the patient-provider relationship as a foundation for further treatment can increase the likelihood that the patient will accept referral for other services. It is important to establish that emotional well-being is part of diabetes management (80).

H. Referral for diabetes management

For a variety of reasons, some people with diabetes and their health care providers do not achieve the desired goals of treatment (Table 6). Intensification of the treatment regimen is suggested and includes identification (or assessment) of barriers to adherence, culturally appropriate and enhanced DSME, comanagement with a diabetes team, change in pharmacological therapy, initiation of or increase in SMBG, more frequent contact with the patient, and referral to an endocrinologist.

I. Intercurrent illness

The stress of illness, trauma, and/or surgery frequently aggravates glycemic control and may precipitate diabetic ketoacidosis (DKA) or nonketotic hyperosmolar state. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose and urine or blood ketones. A vomiting illness accompanied by ketosis may indicate DKA, a life-threatening condition that requires immediate medical care to prevent complications and death; the possibility of DKA should always be considered (83). Marked hyperglycemia requires temporary adjustment of the treatment program and, if accompanied by ketosis, frequent interaction with the diabetes care team. The patient treated with oral glucose-lowering agents or MNT alone may temporarily require insulin. Adequate fluid and caloric intake must be assured. Infection or dehydration is more likely to necessitate hospitalization of the person with diabetes than the person without diabetes. The hospitalized patient should be treated by a physician with expertise in the management of diabetes, and recent studies suggest that achieving very stringent glycemic control may reduce mortality in the immediate postmyocardial infarction period (84). Aggressive glycemic management with insulin may reduce morbidity in patients with severe acute illness (85).

For further information on management of patients in the hospital with DKA or nonketotic hyperosmolar state, refer to the ADA position statement (83).

J. Hypoglycemia

Recommendations

- Glucose (15–20 g) is the preferred treatment for hypoglycemia, although any form of carbohydrate that contains glucose may be used, and treatment effects should be apparent in 15 min. (A)
- Treatment effects on hypoglycemia may only be temporarily corrected. Therefore, plasma glucose should be retested in ~15 min, as additional treatment may be necessary. (B)
- Glucagon should be prescribed for all patients at significant risk of severe hypoglycemia and does not require a health care professional for its administration. (E)

Hypoglycemia, especially in insulin-treated patients, is the leading limiting factor in the glycemic management of type 1 and type 2 diabetes (86). Treatment of hypoglycemia (plasma glucose <70 mg/dl) requires ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Although pure glucose may be the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose. Adding protein to carbohydrate does not

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 11 of 38
Dexcom v. Abbott, IPR2024-00521

affect the glycemic response and does not prevent subsequent hypoglycemia. Adding fat, however, may retard and then prolong the acute glycemic response (87).

Rare situations of severe hypoglycemia (where the individual requires the assistance of another person and cannot be treated with oral carbohydrate) should be treated using emergency glucagon kits, which require a prescription. Those in close contact with, or having custodial care of, people with diabetes, such as family members, roommates, school personnel, child care providers, correctional institution staff, and coworkers, should be instructed in use of such kits. An individual does not need to be a health care professional to safely administer glucagon. Care should be taken to ensure that unexpired glucagon kits are available.

K. Immunization

Recommendations

- Annually provide an influenza vaccine to all diabetic patients ≥6 months of age. (C)
- Provide at least one lifetime pneumococcal vaccine for adults with diabetes. A one-time revaccination is recommended for individuals >64 years of age previously immunized when they were <65 years of age if the vaccine was administered >5 years ago. Other indications for repeat vaccination include nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as after transplantation. (C)

Influenza and pneumonia are common, preventable infectious diseases associated with high mortality and morbidity in the elderly and in people with chronic diseases. There are limited studies reporting the morbidity and mortality of influenza and pneumococcal pneumonia specifically in people with diabetes. Observational studies of patients with a variety of chronic illnesses, including diabetes, show that these conditions are associated with an increase in hospitalizations for influenza and its complications. Based on a case-control series, influenza vaccine has been shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics (88). People with diabetes may be at increased risk of the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, which has a mortality rate as high as 50%.

Safe and effective vaccines are available that can greatly reduce the risk of serious complications from these diseases (88,89). There is sufficient evidence to support that people with diabetes have appropriate serologic and clinical responses to these vaccinations. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends influenza and pneumococcal vaccines for all individuals >65 years of age, as well as for all individuals of any age with diabetes.

For a complete discussion on the prevention of influenza and pneumococcal disease in people with diabetes, consult the technical review and position statement on this subject (90,91).

VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

A. CVD

CVD is the major cause of mortality for individuals with diabetes. It is also a major contributor to morbidity and direct and indirect costs of diabetes. Type 2 diabetes is an independent risk factor for macrovascular disease, and its common coexisting conditions (e.g., hypertension and dyslipidemia) are also risk factors.

Studies have shown the efficacy of reducing cardiovascular risk factors in preventing or slowing CVD. Evidence is summarized in the following sections and reviewed in detail in the ADA technical reviews on hypertension (92), dyslipidemia (93), aspirin therapy (131), and smoking cessation (94) and the consensus statement on CHD in people with diabetes (95). Emphasis should be placed on reducing cardiovascular risk factors, when possible, and clinicians should be alert for signs and symptoms of atherosclerosis.

1. Hypertension/blood pressure control

Recommendations

Screening and diagnosis

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg should have blood pressure confirmed on a separate day. (C)

Goals

- Patients with diabetes should be treated to a systolic blood pressure <130 mmHg. (C)
- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg. (B)

Treatment

- Patients with hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg) should receive drug therapy in addition to lifestyle and behavioral therapy. (A)
- Multiple drug therapy (two or more agents at proper doses) is generally required to achieve blood pressure targets. (B)
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg should be given lifestyle and behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, in addition, be treated with pharmacological agents that block the renin-angiotensin system. (E)
- Initial drug therapy for those with a blood pressure >140/90 mmHg should be with a drug class demonstrated to reduce CVD events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers [ARBs], β-blockers, diuretics, and calcium channel blockers). (A)
- All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If needed to achieve blood pressure targets, a thiazide diuretic should be added. (E)
- If ACE inhibitors, ARBs, or diuretics are used, monitor renal function and serum potassium levels. (E)
  - In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)
  - In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
  - In those with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency, ARBs have been shown to delay the progression of nephropathy. (A)

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 12 of 38
Dexcom v. Abbott, IPR2024-00521

- In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110–129/65–79 mmHg are suggested in the interest of long-term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy. (E)
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications. (E)
- Patients not achieving target blood pressure despite multiple drug therapy should be referred to a physician experienced in the care of patients with hypertension. (E)
- Orthostatic measurement of blood pressure should be performed in people with diabetes and hypertension when clinically indicated. (E)

Hypertension (blood pressure ≥140/90 mmHg) is a common comorbidity of diabetes, affecting the majority of people with diabetes, depending on type of diabetes, age, obesity, and ethnicity. Hypertension is also a major risk factor for CVD and microvascular complications such as retinopathy and nephropathy. In type 1 diabetes, hypertension is often the result of underlying nephropathy. In type 2 diabetes, hypertension may be present as part of the metabolic syndrome (i.e., obesity, hyperglycemia, and dyslipidemia), which is accompanied by high rates of CVD.

Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to <140 mmHg systolic and <80 mmHg diastolic in individuals with diabetes (96–99). Epidemiologic analyses show that blood pressure >115/75 mmHg are associated with increased cardiovascular event rates and mortality in individuals with diabetes (96,100,101). Therefore, a target blood pressure goal of <130/80 mmHg is reasonable if it can be safely achieved.

Although there are no well-controlled studies of diet and exercise in the treatment of hypertension in individuals with diabetes, reducing sodium intake and body weight (when indicated); increasing consumption of fruits, vegetables, and low-fat dairy products; avoiding excessive alcohol consumption; and increasing activity levels have been shown to be effective in reducing blood pressure in nondiabetic individuals (102). These nonpharmacological strategies may also positively affect glycemia and lipid control. Their effects on cardiovascular events have not been well measured.

Lowering of blood pressure with regimens based on antihypertensive drugs, including ACE inhibitors, ARBs, β-blockers, diuretics, and calcium channel blockers, has been shown to be effective in lowering cardiovascular events. Several studies suggest that ACE inhibitors may be superior to dihydropyridine calcium channel blockers (DCCBs) in reducing cardiovascular events (103,104). Additionally, in people with diabetic nephropathy, ARBs may be superior to DCCBs for reducing heart failure but not overall cardiovascular events (105). Conversely, in the recently completed INVEST (International Verapamil-Trandolapril Study) of >22,000 people with CAD and hypertension, the non-DCCB verapamil demonstrated a similar reduction in cardiovascular mortality to a β-blocker. Moreover, this relationship held true in the diabetic subgroup (106).

ACE inhibitors have been shown to improve cardiovascular outcomes in high–cardiovascular risk patients with or without hypertension (107,108). In patients with congestive heart failure (CHF), the addition of ARBs to either ACE inhibitors or other therapies reduces the risk of cardiovascular death or hospitalization for heart failure (109–111). In one study, an ARB was superior to a β-blocker as a therapy to improve cardiovascular outcomes in a subset of diabetic patients with hypertension and left ventricular hypertrophy (112). The compelling effect of ACE inhibitors or ARBs in patients with albuminuria or renal insufficiency provides additional rationale for use of these agents (see section VI, B below).

The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a large randomized trial of different initial blood pressure pharmacological therapies, found no large differences in initial therapy with chlorthalidone, amlodipine, or lisinopril. Diuretics appeared slightly more effective than other agents, particularly for reducing heart failure (113). The α-blocker arm of the ALLHAT was terminated after interim analysis showed that doxazosin was substantially less effective in reducing CHF than diuretic therapy (114).

Before beginning treatment, patients with elevated blood pressure should have their blood pressure reexamined within 1 month to confirm the presence of hypertension. Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg, however, mandates that immediate pharmacological therapy be initiated. Patients with hypertension should be seen as often as needed until the recommended blood pressure goal is obtained and then seen as necessary (96). In these patients, other cardiovascular risk factors, including obesity, hyperlipidemia, smoking, presence of microalbuminuria (assessed before initiation of treatment), and glycemic control, should be carefully assessed and treated. Many patients will require three or more drugs to reach target goals.

During pregnancy in diabetic women with chronic hypertension, target blood pressure goals of systolic blood pressure 110–129 mmHg and diastolic blood pressure 65–79 mmHg are reasonable, as they may contribute to long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they are likely to cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which might reduce uteroplacental perfusion.

2. Dyslipidemia/lipid management

Recommendations

Screening

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (LDL <100 mg/dl, HDL >50 mg/dl, and triglycerides <150 mg/dl), lipid assessments may be repeated every 2 years. (E)

Treatment recommendations and goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; weight loss (if indicated); and increased physical activity has been shown to improve the lipid profile in patients with diabetes. (A)

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 13 of 38
Dexcom v. Abbott, IPR2024-00521

- In individuals without overt CVD
  - The primary goal is an LDL <100 mg/dl (2.6 mmol/l). (A)
  - For those over the age of 40 years, statin therapy to achieve an LDL reduction of 30–40% regardless of baseline LDL levels is recommended. (A)
  - For those under the age of 40 years but at increased risk due to other cardiovascular risk factors who do not achieve lipid goals with lifestyle modifications alone, the addition of pharmacological therapy is appropriate. (C)
- In individuals with overt CVD
  - All patients should be treated with a statin to achieve an LDL reduction of 30–40%. (A)
  - A lower LDL cholesterol goal of <70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option. (B)
- Lower triglycerides to <150 mg/dl (1.7 mmol/l) and raise HDL cholesterol to >40 mg/dl (1.0 mmol/l). In women, an HDL goal 10 mg/dl higher (>50 mg/dl) should be considered. (C)
- Lowering triglycerides and increasing HDL cholesterol with a fibrate is associated with a reduction in cardiovascular events in patients with clinical CVD, low HDL, and near-normal levels of LDL. (A)
- Combination therapy using statins and other lipid-lowering agents may be necessary to achieve lipid targets but has not been evaluated in outcomes studies for either CVD event reduction or safety. (E)
- Statin therapy is contraindicated in pregnancy. (E)

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, which contributes to higher rates of CVD. Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering triglycerides has been shown to reduce macrovascular disease and mortality in patients with type 2 diabetes, particularly in those who have had prior cardiovascular events. In studies using HMG (hydroxymethylglutaryl)-CoA reductase inhibitors (statins), patients with diabetes achieved significant reductions in coronary and cerebrovascular events (115–118). In two studies using the fibric acid derivative gemfibrozil, reductions in cardiovascular end points were also achieved (119,120).

Target lipid levels are shown in Table 6. Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, should allow some patients to reach these lipid levels. Nutrition intervention should be tailored according to each patient's age, type of diabetes, pharmacological treatment, lipid levels, and other medical conditions and should focus on the reduction of saturated fat, cholesterol, and *trans* unsaturated fat intake. Glycemic control can also beneficially modify plasma lipid levels. Particularly in patients with very high triglycerides and poor glycemic control, glucose lowering may be necessary to control hypertriglyceridemia. Pharmacological treatment is indicated if there is an inadequate response to lifestyle modifications and improved glucose control. However, in patients with clinical CVD and LDL >100 mg/dl, pharmacological therapy should be initiated at the same time that lifestyle intervention is started. In patients with diabetes aged <40 years, similar consideration for LDL-lowering therapy should be given if they have increased cardiovascular risk (e.g., additional cardiovascular risk factors or long duration of diabetes). Very little clinical trial data exist for patients in this age-group.

The first priority of pharmacological therapy is to lower LDL cholesterol to a target goal of <100 mg/dl (2.60 mmol/l) or therapy to achieve a reduction in LDL of 30–40%. For LDL lowering, statins are the drugs of choice. Other drugs that lower LDL include nicotinic acid, ezetimbe, bile acid sequestrants, and fenofibrate (121,122).

The Heart Protection Study (118) demonstrated that in individuals with diabetes over the age of 40 years with a total cholesterol >135 mg/dl, LDL reduction of ~30% from baseline with the statin simvastatin was associated with an ~25% reduction in the first event rate for major coronary artery events independent of baseline LDL, preexisting vascular disease, type or duration of diabetes, or adequacy of glycemic control. Similarly, in the CARDS (Coronary Artery Diabetes Study) (124), patients with type 2 diabetes randomized to 10 mg atorvastatin daily had a significant reduction in cardiovascular events including stroke.

Recent clinical trials in high-risk patients, such as those with acute coronary syndromes or previous cardiovascular events (125–127), have demonstrated that more aggressive therapy with high doses of statins to achieve an LDL of <70 mg/dl led to a significant reduction in further events. The risk of side effects with high doses of statins is significantly outweighed by the benefits of such therapy in these high-risk patients. Therefore, a reduction in LDL to a goal of <70 mg/dl is an option in very-high-risk patients with overt CVD (122). The combination of statins with other lipid-lowering drugs such as ezetimibe may allow achievement of the LDL goal with a lower dose of a statin in such patients (128), but no data are available as to whether such combination therapy is more effective than a statin alone in preventing cardiovascular events.

Relatively little data are available on lipid-lowering therapy in subjects with type 1 diabetes. In the Heart Protection Study, ~600 patients with type 1 diabetes had a proportionately similar, but not statistically significant, reduction in risk compared with patients with type 2 diabetes. Although the data are not definitive, consideration should be given for similar lipid-lowering therapy in type 1 diabetic patients as in type 2 diabetic patients, particularly if they have other cardiovascular risk factors or features of the metabolic syndrome.

If the HDL is <40 mg/dl and the LDL between 100 and 129 mg/dl, a fibric acid derivative or niacin might be used. Niacin is the most effective drug for raising HDL but can significantly increase blood glucose at high doses. More recent studies demonstrate that at modest doses (750–2,000 mg/day), significant benefits to LDL, HDL, and triglyceride levels are accompanied by only modest changes in glucose that are generally amenable to adjustment of diabetes therapy (129,130).

Combination therapy, with a statin and a fibrate or statin and niacin, may be efficacious for patients needing treatment for all three lipid fractions, but this combination is associated with an increased risk for abnormal transaminase levels, myositis, or rhabdomyolysis. The risk of rhabdomyolysis seems to be lower when statins are combined with fenofibrate than gemfibrozil. There is also a risk of a rise in plasma creatinine, particularly with fenofibrate. It is important to note that clinical trials with fibrates and niacin have demonstrated benefits in patients who were not being treated with statins and that there are no data available on reduction of events with such combinations. The risks may be greater in patients who are treated with combinations of these drugs with high doses of statins.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 14 of 38
Dexcom v. Abbott, IPR2024-00521

3. Antiplatelet agents

Recommendations

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD. (A)
- Use aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with:
  - Type 2 diabetes at increased cardiovascular risk, including those who are >40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (A)
  - Type 1 diabetes at increased cardiovascular risk, including those who are >40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (C)
- Consider aspirin therapy in people between the age of 30 and 40 years, particularly in the presence of other cardiovascular risk factors. (E)
- Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye's syndrome associated with aspirin use in this population. People <30 years have not been studied. (E)
- Combination therapy using other antiplatelet agents such as clopidrogel in addition to aspirin should be used in patients with severe and progressive CVD. (C)
- Other antiplatelet agents may be a reasonable alternative for high-risk patients with aspirin allergy, with bleeding tendency, who are receiving anticoagulant therapy, with recent gastrointestinal bleeding, and with clinically active hepatic disease who are not candidates for aspirin therapy. (E)

The use of aspirin in diabetes is reviewed in detail in the ADA technical review (131) and position statement (132) on aspirin therapy. Aspirin has been recommended as a primary (133,134) and secondary therapy to prevent cardiovascular events in diabetic and nondiabetic individuals. One large meta-analysis and several clinical trials demonstrate the efficacy of using aspirin as a preventive measure for cardiovascular events, including stroke and myocardial infarction. Many trials have shown an ~30% decrease in myocardial infarction and a 20% decrease in stroke in a wide range of patients, including young and middle-aged patients, patients with and without a history of CVD, males and females, and patients with hypertension.

Dosages used in most clinical trials ranged from 75 to 325 mg/day. There is no evidence to support any specific dose, but using the lowest possible dosage may help reduce side effects. There is no evidence for a specific age at which to start aspirin, but at ages <30 years, aspirin has not been studied.

Clopidogrel has been demonstrated to reduce CVD rates in diabetic individuals (135). Adjunctive therapy in very-high-risk patients or as alternative therapy in aspirin-intolerant patients should be considered.

4. Smoking cessation

Recommendations

- Advise all patients not to smoke. (A)
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. (B)

Issues of smoking in diabetes are reviewed in detail in the ADA technical review (94) and position statement (136) on smoking cessation. A large body of evidence from epidemiological, case-control, and cohort studies provides convincing documentation of the causal link between cigarette smoking and health risks. Cigarette smoking contributes to one of every five deaths in the U.S. and is the most important modifiable cause of premature death. Much of the prior work documenting the impact of smoking on health did not separately discuss results on subsets of individuals with diabetes, suggesting that the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently found a heightened risk of morbidity and premature death associated with the development of macrovascular complications among smokers. Smoking is also related to the premature development of microvascular complications of diabetes and may have a role in the development of type 2 diabetes.

A number of large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of counseling in changing smoking behavior. Such studies, combined with others specific to individuals with diabetes, suggest that smoking cessation counseling is effective in reducing tobacco use (137,138).

The routine and thorough assessment of tobacco use is important as a means of preventing smoking or encouraging cessation. Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse.

5. CHD screening and treatment

Recommendations

- In patients >55 years of age, with or without hypertension but with another cardiovascular risk factor (history of CVD, dyslipidemia, microalbuminuria, or smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events. (A)
- In patients with a prior myocardial infarction or in patients undergoing major surgery, β-blockers, in addition, should be considered to reduce mortality. (A)
- In asymptomatic patients, consider a risk factor evaluation to stratify patients by 10-year risk and treat risk factors accordingly. (B)
- In patients with treated CHF, metformin use is contraindicated. TZDs are associated with fluid retention, and their use can be complicated by the development of CHF. Caution in prescribing TZDs in the setting of known CHF or other heart diseases, as well as in patients with preexisting edema or concurrent insulin therapy, is required. (C)

CHD screening and treatment are reviewed in detail in the ADA consensus statement on CHD in people with diabetes (95). To identify the presence of CHD in diabetic patients without clear or suggestive symptoms of CAD, a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up is recommended. However, a recent study concluded that using current guidelines fails to detect a significant percentage of patients with silent ischemia (69).

At least annually, cardiovascular risk factors should be assessed. These risk factors include dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of micro- or macroalbuminuria. Abnormal risk factors should be treated as described elsewhere in these guidelines. Patients at increased CHD risk should receive aspirin and may warrant an ACE inhibitor.

Candidates for a diagnostic cardiac

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 15 of 38
Dexcom v. Abbott, IPR2024-00521

stress test include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting ECG. The screening of asymptomatic patients remains controversial.

Studies have demonstrated that a significant percentage of patients with diabetes who have no symptoms of CAD have abnormal stress tests, either by ECG or echo and nuclear perfusion imaging. Some of these patients, though clearly not all, have significant coronary stenoses if they proceed to angiography. It has also been demonstrated that patients with silent myocardial ischemia have a poorer prognosis than those with normal stress tests. Their risk is further accentuated if cardiac autonomic neuropathy coexists. Candidates for a screening cardiac stress test include those with *1*) a history of peripheral or carotid occlusive disease and *2*) sedentary lifestyle, age >35 years, and plans to begin a vigorous exercise program. There are no data to suggest that patients who start to increase their physical activity by walking or similar exercise increase their risk of a CVD event and therefore are unlikely to need a stress test.

It has previously been proposed to screen those with two or more additional cardiac risk factors. However, this likely includes the vast majority of patients with type 2 diabetes (given that the risk factors frequently cluster). The DIAD (Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects) study suggested that conventional cardiac risk factors did not help to identify those patients with abnormal perfusion imaging (69).

Current evidence suggests that noninvasive tests can improve assessment of future CHD risk. There is, however, no current evidence that such testing in asymptomatic patients with risk factors improves outcomes or leads to better utilization of treatments (62).

Approximately 1 in 5 will have an abnormal test, and ~1 in 15 will have a major abnormality. More information is needed concerning prognosis, and the value of early intervention (invasive or noninvasive) before widespread screening is recommended. All patients irrespective of their CAD status should have aggressive risk factor modification, including control of glucose, lipids, and blood pressure and prophylactic aspirin therapy.

Patients with abnormal exercise ECG and patients unable to perform an exercise ECG require additional or alternative testing. Currently, stress nuclear perfusion and stress echocardiography are valuable next-level diagnostic procedures. A consultation with a cardiologist is recommended regarding further workup.

When identified, the optimal therapeutic approach to the diabetic patient with silent myocardial ischemia is unknown. Certainly if major CAD is identified, aggressive intervention appears warranted. If minor stenoses are detected, however, it is unknown whether there is any benefit to further invasive evaluation and/or therapy. There are no well-conducted prospective trials with adequate control groups to shed light on this subject. Accordingly, there are no evidence-based guidelines for screening the asymptomatic diabetic patient for CAD.

B. Nephropathy screening and treatment

Recommendations

General recommendations

- To reduce the risk and/or slow the progression of nephropathy, optimize glucose control. (A)
- To reduce the risk and/or slow the progression of nephropathy, optimize blood pressure control. (A)

Screening

- Perform an annual test for the presence of microalbuminuria in type 1 diabetic patients with diabetes duration of ≥5 years and in all type 2 diabetic patients, starting at diagnosis and during pregnancy. (E)
- Serum creatinine should be measured at least annually for the estimation of glomerular filtration rate (GFR) in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine alone should not be used as a measure of kidney function but instead used to estimate GFR and stage the level of chronic kidney disease (CKD). (E)

Treatment

- In the treatment of both micro- and macroalbuminuria, either ACE inhibitors or ARBs should be used except during pregnancy. (A)
- While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:
  - In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)
  - In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
  - In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy. (A)
  - If one class is not tolerated, the other should be substituted. (E)
- Reduction of protein intake to 0.8–1.0 $g \cdot kg\ body\ wt^{-1} \cdot day^{-1}$ in individuals with diabetes and the earlier stages of CKD and to 0.8 $g \cdot kg\ body\ wt^{-1} \cdot day^{-1}$ in the later stages of CKD may improve measures of renal function (urine albumin excretion rate, GFR) and is recommended (B)
- To slow the progression of nephropathy, the use of DCCBs as initial therapy is not more effective than placebo. Their use in nephropathy should be restricted to additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs. (B)
- In the setting of albuminuria or nephropathy, in patients unable to tolerate ACE inhibitors and/or ARBs, consider the use of non-DCCBs, β-blockers, or diuretics for the management of blood pressure. Use of non-DCCBs may reduce albuminuria in diabetic patients, including during pregnancy. (E)
- If ACE inhibitors, ARBs, or diuretics are used, monitor serum potassium levels for the development of hyperkalemia. (B)
- Continued surveillance of microalbuminuria/proteinuria to assess both response to therapy and progression of disease is recommended. (E)
- Consider referral to a physician experienced in the care of diabetic renal disease when the estimated GFR has fallen to <60 ml/min per 1.73 m^2 or if difficulties occur in the management of hypertension or hyperkalemia. (B)

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD). Persistent albuminuria in the

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 16 of 38
Dexcom v. Abbott, IPR2024-00521

Table 8—*Definitions of abnormalities in albumin excretion*

Category	Spot collection (μg/mg creatinine)
Normal	<30
Microalbuminuria	30–299
Macro (clinical)-albuminuria	≥300

Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds. Exercise within 24 h, infection, fever, CHF, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values.

range of 30–299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes. Microalbuminuria is also a well-established marker of increased CVD risk (139,140).

Patients with microalbuminuria who progress to macroalbuminuria (≥300 mg/24 h) are likely to progress to ESRD over a period of years (141,142). Over the past several years, a number of interventions have been demonstrated to reduce the risk and slow the progression of renal disease.

Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to delay the onset of microalbuminuria and the progression of micro- to macroalbuminuria in patients with type 1 (143,144) and type 2 (32,33) diabetes. The UKPDS provided strong evidence that control of blood pressure can reduce the development of nephropathy (97). In addition, large prospective randomized studies in patients with type 1 diabetes have demonstrated that achievement of lower levels of systolic blood pressure (<140 mmHg) resulting from treatment using ACE inhibitors provides a selective benefit over other antihypertensive drug classes in delaying the progression from micro- to macroalbuminuria and can slow the decline in GFR in patients with macroalbuminuria (145–147).

In addition, ACE inhibitors have been shown to reduce severe CVD (i.e., myocardial infarction, stroke, death), thus further supporting the use of these agents in patients with microalbuminuria (107). ARBs have also been shown to reduce the rate of progression from micro- to macroalbuminuria as well as ESRD in patients with type 2 diabetes (148–150). Some evidence suggests that ARBs have a smaller magnitude of rise in potassium compared with ACE inhibitors in people with nephropathy (106). To slow the progression of nephropathy, the use of DCCBs as initial therapy is not more effective than placebo. Their use in nephropathy should be restricted to additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs (105). In the setting of albuminuria or nephropathy, in patients unable to tolerate ACE inhibitors and/or ARBs, consider the use of non-DCCBs, β-blockers, or diuretics for the management of blood pressure (106,151).

Studies in patients with varying stages of nephropathy have shown that protein restriction helps slow the progression of albuminuria, GFR decline, and occurrence of ESRD (152–154). Protein restriction should be considered particularly in patients whose nephropathy seems to be progressing despite optimal glucose and blood pressure control and use of ACE inhibitor and/or ARBs (155).

Screening for microalbuminuria can be performed by three methods: *1*) measurement of the albumin-to-creatinine ratio in a random spot collection (preferred method); *2*) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and *3*) timed (e.g., 4-h or overnight) collection.

The analysis of a spot sample for the albumin-to-creatinine ratio is strongly recommended by most authorities (156,157). The other two alternatives (24-h collection and a timed specimen) are rarely necessary. Measurement of a spot urine for albumin only, whether by immunoassay or by using a dipstick test specific for microalbumin, without simultaneously measuring urine creatinine, is less expensive than the recommended methods but is susceptible to false-negative and -positive determinations as a result of variation in urine concentration due to hydration and other factors.

At least two of three tests measured within a 6-month period should show elevated levels before a patient is designated as having microalbuminuria. Abnormalities of albumin excretion are defined in Table 8.

Screening for microalbuminuria is indicated in pregnancies complicated by diabetes, since microalbuminuria in the absence of urinary tract infection is a strong predictor of superimposed preeclampsia. In the presence of macroalbuminuria or urine dipstick proteinuria, estimation of GFR by serum creatinine (see below) or 24-h urine creatinine clearance is indicated to stage the patient's renal disease, and other tests may be necessary to diagnose preeclampsia.

Information on presence of urine albumin excretion in addition to level of GFR may be used to stage CKD according to the National Kidney Foundation. The current National Kidney Foundation classification (Table 9) is primarily based on GFR levels and therefore differs from some earlier staging systems used by others, in which staging is based primarily on urinary albumin excretion (158). Studies have found decreased GFR in the absence of increase urine albumin excretion in a substantial percentage of adults with diabetes (159,160). Thus, these studies demonstrate that significant decline in GFR may be noted in adults with type 1 and type 2 diabetes in the absence of increased urine albumin excretion. It is now clear that stage 3 or higher CKD (GFR <60 ml/min per 1.73 m^2) occurs in the absence of urine albumin excretion in a sub-

Table 9—*Stages of CKD*

Stage	Description	GFR (ml/min per 1.73 m^2 body surface area)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

*Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests. Adapted from ref. 157a.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 17 of 38
Dexcom v. Abbott, IPR2024-00521

stantial proportion of adults with diabetes. Screening this population for increased urine albumin excretion alone, therefore, will miss a considerable number of CKD cases (158).

Serum creatinine should be measured at least annually for the estimation of GFR in all adults with diabetes regardless of the degree of urine albumin excretion. Serum creatinine alone should not be used as a measure of kidney function, but used to estimate GFR and stage the level of CKD. The GFR can be easily estimated using formulae like the Cockroft-Gault formula or a newer prediction formula developed by Levey et al. (161) using data collected from the MDRD (Modification of Diet and Renal Disease) study. Estimated GFR can easily be calculated by going to www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

The role of annual microalbumuria assessment is less clear after diagnosis of microalbuminuria and institution of ACE inhibitor or ARB therapy and blood pressure control. Most experts, however, recommend continued surveillance to assess both response to therapy and progression of disease. Some experts suggest that reducing urine microalbuminuria to the normal or near-normal range, if possible, may improve renal and cardiovascular prognosis. This approach has not been formally evaluated in prospective trials.

Consider referral to a physician experienced in the care of diabetic renal disease either when the GFR has fallen to <60 ml/min per 1.73 m^2 or if difficulties occur in the management of hypertension or hyperkalemia. It is suggested that consultation with a nephrologist be obtained when the GFR is <30 ml/min per 1.73 m^2. Early referral of such patients has been found to reduce cost and improve quality of care and keep people off dialysis longer (162,163).

C. Retinopathy screening and treatment

Recommendations

General recommendations

- Optimal glycemic control can substantially reduce the risk and progression of diabetic retinopathy. (A)
- Optimal blood pressure control can reduce the risk and progression of diabetic retinopathy. (A)
- Aspirin therapy does not prevent retinopathy or increase the risks of hemorrhage. (A)

Screening

- Adults and adolescents with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 3–5 years after the onset of diabetes. (B)
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes. (B)
- Subsequent examinations for type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist. Less frequent exams (every 2–3 years) may be considered in the setting of a normal eye exam. Examinations will be required more frequently if retinopathy is progressing. (B)
- Women who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum. This guideline does not apply to women who develop GDM because such individuals are not at increased risk for diabetic retinopathy. (B)

Treatment

- Laser therapy can reduce the risk of vision loss in patients with high-risk characteristics (HRCs). (A)
- Promptly refer patients with any level of macular edema, severe NPDR, or any PDR to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. (A)

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. Diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20–74 years. Glaucoma, cataracts, and other disorders of the eye may occur earlier in people with diabetes and should also be evaluated.

Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset of diabetic retinopathy (27,32,33). In addition to glycemic control, several other factors seem to increase the risk of retinopathy. The presence of nephropathy is associated with retinopathy. High blood pressure is an established risk factor for the development of macular edema and is associated with the presence of PDR. Lowering blood pressure, as demonstrated by the UKPDS, has been shown to decrease the progression of retinopathy. Several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy (164). During pregnancy and 1 year postpartum, retinopathy may be transiently aggravated; laser photocoagulation surgery can minimize this risk (165).

Patients with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes. Subsequent examinations for type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Less frequent exams (every 2–3 years) may be considered with the advice of an eye care professional in the setting of a normal eye exam (166–168). Examinations will be required more frequently if retinopathy is progressing.

Examinations can also be done by the taking of retinal photographs (with or without dilation of the pupil) and having these read by experienced experts in this field. In-person exams are still necessary when the photos are unacceptable and for follow-up of abnormalities detected. This technology has it greatest potential in areas where qualified eye care professionals are not available. Results of eye examinations should be documented and transmitted to the referring health care professional.

One of the main motivations for screening for diabetic retinopathy is the established efficacy of laser photocoagulation surgery in preventing visual loss. Two large National Institutes of Health–sponsored trials, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), provide the strongest support for the therapeutic benefit of photocoagulation surgery.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 18 of 38
Dexcom v. Abbott, IPR2024-00521

The DRS tested whether scatter (panretinal) photocoagulation surgery could reduce the risk of vision loss from PDR. Severe visual loss (i.e., best acuity of 5/200 or worse) was seen in 15.9% of untreated vs. 6.4% of treated eyes. The benefit was greatest among patients whose baseline evaluation revealed HRCs (chiefly disc neovascularization or vitreous hemorrhage with any retinal neovascularization). Of control eyes with HRCs, 26% progressed to severe visual loss vs. 11% of treated eyes. Given the risk of a modest loss of visual acuity and of contraction of visual field from panretinal laser surgery, such therapy has been primarily recommended for eyes approaching or reaching HRCs.

The ETDRS established the benefit of focal laser photocoagulation surgery in eyes with macular edema, particularly those with clinically significant macular edema. In patients with clinically significant macular edema after 2 years, 20% of untreated eyes had a doubling of the visual angle (e.g., 20/50 to 20/100) compared with 8% of treated eyes. Other results from the ETDRS indicate that, provided careful follow-up can be maintained, scatter photocoagulation surgery is not recommended for eyes with mild or moderate NPDR. When retinopathy is more severe, scatter photocoagulation surgery should be considered, and usually should not be delayed, if the eye has reached the high-risk proliferative stage. In older-onset patients with severe NPDR or less-than-high-risk PDR, the risk of severe visual loss and vitrectomy is reduced ~50% by laser photocoagulation surgery at these earlier stages.

Laser photocoagulation surgery in both the DRS and the ETDRS was beneficial in reducing the risk of further visual loss, but generally not beneficial in reversing already diminished acuity. This preventive effect and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for a screening program to detect diabetic retinopathy.

For a detailed review of the evidence and further discussion, see the ADA's technical review and position statement on this subject (169,170).

D. Neuropathy screening and treatment (171,172)

Recommendations

- All patients should be screened for distal symmetric polyneuropathy (DPN) at diagnosis and at least annually thereafter, using simple clinical tests. (A)
- Electrophysiological testing is rarely ever needed, except in situations where the clinical features are atypical. (E)
- Once the diagnosis of DPN is established, special foot care is appropriate for insensate feet to decrease the risk of amputation. (B)
- Simple inspection of insensate feet should be performed at 3- to 6-month intervals. An abnormality should trigger referral for special footwear, preventive specialist, or podiatric care. (B)
- Screening for autonomic neuropathy should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Special electrophysiological testing for autonomic neuropathy is rarely needed and may not affect management and outcomes. (E)
- Education of patients about self-care of the feet and referral for special shoes/inserts are vital components of patient management. (B)
- A wide variety of medications is recommended for the relief of specific symptoms related to autonomic neuropathy and are recommended, as they improve the quality of life of the patient. (E)

The diabetic neuropathies are heterogeneous with diverse clinical manifestations. They may be focal or diffuse. Most common among the neuropathies are chronic sensorimotor DPN and autonomic neuropathy. Although DPN is a diagnosis of exclusion, complex investigations to exclude other conditions are rarely needed.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons: *1*) nondiabetic neuropathies may be present in patients with diabetes and may be treatable; *2*) a number of treatment options exist for symptomatic diabetic neuropathy; *3*) up to 50% of DPN may be asymptomatic and patients are at risk of insensate injury to their feet; *4*) autonomic neuropathy may involve every system in the body; and *5*) cardiovascular autonomic neuropathy causes substantial morbidity and mortality. Specific treatment for the underlying nerve damage is currently not available, other than improved glycemic control, which may slow progression but rarely reverses neuronal loss. Effective symptomatic treatments are available for the manifestations of DPN and autonomic neuropathy.

Diagnosis of neuropathy

Patients with diabetes should be screened annually for DPN using tests such as pinprick sensation, temperature and vibration perception (using a 128-Hz tuning fork), and 10-g monofilament pressure sensation at the distal plantar aspect of both great toes and ankle reflexes. Combinations of more than one test have >87% sensitivity in detecting DPN. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers. A minimum of one clinical test should be carried out annually, and the use of two tests will increase diagnostic ability.

Focal and multifocal neuropathy assessment requires clinical examination in the area related to the neurological symptoms.

Diabetic autonomic neuropathy (173)

The symptoms of autonomic dysfunction should be elicited carefully during the history and review of systems, particularly since many of these symptoms are potentially treatable. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure.

Cardiovascular autonomic neuropathy is the most studied and clinically important form of diabetic autonomic neuropathy. Cardiac autonomic neuropathy may be indicated by resting tachycardia (>100 bpm), orthostasis (a fall in systolic blood pressure >20 mmHg upon standing), or other disturbances in autonomic nervous system function involving the skin, pupils, or gastrointestinal and genitourinary systems.

Gastrointestinal disturbances (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, fecal incontinence) are common, and any section of the gastrointestinal tract may be affected. Gastroparesis should be suspected in individuals with erratic glucose control. Upper-gastrointestinal symptoms should lead to consideration of all possible causes, including autonomic dysfunction.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 19 of 38
Dexcom v. Abbott, IPR2024-00521

Evaluation of solid-phase gastric emptying using double-isotope scintigraphy may be done if symptoms are suggestive, but test results often correlate poorly with symptoms. Barium studies or referral for endoscopy may be required to rule out structural abnormalities. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea. Endoscopy may be required to rule out other causes.

Diabetic autonomic neuropathy is also associated with genitourinary tract disturbances, including bladder and/or sexual dysfunction. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder. In men, diabetic autonomic neuropathy may cause loss of penile erection and/or retrograde ejaculation.

Symptomatic treatments

DPN

The first step in management of patients with DPN should be to aim for stable and optimal glycemic control. Although controlled trial evidence is lacking, several observational studies suggest that neuropathic symptoms improve not only with optimization of control, but also with the avoidance of extreme blood glucose fluctuations. Most patients will require pharmacological treatment for painful symptoms: many agents have efficacy confirmed in published randomized controlled trials, though none are specifically licensed for the management of painful-DPN. See Table 10 for examples of agents to treat DPN pain.

Treatment of autonomic neuropathy

A wide variety of agents are used to treat the symptoms of autonomic neuropathy, including metoclopramide for gastroparesis and several medications for bladder and erectile dysfunction. These treatments are frequently used to provide symptomatic relief to patients. Although they do not change the underlying pathology and natural history of the disease process, their use is recommended due to the impact they may have on the quality of life of the patient.

Table 10—*Table of drugs to treat symptomatic DPN*

Class	Examples	Typical doses*
Tricyclic drugs	Amitriptyline	10–75 mg at bedtime
	Nortriptyline	25–75 mg at bedtime
	Imipramine	25–75 mg at bedtime
Anticonvulsants	Gabapentin	300–1,200 mg t.i.d.
	Carbamazepine	200–400 mg t.i.d.
	Pregabalin	100 mg t.i.d.
5-hydroxytryptamine and norepinephrine uptake inhibitor	Duloxitine	60–120 mg daily
Substance P inhibitor	Capsaicin cream	0.025–0.075% applied t.i.d.-q.i.d.

*Dose response may vary; initial doses need to be low and titrated up.

E. Foot care

Recommendations

- Perform a comprehensive foot examination and provide foot self-care education annually on patients with diabetes to identify risk factors predictive of ulcers and amputations. (B)
- The foot examination can be accomplished in a primary care setting and should include the use of a monofilament, tuning fork, palpation, and a visual examination. (B)
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet, especially those with a history of prior ulcer or amputation. (B)
- Refer patients who smoke or with prior lower-extremity complications to foot care specialists for ongoing preventive care and life-long surveillance. (C)
- Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ankle-brachial index (ABI), as many patients with PAD are asymptomatic. (C)
- Refer patients with significant claudication or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options. (C)

Amputation and foot ulceration are the most common consequences of diabetic neuropathy and major causes of morbidity and disability in people with diabetes. Early recognition and management of independent risk factors can prevent or delay adverse outcomes.

The risk of ulcers or amputations is increased in people who have had diabetes >10 years, are male, have poor glucose control, or have cardiovascular, retinal, or renal complications. The following foot-related risk conditions are associated with an increased risk of amputation:

- Peripheral neuropathy with loss of protective sensation
- Altered biomechanics (in the presence of neuropathy)
- Evidence of increased pressure (erythema, hemorrhage under a callus)
- Bony deformity
- Peripheral vascular disease (decreased or absent pedal pulses)
- A history of ulcers or amputation
- Severe nail pathology

All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions. This examination should include assessment of protective sensation, foot structure and biomechanics, vascular status, and skin integrity. People with one or more high-risk foot condition should be evaluated more frequently for the development of additional risk factors. People with neuropathy should have a visual inspection of their feet at every visit with a health care professional. Evaluation of neurological status in the low-risk foot should include a quantitative somatosensory threshold test, using the Semmes-Weinstein 5.07 (10-g) monofilament. The skin should be assessed for integrity, especially between the toes and under the metatarsal heads. The presence of erythema, warmth, or callus formation may indicate areas of tissue damage with impending breakdown. Bony deformities, limitation in joint mobility, and problems with gait and balance should be assessed.

People with neuropathy or evidence of increased plantar pressure may be ad-

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 20 of 38
Dexcom v. Abbott, IPR2024-00521

equately managed with well-fitted walking shoes or athletic shoes. Patients should be educated on the implications of sensory loss and the ways to substitute other sensory modalities (hand palpation, visual inspection) for surveillance of early problems. People with evidence of increased plantar pressure (e.g., erythema, warmth, callus, or measured pressure) should use footwear that cushions and redistributes the pressure. Callus can be debrided with a scalpel by a foot care specialist or other health professional with experience and training in foot care. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra-wide shoes or depth shoes. People with extreme bony deformities (e.g., Charcot foot) who cannot be accommodated with commercial therapeutic footwear may need custom-molded shoes.

Initial screening for PAD should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ABI, as many patients with PAD are asymptomatic. Refer patients with significant or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options (174).

Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. Patients at risk should understand the implications of the loss of protective sensation, the importance of foot monitoring on a daily basis, the proper care of the foot, including nail and skin care, and the selection of appropriate footwear. The patient's understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist in their care. Patients at low risk may benefit from education on foot care and footwear.

For a detailed review of the evidence and further discussion, see the ADA's technical review and position statement on this subject (175,176).

Problems involving the feet, especially ulcers and wound care, may require care by a podiatrist, orthopedic surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes. For a complete discussion on wound care, see the ADA's consensus statement on diabetic foot wound care (177).

VII. DIABETES CARE IN SPECIFIC POPULATIONS

A. Children and adolescents

1. Type 1 diabetes

Although approximately three-quarters of all cases of type 1 diabetes are diagnosed in individuals <18 years of age, historically ADA recommendations for management of type 1 diabetes have pertained most directly to adults with type 1 diabetes. Because children are not simply "small adults," it is appropriate to consider the unique aspects of care and management of children and adolescents with type 1 diabetes. Children with diabetes differ from adults in many respects, including insulin sensitivity related to sexual maturity, physical growth, ability to provide self-care, and unique neurologic vulnerability to hypoglycemia. Attention to such issues as family dynamics, developmental stages, and physiologic differences related to sexual maturity all are essential in developing and implementing an optimal diabetes regimen. Although current recommendations for children and adolescents are less likely to be based on evidence derived from rigorous research because of current and historical restraints placed on conducting research in children, expert opinion and a review of available and relevant experimental data are summarized in a recent ADA statement (178). The following represents a summary of recommendations and guidelines pertaining specifically to the care and management of children and adolescents that are included in that document.

Ideally, the care of a child or adolescent with type 1 diabetes should be provided by a multidisciplinary team of specialists trained in the care of children with pediatric diabetes, although this may not always be possible. At the very least, education of the child and family should be provided by health care providers trained and experienced in childhood diabetes and sensitive to the challenges posed by diabetes in this age-group. At the time of initial diagnosis, it is essential that diabetes education be provided in a timely fashion, with the expectation that the balance between adult supervision and self-care should be defined by, and will evolve according to, physical, psychological, and emotional maturity. MNT should be provided at diagnosis, and at least annually thereafter, by an individual experienced with the nutritional needs of the growing child and the behavioral issues that have an impact on adolescent diets.

a. Glycemic control. While current standards for diabetes management reflect the need to maintain glucose control as near to normal as safely possible, special consideration must be given to the unique risks of hypoglycemia in young children. Glycemic goals need to be modified to take into account the fact that most children <6 or 7 years of age have a form of "hypoglycemic unawareness," in that counterregulatory mechanisms are immature, and young children lack the cognitive capacity to recognize and respond to hypoglycemic symptoms, placing them at greater risk for hypoglycemia and its sequelae. In addition, extensive evidence indicates that near normalization of blood glucose levels is seldom attainable in children and adolescents after the honeymoon (remission) period. The A1C level achieved in the "intensive" adolescent cohort of the DCCT group was >1% higher than that achieved for older patients and current ADA recommendations for patients in general (179). However, the increased frequency of use of basal bolus regimens (including insulin pumps) in youth from infancy through adolescence has been associated with more children reaching ADA blood glucose targets (180,181).

In selecting glycemic goals, the benefits of achieving a lower A1C must be weighed against the unique risks of hypoglycemia and the disadvantages of targeting a higher, though more achievable, goal that may not promote optimal long-term health outcomes. Age-specific glycemic and A1C goals are presented in Table 11.

b. Screening and management of chronic complications in children and adolescents with type 1 diabetes.

i. *Nephropathy*

Recommendations

- Annual screening for microalbuminuria should be initiated once the child is 10 years of age and has had diabetes for 5 years. Screening may be done with a random spot urine sample analyzed for microalbumin-to-creatinine ratio. (E)
- Confirmed, persistently elevated microalbumin levels should be treated

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 21 of 38
Dexcom v. Abbott, IPR2024-00521

Table 11—*Plasma blood glucose and A1C goals for type 1 diabetes by age-group*

Values by age (years)	Plasma blood glucose goal range (mg/dl)		A1C	Rationale
	Before meals	Bedtime/ overnight		
Toddlers and preschoolers (0–6)	100–180	110–200	<8.5% (but >7.5%)	High risk and vulnerability to hypoglycemia
School age (6–12)	90–180	100–180	<8%	Risks of hypoglycemia and relatively low risk of complications prior to puberty
Adolescents and young adults (13–19)	90–130	90–150	<7.5%	• Risk of severe hypoglycemia • Developmental and psychological issues • A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia

Key concepts in setting glycemic goals:
- Goals should be individualized and lower goals may be reasonable based on benefit-risk assessment.
- Blood glucose goals should be higher than those listed above in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a disparity between preprandial blood glucose values and A1C levels.

with an ACE inhibitor, titrated to normalization of microalbumin excretion (if possible). (E)

ii. *Hypertension*

Recommendations
- Treatment of high-normal blood pressure (systolic or diastolic blood pressure consistently above the 90th percentile for age, sex, and height) should include dietary intervention and exercise, aimed at weight control and increased physical activity, if appropriate. If target blood pressure is not reached within 3–6 months of lifestyle intervention, pharmacologic treatment should be initiated. (E)
- Pharmacologic treatment of hypertension (systolic or diastolic blood pressure consistently above the 95th percentile for age, sex, and height or consistently greater than 130/80 mmHg, if 95% exceeds that value) should be initiated as soon as the diagnosis is confirmed. (E)
- ACE inhibitors should be considered for the initial treatment of hypertension. (E)

Hypertension in childhood is defined as an average systolic or diastolic blood pressure ≥95th percentile for age, sex, and height percentile measured on at least three separate days. "High-normal" blood pressure is defined as an average systolic or diastolic blood pressure ≥90th but <95th percentile for age, sex, and height percentile measured on at least 3 separate days. Normal blood pressure levels for age, sex, and height and appropriate methods for determinations are available online at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

iii. *Dyslipidemia*

Recommendations

Screening
- Prepubertal children: a fasting lipid profile should be performed on all children >2 years of age at the time of diagnosis (after glucose control has been established) if there is a family history of hypercholesterolemia (total cholesterol >240 mg/dl), if there is a history of a cardiovascular event before age 55 years, or if family history is unknown. If family history is not of concern, then the first lipid screening should be performed at puberty (>12 years). If values are within the accepted risk levels (LDL <100 mg/dl [2.6 mmol/l]), a lipid profile should be repeated every 5 years. (E)
- Pubertal children (>12 years of age): a fasting lipid profile should be performed at the time of diagnosis (after glucose control has been established). If values fall within the accepted risk levels (LDL <100 mg/dl [2.6 mmol/l]), the measurement should be repeated every 5 years. (E)
- If lipids are abnormal, annual monitoring is recommended in both age-groups. (E)

Treatment
- Treatment should be based on fasting lipid levels (mainly LDL) obtained after glucose control is established. (E)
- Initial therapy should consist of optimization of glucose control and MNT aimed at a decrease in the amount of saturated fat in the diet. (E)
- The addition of a pharmacologic lipid-lowering agents is recommended for LDL >160 mg/dl (4.1 mmol/l), and is also recommended in patients who have LDL cholesterol values of 130–159 mg/dl (3.4–4.1 mmol/l) based on the patient's CVD risk profile, after failure of MNT and lifestyle changes. (E)
- The goal of therapy is an LDL value <100 mg/dl (2.6 mmol/l). (E)

iv. *Retinopathy*

Recommendations
- The first ophthalmologic examination should be obtained once the child is ≥10 years of age and has had diabetes for 3–5 years. (E)
- After the initial examination, annual routine follow-up is generally recommended. Less frequent examinations may be acceptable on the advice of an eye care professional. (E)

Although retinopathy most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration, it has been reported in prepubertal children and with diabetes duration of only 1–2 years. Referrals should be made to eye

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 22 of 38
Dexcom v. Abbott, IPR2024-00521

care professionals with expertise in diabetic retinopathy, an understanding of the risk for retinopathy in the pediatric population, and experience in counseling the pediatric patient and family on the importance of early prevention/intervention.

v. *Celiac disease*

Recommendations

- Children with positive antibodies should be referred to a gastroenterologist for evaluation. (E)
- Children with confirmed celiac disease should have consultation with a dietitian and placed on a gluten-free diet. (E)
- Patients with type 1 diabetes who are or who become symptomatic for celiac disease should be screened, using tTG antibodies, or anti-EMA, with documentation of normal serum IgA levels. (E)

Celiac disease is an immune-mediated disorder that occurs with increased frequency in patients with type 1 diabetes (1–16% of individuals compared with 0.3–1% in the general population) (182,183). Symptoms of celiac disease include diarrhea, weight loss or poor weight gain, growth failure, abdominal pain, chronic fatigue, malnutrition due to malabsorption, and other gastrointestinal problems.

c. Other issues. A major issue deserving emphasis in this age-group is that of "adherence." No matter how sound the medical regimen, it can only be as good as the ability of the family and/or individual to implement it. Family involvement in diabetes remains an important component of optimal diabetes management throughout childhood and into adolescence. Health care providers who care for children and adolescents, therefore, must be capable of evaluating the behavioral, emotional, and psychosocial factors that interfere with implementation and then must work with the individual and family to resolve problems that occur and/or to modify goals as appropriate.

Since a sizable portion of a child's day is spent in school, close communication with school or day care personnel is essential for optimal diabetes management. Information should be supplied to school personnel, so that they may be made aware of the diagnosis of diabetes in the student and of the signs, symptoms, and treatment of hypoglycemia. In most cases it is imperative that blood glucose testing be performed at the school or day care setting before lunch and when signs or symptoms of abnormal blood glucose levels are present. Many children may require support for insulin administration by either injection or continuous subcutaneous insulin infusion (CSII) before lunch (and often also before breakfast) at school or in day care. For further discussion, see the ADA position statement (184) and the report from the NDEP (185).

2. Type 2 diabetes

Finally, the incidence of type 2 diabetes in adolescents has been shown to be increasing, especially in ethnic minority populations (186,187). Distinction between type 1 and type 2 diabetes in children can be difficult, since autoantigens and ketosis may be present in a substantial number of patients with otherwise straightforward type 2 diabetes (including obesity and acanthosis nigricans). Such a distinction at the time of diagnosis is critical since treatment regimens, educational approaches, and dietary counsel will differ markedly between the two diagnoses. It is recommended that screening for the comorbidities and complications of diabetes, including fasting lipid profile, and urine for microalbumin, be obtained at the time of diagnosis of type 2 diabetes. An ophthalmologic examination should be considered. The ADA consensus statement (11) provides guidance on the prevention, screening, and treatment of type 2 diabetes, as well as its comorbidities, in young people.

B. Preconception care

Recommendations

- A1C levels should be normal or as close to normal as possible (<1% above the upper limits of normal) in an individual patient before conception is attempted. (B)
- All women with diabetes and childbearing potential should be educated about the need for good glucose control before pregnancy. They should participate in family planning. (E)
- Women with diabetes who are contemplating pregnancy should be evaluated and, if indicated, treated for diabetic retinopathy, nephropathy, neuropathy, and CVD. (E)
- Among the drugs commonly used in the treatment of patients with diabetes, statins are pregnancy category X and should be discontinued before conception if possible. Based on recent research, ACE inhibitors also should be discontinued before conception (187a). ARBs are category C in the first trimester (maternal benefit may outweigh fetal risk in certain situations), but category D in later pregnancy, and should generally be discontinued before pregnancy. Among the oral antidiabetic agents, metformin and acarbose are classified as category B and all others as category C; potential risks and benefits of oral antidiabetic agents in the preconception period must be carefully weighed, recognizing that sufficient data are not available to establish the safety of these agents in pregnancy. They should generally be discontinued in pregnancy. (E)

Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 and type 2 diabetes. Observational studies indicate that the risk of malformations increases continuously with increasing maternal glycemia during the first 6–8 weeks of gestation, as defined by first-trimester A1C concentrations. There is no threshold for A1C values above which the risk begins or below which it disappears. However, malformation rates above the 1–2% background rate seen in nondiabetic pregnancies appear to be limited to pregnancies in which first-trimester A1C concentrations are >1% above the normal range for a nondiabetic pregnant woman.

Preconception care of diabetes appears to reduce the risk of congenital malformations. Five nonrandomized studies have compared rates of major malformations in infants between women who participated in preconception diabetes care programs and women who initiated intensive diabetes management after they were already pregnant. The preconception care programs were multidisciplinary and designed to train patients in diabetes self-management with diet, intensified insulin therapy, and SMBG. Goals were set to achieve normal blood glucose concentrations, and >80% of subjects achieved normal A1C concentrations before they became pregnant (188–192). In all five studies, the incidence of major congenital malformations in women who participated in preconception care (range 1.0–1.7% of infants) was much lower than the incidence in women

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 23 of 38
Dexcom v. Abbott, IPR2024-00521

who did not participate (range 1.4–10.9% of infants). One limitation of these studies is that participation in preconception care was self-selected by patients rather than randomized. Thus, it is impossible to be certain that the lower malformation rates resulted fully from improved diabetes care. Nonetheless, the overwhelming evidence supports the concept that malformations can be reduced or prevented by careful management of diabetes before pregnancy.

Planned pregnancies greatly facilitate preconception diabetes care. Unfortunately, nearly two-thirds of pregnancies in women with diabetes are unplanned, leading to a persistent excess of malformations in infants of diabetic mothers. To minimize the occurrence of these devastating malformations, standard care for all women with diabetes who have childbearing potential should include *1*) education about the risk of malformations associated with unplanned pregnancies and poor metabolic control and *2*) use of effective contraception at all times, unless the patient is in good metabolic control and actively trying to conceive.

Women contemplating pregnancy need to be seen frequently by a multidisciplinary team experienced in the management of diabetes before and during pregnancy. Teams may vary but should include a diabetologist, an internist or a family physician, an obstetrician, a diabetes educator, a dietitian, a social worker, and other specialists as necessary. The goals of preconception care are to *1*) integrate the patient into the management of her diabetes, *2*) achieve the lowest A1C test results possible without excessive hypoglycemia, *3*) assure effective contraception until stable and acceptable glycemia is achieved, and *4*) identify, evaluate, and treat long-term diabetic complications such as retinopathy, nephropathy, neuropathy, hypertension, and CAD.

For further discussion, see the ADA's technical review (193) and position statement (194) on this subject.

C. Older individuals

Diabetes is an important health condition for the aging population; at least 20% of patients over the age of 65 years have diabetes. The number of older individuals with diabetes can be expected to grow rapidly in the coming decades. A recent publication (195) contains evidence-based guidelines produced in conjunction with the American Geriatric Society. This document contains an excellent discussion of this area, and specific guidelines and language from it have been incorporated below. Unfortunately, there are no long-term studies in individuals >65 years of age demonstrating the benefits of tight glycemic control, blood pressure, and lipid control. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses such as hypertension, CHD, and stroke than those without diabetes. Older adults with diabetes are also at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain.

The care of older adults with diabetes is complicated by their clinical and functional heterogeneity. Some older individuals developed diabetes in middle age and face years of comorbidity; others who are newly diagnosed may have had years of undiagnosed comorbidity or few complications from the disease. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning, but other older individuals with diabetes have little comorbidity and are active. Life expectancies are also highly variable for this population. Clinicians caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals.

All this having been said, patients who can be expected to live long enough to reap the benefits of long-term intensive diabetes management (~10 years) and who are active, cognitively intact, and willing to undertake the responsibility of self-management should be encouraged to do so and be treated using the stated goals for younger adults with diabetes.

There is good evidence from middle-aged and older adults suggesting that multidisciplinary interventions that provide education on medication use, monitoring, and recognizing hypo- and hyperglycemia can significantly improve glycemic control. Although control of hyperglycemia is important, in older individuals with diabetes, greater reductions in morbidity and mortality may result from control of all cardiovascular risk factors rather than from tight glycemic control alone. There is strong evidence from clinical trials of the value of treating hypertension in the elderly. There is less evidence for lipid-lowering and aspirin therapy, although as diabetic patients have such an elevated risk for CVD, aggressive management of lipids and aspirin use when not contraindicated are reasonable interventions.

As noted above, for patients with advanced diabetes complications, life-limiting comorbid illness, or cognitive or functional impairment, it is reasonable to set less intensive glycemic target goals. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. Patients with poorly controlled diabetes may be subject to acute complications of diabetes, including hyperglycemic hyperosmolar coma. Older patients can be treated with the same drug regimens as younger patients, but special care is required in prescribing and monitoring drug therapy. Metformin is often contraindicated because of renal insufficiency or heart failure. Sulfonylureas and other insulin secretagogues can cause hypoglycemia. Insulin can also cause hypoglycemia as well as require good visual and motor skills and cognitive ability of the patient or a caregiver. TZDs should not be used in patients with CHF (New York Heart Association class III and IV). Drugs should be started at the lowest dose and titrated up gradually until targets are reached or side effects develop. As with blood pressure and lipid management, the potential benefits must always be weighed against potential risks.

VIII. DIABETES CARE IN SPECIFIC SETTINGS

A. Diabetes care in the hospital

Recommendations

- All patients with diabetes admitted to the hospital should be identified in the medical record as having diabetes. (E)
- All patients with diabetes should have an order for blood glucose monitoring, with results available to all members of the health care team. (E)
- Goals for blood glucose levels:
  - Critically ill patients: blood glucose levels should be kept as close to 110 mg/dl (6.1 mmol/l) as possible and generally <180 mg/dl (10 mmol/l). These patients will usually require intravenous insulin. (B)
  - Non–critically ill patients: premeal blood glucose levels should be kept as close to 90–130 mg/dl (5.0–7.2 mmol/l; midpoint of range 110 mg/

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 24 of 38
Dexcom v. Abbott, IPR2024-00521

dl) as possible given the clinical situation and postprandial blood glucose levels <180 mg/dl. Insulin should be used as necessary. (E)
- Due to concerns regarding the risk of hypoglycemia, some institutions may consider these blood glucose levels to be overly aggressive for initial targets. Through quality improvement, glycemic goals should systematically be reduced to the recommended levels. (E)

- Scheduled prandial insulin doses should be given in relation to meals and should be adjusted according to point-of-care glucose levels. The traditional sliding-scale insulin regimens are ineffective as monotherapy and are not recommended. (C)
- Using correction dose or "supplemental" insulin to correct premeal hyperglycemia in addition to scheduled prandial and basal insulin is recommended. (C)
- A plan for treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be tracked. (E)
- All patients with diabetes admitted to the hospital should have an A1C obtained for discharge planning if the result of testing in the previous 2–3 months is not available. (E)
- A diabetes education plan including "survival skills education" and follow-up should be developed for each patient. (E)
- Patients with hyperglycemia in the hospital who do not have a diagnosis of diabetes should have appropriate plans for follow-up testing and care documented at discharge. (E)

The management of diabetes in the hospital is extensively reviewed in an ADA technical review by Clement et al. (196). This review forms the basis for these guidelines. In addition, the American Association of Clinical Endocrinologists held a conference on this topic (197), and the recommendations from this meeting (198) were also carefully reviewed and discussed in the formulation of the guidelines that follow. The management of diabetes in the hospital is generally considered secondary in importance compared with the condition that prompted admission (199).

Patients with hyperglycemia fall into three categories:

- Medical history of diabetes: diabetes has been previously diagnosed and acknowledged by the patient's treating physician.
- Unrecognized diabetes: hyperglycemia (fasting blood glucose 126 mg/dl or random blood glucose 200 mg/dl) occurring during hospitalization and confirmed as diabetes after hospitalization by standard diagnostic criteria but unrecognized as diabetes by the treating physician during hospitalization.
- Hospital-related hyperglycemia: hyperglycemia (fasting blood glucose 126 mg/dl or random blood glucose ≥200 mg/dl) occurring during the hospitalization that reverts to normal after hospital discharge.

The prevalence of diabetes in hospitalized adult patients is not precisely known. In the year 2000, 12.4% of hospital discharges in the U.S. listed diabetes as a diagnosis. The prevalence of diabetes in hospitalized adults is conservatively estimated at 12–25%, depending on the thoroughness used in identifying patients. Patients presenting to hospitals may have diabetes, unrecognized diabetes, or hospital-related hyperglycemia. Using the A1C test may be a valuable case-finding tool for identifying diabetes in hospitalized patients. In the year 2003, there were 5.1 million hospitalizations for diabetes as any-listed diagnosis. By way of comparison, in 1980 there were 2.2 million hospitalizations for those having diabetes (200).

A rapidly growing body of literature supports targeted glucose control in the hospital setting with potential for improved mortality, morbidity, and health care economic outcomes. Hyperglycemia in the hospital may result from stress, decompensation of type 1 diabetes, type 2 diabetes, or other forms of diabetes and/or may be iatrogenic due to administration or withholding of pharmacologic agents, including glucocorticoids, vasopressors, etc. Distinction between decompensated diabetes and stress hyperglycemia is often not made.

1. Blood glucose targets

a. General medicine and surgery. Observational studies suggest an association between hyperglycemia and increased mortality. General medical and surgical patients with a blood glucose value(s) >220 mg/dl (12.2 mmol/l) have higher infection rates (201).

When admissions on general medicine and surgery units were studied, patients with new hyperglycemia had significantly increased inhospital mortality, as did patients with known diabetes. In addition, length of stay was higher for the new hyperglycemic group, and both the patients with new hyperglycemia and those with known diabetes were more likely to require intensive care unit (ICU) care and transitional or nursing home care. Better outcomes were demonstrated in patients with fasting and admission blood glucose <126 mg/dl (7 mmol/l) and all random blood glucose levels <200 mg/dl (11.1 mmol/l) (202).

b. CVD and critical care. The relationship of blood glucose levels and mortality in the setting of acute myocardial infarction (AMI) has been reported. A meta-analysis of 15 previously published studies compared in-hospital mortality and CHF in both hyper- and normoglycemic patients with and without diabetes. In subjects without known diabetes whose admission blood glucose was 109.8 mg/dl (6.1 mmol/l), the relative risk for in-hospital mortality was increased significantly. When diabetes was present and admission glucose 180 mg/dl (10 mmol/l), risk of death was moderately increased compared with patients who had diabetes but no hyperglycemia on admission (203). In another study (204), admission blood glucose values were analyzed in consecutive patients with AMI. Analysis revealed an independent association of admission blood glucose and mortality. The 1-year mortality rate was significantly lower in subjects with admission plasma glucose <100.8 mg/dl (5.6 mmol/l) than in those with plasma glucose 199.8 mg/dl (11 mmol/l).

It is important to note that these studies focused more on admission blood glucose as a predictor of outcomes rather than inpatient diabetes or glycemic management per se. Higher admission plasma glucose levels in patients with a prior history of diabetes could reflect the degree of glycemic control experienced in the outpatient setting, thus linking attention to outpatient glycemic control to outcomes in the inpatient population. In patients without a prior history of diabetes, this could represent case finding of patients previously undiagnosed with diabetes who have the disease, an unmasking of risk in a population at high risk for diabetes, or possibly more severe illness at admission.

In the first DIGAMI (Diabetes and In-

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 25 of 38
Dexcom v. Abbott, IPR2024-00521

sulin-Glucose Infusion in Acute Myocardial Infarction) study (84,205), insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with AMI was examined. Intensive subcutaneous insulin therapy for ≥3 months improved long-term survival (84). Mean blood glucose in the intensive insulin intervention arm was 172.8 mg/dl (9.6 mmol/l) (compared with 210.6 mg/dl [11.7 mmol/l] in the "conventional" group). The broad range of blood glucose levels within each arm limits the ability to define specific blood glucose target thresholds.

Finally, two more recent studies (206,207) using an insulin-glucose infusion did not show a reduction in mortality in the intervention groups. However, in both of these studies, blood glucose levels were positively correlated with mortality.

c. Cardiac surgery. Attainment of targeted glucose control in the setting of cardiac surgery is associated with reduced mortality and risk of deep sternal wound infections in cardiac surgery patients with diabetes (208,209) and supports the concept that perioperative hyperglycemia is an independent predictor of infection in patients with diabetes (210), with the lowest mortality in patients with blood glucose <150 mg/dl (8.3 mmol/l) (211).

d. Critical care. A mixed group of patients with and without diabetes admitted to a surgical ICU were randomized to receive intensive insulin therapy (target blood glucose 80–110 mg/dl [4.4–6.1 mmol/l]). The mean blood glucose of 103 mg/dl (5.7 mmol/l) had reduced mortality during the ICU stay and decreased overall in-hospital mortality (85). Hospital and ICU survival were linearly associated with ICU glucose levels, with the highest survival rates occurring in patients achieving an average blood glucose <110 mg/dl (6.1 mmol/l) (212).

The same group subsequently studied a similar population of patients in a medical ICU (213). As in the SICU (Surgical Intensive Care Unit) study, one group received intensive insulin therapy [mean blood glucose 110 mg/dl (6.1 mmol/l)] while the other received conventional therapy [mean blood glucose 161 mg/dl (8.9 mmol/l). The group receiving the intensive therapy had reduced morbidity but not mortality among all patients in the MICU. However, death was reduced for those patients who were treated for longer than 3 days. These patients could not be identified before therapy.

2. Treatment options

a. Noninsulin glucose-lowering agents. No large studies have investigated the potential roles of various oral agents on outcomes in hospitalized patients with diabetes. While the various classes of oral agents are commonly used in the outpatient setting with good response, their use in the inpatient setting presents some specific issues.

i. *Sulfonylureas and meglitinides*. The long action and predisposition to hypoglycemia in patients not consuming their normal nutrition serve as relative contraindications to routine use of sulfonylureas in the hospital for many patients (214). Sulfonylureas do not generally allow rapid dose adjustment to meet the changing inpatient needs. Sulfonylureas also vary in duration of action between individuals and likely vary in the frequency with which they induce hypoglycemia. While the two available meglitinides, repaglinide and neteglinide, theoretically would produce less hypoglycemia than sulfonylureas, lack of clinical trial data for these agents would preclude their use.

ii. *Metformin*. The major limitation to metformin use in the hospital is a number of specific contraindications to its use, many of which occur in the hospital. All of these contraindications relate to lactic acidosis, a potentially fatal complication of metformin therapy. The most common risk factors for lactic acidosis in metformin-treated patients are cardiac disease, including CHF, hypoperfusion, renal insufficiency, old age, and chronic pulmonary disease (215). Recent evidence continues to indicate lactic acidosis is a rare complication (216), despite the relative frequency of risk factors (217). However, in the hospital, where the risk for hypoxia, hypoperfusion, and renal insufficiency is much higher, it still seems prudent to avoid the use of metformin in most patients.

iii. *TZDs*. TZDs are not suitable for initiation in the hospital because of their delayed onset of effect. In addition, they do increase intravascular volume, a particular problem in those predisposed to CHF and potentially a problem for patients with hemodynamic changes related to admission diagnoses (e.g., acute coronary ischemia) or interventions common in hospitalized patients.

iv. *Pramlintide and exenatide*. These drugs work mainly by reducing postprandial hyperglycemia. Therefore, they would not be appropriate for patients not eating (NPO) or with reduced caloric consumption. Furthermore, it would generally be inappropriate to initiate these drugs in the inpatient setting due to all of the differences in normal food intake, in addition to the fact that both of these agents result in nausea as the most common side effect. In general, these agents should be initiated when the patient is not ill in the outpatient setting.

In summary, each of the major classes of oral agents has significant limitations for inpatient use. Additionally, they provide little flexibility or opportunity for titration in a setting where acute changes demand these characteristics. Therefore, insulin, when used properly, may have many advantages in the hospital setting.

b. Insulin. The inpatient insulin regimen must be matched or tailored to the specific clinical circumstance of the individual patient. A recent meta-analysis concluded that insulin therapy in critically ill patients had a beneficial effect on short-term mortality in different clinical settings (218).

i. *Subcutaneous insulin therapy*. Subcutaneous insulin therapy may be used to attain glucose control in most hospitalized patients with diabetes. The components of the daily insulin dose requirement can be met by a variety of insulins, depending on the particular hospital situation. Subcutaneous insulin therapy is subdivided into programmed or scheduled insulin and supplemental or correction-dose insulin. Correction-dose insulin therapy is an important adjunct to scheduled insulin, both as a dose-finding strategy and as a supplement when rapid changes in insulin requirements lead to hyperglycemia. If correction doses are frequently required, it is recommended that the appropriate scheduled insulin doses be increased the following day to accommodate the increased insulin needs (219). There are no studies comparing human regular insulin with rapid-acting analogs for use as correction-dose insulin. However, due to the longer duration with human regular insulin, there is a greater risk of "insulin stacking" when the usual next blood glucose measurement is performed 4–6 h later.

The traditional sliding-scale insulin regimens, usually consisting of regular insulin without any intermediate or long-acting insulins, have been shown to be ineffective when used as monotherapy in patients with an established insulin re-

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 26 of 38
Dexcom v. Abbott, IPR2024-00521

quirement (219–221). Problems cited with sliding-scale insulin regimens are that the sliding-scale regimen prescribed on admission is likely to be used throughout the hospital stay without modification (219). Second, sliding-scale insulin therapy treats hyperglycemia after it has already occurred, instead of preventing the occurrence of hyperglycemia. This "reactive" approach can lead to rapid changes in blood glucose levels, exacerbating both hyper- and hypoglycemia.

ii. *Intravenous insulin infusion*. The only method of insulin delivery specifically developed for use in the hospital is continuous intravenous infusion, using regular crystalline insulin. There is no advantage to using insulin lispro or aspart in an intravenous insulin infusion. The medical literature supports the use of intravenous insulin infusion in preference to the subcutaneous route of insulin administration for several clinical indications among nonpregnant adults. These include DKA and nonketotic hyperosmolar state; general preoperative, intraoperative, and postoperative care; the postoperative period following heart surgery; following organ transplantation; with cardiogenic shock; exacerbated hyperglycemia during high-dose glucocorticoid therapy; patients who are NPO or in critical care illness in general; and as a dose-finding strategy in anticipation of initiation or reinitiation of subcutaneous insulin therapy in type 1 or type 2 diabetes.

Many institutions use insulin infusion algorithms that can be implemented by nursing staff. Algorithms should incorporate the concept that maintenance requirements differ between patients and change over the course of treatment. Although numerous algorithms have been published, there have been no head-to-head comparisons, and thus no single algorithm can be recommended for an individual hospital. Ideally, intravenous insulin algorithms should consider both the current and previous glucose level, the rate of change of plasma glucose, and the current IV insulin infusion rate. For all algorithms, frequent bedside glucose testing is required but the ideal frequency is not known.

iii. *Transition from intravenous to subcutaneous insulin therapy*. There are no specific clinical trials examining how to best transition from intravenous to subcutaneous insulin or which patients with type 2 diabetes may be transitioned to oral agents. For those who will require subcutaneous insulin, it is necessary to administer short- or rapid-acting insulin subcutaneously 1–2 h before discontinuation of the intravenous insulin infusion. An intermediate- or long-acting insulin must be injected 2–3 h before discontinuing the insulin infusion. In transitioning from intravenous insulin infusion to subcutaneous therapy, the caregiver may order subcutaneous insulin with appropriate duration of action to be administered as a single dose or repeatedly to maintain basal effect until the time of day when the choice of insulin or analog preferred for basal effect normally would be provided.

3. Self-management in the hospital

Self-management in the hospital may be appropriate for competent adult patients who have a stable level of consciousness and reasonably stable known daily insulin requirements and successfully conduct self-management of diabetes at home, have physical skills appropriate to successfully self-administer insulin, perform SMBG, and have adequate oral intake. Appropriate patients are those already proficient in carbohydrate counting, use of multiple daily injections of insulin or insulin pump therapy, and sick-day management. The patient and physician in consultation with nursing staff must agree that patient self-management is appropriate under the conditions of hospitalization. For patients who are selected for self-management in the hospital, it is important that basal and bolus doses of insulin with results of bedside glucose monitoring be recorded as part of the patient's hospital medical record.

While many institutions allow patients on an insulin pump to continue these devices in the hospital, others express concern regarding use of a device that nurses are unfamiliar with, particularly in patients who are not able to manage their own pump therapy. If a patient is too ill to self-manage either multiple daily injections or CSII, then appropriate subcutaneous doses can be calculated on the basis of their basal and bolus insulin doses during hospitalization with adjustments for changes in nutritional or metabolic status.

4. Preventing hypoglycemia

Hypoglycemia, especially in insulin-treated patients, is the leading limiting factor in the glycemic management of type 1 and type 2 diabetes (86). In the hospital, multiple additional risk factors for hypoglycemia are present, even among patients who are neither "brittle" nor tightly controlled. Patients who do not have diabetes may experience hypoglycemia in the hospital, in association with factors such as altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis (222). Patients having diabetes may develop hypoglycemia in association with the same conditions (223). Additional triggering events leading to iatrogenic hypoglycemia include sudden reduction of corticosteroid dose, altered ability of the patient to self-report symptoms, reduction of oral intake, emesis, new NPO status, reduction of rate of administration of intravenous dextrose, and unexpected interruption of enteral feedings or parenteral nutrition. Altered consciousness from anesthesia may also alter typical hypoglycemic symptoms.

Despite the preventable nature of many inpatient episodes of hypoglycemia, institutions are more likely to have nursing protocols for the treatment of hypoglycemia than for its prevention.

5. Diabetes care providers

Diabetes management may be effectively offered by primary care physicians or hospitalists, but involvement of appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes (224–227). In the care of diabetes, implementation of standardized order sets for scheduled and correction-dose insulin may reduce reliance on sliding-scale management. A team approach is needed to establish hospital pathways. To implement intravenous infusion of insulin for the majority of patients having prolonged NPO status, hospitals will need multidisciplinary support for using insulin infusion therapy outside of critical care units or will need to develop protocols for subcutaneous insulin therapy that achieve similar glycemic goals (228).

6. DSME

Teaching diabetes self-management to patients in hospitals is a difficult and challenging task. Patients are hospitalized because they are ill, are under increased stress related to their hospitalization and diagnosis, and are in an environment that is not conducive to learning. Ideally, people with diabetes should be taught at a time and place conducive to learning: as an outpatient in a nationally recognized program of diabetes education classes.

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 27 of 38
Dexcom v. Abbott, IPR2024-00521

For the hospitalized patient, diabetes "survival skills" education is generally considered a feasible approach. Patients are taught sufficient information to enable them to go home safely. Those newly diagnosed with diabetes or who are new to insulin and or blood glucose monitoring need to be instructed before discharge to help ensure safe care upon returning home. Those patients hospitalized because of a crisis related to diabetes management or poor care at home need education to hopefully prevent subsequent episodes of hospitalization.

7. MNT

Even though hospital diets continue to be ordered by calorie levels based on the "ADA diet," it has been recommended that the term "ADA diet" no longer be used (229). Since 1994, the ADA has not endorsed any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiologic parameters, and medication usage.

Because of the complexity of nutrition issues, it is recommended that a registered dietitian, knowledgeable and skilled in MNT, serve as the team member who provides MNT. The dietitian is responsible for integrating information about the patient's clinical condition, eating, and lifestyle habits and for establishing treatment goals in order to determine a realistic plan for nutrition therapy (229).

8. Bedside blood glucose monitoring

Implementing intensive diabetes therapy in the hospital setting requires frequent and accurate blood glucose data. This measure is analogous to an additional "vital sign" for hospitalized patients with diabetes. Bedside glucose monitoring using capillary blood has advantages over laboratory venous glucose testing because the results can be obtained rapidly at the "point of care," where therapeutic decisions are made. For this reason, the terms bedside and point-of-care glucose monitoring are used interchangeably.

For patients who are eating, commonly recommended testing frequencies are premeal and at bedtime. For patients not eating, testing every 4–6 h is usually sufficient for determining correction insulin doses. Patients controlled with continuous intravenous insulin typically require hourly blood glucose testing until the blood glucose levels are stable, then every 2 h.

Bedside blood glucose testing is usually performed with portable glucose devices that are identical or similar to devices for home SMBG. Ability to track the occurrence of hypo- and hyperglycemia is necessary.

9. Continuous blood glucose monitoring

The introduction of real-time blood glucose monitoring as a tool for outpatient diabetes management has potential benefit for the inpatient population (230). However, at this time, data are lacking examining this new technology in the acutely ill patient population. Until more studies are published, it is premature to use continuous blood glucose monitoring except in a research setting.

B. Diabetes care in the school and day care setting (184)

Recommendations

- An individualized diabetes medical management plan (DMMP) should be developed by the parent/guardian and the student's diabetes health care team. (E)
- A 504 plan should be developed and implemented by the family, school nurse, and diabetes health care team. (E)
- An adequate number of school personnel should be trained in the necessary diabetes procedures (including monitoring of blood glucose levels and administration of insulin and glucagon) and in the appropriate response to high and low blood glucose levels. These school personnel need not be health care professionals. (E)
- The student with diabetes should have immediate access to diabetes supplies at all times, with supervision as needed. (E)
- The student should be permitted to monitor his or her blood glucose level, as developmentally appropriate and determined by the family and diabetes health care team with input by the school nurse, and take appropriate action to treat hypoglycemia in the classroom or anywhere the student is in conjunction with a school activity if indicated in the student's DMMP. (E)

There are ~206,000 individuals <20 years of age with diabetes in the U.S., most of whom attend school and/or some type of day care and need knowledgeable staff to provide a safe environment. Despite legal protections, children in the school and day care setting still face discrimination. Parents and the health care team should provide school systems and day care providers with the information necessary by developing an individualized DMMP, including information necessary for children with diabetes to participate fully and safely in the school/day care experience. Appropriate diabetes care in the school and day care setting is necessary for the child's immediate safety, long-term well-being, and optimal academic performance.

An adequate number of school personnel should be trained in the necessary diabetes procedures (e.g., blood glucose monitoring and insulin and glucagon administration) and in the appropriate response to high and low blood glucose levels. This will ensure that at least one adult is present to perform these procedures in a timely manner while the student is at school, on field trips, and during extracurricular activities or other school-sponsored events. These school personnel need not be health care professionals.

The student with diabetes should have immediate access to diabetes supplies at all times, with supervision as needed. A student with diabetes should be able to obtain a blood glucose level and respond to the results as quickly and conveniently as possible, minimizing the need for missing instruction in the classroom. Accordingly, a student who is capable of doing so should be permitted to monitor his or her blood glucose level and take appropriate action to treat hypoglycemia in the classroom or designated area adjacent to the classroom or anywhere the student is in conjunction with a school activity. The student's desire for privacy during testing should also be accommodated.

C. Diabetes care at diabetes camps (231)

Recommendations

- Each camper should have a standardized medical form completed by his/her family and the physician managing the diabetes. (E)
- It is imperative that the medical staff is led by someone with expertise in managing type 1 and type 2 diabetes and includes a nursing staff (including diabetes educators and diabetes clinical nurse specialists) and registered dietitians with expertise in diabetes. (E)
- All camp staff, including medical, nurs-

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 28 of 38
Dexcom v. Abbott, IPR2024-00521

ing, nutrition, and volunteer, should undergo background testing to ensure appropriateness in working with children. (E)

The concept of specialized residential and day camps for children with diabetes has become widespread throughout the U.S. and many other parts of the world. The mission of camps specialized for children and youth with diabetes is to allow for a camping experience in a safe environment. An equally important goal is to enable children with diabetes to meet and share their experiences with one another while they learn to be more personally responsible for their disease. For this to occur, a skilled medical and camping staff must be available to ensure optimal safety and an integrated camping/educational experience.

The diabetes camping experience is short term and is most often associated with increased physical activity relative to that experienced while at home. Thus, goals of glycemic control are more related to the avoidance of extremes in blood glucose levels than to the optimization of intensive glycemic control while away at camp.

Each camper should have a standardized medical form completed by his/her family and the physician managing the diabetes that details the camper's past medical history, immunization record, and diabetes regimen. The home insulin dosage should be recorded for each camper, including number and timing of injections or basal and bolus dosages given by CSII and type(s) of insulin used.

During camp, a daily record of the camper's progress should be made. All blood glucose levels and insulin dosages should be recorded. To ensure safety and optimal diabetes management, multiple blood glucose determinations should be made throughout each 24-h period: before meals, at bedtime, after or during prolonged and strenuous activity, and in the middle of the night when indicated for prior hypoglycemia. If major alterations of a camper's regimen appear to be indicated, it is important to discuss this with the camper and the family in addition to the child's local physician. The record of what transpired during camp should be discussed with the family when the camper is picked up.

A formal relationship with a nearby medical facility should be secured for each camp so that camp medical staff have the ability to refer to this facility for prompt treatment of medical emergencies. It is imperative that the medical staff is led by someone with expertise in managing type 1 and type 2 diabetes. Nursing staff should include diabetes educators and diabetes clinical nurse specialists. Registered dietitians with expertise in diabetes should also have input into the design of the menu and the education program. All camp staff, including medical, nursing, nutrition, and volunteer, should undergo background testing to ensure appropriateness in working with children.

D. Diabetes management in correctional institutions (232)

Recommendations

- Patients with a diagnosis of diabetes should have a complete medical history and undergo an intake physical examination by a licensed health professional in a timely manner. (E)
- Insulin-treated patients should have a capillary blood glucose (CBG) determination within 1–2 h of arrival. (E)
- Medications and MNT should be continued without interruption upon entry into the correctional environment. (E)
- Correctional staff should be trained in the recognition, treatment, and appropriate referral for hypo- and hyperglycemia. (E)
- Train staff to recognize symptoms and signs of serious metabolic decompensation and to immediately refer the patient for appropriate medical care. (E)
- Institutions should implement a policy requiring staff to notify a physician of all CBG results outside of a specified range, as determined by the treating physician. (E)
- Identify patients with type 1 diabetes who are at high risk for DKA. (E)
- In the correctional setting, policies and procedures need to be developed and implemented to enable CBG monitoring to occur at the frequency necessitated by the individual patient's glycemic control and diabetes regimen. (E)
- Include diabetes in correctional staff education programs. (E)
- For all interinstitutional transfers, complete a medical transfer summary to be transferred with the patient. (E)
- Diabetes supplies and medication should accompany the patient during transfer. (E)
- Begin discharge planning with adequate lead time to insure continuity of care and facilitate entry into community diabetes care. (E)

At any given time, >2 million people are incarcerated in prisons and jails in the U.S. It is estimated that nearly 80,000 of these inmates have diabetes. In addition, many more people with diabetes pass through the corrections system in a given year.

People with diabetes in correctional facilities should receive care that meets national standards. Correctional institutions have unique circumstances that need to be considered so that all standards of care may be achieved. Correctional institutions should have written policies and procedures for the management of diabetes and for training of medical and correctional staff in diabetes care practices.

Reception screening should emphasize patient safety. In particular, rapid identification of all insulin-treated individuals with diabetes is essential in order to identify those at highest risk for hypo- and hyperglycemia and DKA. All insulin-treated patients should have a CBG determination within 1–2 h of arrival. Patients with a diagnosis of diabetes should have a complete medical history and physical examination by a licensed health care provider with prescriptive authority in a timely manner. It is essential that medication and MNT be continued without interruption upon entry into the correctional system, as a hiatus in either medication or appropriate nutrition may lead to either severe hypo- or hyperglycemia.

All patients must have access to prompt treatment of hypo- and hyperglycemia. Correctional staff should be trained in the recognition and treatment of hypo- and hyperglycemia, and appropriate staff should be trained to administer glucagon. Institutions should implement a policy requiring staff to notify a physician of all CBG results outside of a specified range, as determined by the treating physician.

Correctional institutions should have systems in place to ensure that insulin administration and meals are coordinated to prevent hypo- and hyperglycemia, taking into consideration the transport of residents off site and the possibility of emergency schedule changes.

Monitoring of CBG is a strategy that allows caregivers and people with diabetes to evaluate diabetes management regimens. The frequency of monitoring will

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 29 of 38
Dexcom v. Abbott, IPR2024-00521

vary by patients' glycemic control and diabetes regimens. Policies and procedures should be implemented to ensure that the health care staff has adequate knowledge and skills to direct the management and education of individuals with diabetes.

Patients in jails may be housed for a short period of time before being transferred or released, and it is not unusual for patients in prison to be transferred within the system several times during their incarceration. Transferring a patient with diabetes from one correctional facility to another requires a coordinated effort as does planning for discharge.

E. Emergency and disaster preparedness

People with diabetes should always be prepared for emergencies whether natural or otherwise, affecting the nation/state or just them and their families. Such preparedness will lessen the impact an emergency may have on their condition. It is recommended that people with diabetes keep a waterproof and insulated disaster kit ready with items critically important to their self-management. These include glucose testing strips, lancets, and a glucose-testing meter; medications including insulin in a cool bag; syringes; glucose tabs or gels; antibiotic ointments/creams for external use; and glucagon emergency kits. In addition, it may be important to carry a list of contacts for national organizations, such as the ADA, through their help lines or the Internet, and photocopies of relevant medical information, particularly medication lists, and recent lab tests/procedures if available. If possible, prescription numbers should be noted, since many chain pharmacies throughout the country may be able to refill medications based on the prescription number alone. This disaster kit should be reviewed and replenished at least twice yearly.

IX. HYPOGLYCEMIA AND EMPLOYMENT/LICENSURE

Recommendations

- People with diabetes should be individually considered for employment based on the requirements of the specific job and the individual's medical condition, treatment regimen, and medical history. (E)

Any person with diabetes, whether insulin treated or non–insulin treated, should be eligible for any employment for which he/she is otherwise qualified. Despite the significant medical and technological advances made in managing diabetes, discrimination in employment and licensure against people with diabetes still occurs. This discrimination is often based on apprehension that the person with diabetes may present a safety risk to the employer or the public, a fear sometimes based on misinformation or lack of up-to-date knowledge about diabetes. Perhaps the greatest concern is that hypoglycemia will cause sudden unexpected incapacitation. However, most people with diabetes can manage their condition in such a manner that there is minimal risk of incapacitation from hypoglycemia.

Because the effects of diabetes are unique to each individual, it is inappropriate to consider all people with diabetes the same. People with diabetes should be individually considered for employment based on the requirements of the specific job. Factors to be weighed in this decision include the individual's medical condition, treatment regimen (MNT, oral glucose-lowering agent, and/or insulin), and medical history, particularly in regard to the occurrence of incapacitating hypoglycemic episodes.

X. THIRD-PARTY REIMBURSEMENT FOR DIABETES CARE, SELF-MANAGEMENT EDUCATION, AND SUPPLIES (233)

Recommendations

- Patients and practitioners should have access to all classes of antidiabetic medications, equipment, and supplies without undue controls. (E)
- MNT and DSME should be covered by insurance and other payors. (E)

To achieve optimal glucose control, the person with diabetes must be able to access health care providers who have expertise in the field of diabetes. Treatments and therapies that improve glycemic control and reduce the complications of diabetes will also significantly reduce health care costs. Access to the integral components of diabetes care, such as health care visits, diabetes supplies and medications, and self-management education, is essential. All medications and supplies, such as syringes, strips, and meters, related to the daily care of diabetes must also be reimbursed by third-party payors.

It is recognized that the use of formularies, prior authorization, and related provisions, such as competitive bidding, can manage provider practices as well as costs to the potential benefit of payors and patients. However, any controls should ensure that all classes of antidiabetic agents with unique mechanisms of action and all classes of equipment and supplies designed for use with such equipment are available to facilitate achieving glycemic goals and to reduce the risk of complications. To reach diabetes treatment goals, practitioners should have access to all classes of antidiabetic medications, equipment, and supplies without undue controls. Without appropriate safeguards, these controls could constitute an obstruction of effective care.

Medicare and many other third-party payors cover DSME (diabetes self-management training [DSMT]) and MNT. The qualified beneficiary, who meets the diagnostic criteria and medical necessity, can receive an initial benefit of 10 h of DSMT and 3 h of MNT with a potential total of 13 h of initial education as long as the services are not provided on the same date. However, not all Medicare beneficiaries with a diagnosis of diabetes will qualify for both MNT and DSMT benefits. More information on Medicare policy, including follow-up benefits, is available at www.diabetes.org/for-health-professionals-and-scientists/recognition.jsp. Or visit CMS websites: DSME, www.cms.hhs.gov/DiabetesSelfManagement; and diabetes MNT, www.cms.hhs.gov/MedicalNutritionTherapyreimbursement.

XI. STRATEGIES FOR IMPROVING DIABETES CARE

The implementation of the standards of care for diabetes has been suboptimal in most clinical settings. A recent report (26) indicated that only 37% of adults with diagnosed diabetes achieved an A1C of <7%, only 36% had a blood pressure <130/80 mmHg, and just 48% had a cholesterol <200 mg/dl. Most distressing was that only 7.3% of diabetes subjects achieved all three treatment goals.

While numerous interventions to improve adherence to the recommended standards have been implemented, the challenge of providing uniformly effective diabetes care has thus far defied a simple solution. A major contributor to suboptimal care is a delivery system that too often is fragmented, lacks clinical information capabilities, often duplicates services, and is poorly designed for the delivery of

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 30 of 38
Dexcom v. Abbott, IPR2024-00521

chronic care. The Institute of Medicine has called for changes so that delivery systems provide care that is evidence based, patient centered, and systems oriented and takes advantage of information technologies that foster continuous quality improvement. Collaborative, multidisciplinary teams should be best suited to provide such care for people with chronic conditions like diabetes and to empower patients' performance of appropriate self-management. Alterations in reimbursement that reward the provision of quality care, as defined by the attainment of quality measures developed by such activities as the ADA/National Committee for Quality Assurance Diabetes Provider Recognition Program will also be required to achieve desired outcome goals.

The NDEP recently launched a new online resource to help health care professionals better organize their diabetes care. The www.betterdiabetescare.nih.gov website should help users design and implement more effective health care delivery systems for those with diabetes.

In recent years, numerous health care organizations, ranging from large health care systems such as the U.S. Veteran's Administration to small private practices, have implemented strategies to improve diabetes care. Successful programs have published results showing improvement in important outcomes such as A1C measurements and blood pressure and lipid determinations as well as process measures such as provision of eye exams. Successful interventions have been focused at the level of health care professionals, delivery systems, and patients. Features of successful programs reported in the literature include:

- Improving health care professional education regarding the standards of care through formal and informal education programs.
- Delivery of DSME, which has been shown to increase adherence to standard of care.
- Adoption of practice guidelines, with participation of health care professionals in the process. Guidelines should be readily accessible at the point of service, such as on patient charts, in examining rooms, in "wallet or pocket cards," on PDAs, or on office computer systems. Guidelines should begin with a summary of their major recommendations instructing health care professionals what to do and how to do it.
- Use of checklists that mirror guidelines have been successful at improving adherence to standards of care.
- Systems changes, such as provision of automated reminders to health care professionals and patients, reporting of process and outcome data to providers, and especially identification of patients at risk because of failure to achieve target values or a lack of reported values.
- Quality improvement programs combining continuous quality improvement or other cycles of analysis and intervention with provider performance data.
- Practice changes, such as clustering of dedicated diabetes visits into specific times within a primary care practice schedule and/or visits with multiple health care professionals on a single day and group visits.
- Tracking systems with either an electronic medical record or patient registry have been helpful at increasing adherence to standards of care by prospectively identifying those requiring assessments and/or treatment modifications. They likely could have greater efficacy if they suggested specific therapeutic interventions to be considered for a particular patient at a particular point in time (234).
- A variety of nonautomated systems, such as mailing reminders to patients, chart stickers, and flow sheets, have been useful to prompt both providers and patients.
- Availability of case or (preferably) care management services, usually by a nurse. Nurses, pharmacists, and other nonphysician health care professionals using detailed algorithms working under the supervision of physicians and/or nurse education calls have also been helpful. Similarly dietitians using MNT guidelines have been demonstrated to improve glycemic control.
- Availability and involvement of expert consultants, such as endocrinologists and diabetes educators.

Evidence suggests that these individual initiatives work best when provided as components of a multifactorial intervention. Therefore, it is difficult to assess the contribution of each component; however, it is clear that optimal diabetes management requires an organized, systematic approach and involvement of a coordinated team of health care professionals.

References

1. Bode BW (Ed.):*Medical Management of Type 1 Diabetes*. Alexandria, VA, American Diabetes Association, 2004
2. Burant CF (Ed.):*Medical Management of Type 2 Diabetes*. Alexandria, VA, American Diabetes Association, 2004
3. Klingensmith GJ (Ed.): *Intensive Diabetes Management*. Alexandria, VA, American Diabetes Association, 2003
4. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
5. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
6. Engelgau MM, Narayan KM, Herman WH: Screening for type 2 diabetes. *Diabetes Care* 23:1563–1580, 2000
7. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC: The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 23:1108–1112, 2000
8. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346: 393–403, 2002
9. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
10. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
11. American Diabetes Association: Type 2 diabetes in children and adolescents (Consensus Statement). *Diabetes Care* 23:381–389, 2000
12. Harris R, Donahue K, Rathore SS, Frame P, Woolf SH, Lohr KN: Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 138: 215–229, 2003
13. US Preventive Services Task Force:

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 31 of 38
Dexcom v. Abbott, IPR2024-00521

Screening for type 2 diabetes mellitus in adults: recommendations and rationale. *Ann Intern Med* 138:212–214, 2003
14. American Diabetes Association: Gestational diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1):S88–S90, 2004
15. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002
16. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
17. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V: The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 49: 289–297, 2006
18. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006
19. American Diabetes Association: Consensus statement on self-monitoring of blood glucose. *Diabetes Care* 10:95–99, 1987
20. American Diabetes Asociation: Self-monitoring of blood glucose. *Diabetes Care* 17:81–86, 1994
21. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 28:1510–1517, 2005
22. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M: Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 48:436–472, 2002
23. Cagliero E, Levina EV, Nathan DM: Immediate feedback of HbA_{1c} levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. *Diabetes Care* 22:1785–1789, 1999
24. Miller CD, Barnes CS, Phillips LS, Ziemer DC, Gallina DL, Cook CB, Maryman SD, El Kebbi IM: Rapid A1c availability improves clinical decision-making in an urban primary care clinic. *Diabetes Care* 26:1158–1163, 2003
25. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE: Defining the relationship between plasma glucose and HbA_{1c}: analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial. *Diabetes Care* 25:275–278, 2002
26. Saydah SH, Fradkin J, Cowie CC: Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 291:335–342, 2004
27. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986, 1993
28. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
29. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 342:381–389, 2000
30. Cefalu WT: Glycemic control and cardiovascular disease: should we reassess clinical goals? *N Engl J Med* 353:2707–2709, 2005
31. Lawson ML, Gerstein HC, Tsui E, Zinman B: Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Care* 22 (Suppl. 2):B35–B39, 1999
32. UKPDS: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837–853, 1998
33. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
34. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
35. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH: Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 141: 421–431, 2004
36. American Diabetes Association: Postprandial blood glucose (Consensus Statement). *Diabetes Care* 24:775–778, 2001
37. Metzger BE, Coustan DR: Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus: the Organizing Committee. *Diabetes Care* 21 (Suppl. 2): B161–B167, 1998
38. Jovanovic-Peterson L. (Ed.): *Medical Management of Pregnancy Complicated by Diabetes*. 3rd ed. Alexandria, VA, American Diabetes Association, 2000
39. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963–1972, 2006
40. DeWitt DE, Hirsch IB: Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 289: 2254–2264, 2003
41. Mooradian AD, Bernbaum M, Albert SG: Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 145:125–134, 2006
42. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML: Nutrition recommendations and interventions for diabetes–2006: a position statement of the American Diabetes Association. *Diabetes Care* 29:2140–2157, 2006
43. U.S. Department of Health and Human Services, U.S. Department of Agriculture: *Dietary Guidelines for Americans*. Washington, DC, U.S. Government Printing Office, 2005
44. Institute of Medicine: *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, D.C., National Academies Press, 2002
45. Piette JD, Glasgow RE: Strategies for improving behavioral and health outcomes among people with diabetes: self managemnt education. In *Evidence-Based Diabetes Care*. Gerstein HC, Hayes RB, Eds. Ontario, Canada, BC Decker, 2000
46. Norris SL, Engelgau MM, Narayan KM: Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care* 24:561–587, 2001
47. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM: Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care* 25:1159–1171,

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 32 of 38
Dexcom v. Abbott, IPR2024-00521

2002
48. Gary TL, Genkinger JM, Guallar E, Peyrot M, Brancati FL: Meta-analysis of randomized educational and behavioral interventions in type 2 diabetes. *Diabetes Educ* 29:488–501, 2003
49. Steed L, Cooke D, Newman S: A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. *Patient Educ Couns* 51:5–15, 2003
50. Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA: Diabetes patient education: a meta-analysis and meta-regression. *Patient Educ Couns* 52:97–105, 2004
51. Warsi A, Wang PS, LaValley MP, Avorn J, Solomon DH: Self-management education programs in chronic disease: a systematic review and methodological critique of the literature. *Arch Intern Med* 164:1641–1649, 2004
52. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C: Physical activity/exercise and type 2 diabetes (Technical Review). *Diabetes Care* 27:2518–2539, 2004
53. Wasserman DH, Zinman B: Exercise in individuals with IDDM. *Diabetes Care* 17:924–937, 1994
54. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion: *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA, Centers for Disease Control and Prevention, 1996
55. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ: Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 286:1218–1227, 2001
56. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ: Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* 46:1071–1081, 2003
57. Albright A, Franz M, Hornsby G, Kriska A, Marrero D, Ullrich I, Verity LS: American College of Sports Medicine position stand: exercise and type 2 diabetes. *Med Sci Sports Exerc* 32:1345–1360, 2000
58. Ivy JL: Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. *Sports Med* 24:321–336, 1997
59. Dunstan DW, Daly RM, Owen N, Jolley D, de Court, Shaw J, Zimmet P: High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care* 25:1729–1736, 2002
60. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME: A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care* 25:2335–2341, 2002
61. Fowler-Brown A, Pignone M, Pletcher M, Tice JA, Sutton SF, Lohr KN: Exercise tolerance testing to screen for coronary heart disease: a systematic review for the technical support for the U.S. Preventive Services Task Force. *Ann Intern Med* 140: W9–W24, 2004
62. US Preventive Services Task Force: Screening for coronary heart disease: recommendation statement. *Ann Intern Med* 140:569–572, 2004
63. Berger M, Berchtold P, Cuppers HJ, Drost H, Kley HK, Muller WA, Wiegelmann W, Zimmerman-Telschow H, Gries FA, Kruskemper HL, Zimmermann H: Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. *Diabetologia* 13:355–365, 1977
64. American Diabetes Association: Physical activity/exercise and diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1): S58–S62, 2004
65. Berger M: Adjustment of insulin and oral agent therapy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 365–376
66. Aiello LP, Wong J, Cavallerano J, Bursell SE, Aiello LM: Retinopathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 401–413
67. Vinik A, Erbas T: Neuropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, Anerican Diabetes Association, 2002, p. 463–496
68. Levin ME: The diabetic foot. In *Handbook of Exercise in Diabetes*. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 385–399
69. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE: Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 27:1954–1961, 2004
70. Valensi P, Sachs RN, Harfouche B, Lormeau B, Paries J, Cosson E, Paycha F, Leutenegger M, Attali JR: Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. *Diabetes Care* 24:339–343, 2001
71. Mogensen CE: Nephropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 433–449
72. Anderson RJ, Grigsby AB, Freedland KE, de Groot M, McGill JB, Clouse RE, Lustman PJ: Anxiety and poor glycemic control: a meta-analytic review of the literature. *Int J Psychiatry Med* 32:235–247, 2002
73. Jacobson AM: Depression and diabetes. *Diabetes Care* 16:1621–1623, 1993
74. Lustman PJ, Griffith LS, Clouse RE, Cryer PE: Psychiatric illness in diabetes mellitus: relationship to symptoms and glucose control. *J Nerv Ment Dis* 174:736–742, 1986
75. Rubin RR, Peyrot M: Psychosocial problems and interventions in diabetes: a review of the literature. *Diabetes Care* 15: 1640–1657, 1992
76. Surwit RS, Schneider MS, Feinglos MN: Stress and diabetes mellitus. *Diabetes Care* 15:1413–1422, 1992
77. Young-Hyman D: Psycosocial factors affecting adherence, quality of life, and well-being: helping patients cope. In *Medical Management of Type 1 Diabetes*. 4th ed. Bode B, Ed. Alexandria, VA, American Diabetes Association, 2004, p. 162–182
78. Anderson BJ, Auslander WF, Jung KC, Miller JP, Santiago JV: Assessing family sharing of diabetes responsibilities. *J Pediatr Psychol* 15:477–492, 1990
79. Clark CM Jr, Fradkin JE, Hiss RG, Lorenz RA, Vinicor F, Warren-Boulton E: The National Diabetes Education Program, changing the way diabetes is treated: comprehensive diabetes care. *Diabetes Care* 24:617–618, 2001
80. McCulloch DK, Glasgow RE, Hampson SE, Wagner E: A systematic approach to diabetes management in the post-DCCT era. *Diabetes Care* 17:765–769, 1994
81. Rubin RR, Peyrot M: Psychological issues and treatments for people with diabetes. *J Clin Psychol* 57:457–478, 2001
82. Marcus MD, Wing RR: Eating disorders and diabetes. In *Neuropsychological and Behavioral Aspects of Diabetes*. Holmes CS, Ed. New York, Springer-Verlag, 1990, p. 102–121
83. American Diabetes Association: Hyperglycemic crises in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1): S94–S102, 2004
84. Malmberg K: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus: DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 314:1512–1515, 1997
85. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 33 of 38
Dexcom v. Abbott, IPR2024-00521

the critically ill patients. *N Engl J Med* 345:1359–1367, 2001
86. Cryer PE: Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937–948, 2002
87. Gannon MC, Nuttall FQ: Protein and diabetes. In *American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes*. Franz MJ, Bantle JP, Eds. Alexandria, VA, American Diabetes Association, 1999, p. 107–125
88. Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT: Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect* 119:335–341, 1997
89. Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA: Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 51:1–31, 2002
90. Smith SA, Poland GA: Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 23:95–108, 2000
91. American Diabetes Association: Influenza and pneumococcal immunization in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S111–S113, 2004
92. Arauz-Pacheco C, Parrott MA, Raskin P: The treatment of hypertension in adult patients with diabetes. *Diabetes Care* 25: 134–147, 2002
93. Haffner SM: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21:160–178, 1998
94. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes. *Diabetes Care* 22: 1887–1898, 1999
95. American Diabetes Asociation: Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. *Diabetes Care* 21: 1551–1559, 1998
96. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289:2560–2572, 2003
97. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998
98. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial: HOT Study Group. *Lancet* 351:1755–1762, 1998
99. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR: Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 321:412–419, 2000
100. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360:1903–1913, 2002
101. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16: 434–444, 1993
102. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER III, Simons-Morton DG, Karanja N, Lin PH: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet: DASH-Sodium Collaborative Research Group. *N Engl J Med* 344:3–10, 2001
103. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F: Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 21:597–603, 1998
104. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW: The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 338:645–652, 1998
105. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, Drury PL, Esmatjes E, Hricik D, Parikh CR, Raz I, Vanhille P, Wiegmann TB, Wolfe BM, Locatelli F, Goldhaber SZ, Lewis EJ: Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 138:542–549, 2003
106. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 290: 2805–2816, 2003
107. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–259, 2000
108. PROGRESS Collaborative Group: Randomised trial of a perindopril based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 358:1033–1041, 2001
109. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 362:759–766, 2003
110. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 362: 772–776, 2003
111. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 362:767–771, 2003
112. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359: 1004–1010, 2002
113. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002
114. ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 283:1967–1975, 2000
115. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 34 of 38
Dexcom v. Abbott, IPR2024-00521

G: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614–620, 1997
116. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 335:1001–1009, 1996
117. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349–1357, 1998
118. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–2016, 2003
119. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al.: Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 317:1237–1245, 1987
120. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341:410–418, 1999
121. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
122. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110:227–239, 2004
124. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364:685–696, 2004
125. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495–1504, 2004
126. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E: Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 292:1307–1316, 2004
127. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN: Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 291:1071–1080, 2004
128. Ballantyne CM, Grundy SM, Oberman A, Kreisberg RA, Havel RJ, Frost PH, Haffner SM: Hyperlipidemia: diagnostic and therapeutic perspectives. *J Clin Endocrinol Metab* 85:2089–2112, 2000
129. Elam MB, Hunninghake DB, Davis KB, Garg R, Johnson C, Egan D, Kostis JB, Sheps DS, Brinton EA: Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial: Arterial Disease Multiple Intervention Trial. *JAMA* 284:1263–1270, 2000
130. Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, Ganda OP, Rosenson RS, Buse JB, Robertson DD, Sheehan JP: Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial. *Arch Intern Med* 162:1568–1576, 2002
131. Colwell JA: Aspirin therapy in diabetes (Technical Review). *Diabetes Care* 20:1767–1771, 1997
132. American Diabetes Association: Aspirin therapy in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S72–S73, 2004
133. Hayden M, Pignone M, Phillips C, Mulrow C: Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 136: 161–172, 2002
134. US Preventive Services Task Force: Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 136:157–160, 2002
135. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ: Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 90:625–628, 2002
136. American Diabetes Association: Smoking and diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S74–S75, 2004
137. US Preventive Services Task Force: Counseling to prevent tobacco use. In *Guide to Clinical Preventive Services*. 2nd ed. Baltimore, MD, Williams & Wilkins, 1996, p. 597–609
138. Fiore M, Bailey W, Cohen S: *Smoking Cessation: Clinical Practice Guideline Number 18*. Rockville, MD, U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1996
139. Garg JP, Bakris GL: Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med* 7:35–43, 2002
140. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS: Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110:32–35, 2004
141. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH: Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 314:783–788, 1997
142. Ravid M, Lang R, Rachmani R, Lishner M: Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med* 156:286–289, 1996
143. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
144. The Diabetes Control and Complications Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 47:1703–1720, 1995
145. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: the Collaborative Study Group. *N Engl J Med* 329:1456–1462,

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 35 of 38
Dexcom v. Abbott, IPR2024-00521

1993
146. Laffel LM, McGill JB, Gans DJ: The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria: North American Microalbuminuria Study Group. *Am J Med* 99:497–504, 1995
147. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J: Preserving renal function in adults with hypertension and diabetes: a consensus approach: National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 36:646–661, 2000
148. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
149. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
150. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345:870–878, 2001
151. Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH Jr, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ: Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA* 289:2073–2082, 2003
152. Pijls LT, de Vries H, Donker AJ, van Eijk JT: The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Nephrol Dial Transplant* 14:1445–1453, 1999
153. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 124:627–632, 1996
154. Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH: Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 62:220–228, 2002
155. Kasiske BL, Lakatua JD, Ma JZ, Louis TA: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 31: 954–961, 1998
156. Eknoyan G, Hostetter T, Bakris GL, Hebert L, Levey AS, Parving HH, Steffes MW, Toto R: Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK). *Am J Kidney Dis* 42: 617–622, 2003
157. Meigs JB, Larson MG, D'Agostino RB, Levy D, Clouse ME, Nathan DM, Wilson PW, O'Donnell CJ: Coronary artery calcification in type 2 diabetes and insulin resistance: the Framingham Offspring Study. *Diabetes Care* 25:1313–1319, 2002
157a. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 39 (2 Suppl. 1):S1–S266, 2002
158. Kramer H, Molitch ME: Screening for kidney disease in adults with diabetes. *Diabetes Care* 28:1813–1816, 2005
159. Kramer HJ, Nguyen QD, Curhan G, Hsu CY: Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 289:3273–3277, 2003
160. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, Jerums G: Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 43:649–655, 1994
161. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation: Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130:461–470, 1999
162. Levinsky NG: Specialist evaluation in chronic kidney disease: too little, too late. *Ann Intern Med* 137:542–543, 2002
163. American Diabetes Association: Nephropathy in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S79–S83, 2004
164. Fong DS, Aiello LP, Ferris FL III, Klein R: Diabetic retinopathy. *Diabetes Care* 27: 2540–2553, 2004
165. The Diabetes Control and Complications Trial Research Group: Effect of pregnancy on microvascular complications in the Diabetes Control and Complications Trial. *Diabetes Care* 23:1084–1091, 2000
166. Vijan S, Hofer TP, Hayward RA: Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. *JAMA* 283:889–896, 2000
167. Klein R: Screening interval for retinopathy in type 2 diabetes. *Lancet* 361:190–191, 2003
168. Younis N, Broadbent DM, Vora JP, Harding SP: Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. *Lancet* 361:195–200, 2003
169. American Diabetes Association: Retinopathy in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S84–S87, 2004
170. Ciulla TA, Amador AG, Zinman B: Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 26:2653–2664, 2003
171. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D: Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 28:956–962, 2005
172. Vinik AI, Mehrabyan A: Diabetic neuropathies (Review). *Med Clin North Am* 88:947–999, xi, 2004
173. Vinik AI, Maser RE, Mitchell BD, Freeman R: Diabetic autonomic neuropathy. *Diabetes Care* 26:1553–1579, 2003
174. American Diabetes Association: Peripheral arterial disease in people with diabetes (Consensus Statement). *Diabetes Care* 26:3333–3341, 2003
175. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM: Preventive foot care in people with diabetes. *Diabetes Care* 21:2161–2177, 1998
176. American Diabetes Association: Preventive foot care in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S63–S64, 2004
177. American Diabetes Association: Consensus Development Conference on Diabetic Foot Wound Care: 7–8 April 1999, Boston, Massachusetts. *Diabetes Care* 22:1354–1360, 1999
178. Silverstein J, Klingensmith G, Copeland KC, Plotnick L, Kaufman F, Laffel L, Deeb LC, Grey M, Anderson BJ, Holzmeister LA, Clark NG, American Diabetes Association: Care of children and adolescents with type 1 diabetes mellitus: a statement of the American Diabetes Association. *Diabetes Care* 28:186–212, 2005
179. American Diabetes Association: Standards of medical care in diabetes (Position Statement). *Diabetes Care* 28:S4–S36, 2005
180. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV: A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 27:1554–1558, 2004
181. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M: Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics* 117:2126–2131, 2006

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 36 of 38
Dexcom v. Abbott, IPR2024-00521

182. Holmes GK: Screening for coeliac disease in type 1 diabetes. *Arch Dis Child* 87:495–498, 2002
183. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ: Celiac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 33:197–214, xi, 2004
184. American Diabetes Association: Diabetes care in the school and day care setting (Position Statement). *Diabetes Care* 30 (Suppl. 1):S66–S73, 2007
185. National Diabetes Education Program. Helping the student with diabetes succeed: a guide for school personnel [article online], 2006. Available from http://ndep.nih.gov/diabetes/pubs/Youth_NDEPSchoolGuide.pdf
186. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136:664–672, 2000
187. Gahagan S, Silverstein J: Prevention and treatment of type 2 diabetes mellitus in children, with special emphasis on American Indian and Alaska Native children: American Academy of Pediatrics Committee on Native American Child Health. *Pediatrics* 112:e328, 2003
187a. Cooper WP, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA: Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 354:2443–2441, 2006
188. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD: Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 265:731–736, 1991
189. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M: Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol* 155:293–297, 1986
190. Rosenn B, Miodovnik M, Combs CA, Khoury J, Siddiqi TA: Pre-conception management of insulin-dependent diabetes: improvement of pregnancy outcome. *Obstet Gynecol* 77:846–849, 1991
191. Tchobroutsky C, Vray MM, Altman JJ: Risk/benefit ratio of changing late obstetrical strategies in the management of insulin-dependent diabetic pregnancies: a comparison between 1971–1977 and 1978–1985 periods in 389 pregnancies. *Diabetes Metab* 17:287–294, 1991
192. Willhoite MB, Bennert HW Jr, Palomaki GE, Zaremba MM, Herman WH, Williams JR, Spear NH: The impact of preconception counseling on pregnancy outcomes: the experience of the Maine Diabetes in Pregnancy Program. *Diabetes Care* 16:450–455, 1993
193. Kitzmiller JL, Buchanan TA, Kjos S, Combs CA, Ratner RE: Pre-conception care of diabetes, congenital malformations, and spontaneous abortions. *Diabetes Care* 19:514–541, 1996
194. American Diabetes Association: Preconception care of women with diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S76–S78, 2004
195. Brown AF, Mangione CM, Saliba D, Sarkisian CA: Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 51:S265–S280, 2003
196. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsh IB: Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 27: 553–591, 2004
197. American Association of Clinical Endocrinologists: Inpatient diabetes and metabolic control: conference proceedings. *Endocr Pract* 10 (Suppl. 2): 1–108, 2004
198. Garber AJ, Moghissi ES, Bransome ED Jr, Clark NG, Clement S, Cobin RH, Furnary AP, Hirsch IB, Levy P, Roberts R, van den Berghe G, Zamudio V: American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 10 (Suppl. 2): 4–9, 2004
199. ACE/ADA Task Force on Inpatient Diabetes: American College of Endocrinology and American Diabetes Association Consensus Statement on Inpatient Diabetes and Glycemic Control. *Diabetes Care* 29:1955–1962, 2006
200. Centers for Disease Control and Prevention: *Hospitalizations for Diabetes as Any-Listed Diagnosis: National Diabetes Surveillance System*. Atlanta, GA, Centers for Disease Control and Prevention, 2003
201. Pomposelli JJ, Baxter JK III, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA, Bistrian BR: Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr* 22:77–81, 1998
202. Fritsche A, Schweitzer MA, Haring HU: Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 138:952–959, 2003
203. Capes SE, Hunt D, Malmberg K, Gerstein HC: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355:773–778, 2000
204. Bolk J, van der PT, Cornel JH, Arnold AE, Sepers J, Umans VA: Impaired glucose metabolism predicts mortality after a myocardial infarction. *Int J Cardiol* 79: 207–214, 2001
205. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57–65, 1995
206. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenstrom A: Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 26:650–661, 2005
207. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K, Tai J, Orlandini A, Pogue J, Liu L: Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 293:437–446, 2005
208. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A: Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* 67:352–360, 1999
209. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 125: 1007–1021, 2003
210. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL: Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 22:1408–1414, 1999
211. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A: Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg* 63:356–361, 1997
212. van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P: Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med* 31:359–366, 2003
213. van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449–461, 2006

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 37 of 38
Dexcom v. Abbott, IPR2024-00521

214. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El Kebbi IM: Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 161:1653–1659, 2001
215. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA: Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 338:265–266, 1998
216. Misbin RI: The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care* 27:1791–1793, 2004
217. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med* 163:2594–2602, 2003
218. Pittas AG, Siegel RD, Lau J: Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med* 164:2005–2011, 2004
219. Queale WS, Seidler AJ, Brancati FL: Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Arch Intern Med* 157:545–552, 1997
220. Gearhart JG, Duncan JL III, Replogle WH, Forbes RC, Walley EJ: Efficacy of sliding-scale insulin therapy: a comparison with prospective regimens. *Fam Pract Res J* 14:313–322, 1994
221. Walts LF, Miller J, Davidson MB, Brown J: Perioperative management of diabetes mellitus. *Anesthesiology* 55:104–109, 1981
222. Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M: Hypoglycemia in hospitalized nondiabetic older patients. *J Am Geriatr Soc* 46:978–982, 1998
223. Fischer KF, Lees JA, Newman JH: Hypoglycemia in hospitalized patients: causes and outcomes. *N Engl J Med* 315:1245–1250, 1986
224. Markovitz LJ, Wiechmann RJ, Harris N, Hayden V, Cooper J, Johnson G, Harelstad R, Calkins L, Braithwaite SS: Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract* 8:10–18, 2002
225. Levetan CS, Salas JR, Wilets IF, Zumoff B: Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. *Am J Med* 99:22–28, 1995
226. Levetan CS, Passaro MD, Jablonski KA, Ratner RE: Effect of physician specialty on outcomes in diabetic ketoacidosis. *Diabetes Care* 22:1790–1795, 1999
227. Koproski J, Pretto Z, Poretsky L: Effects of an intervention by a diabetes team in hospitalized patients with diabetes. *Diabetes Care* 20:1553–1555, 1997
228. Furnary AP, Braithwaite SS: Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. *Am J Cardiol* 98:557–564, 2006
229. American Diabetes Association: Diabetes nutrition recommendations for health care institutions (Position Statement). *Diabetes Care* 27 (Suppl. 1):S55–S57, 2004
230. De Block C, Manuel YK, Van Gaal L, Rogiers P: Intensive insulin therapy in the intensive care unit: assessment by continuous glucose monitoring. *Diabetes Care* 29:1750–1756, 2006
231. American Diabetes Association: Diabetes care at diabetes camps (Position Statement). *Diabetes Care* 30 (Suppl. 1): S74–S76, 2007
232. American Diabetes Association: Diabetes management in correctional institutions (Position Statement). *Diabetes Care* 30 (Suppl. 1):S77–S84, 2007
233. American Diabetes Association: Third-party reimbursement for diabetes care, self-management education, and supplies (Position Statement). *Diabetes Care* 30 (Suppl. 1):S86–S87, 2007
234. O'Connor PJ: Electronic medical records and diabetes care improvement: are we waiting for Godot? (Editorial). *Diabetes Care* 26:942–943, 2003

Downloaded from http://diabetesjournals.org/care/article-pdf/30/suppl_1/S4/595396/zdc10107000s4.pdf by guest on 24 September 2024

ABBOTT Exhibit 2235 - Page 38 of 38
Dexcom v. Abbott, IPR2024-00521