

Standards of Medical Care in Diabetes—2008

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 screening, 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 exist-

ing 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 (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 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) (diabetes 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 of diabetes

Recommendations

- The fasting plasma glucose (FPG) test 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 the FPG to diagnose diabetes, it is poorly reproducible and difficult to perform in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG is the preferred diagnostic test. Although the FPG is less sensitive than the OGTT, the vast majority of people who do not meet diagnostic criteria for diabetes by the FPG but would by the OGTT will have an A1C value well below 7.0% (6).

Although the OGTT is not recommended for routine clinical use, it may be

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 2007.

Abbreviations: ABI, ankle-brachial index; ACE, angiotensin-converting enzyme; ADAG, A1C-Derived Average Glucose; 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; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; DMMP, diabetes medical management plan; DPN, distal symmetric polyneuropathy; DPP, Diabetes Prevention Program; DRS, Diabetic Retinopathy Study; DSME, diabetes self-management education; DSMT, diabetes self-management training; eAG, estimated average glucose; ECG, electrocardiogram; EDIC, Epidemiology of Diabetes Interventions and Complications; ERP, education recognition program; 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; ICU, intensive care unit; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MICU, medical ICU; 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; RAS, renin-angiotensin system; RDA, recommended dietary allowance; SICU, surgical ICU; SMBG, self-monitoring of blood glucose; TSH, thyroid-stimulating hormone; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study.

DOI: 10.2337/dc08-S012

© 2008 by the American Diabetes Association.

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

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

useful for further evaluation of patients in whom diabetes is still strongly suspected but who have normal FPG or impaired fasting glucose (IFG) (see Section 1.C).

Due to lack of evidence on prognostic significance and diagnostic thresholds, the use of the A1C for the diagnosis of diabetes is not recommended at this time.

C. Diagnosis of pre-diabetes

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 the FPG or the 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)

IFG and IGT have been officially termed “pre-diabetes.” Both categories of pre-diabetes are risk factors for future diabetes and for cardiovascular disease (CVD) (7).

II. TESTING FOR PRE-DIABETES AND DIABETES IN ASYMPTOMATIC PATIENTS

Recommendations

- Testing to detect pre-diabetes and type 2 diabetes in asymptomatic people should be considered in adults who are overweight or obese (BMI ≥ 25 kg/m²) and who have one or more additional

risk factors for diabetes (Table 3). In those without these risk factors, testing should begin at age 45. (B)

- If tests are normal, repeat testing should be carried out at least at 3-year intervals. (E)
- To test for pre-diabetes or diabetes, either an FPG test or a 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)
- In those identified with pre-diabetes, identify and, if appropriate, treat other CVD risk factors. (B)

For many illnesses, there is a major distinction between screening and diagnostic testing. However, for diabetes, the same tests would be used for “screening” as for diagnosis. Type 2 diabetes has a long asymptomatic phase and significant clinical risk markers. Diabetes may be identified anywhere along a spectrum of clinical scenarios ranging from a seemingly low-risk individual who happens to have glucose testing, to a higher-risk individual who the provider tests because of high suspicion of diabetes, to the symptomatic patient. The discussion herein is primarily framed as testing for diabetes in those without symptoms. Testing for diabetes will also detect individuals with pre-diabetes.

A. Testing for pre-diabetes and type 2 diabetes in adults

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Although the effectiveness of early identification of pre-diabetes and diabetes

Table 2—Criteria for the diagnosis of diabetes

| | | |
|----|---|----|
| 1. | FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.* | OR |
| 2. | Symptoms of hyperglycemia 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 hyperglycemia include polyuria, polydipsia, and unexplained weight loss. | 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.* | |

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day (5).

Table 3—Criteria for testing for pre-diabetes and diabetes in asymptomatic adult individuals

- Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m²*) and have additional risk factors:
 - physical inactivity
 - first-degree relative with diabetes
 - members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, and Pacific Islander)
 - women who delivered a baby weighing >9 lb or were diagnosed with GDM
 - hypertension ($\geq 140/90$ mmHg or on therapy for hypertension)
 - HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
 - women with polycystic ovarian syndrome (PCOS)
 - IGT or IFG on previous testing
 - other clinical conditions associated with insulin resistance (e.g., severe obesity and acanthosis nigricans)
 - history of CVD
- In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at age 45 years
- If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

*At-risk BMI may be lower in some ethnic groups.

through mass testing of asymptomatic individuals has not been definitively proven (and rigorous trials to provide such proof are unlikely to occur), pre-diabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common, increasing in prevalence, and impose significant public health burdens. There is a long presymptomatic phase before the diagnosis of type 2 diabetes is usually made. Relatively simple tests are available to detect preclinical disease (8). Additionally, the duration of glycemic burden is a strong predictor of adverse outcomes, and effective interventions exist to prevent progression of pre-diabetes to diabetes (see Section IV) and to reduce risk of complications of diabetes (see Section VI).

Recommendations for testing for pre-diabetes and diabetes in asymptomatic, undiagnosed adults are listed in Table 3. Testing should be considered in all adults with BMI ≥ 25 kg/m² and one or more risk factors for diabetes. Because age is a major risk factor for diabetes, testing of those without other risk factors should begin no later than age 45.

Either FPG testing or the 2-h OGTT is appropriate for testing. The 2-h OGTT identifies people with either IFG or IGT and, thus, more prediabetic people at increased risk for the development of diabetes and CVD. It should be noted that the two tests do not necessarily detect the same prediabetic individuals (9). The efficacy of interventions for primary prevention of type 2 diabetes (10–16) has primarily been demonstrated among in-

dividuals with IGT, not among individuals with IFG (who do not also have IGT). As noted in the diagnosis section (I.B), the FPG test is more convenient, more reproducible, less costly, and easier to administer than the 2-h OGTT (4,5). An OGTT may be useful in patients with IFG to better define the risk of diabetes.

The appropriate interval between tests is not known (17). The rationale for the 3-year interval is that false negatives will be repeated before substantial time elapses, and there is little likelihood that an individual will develop significant complications of diabetes within 3 years of a negative test result.

Because of the need for follow-up and discussion of abnormal results, testing should be carried out within the health care setting. Community screening outside a health care setting is not recommended because people with positive tests may not seek appropriate follow-up testing and care, and, conversely, there may be failure to ensure appropriate repeat testing for individuals who test negative. 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 (18,19).

B. Testing for type 2 diabetes in children

The incidence of type 2 diabetes in adolescents has increased dramatically in the last decade, especially in minority populations (20), although the disease remains

rare in the general population (21). Consistent with recommendations for adults, children and youth at increased risk for the presence or the development of type 2 diabetes should be tested (22). The recommendations of the ADA consensus statement on type 2 diabetes in children and youth are summarized in Table 4.

C. Screening for type 1 diabetes

Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels, and most cases are diagnosed soon after the onset of hyperglycemia. Widespread clinical testing of asymptomatic individuals for the presence of autoantibodies related to type 1 diabetes cannot currently be recommended as a means to identify individuals at risk, for several reasons: 1) cutoff values for the immune marker assays have not been completely established or standardized for clinical settings; 2) there is no consensus as to what follow-up testing should be undertaken when a positive autoantibody test result is obtained; and 3) because the incidence of type 1 diabetes is low, testing of healthy individuals will identify only a very small number ($<0.5\%$) who at that moment may be “prediabetic.” Finally, though clinical studies are being conducted to test various methods of preventing type 1 diabetes in high-risk individuals, no effective intervention has yet been identified. If studies uncover an effective means of preventing type 1 diabetes, targeted screening (e.g., siblings of type 1 children) may be appropriate in the future.

Table 4—Testing for type 2 diabetes in asymptomatic children

| Criteria |
|--|
| <ul style="list-style-type: none"> • 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: |
| <ul style="list-style-type: none"> • Family history of type 2 diabetes in first- or second-degree relative • Race/ethnicity (e.g., Native American, African American, Latino, Asian American, and Pacific Islander) • Signs of insulin resistance or conditions associated with insulin resistance (e.g., 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 |

III. DETECTION AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS (GDM)

Recommendations

- Screen for GDM 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)

Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (4). Although most cases resolve with delivery, the definition applies whether or not the condition persists after pregnancy and does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. Approximately 7% of all pregnancies (ranging from 1 to 14% depending on the population studied and the diagnostic tests used) are complicated by GDM, resulting in more than 200,000 cases annually.

Because of the risks of GDM to the mother and neonate, screening and diagnosis are warranted. The screening and diagnostic strategies, based on the 2004 ADA position statement on gestational diabetes mellitus (23), are outlined in Table 5.

Results of the Hyperglycemia and Adverse Pregnancy Outcomes study were reported at ADA's 67th Annual Scientific Sessions in June 2007. This large-scale (~25,000 pregnant women), multinational, epidemiologic study demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results may call for careful reconsideration of the diagnostic criteria for GDM.

Because women with a history of GDM have a greatly increased subsequent risk for diabetes (24), they should be screened for diabetes 6–12 weeks postpartum, using standard criteria, and should be followed up with subsequent screening for the development of diabetes or pre-diabetes, as outlined in Section II. For information on the National Diabetes Education Program (NDEP) campaign to prevent type 2 diabetes in women with

Table 5—Screening for and diagnosis of GDM

Carry out GDM risk assessment at the first prenatal visit.

Women at very high risk for GDM should be screened for diabetes as soon as possible after the confirmation of pregnancy. Criteria for very high risk are:

- Severe obesity
- Prior history of GDM or delivery of large-for-gestational-age infant
- Presence of glycosuria
- Diagnosis of PCOS
- Strong family history of type 2 diabetes

Screening/diagnosis at this stage of pregnancy should use standard diagnostic testing (Table 2)

All women of higher than low risk of GDM, including those above not found to have diabetes early in pregnancy, should undergo GDM testing at 24–28 weeks of gestation.

Low risk status, which does not require GDM screening, is defined as women with *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 obstetrical outcome

Two approaches may be followed for GDM screening at 24–28 weeks:

1. Two-step approach:

A. Perform initial screening by measuring plasma or serum glucose 1 h after a 50-g oral glucose load. A glucose threshold after 50-g load of ≥ 140 mg/dl identifies ~ 80% of women with GDM, while the sensitivity is further increased to ~ 90% by a threshold of ≥ 130 mg/dl.

B. Perform a diagnostic 100-g OGTT on a separate day in women who exceed the chosen threshold on 50-g screening.

2. One-step approach (may be preferred in clinics with high prevalence of GDM): Perform a diagnostic 100-g OGTT in all women to be tested at 24–28 weeks.

The 100-g OGTT should be performed in the morning after an overnight fast of at least 8 h.

A diagnosis of GDM requires at least two of the following plasma glucose values:

Fasting: ≥ 95 mg/dl (≥ 5.3 mmol/l)

1 h: ≥ 180 mg/dl (≥ 10.0 mmol/l)

2 h: ≥ 155 mg/dl (≥ 8.6 mmol/l)

3 h: ≥ 140 mg/dl (≥ 7.8 mmol/l)

GDM, go to www.ndep.nih.gov/diabetes/pubs/NeverTooEarly_Tipsheet.pdf.

IV. PREVENTION/DELAY OF TYPE 2 DIABETES

Recommendations

- Patients with IGT (A) or IFG (E) should be given counseling on weight loss of 5–10% of body weight, as well as on increasing physical activity to at least 150 min/week of moderate activity such as walking.
- Follow-up counseling appears to be important for success. (B)
- Based on potential cost savings of diabetes prevention, such counseling should be covered by third-party payors. (E)
- In addition to lifestyle counseling, metformin may be considered in those who are at very high risk (combined IFG and

IGT plus other risk factors) and who are obese and under 60 years of age. (E)

- Monitoring for the development of diabetes in those with pre-diabetes should be performed every year. (E)

Randomized controlled trials have shown that individuals at high risk for developing diabetes (those with IFG, IGT, or both) can be given interventions that significantly decrease the rate of onset of diabetes (10–16). These interventions include an intensive lifestyle modification program that has been shown to be very effective (~58% reduction after 3 years), and use of the pharmacologic agents metformin, acarbose, orlistat, and rosiglitazone, each of which has been shown to decrease incident diabetes to various degrees. A summary of major diabetes prevention trials is shown in Table 6.

Based on the results of clinical trials and the known risks of progression of

Table 6—Therapies proven effective in diabetes prevention trials

| Study (reference)‡ | n | Population | Age (years) | Duration (years) | Follow up | Intervention (daily dose) | Control subjects (%/year) | Relative risk |
|--------------------|--------|--|-------------|------------------|-----------|---------------------------|---------------------------|-------------------|
| Finnish DPS (15) | 522 | IGT, BMI \geq 25 kg/m ² | 55 | 3.2 | 92 | Individual diet/exercise | 6 | 0.42 (0.30–0.70) |
| DPP (14) | 2,161* | IGT, BMI \geq 24 kg/m ² , FPG >5.3 (95) | 51 | 3 | 93 | Individual diet/exercise | 10 | 0.42 (0.34–0.52) |
| Pan et al. (22) | 259* | IGT (randomized groups) | 45 | 6 | 92 | Group diet/exercise | 16 | 0.62 (0.44–0.86) |
| Kosaka et al. (23) | 458 | IGT (men), BMI = 24 kg/m ² | ~55 | 4 | 92 | Individual diet/exercise | 2 | 0.33 (0.10–1.0)† |
| Indian DPP (24) | 269* | IGT | 46 | 2.5 | 95 | Individual diet/exercise | 22 | 0.71 (0.63–0.79) |
| DPP (14) | 2,155* | IGT, BMI >24 kg/m ² , FPG >5.3 | 51 | 2.8 | 93 | Metformin (1,700 mg) | 10 | 0.69 (0.57–0.83) |
| Indian DPP (24) | 269* | IGT | 46 | 2.5 | 95 | Metformin (500 mg) | 22 | 0.74 (0.65–0.81) |
| STOP NIDDM (16) | 1,419 | IGT, FPG >5.6 | 54 | 3.2 | 96 | Acarbose (300 mg) | 13 | 0.75 (0.63–0.90) |
| XENDOS (18) | 3,277 | BMI >30 kg/m ² | 43 | 4 | 43 | Orlistat (360 mg) | 2 | 0.63 (0.46–0.86) |
| DPP (25) | 1,067* | IGT, BMI >24 kg/m ² , FPG >5.3 | 51 | 0.9 | 93 | Troglitazone (400 mg) | 12 | 0.25 (0.14–0.43)† |
| TRIPOD (26) | 266 | Previous GDM | 35 | 2.5 | 67 | Troglitazone (400 mg) | 12 | 0.45 (0.25–0.83) |
| DREAM (17) | 5,269 | IGT or IFG | 55 | 3.0 | 94 | Rosiglitazone (8 mg) | 9 | 0.40 (0.35–0.46) |

Reprinted with permission (25). *Number of participants in the indicated comparisons and not the total randomized; †calculated from information in the article; ‡references are numbered as in original publication (25). DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; GDM, gestational diabetes mellitus; STOP, Study to Prevent Non-Insulin Dependent Diabetes; TRIPOD, Troglitazone in Prevention of Diabetes; XENDOS, Xenical in the prevention of Diabetes in Obese Subjects.

pre-diabetes to diabetes, an ADA consensus development panel in 2007 (7) concluded that persons with pre-diabetes (IGT and/or IFG) should be counseled on lifestyle changes with goals similar to those of the Diabetes Prevention Program (DPP) (5–10% weight loss and moderate physical activity of ~30 min/day). Regarding the more difficult issue of drug therapy for diabetes prevention, the consensus panel felt that metformin should be the only drug considered for use in diabetes prevention. For other drugs, the issues of cost, side effects, and lack of persistence of effect in some studies led the panel to not recommend their use for diabetes prevention. Metformin use was recommended only for very high-risk individuals (combined IGT and IFG, and with at least one other risk factor). In addition, the panel highlighted the evidence that in the DPP, treatment with metformin had the most relative effectiveness in those with BMI of at least 35 kg/m² and those under age 60.

V. DIABETES CARE

A. Initial evaluation

A complete medical evaluation should be performed to classify the diabetes, detect the presence of diabetes complications, review previous treatment and glycemic control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care. Laboratory tests appropriate to the evaluation of each patient's medical condition should be performed. A focus on the components of comprehensive care (Table 7) 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 physician, and other members of the health care team. 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. 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 compli-

Table 7—Components of the comprehensive diabetes evaluation

| | |
|--|--|
| Medical history | <ul style="list-style-type: none"> • Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding) • Eating patterns, nutritional status, and weight history; growth and development in children and adolescents • Diabetes education history • Review of previous treatment regimens and response to therapy (A1C records) • Current treatment of diabetes, including medications, meal plan, physical activity patterns, and results of glucose monitoring and patient's use of data • DKA frequency, severity, and cause • Hypoglycemic episodes <ul style="list-style-type: none"> • Hypoglycemia awareness • Any severe hypoglycemia: frequency and cause • History of diabetes-related complications <ul style="list-style-type: none"> • Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis) • Macrovascular: CHD, cerebrovascular disease, PAD • Other: psychosocial problems,* dental disease* |
| Physical examination | <ul style="list-style-type: none"> • Height, weight, BMI • Blood pressure determination, including orthostatic measurements when indicated • Fundoscopic examination* • Thyroid palpation • Skin examination (for acanthosis nigricans and insulin injection sites) • Comprehensive foot examination: <ul style="list-style-type: none"> • Inspection • Palpation of dorsalis pedis and posterior tibial pulses • Presence/absence of patellar and Achilles reflexes • Determination of proprioception, vibration, and monofilament sensation |
| Laboratory evaluation | <ul style="list-style-type: none"> • A1C, if results not available within past 2–3 months |
| If not performed/available within past year: | <ul style="list-style-type: none"> • Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides • Liver function tests • Test for urine albumin excretion with spot urine albumin-to-creatinine ratio • Serum creatinine and calculated GFR • Thyroid-stimulating hormone in type 1 diabetes, dyslipidemia or women over age 50 |
| Referrals | <ul style="list-style-type: none"> • Annual dilated eye exam • Family planning for women of reproductive age • Registered dietitian for MNT • Diabetes self-management education • Dental examination • Mental health professional, if needed |

*See appropriate referrals for these categories.

cations of diabetes or other medical conditions.

C. Glycemic control

1. Assessment of glycemic control.

Two primary techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control: patient self-monitoring of blood glucose (SMBG) and A1C measurement. In addition, in recent years technologies for continuous monitoring of interstitial glucose have entered the market.

a. Self-monitoring of blood glucose

Recommendations

- SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. (A)
- For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) alone, SMBG may be useful in achieving glycemic goals. (E)
- To achieve postprandial glucose tar-

gets, postprandial SMBG may be appropriate. (E)

- When prescribing SMBG, ensure that patients receive initial instruction in, and routine follow-up evaluation of, SMBG technique and their ability to use data to adjust therapy. (E)
- Continuous glucose monitoring may be a supplemental tool to SMBG for selected patients with type 1 diabetes, especially those with hypoglycemia unawareness. (E)

ADA's consensus and position statements on SMBG provide a comprehensive review of the subject (26,27). Major clinical trials of insulin-treated patients that demonstrated the benefits of intensive 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 (particularly prandial insulin doses), MNT, and physical activity.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the patients. 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. For this population, it is often difficult to reach A1C targets safely without hypoglycemia with the minimum of three daily tests. The optimal frequency and timing of SMBG for patients with type 2 diabetes on noninsulin therapy is not known but should be sufficient to facilitate reaching glucose goals. A meta-analysis of SMBG in non-insulin-treated patients with type 2 diabetes concluded that some regimen of SMBG 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 difficult to assess the contribution of SMBG alone to improved control (28).

Because the accuracy of SMBG is instrument and user dependent (29), it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, optimal use of SMBG requires proper in-

Table 8—Summary of glycemic recommendations for adults with diabetes

| | |
|--|-------------------------------|
| A1C | <7.0%* |
| Preprandial capillary plasma glucose | 70–130 mg/dl (3.9–7.2 mmol/l) |
| Peak postprandial capillary plasma glucose† | <180 mg/dl (<10.0 mmol/l) |
| Key concepts in setting glycemic goals: | |
| <ul style="list-style-type: none"> • A1C is the primary target for glycemic control • Goals should be individualized based on: <ul style="list-style-type: none"> • duration of diabetes • pregnancy status • age • comorbid conditions • hypoglycemia unawareness • individual patient considerations • More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of 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.

terpretation 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, and these skills should be re-evaluated periodically.

In recent years, methods to sample interstitial fluid glucose (which correlates highly with blood glucose) in a continuous and minimally invasive way have been developed. Most microdialysis systems are inserted subcutaneously, while an early system employed “reverse iontophoresis” to move glucose across the skin. The concentration of glucose is then measured by a glucose oxidase electrode detector. These systems require calibration with SMBG readings, and the latter are still recommended for making treatment decisions. Continuous glucose sensors have alarms for hypo- and hyperglycemia. Small studies in selected patient populations have shown good correlation of readings with SMBG and decreases in the mean time spent in hypo- and hyperglycemic ranges compared with blinded sensor use (30). Although continuous glucose sensors would seem to show great promise in diabetes management, as yet no rigorous controlled trials have demonstrated improvements in long-term glycemia.

b. A1C

Recommendations

- Perform the A1C test at least two times a year in patients who are meeting treat-

ment 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)

Because A1C is thought to reflect average glycemia over several months (29), and has strong predictive value for diabetes complications (10,31), A1C testing should be performed routinely in all patients with diabetes, at initial assessment and then as part of continuing care. Measurement approximately every 3 months determines whether a patient's glycemic targets (Table 8) have been reached and maintained. 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. Some patients with stable glycemia well within target may do well with testing only twice per year, while unstable or highly intensively managed patients (e.g., pregnant type 1 women) may be tested more frequently than every 3 months. The availability of the A1C result at the time that the patient is seen (point-of-care testing) has been reported to result in increased intensification of therapy and improvement in glycemic control (32,33).

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 (29). In addition, A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability (especially type 1 diabetic patients, or type 2 diabetic patients with severe insulin deficiency), glycemic control is best judged by the combination of results of SMBG testing and the A1C. The A1C may also serve as a check on the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

Table 9 contains the correlation between A1C levels and mean plasma glucose levels based on data from the Diabetes Control and Complications Trial (DCCT) (34). The correlation is based on relatively sparse data from a primarily Caucasian type 1 diabetic population. Preliminary results of the multicenter A1C-Derived Average Glucose (ADAG) Trial, presented at the European Association for the Study of Diabetes meeting in September 2007, confirmed a close correlation of A1C with mean glucose in patients with type 1, type 2, or no diabetes. Final results of this study, not available at the time this statement was completed, should allow more accurate reporting of the estimated average glucose (eAG) and improve patients' understanding of this measure of glycemia. An updated version of Table 9, based on final results of the ADAG Trial, will be available at www.diabetes.org after publication of the study's findings in 2008.

Table 9—Correlation between A1C level and mean plasma glucose levels on multiple testing over 2–3 months

| A1C (%) | Mean plasma glucose | |
|---------|---------------------|--------|
| | 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 |

These estimates are based on DCCT data (34). An updated version of this table, based on final results of the ADAG Trial, will be available at www.diabetes.org after publication of the study's findings in 2008.

2. Glycemic goals

Recommendations

- Lowering A1C to an average of ~7% has clearly been shown to reduce microvascular and neuropathic complications of diabetes and, possibly, macrovascular disease. Therefore, the A1C goal for nonpregnant adults in general is <7%. (A)
- Epidemiologic studies have suggested an incremental (albeit, in absolute terms, a small) benefit to lowering A1C from 7% into the normal range. Therefore, the A1C goal for selected individual patients is as close to normal (<6%) as possible without significant hypoglycemia. (B)
- Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, children, individuals with comorbid conditions, and those with longstanding diabetes and minimal or stable microvascular complications. (E)

Glycemic control is fundamental to the management of diabetes. The DCCT, a prospective, randomized, controlled trial of intensive versus standard glycemic control in type 1 diabetes, showed definitively that improved glycemic control is associated with sustained decreased rates of microvascular (retinopathy and nephropathy) as well as neuropathic complications (35). Follow up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown persistence of this effect in previously intensively treated subjects, even though their glycemic control has been equivalent to that of previous standard arm subjects during follow-up (36,37). In addition, EDIC has shown a significant reduction of the rate of cardiovascular outcomes in the previous intensive arm (38).

In type 2 diabetes, the Kumamoto study (39) and the UK Prospective Diabetes Study (UKPDS) (40,41) demonstrated significant reductions in microvascular and neuropathic complications with intensive therapy. The potential of intensive glycemic control to reduce CVD in type 2 diabetes is supported by epidemiological studies (31,40–42) and a meta-analysis (43), but has not yet been demonstrated in a randomized clinical trial. Several large trials are currently under way to address this issue.

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, most notably in the DCCT, and to lead to weight gain (31,44).

Epidemiological analyses of the DCCT and UKPDS (31,35) demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair or good control. These analyses also suggest that further lowering of A1C from 7 to 6% is associated with further reduction in the risk of complications, albeit the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycemia (particularly in those with type 1 diabetes) and the relatively much greater effort required to achieve near-normoglycemia, the risks of lower targets may outweigh the potential benefits on a population level. However, selected individual patients, especially those with little comorbidity and long life expectancy (who may reap the benefits of further lowering of glycemia below 7%) may, at patient and provider judgment, have glycemic targets as close to normal as possible without significant hypoglycemia becoming a barrier.

Recommended glycemic goals for nonpregnant individuals are shown in Table 8. The recommendations are based on data for A1C. The listed blood glucose goals are levels that appear to correlate with achievement of an A1C of <7%. Less stringent treatment goals may be appropriate for patients with limited life expectancies, in children, and in individuals with comorbid conditions. Severe or frequent hypoglycemia is an indication for the modification of treatment regimens, including setting higher glycemic goals.

Neither the DCCT nor the UKPDS addressed patient populations with long durations of diabetes. Clinical experience suggests that it is uncommon for significant microvascular disease to begin after 20–30 years of diabetes. Furthermore, hypoglycemia unawareness becomes more prevalent with long duration of diabetes. Therefore, in patients with longstanding diabetes (three or more decades) and minimal or stable microvascular complications, the risk-to-benefit ratio for stringent A1C goals appears high.

The issue of pre- versus postprandial SMBG targets is complex (45). Elevated postchallenge (2-h OGTT) glucose values have been associated with increased cardiovascular risk independent of FPG in some epidemiological studies. In diabetic subjects, some surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia (46). It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being higher at A1C levels that are closer to 7%. However, outcome studies have clearly shown A1C to be the primary predictor of complications, and the glycemic control trials such as the DCCT relied overwhelmingly on preprandial SMBG. Thus, a reasonable recommendation is: In individuals who have premeal glucose values within target but have A1C values above target, monitoring postprandial plasma glucose (PPG) 1–2 h after the start of the meal and treatment aimed at reducing PPG values to <180 mg/dl will likely lower A1C and may improve outcomes.

In regard to glycemic control for women with GDM, recommendations from the Fourth International Workshop-Conference on Gestational Diabetes Mellitus (47) suggested lowering maternal capillary whole-blood glucose concentrations to:

- Preprandial: ≤95 mg/dl (5.3 mmol/l), and either:
 - 1-h postmeal: ≤140 mg/dl (7.8 mmol/l) or
 - 2-h postmeal: ≤120 mg/dl (6.7 mmol/l)

Comparable plasma-referenced capillary blood glucose values suggested in the ADA Position Statement on GDM (14) are:

- Preprandial: ≤105 mg/dl (5.8 mmol/l), and either:
 - 1-h postmeal: ≤155 mg/dl (8.6 mmol/l) or
 - 2-h postmeal: ≤130 mg/dl (7.2 mmol/l)

3. Approach to treatment

a. Therapy for type 1 diabetes. The DCCT clearly showed that intensive insulin therapy (three or more injections per day of insulin or continuous subcutaneous insulin infusion [CSII, or insulin

pump therapy) was a key part of improved glycemia and better outcomes (35). At the time of the study, therapy was carried out with short- and intermediate-acting human insulins. Despite better microvascular outcomes, intensive insulin therapy was associated with a marked increase in severe hypoglycemia (62 episodes per 100 patient-years of therapy). Since the time of the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs were designed to be more “physiological” in their pharmacokinetics and pharmacodynamics, and are associated with less hypoglycemia with equal A1C lowering in type 1 diabetes (48,49).

Therefore, recommended therapy for type 1 diabetes consists of the following components: 1) use of multiple dose insulin injections (3–4 injections per day of basal and prandial insulin) or CSII therapy; 2) matching of prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated activity; and 3) for many patients (especially if hypoglycemia is a problem), use of insulin analogs. There are excellent reviews available that guide the initiation and management of insulin therapy to achieve desired glycemic goals (3,48,50).

b. Therapy for type 2 diabetes. ADA and the European Association for the Study of Diabetes published a consensus statement on the approach to management of hyperglycemia in individuals with type 2 diabetes (51). Highlights of this approach are 1) intervention at the time of diagnosis with metformin in combination with lifestyle changes (MNT and exercise) and 2) continuing timely augmentation of 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). The overall objective is to achieve and maintain glycemic levels as close to the nondiabetic range as possible and to change interventions at as rapid a pace as titration of medications allows.

The algorithm took into account the evidence for A1C-lowering of the individual interventions, their synergies, and their expense. Of note, the consensus algorithm was developed before publications that raised concerns about increased risk of myocardial infarction with use of rosiglitazone (52,53) and before addition of black box warnings about congestive heart failure (CHF) for both rosiglitazone

and pioglitazone. This new information may prompt greater caution in using the thiazolidinediones. Other medications such as pramlintide, exenatide, α -glucosidase inhibitors, the glinides, and dipeptidyl peptidase IV inhibitors were not included in the consensus algorithm, owing to less glucose-lowering effectiveness, limited clinical data, and/or relative expense. However, they may be appropriate choices in individual patients to achieve glycemic goals. Initiation of insulin at time of diagnosis is recommended for individuals presenting with weight loss or other severe hyperglycemic symptoms or signs. For a list of currently approved diabetes medications, see http://ndep.nih.gov/diabetes/pubs/Drug_tables_supplement.pdf.

D. MEDICAL NUTRITION THERAPY (MNT)

General recommendations

- 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)

Energy balance, overweight, and obesity

- 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)
- For weight loss, either low-carbohydrate or low-fat calorie-restricted diets may be effective in the short term (up to 1 year). (A)
- For patients on low-carbohydrate diets, monitor lipid profiles, renal function, and protein intake (in those with nephropathy), and adjust hypoglycemic therapy as needed. (E)
- Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintenance of weight loss. (B)

Primary prevention of diabetes

- Among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight

loss (7% body weight) and regular physical activity (150 min/week), with dietary strategies including reduced calories and reduced intake of dietary fat, can reduce the risk for developing diabetes and are therefore recommended. (A)

- Individuals at high risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake). (B)

Dietary fat intake in diabetes management

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

Carbohydrate intake in diabetes management

- Monitoring carbohydrate intake, 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)

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. ADA recognizes

that, in addition to its important role in preventing and controlling diabetes, nutrition is an essential component of an overall healthy lifestyle. A full review of the evidence regarding nutrition in preventing and controlling diabetes and its complications and additional nutrition-related recommendations can be found in the ADA position statement, "Nutrition Recommendations and Interventions for Diabetes," published in 2007 and updated for 2008 (54). 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.

Clinical trials/outcome studies of MNT have reported decreases in A1C of ~1% in type 1 diabetes and 1–2% in type 2 diabetes, depending on the duration of diabetes (55,56). Meta-analyses of studies in nondiabetic, free-living subjects report that MNT reduces LDL cholesterol by 15–25 mg/dl (57), while clinical trials support a role for lifestyle modification in treating hypertension (58).

Because of the effects of obesity on insulin resistance, weight loss is an important therapeutic objective for overweight or obese individuals with pre-diabetes or diabetes (59). Short-term studies have demonstrated that moderate weight loss (5% of body weight) in subjects with type 2 diabetes is associated with decreased insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure (60); longer-term studies (≥ 52 weeks) showed mixed effects on A1C in adults with type 2 diabetes (61–63), and results were confounded by pharmacologic weight loss therapy. Sustained weight loss is difficult for most people to accomplish. However, the multifactorial intensive lifestyle intervention employed in the DPP, which included reduced intake of fat and calories, led to weight loss averaging 7% at 6 months and maintenance of 5% weight loss at 3 years, and these outcomes were associated with a 58% reduction in the incidence of type 2 diabetes (10). The Look AHEAD (Action for Health in Diabetes) study is a large clinical trial designed to determine whether long-term weight loss will improve glycemia and prevent cardiovascular events in subjects with type 2 diabetes. One-year results of

the intensive lifestyle intervention in this trial show an average 8.6% weight loss, significant reduction of A1C, and reduction in several CVD risk factors (64). When completed, the Look AHEAD study should provide insight into the effects of long-term weight loss on important clinical outcomes.

The optimal macronutrient distribution of weight loss diets has not been established. Although low-fat diets have traditionally been promoted for weight loss, several randomized controlled trials found that subjects on low-carbohydrate diets (<130 g/day of carbohydrate) lost more weight at 6 months than subjects on low-fat diets (65,66); however, at 1 year, the difference in weight loss between the low-carbohydrate and low-fat diets was not significant and weight loss was modest with both diets. Another study of overweight women randomized to one of four diets showed significantly more weight loss at 12 months with the Atkins low-carbohydrate diet than with higher-carbohydrate diets (67). Changes in serum triglyceride and HDL cholesterol were more favorable with the low-carbohydrate diets. In one study, those subjects with type 2 diabetes demonstrated a greater decrease in A1C with a low-carbohydrate diet than with a low-fat diet (66). A recent meta-analysis showed that at 6 months, low-carbohydrate diets were associated with greater improvements in triglyceride and HDL cholesterol concentrations than low-fat diets; however, LDL cholesterol was significantly higher on the low-carbohydrate diets (68).

The recommended dietary allowance (RDA) for digestible carbohydrate is 130 g/day and is based on providing adequate glucose as the required fuel for the central nervous system without reliance on glucose production from ingested protein or fat. Although brain fuel needs can be met on lower-carbohydrate diets, long-term metabolic effects of very-low-carbohydrate diets are unclear, and such diets eliminate many foods that are important sources of energy, fiber, vitamins, and minerals and are important in dietary palatability (69).

Although numerous studies have attempted to identify the optimal mix of macronutrients for meal plans of people with diabetes, it is unlikely that one such combination of macronutrients exists. The best mix of carbohydrate, protein, and fat appears to vary depending on individual circumstances. For those indi-

viduals seeking guidance on macronutrient distribution in healthy adults, the Dietary Reference Intakes (DRIs) may be helpful (69). It must be clearly recognized that regardless of the macronutrient mix, total caloric intake must be appropriate to weight management goal. Further, individualization of the macronutrient composition will depend on the metabolic status of the patient (e.g., lipid profile, renal function).

The primary goal with respect to dietary fat in individuals with diabetes is to limit saturated fatty acids, *trans* fatty acids, and cholesterol intake so as to reduce risk for CVD. Saturated and *trans* fatty acids are the principal dietary determinants of plasma LDL cholesterol. There is a lack of evidence on the effects of specific fatty acids on people with diabetes, so the recommended goals are consistent with those for individuals with CVD (70).

The FDA has approved five nonnutritive sweeteners for use in the U.S.: acesulfame potassium, aspartame, neotame, saccharin, and sucralose. Before being allowed on the market, all underwent rigorous scrutiny and were shown to be safe when consumed by the public, including people with diabetes and women during pregnancy. Reduced-calorie sweeteners approved by the FDA include sugar alcohols (polyols) such as erythritol, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol, tagatose, and hydrogenated starch hydrolysates. The use of sugar alcohols appears to be safe; however, they may cause diarrhea, especially in children.

Reimbursement for MNT

MNT, when delivered by a registered dietitian according to nutrition practice guidelines, is reimbursed as part of the Medicare program as overseen by the Centers for Medicare and Medicaid Services (CMS) (www.cms.hhs.gov/medicalnutritiontherapy).

E. DSME

Recommendations

- People with diabetes should receive DSME according to national standards when their diabetes is diagnosed and as needed thereafter. (B)
- Self-management behavior change is the key outcome of DSME and should be measured and monitored as part of care. (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 (71–77), and the National Standards for DSME (78) 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 as treatment advances become available. DSME helps patients optimize metabolic control, prevent and manage complications, and maximize quality of life, in a cost-effective manner (79).

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 and improved self-care behavior (72), improved clinical outcomes such as lower A1C (73,74,76,77,80), lower self-reported weight (72), and improved quality of life (75). Better outcomes were reported for DSME interventions that were longer and included follow-up support (72), that were tailored to individual needs and preferences (71), and that addressed psychosocial issues (71,72,76). Both individual and group approaches have been found effective (81,82). There is increasing evidence for the role of a community health worker in delivering diabetes education in addition to the core team (83).

The National Standards for DSME

ADA-recognized DSME programs have staff who must be certified diabetes educators or have recent experience in diabetes education and management. The curriculum of ADA-recognized DSME programs must cover all nine areas of diabetes management, with the assessed needs of the individual determining which areas are addressed. The ADA Education Recognition Program (ERP) is a mechanism to ensure that diabetes education programs meet the National Standards and provide quality diabetes care.

Reimbursement for DSME

DSME, when provided by a program that meets ADA ERP standards, 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

- People with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate). (A)
- In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance training three times per week. (A)

ADA technical reviews on exercise in patients with diabetes have summarized the value of exercise in the diabetes management plan (84,85). 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 (10–12). Structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even with no significant change in BMI (86). Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness (87).

Frequency and type of exercise

A U.S. Surgeon General's report (88) recommended that most adults accumulate at least 30 min of moderate-intensity activity on most, ideally all, days of the week. The studies included in the meta-analysis of effects of exercise interventions on glycemic control (86) had a mean number of sessions per week of 3.4, with a mean of 49 min per session. The DPP lifestyle intervention, which included 150 min per week of moderate-intensity exercise, had a beneficial effect on glycemia in those with pre-diabetes. Therefore, it seems reasonable to recommend ~150 min of exercise per week for people with diabetes.

Resistance exercise improves insulin sensitivity to about the same extent as aerobic exercise (89). Clinical trials have provided strong evidence for the A1C-

lowering value of resistance training in older adults with type 2 diabetes (90,91), and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (92).

Evaluation of the diabetic patient before recommending an exercise program

Prior guidelines suggested that before recommending a program of physical activity, the provider should assess patients with multiple cardiovascular risk factors for coronary artery disease (CAD). As discussed more fully in Section VI.A.5, the area of screening asymptomatic diabetic patients for CAD remains unclear, and a recent ADA consensus statement on this issue concluded that routine screening is not recommended (93). Providers should use clinical judgment in this area. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and increase the intensity and duration slowly.

Providers should assess patients for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy or history of foot lesions, and advanced retinopathy. The patient's age and previous physical activity level should be considered.

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 (94); therefore, vigorous activity should be avoided in the presence of ketosis. However, it is not necessary to postpone exercise based simply on hyperglycemia, provided the patient feels well and urine and/or blood ketones are negative.

Hypoglycemia. In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. For individuals on these therapies, added carbohydrate should be ingested if pre-exercise glucose levels are <100 mg/dl (5.6 mmol/l) (95,96). Hypoglycemia is rare in diabetic individuals who are not treated with insulin or insulin secretagogues, and no preventive measures for hypoglycemia are usually advised in these cases.

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 (97).

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 (98,99).

Autonomic neuropathy. Autonomic neuropathy can increase the risk of exercise-induced injury or adverse event through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and unpredictable carbohydrate delivery from gastroparesis predisposing to hypoglycemia (98). Autonomic neuropathy is also strongly associated with CVD in people with diabetes (100,101). People with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Albuminuria and nephropathy. Physical activity can acutely increase urinary protein excretion. However, there is no evidence that vigorous exercise increases the rate of progression of diabetic kidney disease; thus, there is likely no need for any specific exercise restrictions for people with diabetic kidney disease (102).

G. Psychosocial assessment and care

Recommendations

- Assessment of psychological and social situation should be included as an ongoing part of the medical management of diabetes. (E)
- Psychosocial screening and follow-up 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)
- Screen for psychosocial problems such as depression, anxiety, eating disorders, and cognitive impairment when

adherence to the medical regimen is poor. (E)

Psychological and social problems can impair the individual's (103–108) or family's (109) ability to carry out diabetes care tasks and can therefore compromise health status. 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.

Key opportunities for screening of psychosocial status occur at diagnosis, during regularly scheduled management visits, during hospitalizations, at discovery of complications, or when problems with glucose control, quality of life, or adherence are identified (110). 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 (105,107).

Issues known to impact self-management and health outcomes include but are not limited to: attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional) (106), and psychiatric history (107,110,111). Screening tools are available for a number of these areas (112). Indications for referral to a mental health specialist familiar with diabetes management may include gross noncompliance with medical regimen (by self or others) (111), depression with the possibility of self-harm (104,113), debilitating anxiety (alone or with depression), indications of an eating disorder (114), and cognitive functioning that significantly impairs judgment (113). It is preferable to incorporate psychological assessment and treatment into routine care rather than wait for identification of a specific problem or deterioration in psychological status (115). 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 (110).

H. When treatment goals are not met

For a variety of reasons, some people with diabetes and their health care providers

do not achieve the desired goals of treatment (Table 8). Intensification of the treatment regimen is suggested and may include assessment of barriers to adherence including income; educational attainment; and competing demands, including those related to family responsibilities and family dynamics; culturally appropriate and enhanced DSME; co-management with a diabetes team; referral to a medical social worker for assistance with insurance coverage; 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, both of which are life-threatening conditions that require immediate medical care to prevent complications and death (116). Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose and (in ketosis-prone patients) urine or blood ketones. Marked hyperglycemia requires temporary adjustment of the treatment program and—if accompanied by ketosis, vomiting, or alteration in the level of consciousness—immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or MNT alone may temporarily require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration is more likely to necessitate hospitalization of the person with diabetes than the person without diabetes.

The hospitalized patient should be treated by a physician with expertise in the management of diabetes. For further information on management of patients with hyperglycemia in the hospital, see Section VIII.A. For further information on management of DKA or nonketotic hyperosmolar state, refer to the ADA position statement on hyperglycemic crises (116).

J. Hypoglycemia

Recommendations

- Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia, although any form of carbohydrate that contains glucose may be used. If SMBG 15 min after

treatment shows continued hypoglycemia, the treatment should be repeated. Once SMBG glucose returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. (E)

- Glucagon should be prescribed for all individuals at significant risk of severe hypoglycemia, and caregivers or family members of these individuals should be instructed in its administration. Glucagon administration is not limited to health care professionals. (E)
- Individuals with hypoglycemia unawareness or one or more episodes of severe hypoglycemia should be advised to raise their glycemic targets to strictly avoid further hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. (B)

Hypoglycemia is the leading limiting factor in the glycemic management of type 1 and insulin-treated type 2 diabetes (117). 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 is the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose. Protein added to carbohydrate does not impair the glycemic response, but also has no benefit in preventing subsequent hypoglycemia. Added fat may retard and then prolong the acute glycemic response (118). Ongoing activity of insulin or insulin secretagogues may lead to recurrence of hypoglycemia unless further food is ingested after recovery.

Severe hypoglycemia (where the individual requires the assistance of another person and cannot be treated with oral carbohydrate due to confusion or unconsciousness) should be treated using emergency glucagon kits, which require a prescription. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, child care providers, correctional institution staff, or coworkers) should be instructed 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.

Prevention of hypoglycemia is a crit-

ical component of diabetes management. Teaching people with diabetes to balance insulin use, carbohydrate intake, and exercise is a necessary but not always sufficient strategy. In type 1 diabetes and severely insulin-deficient type 2 diabetes, the syndrome of hypoglycemia unawareness, or hypoglycemia-associated autonomic failure, can severely compromise stringent diabetes control and quality of life. The deficient counter-regulatory hormone release and autonomic responses in this syndrome are both risk factors for, and caused by, hypoglycemia. A corollary to this “vicious cycle” is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counter-regulation and awareness to some extent in many patients (117,119,120). Hence, patients with one or more episodes of severe hypoglycemia may benefit from at least short-term relaxation of glycemic targets.

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 ≥ 65 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. Though 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. 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% (121).

Safe and effective vaccines are available that can greatly reduce the risk of serious complications from these diseases (122,123). In a case-control series, influenza vaccine was shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics (122). 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 of any age with diabetes (<http://www.cdc.gov/vaccines/recs>). 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 (121,124).

VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

A. CVD

CVD is the major cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for CVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling cardiovascular risk factors in preventing or slowing CVD in people with diabetes. Evidence is summarized in the following sections and reviewed in detail in the ADA technical reviews on hypertension (125), dyslipidemia (126), aspirin therapy (127), and smoking cessation (128), and in the AHA/ADA scientific statement on prevention of CVD in people with diabetes (129). Emphasis should be placed on reducing cardiovascular risk factors, 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. Repeat systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg confirms a diagnosis of hypertension. (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 a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg may be given lifestyle therapy alone for a maximum of 3 months and then, if targets are not achieved, be treated with addition of pharmacological agents. (E)
- Patients with more severe hypertension (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg) at diagnosis or follow-up should receive pharmacologic therapy in addition to lifestyle therapy. (A)
- Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (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 to those with an estimated glomerular filtration rate (GFR) (see below) ≥ 50 ml/min per 1.73 m² and a loop diuretic for those with an estimated GFR < 50 ml/min per 1.73 m². (E)
- Multiple drug therapy (two or more agents at maximal doses) is generally required to achieve blood pressure targets. (B)
- If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be closely monitored. (E)
- 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)

Hypertension is a common comorbidity of diabetes, affecting the majority of patients, with prevalence depending on type of diabetes, age, obesity, and ethnicity. Hypertension is a major risk factor for both CVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2 diabetes it usually coexists with other cardiometabolic risk factors.

Screening and diagnosis

Measurement of blood pressure in the office should follow the guidelines established for nondiabetic individuals: measurement in the seated position, with feet on the floor and arm supported at heart level, and after 5 min of rest. Elevated values should be confirmed on a separate day. Because of the clear synergistic risks of hypertension and diabetes, the diagnostic cut-off for a diagnosis of hypertension is lower in people with diabetes (blood pressure $\geq 130/80$) than those without diabetes (blood pressure $\geq 140/90$ mmHg) (130).

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide additional evidence of “white coat” and masked hypertension and other discrepancies between office and “true” blood pressure, and in studies in nondiabetic populations, home measurements may better correlate with CVD risk than office measurements (131,132). However, the preponderance of the clear evidence of benefits of treatment of hypertension in people with diabetes is based on office measurements.

Treatment goals

Randomized clinical trials have demonstrated the benefit (reduction of coronary heart disease [CHD] events, stroke, and nephropathy) of lowering blood pressure to < 140 mmHg systolic and < 80 mmHg diastolic in individuals with diabetes (130,133–135). Epidemiologic analyses show that blood pressures $> 115/75$ mmHg are associated with increased cardiovascular event rates and mortality in individuals with diabetes (130,136,137). Therefore, a target blood pressure goal of $< 130/80$ mmHg is reasonable if it can be safely achieved. The ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is designed to determine whether lowering systolic blood pressure to < 120 mmHg provides greater cardio-

vascular protection than a systolic blood pressure level of < 140 mmHg in patients with type 2 diabetes (www.accord.org).

Treatment strategies

Although there are no well-controlled studies of diet and exercise in the treatment of hypertension in individuals with diabetes, studies in nondiabetic individuals have shown antihypertensive effects similar to pharmacologic monotherapy of reducing sodium intake and excess body weight; increasing consumption of fruits, vegetables, and low-fat dairy products; avoiding excessive alcohol consumption; and increasing activity levels (130,138). These nonpharmacological strategies may also positively affect glycemia and lipid control. Their effects on cardiovascular events have not been established. An initial trial of nonpharmacologic therapy may be reasonable in diabetic individuals with mild hypertension (systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg). If the blood pressure is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic at the time of diagnosis, pharmacologic therapy should be initiated along with nonpharmacologic therapy (130).

Lowering of blood pressure with regimens based on a variety of antihypertensive drugs, including ACE inhibitors, ARBs, β -blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events. Several studies suggested that ACE inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events (139–141). However, a variety of other studies have shown no specific advantage to ACE inhibitors as initial treatment of hypertension in the general hypertensive population, but rather an advantage on cardiovascular outcomes of initial therapy with low-dose thiazide diuretics (130, 142,143).

In people with diabetes, inhibitors of the renin-angiotensin system (RAS) may have unique advantages for initial or early therapy of hypertension. In a nonhypertension trial of high-risk individuals, including a large subset with diabetes, an ACE inhibitor reduced CVD outcomes (144). In patients with CHF, including diabetic subgroups, ARBs have been shown to reduce major CVD outcomes (145–148), and in type 2 diabetic patients with significant nephropathy, ARBs were superior to calcium channel blockers for

reducing heart failure (149–151). Although evidence for distinct advantages of RAS inhibitors on CVD outcomes in diabetes remains conflicting (133,152), the high CVD risks associated with diabetes, and the high prevalence of undiagnosed CVD, may still favor recommendations for their use as first-line hypertension therapy in people with diabetes (130). The compelling benefits of RAS inhibitors in diabetic patients with albuminuria or renal insufficiency provide additional rationale for use of these agents (see Section VI. B below).

An important caveat is that most patients with hypertension require multi-drug therapy to reach treatment goals, especially diabetic patients whose targets are lower. Many patients will require three or more drugs to reach target goals (130).

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 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 (153).

2. Dyslipidemia/lipid management

Recommendations

Screening

- In most adult patients, measure fasting lipid profile at least annually. In adults with low-risk lipid values (LDL cholesterol <100 mg/dl, HDL cholesterol >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 should be recommended to improve the lipid profile in patients with diabetes. (A)
- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:
 - with overt CVD (A)
 - without CVD who are over the age of 40 and have one or more other CVD risk factors. (A)
- For lower-risk patients than those specified above (e.g., without overt CVD and under the age of 40), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dl or in those with multiple CVD risk factors (E)
- In individuals without overt CVD, the primary goal is an LDL cholesterol <100 mg/dl (2.6 mmol/l). (A)
- In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dl (1.8

mmol/l), using a high dose of a statin, is an option. (E)

- If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~40% from baseline is an alternative therapeutic goal. (A)
- Triglycerides levels <150 mg/dl (1.7 mmol/l) and HDL cholesterol >40 mg/dl (1.0 mmol/l) in men and >50 mg/dl (1.3 mmol/l) in women are desirable. However, LDL cholesterol-targeted statin therapy remains the preferred strategy. (C)
- Combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety. (E)
- Statin therapy is contraindicated in pregnancy. (E)

Evidence for benefits of lipid-lowering therapy

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, which contributes to their high risk of CVD. For the past decade or more, multiple clinical trials demonstrated significant effects of pharmacologic (primarily statin) therapy on CVD outcomes in subjects with CHD and for primary CVD prevention (154). Sub-analyses of diabetic subgroups of larger trials (155–159) and trials specifically in subjects with diabetes (160,161) showed significant primary and secondary prevention of CVD events ± CHD deaths in diabetic populations. As shown in Table 10, and similar to findings in nondiabetic subjects, re-

Table 10—Reduction in 10-year risk of major CVD end points (CHD death/nonfatal MI) in major statin trials, or substudies of major trials, in diabetic subjects (n = 16,032)

| Study (ref.) | CVD prevention | Statin dose and comparator | RRR | ARR | LDL cholesterol reduction |
|----------------------------|----------------|----------------------------------|---------------------|-------|---------------------------|
| 4S-DM (155) | 2 ^o | Simvastatin 20–40 mg vs. placebo | 85.7 to 43.2% (50%) | 42.5% | 186 to 119 mg/dl (36%) |
| ASPEN 2 ^o (160) | 2 ^o | Atorvastatin 10 mg vs. placebo | 39.5 to 24.5% (34%) | 12.7% | 112 to 79 mg/dl (29%) |
| HPS-DM (156) | 2 ^o | Simvastatin 40 mg vs. placebo | 43.8 to 36.3% (17%) | 7.5% | 123 to 84 mg/dl (31%) |
| CARE-DM (157) | 2 ^o | Pravastatin 40 mg vs. placebo | 40.8 to 35.4% (13%) | 5.4% | 136 to 99 mg/dl (27%) |
| TNT-DM (158) | 2 ^o | Atorvastatin 80 mg vs. 10 mg | 26.3 to 21.6% (18%) | 4.7% | 99 to 77 mg/dl (22%) |
| HPS-DM (156) | 1 ^o | Simvastatin 40 mg vs. placebo | 17.5 to 11.5% (34%) | 6.0% | 124 to 86 mg/dl (31%) |
| CARDS (161) | 1 ^o | Atorvastatin 10 mg vs. placebo | 11.5 to 7.5% (35%) | 4% | 118 to 71 mg/dl (40%) |
| ASPEN 1 ^o (160) | 1 ^o | Atorvastatin 10 mg vs. placebo | 11.0 to 7.9% (19%) | 1.9% | 114 to 80 mg/dl (30%) |
| ASCOT-DM (159) | 1 ^o | Atorvastatin 10 mg vs. placebo | 11.1 to 10.2% (8%) | 0.9% | 125 to 82 mg/dl (34%) |

Studies were of differing lengths (3.3–5.4 years) and used somewhat different outcomes, but all reported rates of CVD death and nonfatal MI. In this tabulation, results of the statin on 10-year risk of major CVD end points (CHD death/nonfatal MI) are listed for comparison between studies. Correlation between 10-year CVD risk of the control group and the ARR with statin therapy is highly significant ($P = 0.0007$). Analyses provided by Craig Williams, Pharm.D., Oregon Health & Science University, 2007. ARR, absolute risk reduction; RRR, relative risk reduction.

Table 11—Summary of recommendations for glycemic, blood pressure, and lipid control for adults with diabetes

| | |
|-----------------|---------------------------|
| A1C | <7.0%* |
| Blood pressure | <130/80 mmHg |
| Lipids | |
| LDL cholesterol | <100 mg/dl (<2.6 mmol/l)† |

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option.

duction in “hard” CVD outcomes (CHD death and nonfatal myocardial infarction) can be more clearly seen in diabetic subjects with high baseline CVD risk (known CVD and/or very high LDL cholesterol levels), but overall the benefits of statin therapy in people with diabetes at moderate or high risk for CVD are convincing.

Low HDL cholesterol levels, which are often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in persons with type 2 diabetes. However, the evidence base for drugs that target these lipid fractions is significantly less robust than that for statin therapy (162). In a study conducted in a nondiabetic cohort, nicotinic acid reduced CVD outcomes (163). Gemfibrozil has been shown to decrease rates of CVD events in subjects without diabetes (164,165) and in the diabetic subgroup in one of the larger trials (164). However, in a large trial specific to diabetic patients, fenofibrate failed to reduce overall cardiovascular outcomes (166).

Dyslipidemia treatment and target lipid levels

For most patients with diabetes, the first priority of dyslipidemia therapy (unless severe hypertriglyceridemia is the immediate issue) is to lower LDL cholesterol to a target goal of <100 mg/dl (2.60 mmol/l) (167). Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, may allow some patients to reach lipid goals. 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.

In those with clinical CVD or over aged 40 with other CVD risk factors, pharmacological treatment should be added to lifestyle therapy regardless of

baseline lipid levels. Statins are the drugs of choice for lowering LDL cholesterol.

In patients other than those described above, statin treatment should be considered if there is an inadequate LDL cholesterol response to lifestyle modifications and improved glucose control, or if the patient has increased cardiovascular risk (e.g., multiple cardiovascular risk factors or long duration of diabetes). Very little clinical trial evidence exists for type 2 diabetic patients under the age of 40 or for type 1 diabetic patients of any age. In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 patients with type 1 diabetes had a proportionately similar (though not statistically significant) reduction in risk to patients with type 2 diabetes (156). Although the data are not definitive, consideration should be given to similar lipid-lowering goals in type 1 diabetic patients as in type 2 diabetic patients, particularly if they have other cardiovascular risk factors.

Alternative LDL cholesterol goals

Virtually all trials of statins and CVD outcome tested specific doses of statins against placebo, other doses of statin, or other statins, rather than aiming for specific LDL cholesterol goals (168). As can be seen in Table 10, placebo-controlled trials generally achieved LDL cholesterol reductions of 30–40% from baseline. Hence, LDL cholesterol lowering of this magnitude is an acceptable outcome for patients who cannot reach LDL cholesterol goals due to severe baseline elevations in LDL cholesterol and/or intolerance of maximal, or any, statin doses.

Recent clinical trials in high-risk patients, such as those with acute coronary syndromes or previous cardiovascular events (169–171), have demonstrated that more aggressive therapy with high doses of statins to achieve an LDL cholesterol of <70 mg/dl led to a significant reduction in further events. Therefore, a reduction in LDL cholesterol to a goal of

<70 mg/dl is an option in very-high-risk diabetic patients with overt CVD (172).

The addition of other drugs such as ezetimibe to statins may achieve lower LDL cholesterol goals, but no data are available as to whether such combination therapy is more effective than a statin alone in preventing cardiovascular events.

Treatment of other lipoprotein fractions

Severe hypertriglyceridemia may warrant immediate therapy of this abnormality with lifestyle and usually pharmacologic therapy (fibric acid derivative or niacin) to reduce the risk of acute pancreatitis. In the absence of severe hypertriglyceridemia, therapy targeting HDL cholesterol or triglycerides has intuitive appeal but lacks the evidence base of statin therapy (162). If the HDL cholesterol is <40 mg/dl and the LDL cholesterol between 100 and 129 mg/dl, gemfibrozil or niacin might be used, especially if a patient is intolerant to statins. Niacin is the most effective drug for raising HDL cholesterol. It can significantly increase blood glucose at high doses, but recent studies demonstrate that at modest doses (750–2,000 mg/day), significant improvements in LDL cholesterol, HDL cholesterol, and triglyceride levels are accompanied by only modest changes in glucose that are generally amenable to adjustment of diabetes therapy (173,174).

Combination therapy, with a statin and a fibrate or statin and niacin, may be efficacious for 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 is higher with higher doses of statins and with renal insufficiency, and seems to be lower when statins are combined with fenofibrate than gemfibrozil (175). Several ongoing trials may provide much-needed evidence for the effects of combination therapy on cardiovascular outcomes.

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 1 or 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)

- Aspirin therapy is not recommended in people under 30 years of age, due to lack of evidence of benefit, and is contraindicated in patients under the age of 21 years because of the associated risk of Reye's syndrome. (E)
- Combination therapy using other antiplatelet agents such as clopidogrel 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 (127) and position statement (176) on this topic. Aspirin has been recommended for primary (177,178) and secondary (179,180) prevention of cardiovascular events in high-risk 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 little evidence to support any specific dose, but using the lowest possible dosage may help reduce side effects (181). Conversely, a randomized trial of 100 mg of aspirin daily showed less of a primary prevention effect, without statistical significance, in the large diabetic subgroup in contrast to significant benefit in those without diabetes (182), raising the issue of aspirin resistance in those with diabetes. 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 events in diabetic individuals (183). 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 (128) and position statement (184) on this topic. 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 CVD and premature death 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 smoking cessation counseling in changing smoking behavior and reducing tobacco use. 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 (185,186).

5. CHD screening and treatment

Recommendations

Screening

- In asymptomatic patients, evaluate risk factors to stratify patients by 10-year risk, and treat risk factors accordingly. (B)

Treatment

- In patients with known CVD, ACE inhibitor, aspirin, and statin therapy (if not contraindicated) should be used to

reduce the risk of cardiovascular events. (A)

- In patients with a prior myocardial infarction, add β -blockers (if not contraindicated) to reduce mortality. (A)
- In patients >40 years of age with another cardiovascular risk factor (hypertension, family history, dyslipidemia, microalbuminuria, cardiac autonomic neuropathy, or smoking), ACE inhibitor, aspirin, and statin therapy (if not contraindicated) should be used to reduce the risk of cardiovascular events. (B)
- In patients with treated CHF, metformin and thiazolidinedione (TZD) use are contraindicated. (C)

CHD screening and treatment are reviewed in detail in the ADA consensus statement on CHD in people with diabetes (187), and screening for CAD is reviewed in a recently updated consensus statement (93). To identify the presence of CAD in diabetic patients without clear or suggestive symptoms, a risk factor-based approach to the initial diagnostic evaluation and subsequent follow-up has intuitive appeal. However, recent studies concluded that using this approach fails to identify which patients will have silent ischemia on screening tests (100,188).

Cardiovascular risk factors should be assessed at least once a year. 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, statin, and ACE inhibitor therapy, unless there are contraindications to a particular drug class.

Candidates for a further cardiac testing include those with 1) typical or atypical cardiac symptoms and 2) an abnormal resting electrocardiogram (ECG). The screening of asymptomatic patients remains controversial, especially as intensive medical therapy, indicated in diabetic patients at high risk for CVD, has an increasing evidence base for providing equal outcomes to invasive revascularization, including in diabetic patients (189). There is also recent preliminary evidence that silent myocardial ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (190).

B. Nephropathy screening and treatment

Recommendations

General recommendations

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

Screening

- Perform an annual test to assess urine albumin excretion in type 1 diabetic patients with diabetes duration of ≥ 5 years and in all type 2 diabetic patients, starting at diagnosis. (E)
- Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present. (E)

Treatment

- In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. (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, both 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 $0.8\text{--}1.0$ 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

(e.g., urine albumin excretion rate and GFR) and is recommended (B)

- When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia. (E)
- Continued monitoring of urine albumin excretion to assess both response to therapy and progression of disease is recommended. (E)
- Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (active urine sediment, absence of retinopathy, rapid decline in GFR), difficult management issues, or advanced kidney disease. (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 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 (191,192). Patients with microalbuminuria who progress to macroalbuminuria (≥ 300 mg/24 h) are likely to progress to ESRD (193,194). However, 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 (195,196) and type 2 (40,41) diabetes. The UKPDS provided strong evidence that control of blood pressure can reduce the development of nephropathy (133). 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 (150, 151,197). In type 2 diabetes with hypertension and normoalbuminuria, ACE inhibition has been demonstrated to de-

lay progression to microalbuminuria (198).

In addition, ACE inhibitors have been shown to reduce major CVD outcomes (i.e., myocardial infarction, stroke, death) in patients with diabetes (144), thus further supporting the use of these agents in patients with microalbuminuria, a CVD risk factor. 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 (199–201). Some evidence suggests that ARBs have a smaller magnitude of rise in potassium compared with ACE inhibitors in people with nephropathy (202,203). Other drugs, such as diuretics, calcium channel blockers, and β -blockers, should be used as additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs (149), or as alternate therapy in the rare individual unable to tolerate ACE inhibitors or ARBs.

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 (204–207). 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 (207).

Assessment of albuminuria status and renal function

Screening for microalbuminuria can be performed by measurement of the albumin-to-creatinine ratio in a random spot collection (preferred method); 24-h or timed collections are more burdensome and add little to prediction or accuracy (208,209). 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 somewhat less expensive but susceptible to false-negative and -positive determinations as a result of variation in urine concentration due to hydration and other factors.

Abnormalities of albumin excretion are defined in Table 12. 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 hy-

Table 12—Definitions of abnormalities in albumin excretion

| Category | Spot collection ($\mu\text{g}/\text{mg}$ creatinine) |
|------------------------------|---|
| Normal | <30 |
| Microalbuminuria | 30–299 |
| Macro (clinical)-albuminuria | 300 |

pertension may elevate urinary albumin excretion over baseline values.

Information on presence of abnormal urine albumin excretion in addition to level of GFR may be used to stage CKD. The National Kidney Foundation classification (Table 13) is primarily based on GFR levels and therefore differs from other systems in which staging is based primarily on urinary albumin excretion (210). Studies have found decreased GFR in the absence of increased urine albumin excretion in a substantial percentage of adults with diabetes (211,212). Epidemiologic evidence suggests that a substantial fraction of those with chronic kidney disease in the setting of diabetes have little or no detectable albuminuria (211). Serum creatinine should therefore be measured at least annually in all adults with diabetes, regardless of the degree of urine albumin excretion.

Serum creatinine should be used to estimate GFR and to stage the level of CKD, if present. GFR can be estimated using formulae such as the Cockcroft-Gault equation or a prediction formula using data from the Modification of Diet and Renal Disease study (213). GFR calculators are available at <http://www.nkdep.nih.gov>. Many clinical laboratories now report estimated GFR in addition to serum creatinine.

The role of continued annual quantitative assessment of albumin excretion after diagnosis of microalbuminuria and institution of ACE inhibitor or ARB therapy and blood pressure control is unclear. Continued surveillance can assess both response to therapy and progression of disease. Some suggest that reducing abnormal albuminuria (>30 mg/g) to the normal or near-normal range may improve renal and cardiovascular prognosis, but this approach has not been formally evaluated in prospective trials.

Complications of kidney disease correlate with level of kidney function. When the estimated GFR is <60 ml/min per 1.73 m², screening for anemia, malnutrition, and metabolic bone disease is indicated. Early vaccination against hepatitis

B is indicated in patients likely to progress to end-stage kidney disease.

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (active urine sediment, absence of retinopathy, rapid decline in GFR), difficult management issues, or advanced kidney disease. The threshold for referral may vary depending on the frequency with which a provider encounters diabetic patients with significant kidney disease. Consultation with a nephrologist when stage 4 CKD develops has been found to reduce cost, improve quality of care, and keep people off dialysis longer (214,215). However, nonrenal specialists should not delay educating their patients about the progressive nature of diabetic kidney disease; the renal preservation benefits of aggressive treatment of blood pressure, blood glucose, and hyperlipidemia; and the potential need for renal replacement therapy.

C. Retinopathy screening and treatment

Recommendations

General recommendations

- To reduce the risk or slow the progression of retinopathy, optimize glycemic control. (A)
- To reduce the risk or slow the progression of retinopathy, optimize blood pressure control. (A)

Table 13—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. 209.

Screening

- Adults and adolescents with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. (B)
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist 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 following one or more normal eye exams. Examinations will be required more frequently if retinopathy is progressing. (B)
- Women with pre-existing diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and 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. (B)

Treatment

- 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)
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR, clinically significant macular edema, and in some cases of severe NPDR. (A)
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as this therapy does

not increase the risk of retinal hemorrhage. (A)

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

In addition to duration of diabetes, other factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (216), the presence of nephropathy (217), and hypertension (218). Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy (35,40,41). Lowering blood pressure has been shown to decrease the progression of retinopathy (133). Several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy (219,220); laser photocoagulation surgery can minimize this risk (220).

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

The DRS (221) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes. The benefit was greatest among patients whose baseline evaluation revealed high-risk characteristics (chiefly disc neovascularization or vitreous hemorrhage). Given the risks of modest loss of visual acuity and contraction of the visual field from panretinal laser surgery, such therapy is primarily recommended for eyes with PDR approaching or having high-risk characteristics.

The ETDRS (222) established the benefit of focal laser photocoagulation surgery in eyes with macular edema, particularly those with clinically significant macular edema, with reduction of dou-

bling of the visual angle (e.g., 20/50 to 20/100) from 20% in untreated eyes to 8% in treated eyes. The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR, but not for mild or moderate NPDR. In older-onset patients with severe NPDR or less-than-high-risk PDR, the risk of severe visual loss or vitrectomy was reduced ~50% by early laser photocoagulation surgery at these stages.

Laser photocoagulation surgery in both trials 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.

As retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia (223), patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the onset of diabetes. Patients with type 2 diabetes, who generally have had years of undiagnosed diabetes (224) and who have a significant risk of prevalent diabetic retinopathy at the time of diabetes diagnosis, should have an initial dilated and comprehensive eye examination soon after diagnosis. Examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Subsequent examinations for type 1 and type 2 diabetic patients are generally repeated annually. Less frequent exams (every 2–3 years) may be cost-effective after one or more normal eye exams (225–227), while examinations will be required more frequently if retinopathy is progressing.

Examinations can also be done with retinal photographs (with or without dilation of the pupil) read by experienced experts. In-person exams are still necessary when the photos are unacceptable and for follow-up of abnormalities detected. This technology has great potential in areas where qualified eye care professionals are not available, and may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be utilized for more complex examinations and for therapy (228).

Results of eye examinations should be documented and transmitted to the referring health care professional. For a detailed review of the evidence and further

discussion of diabetic retinopathy, see ADA's technical review and position statement on this subject (229,230).

D. Neuropathy screening and treatment

Recommendations

- All patients should be screened for distal symmetric polyneuropathy (DPN) at diagnosis and at least annually thereafter, using simple clinical tests. (B)
- Electrophysiological testing is rarely needed, except in situations where the clinical features are atypical. (E)
- Educate all patients about self-care of the feet. For those with DPN, facilitate enhanced foot care education and refer for special footwear. (B)
- Screening for signs and symptoms of autonomic neuropathy should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Special testing is rarely needed and may not affect management or outcomes. (E)
- Medications for the relief of specific symptoms related to DPN and autonomic neuropathy 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 (231).

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 not reverse neuronal loss. Effective symptomatic treatments are available for some

Table 14—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 | Duloxetine† | 60–120 mg daily |
| Substance P inhibitor | Capsaicin cream | 0.025–0.075% applied t.i.d. or q.i.d. |

*Dose response may vary; initial doses need to be low and titrated up; †has FDA indication for treatment of painful diabetic neuropathy.

manifestations of DPN and autonomic neuropathy (231).

Diagnosis of neuropathy

Distal symmetric polyneuropathy

Patients with diabetes should be screened annually for DPN using tests such as pin-prick sensation, vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of 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 (231).

Diabetic autonomic neuropathy

The symptoms and signs of autonomic dysfunction should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, “brittle diabetes,” and hypoglycemic autonomic failure (232).

Cardiovascular autonomic neuropathy, a CVD risk factor (93), is the most studied and clinically important form of diabetic autonomic neuropathy. Cardiovascular 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 (232).

Gastrointestinal neuropathies (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 or with upper gastrointestinal symptoms without other identified cause. 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. Constipation is the most common lower gastrointestinal symptom but can alternate with episodes of diarrhea (232).

Diabetic autonomic neuropathy is also associated with genitourinary tract disturbances. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder (232).

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. Patients with painful DPN may benefit from pharmacological treatment of their symptoms: many agents have efficacy confirmed in published randomized controlled trials, with several FDA-approved for the management of painful

DPN. See Table 14 for examples of agents to treat DPN pain.

Treatment of autonomic neuropathy

Gastroparesis symptoms may improve with dietary changes and prokinetic agents such as metoclopramide or erythromycin. Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. Interventions for other manifestations of autonomic neuropathy are described in the ADA statement on neuropathy (231). As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process, but may have a positive impact on the quality of life of the patient.

E. Foot care

Recommendations

- For all patients with diabetes, perform an annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations. 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)
- Provide general foot self-care education to all patients with diabetes. (B)
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet, especially for those with a history of prior ulcer or amputation. (B)
- Refer patients who smoke, have loss of protective sensation and structural abnormalities, or have history of 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, consequences of diabetic neuropathy and/or PAD, are common and major causes of morbidity and disability in people with diabetes. Early recognition and manage-

ment of 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
- PAD (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. 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. Patients at low risk may benefit from education on foot care and footwear.

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 one or more high-risk foot conditions 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.

People with neuropathy (e.g., erythema, warmth, callus, or measured pressure) or evidence of increased plantar pressure may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute 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 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. A diagnostic ABI should be performed in any patient with symptoms of PAD. Due to the high estimated prevalence of PAD in patients with diabetes and the fact that many patients with PAD are asymptomatic, an ADA consensus statement on PAD (233) suggested that a screening ABI be performed in patients older than 50 years of age and be considered in patients younger than 50 years who have other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years). Refer patients with significant symptoms or a positive ABI for further vascular assessment, and consider exercise, medication, and surgical options (233).

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. Patients with loss of protective sensation should be educated on ways to substitute other sensory modalities (hand palpation, visual inspection) for surveillance of early foot problems. 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.

For a detailed review of the evidence and further discussion, see ADA's technical review and position statement on preventive foot care (234,235).

Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes. For a complete discussion, see ADA's consensus statement on diabetic foot wound care (236).

VII. DIABETES CARE IN SPECIFIC POPULATIONS

A. Children and adolescents

1. Type 1 diabetes

Three-quarters of all cases of type 1 diabetes are diagnosed in individuals <18 years of age. 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 are all essential in developing and implementing an optimal diabetes regimen. Although recommendations for children and adolescents are less likely to be based on clinical trial evidence, 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 (237).

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. 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 is 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

Recommendations

- Consider age when setting glycemic goals in children and adolescents with type 1 diabetes, with less stringent goals for younger children. (E)

Table 15—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% | <ul style="list-style-type: none"> • 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 discrepancy between pre-prandial blood glucose values and A1C levels.

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.” Their counterregulatory mechanisms are immature, and they may lack the cognitive capacity to recognize and respond to hypoglycemic symptoms, placing them at greater risk for severe hypoglycemia and its sequelae. In addition, and unlike the case in adults, children younger than 5 years of age are at risk for permanent cognitive impairment after episodes of severe hypoglycemia (238–240). 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 by adult DCCT subjects and above current ADA recommendations for patients in general. 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 (241,242) in those families in which both parents and the child with diabetes are motivated to perform the required diabetes-related tasks.

In selecting glycemic goals, the bene-

fits on long-term health outcomes of achieving a lower A1C must be weighed against the unique risks of hypoglycemia and the difficulties achieving near-normoglycemia in children and youth. Age-specific glycemic and A1C goals are presented in Table 15.

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

i. Nephropathy

Recommendations

- Annual screening for microalbuminuria, with a random spot urine sample for microalbumin-to-creatinine ratio, should be initiated once the child is 10 years of age and has had diabetes for 5 years. (E)
- Confirmed, persistently elevated microalbumin levels on two additional urine specimens should be treated 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 with 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 >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 \geq 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 \geq 90th but <95th percentile for age, sex, and height percentile measured on at least three 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

- If there is a family history of hypercholesterolemia (total cholesterol >240 mg/dl) or a cardiovascular event before

age 55 years, or if family history is unknown, then a fasting lipid profile should be performed on children >2 years of age soon after diagnosis (after glucose control has been established). If family history is not of concern, then the first lipid screening should be performed at puberty (≥ 10 years). All children diagnosed with diabetes at or after puberty should have a fasting lipid profile performed soon after diagnosis (after glucose control has been established). (E)

- For both age groups, if lipids are abnormal, annual monitoring is recommended. If LDL cholesterol values are within the accepted risk levels (< 100 mg/dl [2.6 mmol/l]), a lipid profile should be repeated every 5 years. (E)

Treatment

- Initial therapy should consist of optimization of glucose control and MNT using a Step 2 American Heart Association diet aimed at a decrease in the amount of saturated fat in the diet. (E)
- After the age of 10, the addition of a statin is recommended in patients who, after MNT and lifestyle changes, have LDL cholesterol > 160 mg/dl (4.1 mmol/l) or have LDL cholesterol > 130 mg/dl (3.4 mmol/l) and one or more CVD risk factors. (E)
- The goal of therapy is an LDL cholesterol value < 100 mg/dl (2.6 mmol/l). (E)

People diagnosed with type 1 diabetes in childhood have a high risk of early subclinical (243–245) and clinical (246) CVD. Although intervention data are lacking, the American Heart Association (AHA) categorizes type 1 children in the highest tier for cardiovascular risk, and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (247). Initial therapy should be with a Step 2 AHA diet, which restricts saturated fat to 7% of total calories and restricts dietary cholesterol to 200 mg/day. Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (248,249).

For children over the age of 10 with persistent elevation of LDL cholesterol despite lifestyle therapy, statins should be considered. Neither long-term safety nor cardiovascular outcome efficacy has been established for children. However, recent studies have shown short-term safety

equivalent to that seen in adults, as well as efficacy in lowering LDL cholesterol levels, improving endothelial function, and causing regression of carotid intimal thickening (250–252). No statin is approved for use under the age of 10, and statin treatment should generally not be used in type 1 children before this age.

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 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

- Patients with type 1 diabetes who become symptomatic for celiac disease should be tested by measuring tissue transglutaminase or anti-endomysial antibodies, with documentation of normal serum IgA levels. (E)
- 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 be placed on a gluten-free diet. (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) (253,254). Symptoms of celiac disease include diarrhea, weight loss or poor weight gain, growth failure, abdominal pain, chronic fatigue, malnutrition due to mal-

absorption and other gastrointestinal problems, and unexplained hypoglycemia or erratic blood glucose concentrations.

vi. Hypothyroidism

Recommendations

- Patients with type 1 diabetes should be screened for thyroid peroxidase and thyroglobulin antibodies at diagnosis. (E)
- Thyroid-stimulating hormone (TSH) concentrations should be measured after metabolic control has been established. If normal, they should be rechecked every 1–2 years, or if the patient develops symptoms of thyroid dysfunction, thyromegaly, or an abnormal growth rate. Free T4 should be measured if TSH is abnormal. (E)

Auto-immune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes (255). The presence of thyroid auto-antibodies is predictive of thyroid dysfunction (generally hypothyroidism, but less commonly hyperthyroidism) (256). Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia (257) and with reduced linear growth (258). Hyperthyroidism alters glucose metabolism, potentially resulting in deterioration of metabolic control.

c. “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.

d. School and day care.

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, safety, and maximal academic opportunities. See Section VIII.B, “Diabetes Care in the School and Day Care Setting,” for further discussion.

2. Type 2 diabetes

The incidence of type 2 diabetes in adolescents is increasing, especially in ethnic minority populations (20). 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 features of 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. Because type 2 diabetes has a significant incidence of hypertension, dyslipidemia, and microalbuminuria at diagnosis (259), it is recommended that screening for the comorbidities and complications of diabetes, including fasting lipid profile, microalbuminuria assessment, and dilated eye examinations, begin at the time of diagnosis. The ADA consensus statement (22) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in young people.

B. Preconception care

Recommendations

- A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted. (B)
- All women with diabetes and child-bearing potential should be educated about the need for good glucose control before pregnancy and 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)
- Medications used by such women should be evaluated before conception, since drugs commonly used to treat diabetes and its complications may be contraindicated or not recommended in pregnancy, including statins, ACE inhibitors, ARBs, and most noninsulin therapies. (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 below which risk disappears entirely. However, malformation rates above the 1–2% background rate of 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 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 (260–264). 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 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 rather than randomized. Thus, it is impossible to be certain that the lower malformation rates resulted fully from improved diabetes care. Nonetheless, the 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 child-bearing 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 has good metabolic control and is actively trying to conceive.

Women contemplating pregnancy need to be seen frequently by a multidisciplinary team experienced in the man-

agement of diabetes before and during pregnancy. The goals of preconception care are to 1) involve and empower the patient in the management of her diabetes, 2) achieve the lowest A1C test results possible without excessive hypoglycemia, 3) ensure 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 CHD.

Among the drugs commonly used in the treatment of patients with diabetes, a number may be relatively or absolutely contraindicated during pregnancy. Statins are category X (contraindicated for use in pregnancy) and should be discontinued before conception, as should ACE inhibitors (265). ARBs are category C (risk cannot be ruled out) in the first trimester, but category D (positive evidence of risk) in later pregnancy, and should generally be discontinued before pregnancy. Among the oral antidiabetic agents, metformin and acarbose are classified as category B (no evidence of risk in humans) and all others as category C. Potential risks and benefits of oral antidiabetic agents in the preconception period must be carefully weighed, recognizing that data are insufficient to establish the safety of these agents in pregnancy.

For further discussion of preconception care, see ADA's technical review (266) and position statement (267) on this subject.

C. Older adults

Recommendations

- Older adults who are functional, cognitively intact, and have significant life expectancy should receive diabetes treatment using goals developed for younger adults. (E)
- Glycemic goals for older adults who do not meet the above criteria may be relaxed using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. (E)
- Other cardiovascular risk factors should be treated in older adults with consideration of the timeframe of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid and aspirin therapy may benefit those with life expectancy at least equal to the

timeframe of primary or secondary prevention trials. (E)

- Screening for diabetic complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment. (E)

Diabetes is an important health condition for the aging population. At least 20% of patients over the age of 65 years have diabetes, and this number can be expected to grow rapidly in the coming decades. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses such as hypertension, 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 American Geriatric Society's guidelines for improving the care of the older person with diabetes mellitus (268) have influenced the following discussion and recommendations. The care of older adults with diabetes is complicated by their clinical and functional heterogeneity. Some older individuals developed diabetes years earlier and may have significant complications; others who are newly diagnosed may have had years of undiagnosed diabetes with resultant complications or may have 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. Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable for this population, but often longer than clinicians realize. Providers caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals.

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid control. Patients who can be expected to live long enough to reap the benefits of long-term intensive diabetes management and who are active, have good cognitive function, and are willing to undertake the responsibility of self-management should be encouraged to do

so and be treated using the goals for younger adults with diabetes.

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

Although control of hyperglycemia may be important in older individuals with diabetes, greater reductions in morbidity and mortality may result from control of other cardiovascular risk factors than from tight glycemic control alone. There is strong evidence from clinical trials of the value of treating hypertension in the elderly (269). There is less evidence for lipid-lowering and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the timeframes seen in clinical trials.

Special care is required in prescribing and monitoring pharmacologic therapy in older adults. Metformin is often contraindicated because of renal insufficiency or significant heart failure. TZDs can cause fluid retention, which may exacerbate or lead to heart failure. They are contraindicated in patients with CHF (New York Heart Association class III and IV), and if used at all should be used very cautiously in those with, or at risk for, milder degrees of CHF. Sulfonylureas, other insulin secretagogues, and insulin can cause hypoglycemia. Insulin use requires that patients or caregivers have good visual and motor skills and cognitive ability. Drugs should be started at the lowest dose and titrated up gradually until targets are reached or side effects develop.

Screening for diabetic complications in older adults also should be individualized. Particular attention should be paid to complications that can develop over short periods of time and/or that would significantly impair functional status, such as visual and lower-extremity complications.

VIII. DIABETES CARE IN SPECIFIC SETTINGS

A. Diabetes care in the hospital

Recommendations

- All patients with diabetes admitted to the hospital should have their diabetes clearly identified in the medical record. (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 <140 mg/dl (7.8 mmol/l). (A) These patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia. (E)
 - Non-critically ill patients: there is no clear evidence for specific blood glucose goals. Since cohort data suggest that outcomes are better in hospitalized patients with fasting glucose <126 mg/dl and all random glucoses <180–200, these goals are reasonable if they can be safely achieved. Insulin is the preferred drug to treat hyperglycemia in most cases. (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 appropriately timed 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 generally not recommended. (C)
- Using correction dose or “supplemental” insulin to correct premeal hyperglycemia in addition to scheduled prandial and basal insulin is recommended. (E)
- Glucose monitoring with orders for correction insulin should be initiated in any patient not known to be diabetic who receives therapy associated with high risk for hyperglycemia, including high-dose glucocorticoids therapy, ini-

tiation of enteral or parenteral nutrition, or other medications such as octreotide or immunosuppressive medications. (B) If hyperglycemia is documented and persistent, initiation of basal/bolus insulin therapy may be necessary. Such patients should be treated to the same glycemic goals as patients with known diabetes. (E)

- 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 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 (270). This review, as well as a consensus statement by the American Association of Clinical Endocrinologists (AACE) with cosponsorship by ADA (271,272) and a report of a joint ADA-AACE task force on the topic (273), forms the basis for the discussion and guidelines in this section.

The literature on hospitalized patients with hyperglycemia typically describes 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 \geq 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, but this is likely an underestimate. The prevalence of diabetes in hospitalized adults is conservatively estimated at 12–25%, depending on the thoroughness used in identifying patients. In the year 2003, there were 5.1 million hospitalizations with diabetes as a listed diagnosis, a 2.3-fold increase over 1980 rates (274).

The management of hyperglycemia in the hospital was traditionally considered secondary in importance to the condition that prompted admission (273).

A rapidly growing body of literature supports targeted glucose control in the hospital setting for potential improved mortality, morbidity, and health economic outcomes. Hyperglycemia in the hospital may result from stress; decompensation of type 1, type 2, or other forms of diabetes; and/or may be iatrogenic due to withholding of antihyperglycemic medications or administration of hyperglycemia-provoking agents such as glucocorticoids or vasopressors.

1. In-hospital hyperglycemia and outcomes

a. General medicine and surgery. Observational studies suggest an association between hyperglycemia and increased mortality. Surgical patients with at least one blood glucose value >220 mg/dl (12.2 mmol/l) on the first postoperative day have significantly higher infection rates (275).

When admissions on general medicine and surgery units were studied, patients with new hyperglycemia had significantly increased in-hospital mortality, as did patients with known diabetes. In addition, length of stay was higher for the new hyperglycemic group, and patients in either hyperglycemic group 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) (276).

b. CVD and critical care. A significant relationship exists between blood glucose levels and mortality in the setting of acute myocardial infarction. A meta-analysis of 15 studies compared in-hospital mortality in both hyper- and normoglycemic patients with and without diabetes. In subjects without known diabetes whose

admission blood glucose averaged 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 averaged 180 mg/dl (10 mmol/l), risk of death was moderately increased compared with patients who had diabetes but less hyperglycemia on admission (277). Another study (278) demonstrated a strong independent relationship between admission blood glucose values and both in-hospital and 1-year mortality; rates were 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).

These studies focused on admission blood glucose as a predictor of outcomes, rather than inpatient glycemic management per se. Higher admission plasma glucose levels in patients with a prior history of diabetes could reflect the degree of glycemic control in the outpatient setting, thus linking outpatient glycemic control to outcomes in the inpatient population. In patients without a prior history of diabetes, admission hyperglycemia could represent case finding of patients with previously undiagnosed diabetes, an unmasking of risk in a population at high risk for diabetes, or more severe illness at admission.

In the initial Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction study (279,280), insulin-glucose infusion followed by at least 3 months of subcutaneous insulin treatment in diabetic patients with acute myocardial infarction improved long-term survival. 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.

Three more recent studies (281–283) using an insulin-glucose infusion did not show a reduction in mortality in the intervention groups. However, in each of these studies, blood glucose levels were positively correlated with mortality. In the Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study, a decrease in both CHF and reinfarction was observed in the group receiving intensive insulin therapy for at least 24 h.

c. Cardiac surgery. Attainment of targeted glucose control in patients with diabetes undergoing cardiac surgery is

associated with reduced mortality and risk of deep sternal wound infections (284,285) and supports the concept that perioperative hyperglycemia is an independent predictor of infection in patients with diabetes (286), with the lowest mortality in patients with blood glucose <150 mg/dl (8.3 mmol/l) (287).

d. Critical care. A mixed group of patients with and without diabetes admitted to a surgical ICU (SICU) were randomized to receive intensive insulin therapy (target blood glucose 80–110 mg/dl [4.4–6.1 mmol/l]) or conventional therapy. Intensive insulin therapy achieved a mean blood glucose of 103 mg/dl (5.7 mmol/l) and was associated with reduced mortality during the ICU stay and decreased overall in-hospital mortality (288). 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) (289).

A subsequent study of a similar intervention in patients in a medical ICU (MICU) (290) showed that the group receiving intensive insulin therapy had reduced morbidity but no difference in mortality overall. Death rates were significantly lower in those patients who were treated for >3 days; these patients could not be identified before therapy. A recent meta-analysis concluded that insulin therapy in critically ill patients had a beneficial effect on short-term mortality in different clinical settings (291).

2. Glycemic targets in hospitalized patients

There is relatively strong evidence from randomized controlled trials for a glycemic target of blood glucose <110 mg/dl (6.1 mmol/l) in patients in critical care units (288–290). However, the incidence of severe hyperglycemia (blood glucose <40 mg/dl) in the MICU study was 18.7%, much greater than the 5.1% observed in the SICU population. The identification of hypoglycemia as an independent risk factor for death in the MICU population may merit caution in widely promoting the 80–110 mg/dl target range for all critically ill populations (292). Two recent trials were discontinued because of difficulty achieving desired target ranges of blood glucose and unacceptably high rates of hypoglycemia (293,293a).

For patients on general medical-surgical units, the evidence for specific

glycemic goals is less definitive. Epidemiologic and physiologic data suggest that lower blood glucose levels are associated with improved outcomes. Glycemic targets similar to those of outpatients may be difficult to achieve in the hospital due to the effects of stress hyperglycemia, altered nutritional intake, and multiple interruptions to medical care. Blood glucose levels shown to be associated with improved outcomes in these patients (fasting glucose <126 mg/dl and all blood glucose readings <180–200 mg/dl) would appear reasonable, if they can be safely achieved.

In both the critical care and non-critical care venue, glycemic goals must take into account the individual patient's situation as well as hospital system support for achieving these goals. A continuous quality improvement strategy may facilitate gradual improvement in mean glycemia hospital-wide.

3. Treatment options in hospitalized patients

a. Noninsulin glucose-lowering agents. No large studies have investigated the potential roles of various noninsulin glucose-lowering agents on outcomes of hospitalized patients with diabetes. Use of the various noninsulin classes in the inpatient setting presents some specific issues.

The long action of sulfonylureas and their predisposition to hypoglycemia in patients not consuming their normal nutrition serve as relative contraindications to routine use of these agents in the hospital (294). While the meglitinides, repaglinide and neteglinide, theoretically would produce less hypoglycemia than sulfonylureas, lack of clinical trial data for these agents, and the fact that they are primarily prandial in effect, would preclude their use. The major limitation to metformin use in the hospital is a number of specific contraindications to its use, related to risk of lactic acidosis, many of which occur in the hospital. 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 (295). Lactic acidosis is a rare complication in the outpatient setting (296), despite the relative frequency of risk factors (297). However, in the hospital the risks of hypoxia, hypoperfusion, and renal insufficiency are much higher, and it is prudent to avoid the use of metformin in most patients.

TZDs are not suitable for initiation in the hospital because of their delayed onset of effect. In addition, they 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. Pramlintide and exenatide work mainly by reducing postprandial hyperglycemia, so they would not be appropriate for patients not eating (NPO) or with reduced caloric consumption. Furthermore, initiation of these drugs in the inpatient setting would be problematic, due to alterations in normal food intake and their propensity to induce nausea initially. There is limited experience and no published data on the DPP-IV inhibitors in the hospital setting, but there are no specific safety concerns. They are mainly effective on postprandial glucose and therefore would have limited effect in patients who are not eating.

In summary, each of the major classes of noninsulin glucose-lowering drugs has significant limitations for inpatient use. Additionally, they provide little flexibility or opportunity for titration in a setting where acute changes often demand these characteristics. Therefore insulin, when used properly, is preferred for the majority of hyperglycemic patients in the hospital setting.

b. Insulin

i. Subcutaneous insulin therapy. Subcutaneous insulin therapy may be used to attain glucose control in most hospitalized patients with diabetes outside of the critical care arena. 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 should cover both basal and nutritional needs, and is subdivided into 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, the appropriate scheduled insulin doses should be increased to accommodate the increased insulin needs. There are no studies comparing human regular insulin with rapid-acting analogs for use as correction-dose insulin.

The traditional “sliding-scale” insulin regimens, usually consisting of regular in-

sulin without any intermediate or long-acting insulins, have been shown to be ineffective when used as monotherapy in patients with an established insulin requirement (298–300). One problem with sliding-scale insulin regimens is that the sliding-scale regimen prescribed on admission is likely to be used throughout the hospital stay without modification, even when control remains poor. Additionally, 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.

A recent study demonstrated the safety and efficacy of using basal-bolus insulin therapy utilizing weight-based dosing in insulin-naïve hospitalized patients with type 2 diabetes (301). Glycemic control, defined as a mean blood glucose <140 mg/dl, was achieved in 68% of patients receiving basal-bolus insulin versus only 38% of those receiving sliding-scale insulin alone. There were no differences in hypoglycemia between the two groups. It is important to note that the patients in this study were obese, and the doses used in this study ($0.4\text{--}0.5 \text{ units} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) are higher than what may be required in patients who are more sensitive to insulin, such as those who are lean or who have type 1 diabetes.

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 rapid-acting analogs, the structural modifications of which increase the rate of absorption from subcutaneous depots, 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; type 1 diabetic patients who are NPO; or in critical care illness in general. It may be used 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. Although numerous algorithms have been published, there have been no head-to-head comparisons between insulin infusion strategies. Algorithms should incorporate the concepts that maintenance requirements differ between patients and change over the course of treatment. Ideally, intravenous insulin algorithms should consider both the current and previous glucose level, the rate of change of plasma glucose, and the current intravenous 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. For those who will require subcutaneous insulin, the very short half-life of intravenous insulin necessitates administering the first dose of subcutaneous insulin before discontinuation of the intravenous insulin infusion. If short- or rapid-acting insulin is used, it should be injected 1–2 h before stopping the infusion. If intermediate- or long-acting insulin is used alone, it should be injected 2–3 h before. A combination of short-/rapid- and intermediate-/long-acting insulin is usually preferred. Basal insulin therapy can be initiated at any time of the day, and should not be withheld to await a specific dosing time, such as bedtime. A recent clinical trial demonstrated that a regimen using 80% of the intravenous insulin requirement over the preceding 24 h, divided into basal and bolus insulin components, was effective at achieving blood glucose levels between 80 and 150 mg/dl following discontinuation of the intravenous insulin (302).

4. Self-management in the hospital

Self-management of diabetes in the hospital may be appropriate for competent adult patients who have a stable level of consciousness, have reasonably stable daily insulin requirements, successfully conduct self-management of diabetes at home, have physical skills needed to successfully self-administer insulin and perform SMBG, have adequate oral intake, and are proficient in carbohydrate counting, use of multiple daily insulin injections 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 conducting self-management in the hospital, it is imperative that basal, prandial, and correction doses of insulin and results of bedside glucose monitoring are recorded as part of the patient's hospital medical record. While many institutions allow patients on insulin pumps to continue these devices in the hospital, others express concern regarding use of a device unfamiliar to staff, 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 needs during hospitalization, with adjustments for changes in nutritional or metabolic status.

5. Preventing hypoglycemia

Hypoglycemia, especially in insulin-treated patients, is the leading limiting factor in the glycemic management of type 1 and type 2 diabetes (117). In the hospital, multiple additional risk factors for hypoglycemia are present, even among patients who are neither “brittle” nor tightly controlled. Patients with or without diabetes may experience hypoglycemia in the hospital in association with altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis (303,304). 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, inappropriate timing of short- or rapid-acting insulin in relation to meals, reduction of rate of administration of intravenous dextrose, and unexpected interruption of enteral feedings or parenteral nutrition.

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. Tracking such episodes and analyzing their causes are important quality improvement activities.

6. Diabetes care providers in the hospital

Inpatient diabetes management may be effectively provided by primary care physicians, endocrinologists, or hospitalists, but involvement of appropriately trained specialists or specialty teams may reduce

length of stay, improve glycemic control, and improve outcomes (305–308). 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 achieve glycemic targets associated with improved hospital outcomes, 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 effectively and safely achieve glycemic targets (309).

7. DSME in the hospital

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

For the hospitalized patient, diabetes “survival skills” education is generally a feasible approach. Patients receive sufficient information and training 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 prevent subsequent episodes of hospitalization.

8. MNT in the hospital

Hospital diets continue to be ordered by calorie levels based on the “ADA diet.” However, since 1994 the ADA has not endorsed any single meal plan or specified percentages of macronutrients, and the term “ADA diet” should no longer be used. Current nutrition recommendations advise individualization based on treatment goals, physiologic parameters, and medication usage. Because of the complexity of nutrition issues in the hospital, a registered dietitian, knowledgeable and skilled in MNT, should serve as an inpatient team member. 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 (310,311).

9. 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.

Bedside blood glucose testing is usually performed with portable meters that are similar or identical to devices for home SMBG. Staff training and ongoing quality control activities are important components of ensuring accuracy of the results. Ability to track the occurrence of hypo- and hyperglycemia is necessary. Results of bedside glucose tests should be readily available to all members of the care team.

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 on continuous intravenous insulin typically require hourly blood glucose testing until the blood glucose levels are stable, then every 2 h.

10. Continuous blood glucose monitoring in the hospital

The introduction of real-time blood glucose monitoring as a tool for outpatient diabetes management has potential benefit for the inpatient population (312). 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 in the hospital except in a research setting.

B. Diabetes care in the school and day care setting

Recommendations

- An individualized diabetes medical management plan (DMMP) should be developed by the parent/guardian and the student’s 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)

- As specified in the DMMP and as developmentally appropriate, the student with diabetes should have immediate access to diabetes supplies at all times, should be permitted to monitor his or her blood glucose level, and should be able to take appropriate action to treat hypoglycemia in the classroom or anywhere the student may be in conjunction with a school activity. (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, including coverage of children with diabetes under Section 504 of the Individuals with Disabilities Education Act of 1991, children in the school and day care setting still face discrimination. The ADA position statement on diabetes care in the school and day care setting (313) provides the legal and medical justifications for the recommendations provided herein.

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. Parents and the health care team should provide school systems and day care providers with the information necessary for children with diabetes to participate fully and safely in the school/day care experience by developing an individualized DMMP.

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 responses to high and low blood glucose levels to 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 participating in school-sponsored extracurricular activities. These school personnel need not be health care professionals, although the school nurse may be instrumental in training nonmedical individuals.

The student with diabetes should have immediate access to diabetes supplies at all times, with supervision as needed. The student should be able to ob-

tain a blood glucose level and respond to the results as quickly and conveniently as possible, minimizing the need for missing instruction in the classroom and avoiding the risk of worsening hypoglycemia if the child must go somewhere else for treatment. The student's desire for privacy during testing and insulin administration should also be accommodated.

ADA and partner organizations have developed tools for school personnel to provide a safe and nondiscriminatory educational environment for all students with diabetes (314,315).

C. Diabetes care at diabetes camps

Recommendations

- Each camper should have a standardized medical form completed by his/her family and the physician managing the diabetes. (E)
- Camp medical staff should be led by with a physician with expertise in managing type 1 and type 2 diabetes, and includes nurses (including diabetes educators and diabetes clinical nurse specialists) and registered dietitians with expertise in diabetes. (E)
- All camp staff, including physicians, nurses, dietitians and volunteers, 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 diabetes camps is to provide 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 (316).

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 type(s) of insulin used, number and timing of injections and the correction factor and carbohydrate ratios used for determining bolus dosages for basal-bolus regimens. Campers using CSII

should also have their basal rates specified. Because camp is often associated with more physical activity than experienced at home, the insulin dose may have to be decreased during camp (316).

The diabetes camping experience is short-term, with food and activity different than the home environment. Thus, goals of glycemic control at camp are to avoid extremes in blood glucose levels rather than attempting optimization of intensive glycemic control (316).

During camp, a daily record of the camper's progress should be made, including all blood glucose levels and insulin dosages. 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 at the end of the camp session and a copy sent to the child's physician (316).

Each camp should secure a formal relationship with a nearby medical facility so that camp medical staff can refer to this facility for prompt treatment of medical emergencies. ADA requires that the camp medical director be a physician 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 have input into the design of the menu and the education program. All camp staff, including medical, nursing, nutrition, and volunteer staff, should undergo background testing to ensure appropriateness in working with children (316).

D. Diabetes management in correctional institutions

Recommendations

- Correctional staff should be trained in the recognition, treatment, and appropriate referral for hypo- and hyperglycemia, including serious metabolic decompensation. (E)
- 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 upon entry. Insulin-treated patients should have a capillary blood glucose (CBG) determination within 1–2 h of arrival. Staff should identify patients with type 1 diabetes who are at high risk for DKA with omission of insulin. (E)

- Medications and MNT should be continued without interruption upon entry into the correctional environment. (E)
- In the correctional setting, policies and procedures should enable CBG monitoring to occur at the frequency necessitated by the patient's glycemic control and diabetes regimen, and should require staff to notify a physician of all CBG results outside of a specified range, as determined by the treating physician. (E)
- For all inter-institutional transfers, a medical transfer summary should be transferred with the patient, and diabetes supplies and medication should accompany the patient. (E)
- Correctional staff should begin discharge planning with adequate lead time to ensure 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., and 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 (317).

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 (317).

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 medica-

tion 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 hyper- or hypoglycemia (317).

Patients must have access to prompt treatment of hypo- and hyperglycemia. Correctional staff should be trained in the recognition and treatment of these conditions, 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 (317).

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. The frequency of CBG monitoring will vary by patients' glycemic control and diabetes regimens. Policies and procedures should ensure that the health care staff has adequate knowledge and skills to direct the management and education of individuals with diabetes (317).

Patients in jails may be housed for a short period of time before being transferred or released, and patients in prison may 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. The ADA Position Statement on Diabetes Management in Correctional Institutions (317) should be consulted for more information on this topic.

E. Emergency and disaster preparedness

Recommendations

- People with diabetes should maintain a disaster kit that includes items important to their diabetes self-management and continuing medical care. (E)
- The kit should be reviewed and replenished at least twice yearly. (E)

The difficulties encountered by people with diabetes and their health care providers in the wake of Hurricane Katrina (318) highlight the need for people with diabetes to be prepared for emergencies, whether natural or otherwise, affecting a

region or just their household. 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 may 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; glucagon emergency kits; 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 will refill medications based on the prescription number alone. In addition, it may be important to carry a list of contacts for national organizations, such as the American Red Cross and ADA. This disaster kit should be reviewed and replenished at least twice yearly (319).

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 (320).

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, noninsulin drugs, and/or insulin), and medical history, particularly in regard to the occurrence of incapacitating hypoglycemic episodes (320).

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

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 have access to 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 related to the daily care of diabetes, such as syringes, strips, and meters, must also be reimbursed by third-party payors (321).

It is recognized that the use of formularies, prior authorization, and 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. Without appropriate safeguards, undue controls could constitute an obstruction of effective care (321).

Medicare and many other third-party payors cover DSME (the CMS term is 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 benefits. However, not all Medicare beneficiaries with 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 on the CMS Web sites: www.cms.hhs.gov/DiabetesSelfManagement (DSME) and www.cms.hhs.gov/MedicalNutritionTherapy (diabetes MNT) reimbursement.

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 (322) 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 total cholesterol <200 mg/dl. Most distressing was that only 7.3% of people with diabetes 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 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 programs 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

Web site 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 process measures such as measurement of A1C, lipids, and blood pressure. Effects on important intermediate outcomes, such as mean A1C for populations, have been more difficult to demonstrate (323–325) although examples do exist (326–330). 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 elec-

tronic 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 (331).

- 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 (332). 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. *Medical Management of Type 1 Diabetes*. Alexandria, VA, American Diabetes Association, 2004
2. *Medical Management of Type 2 Diabetes*. Alexandria, VA, American Diabetes Association, 2004
3. *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. Davidson MB, Schriger DL, Peters AL, Lorber B: Relationship between fasting plasma glucose and glycosylated hemo-

- globin: potential for false-positive diagnoses of type 2 diabetes using new diagnostic criteria. *JAMA* 281:1203–1210, 1999
7. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B: Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 30:753–759, 2007
 8. Engelgau MM, Narayan KM, Herman WH: Screening for type 2 diabetes. *Diabetes Care* 23:1563–1580, 2000
 9. 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
 10. 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
 11. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukkaanniemi 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
 12. 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
 13. 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
 14. 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
 15. 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
 16. 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
 17. Johnson SL, Tabaei BP, Herman WH: The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the U.S. population 45–74 years of age. *Diabetes Care* 28:307–311, 2005
 18. 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
 19. USPSTF: Screening for type 2 diabetes mellitus in adults: recommendations and rationale. *Ann Intern Med* 138:212–214, 2003
 20. Dabelea D, Bell RA, D'Agostino RB, Jr, Imperatore G, Johansen JM, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ, Waitzfelder B: Incidence of diabetes in youth in the United States. *JAMA* 297:2716–2724, 2007
 21. Liese AD, D'Agostino RB, Jr, Hamman RF, Kilgo PD, Lawrence JM, Liu LL, Loots B, Linder B, Marcovina S, Rodriguez B, Standiford D, Williams DE: The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics* 118:1510–1518, 2006
 22. American Diabetes Association: Type 2 diabetes in children and adolescents (Consensus Statement). *Diabetes Care* 23:381–389, 2000
 23. American Diabetes Association: Gestational diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1):S88–S90, 2004
 24. Kim C, Newton KM, Knopp RH: Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 25:1862–1868, 2002
 25. Gerstein HC: Point: If it is important to prevent type 2 diabetes, it is important to consider all proven therapies within a comprehensive approach. *Diabetes Care* 30:432–434, 2007
 26. American Diabetes Association: Consensus statement on self-monitoring of blood glucose. *Diabetes Care* 10:95–99, 1987
 27. American Diabetes Association: Self-monitoring of blood glucose. American Diabetes Association. *Diabetes Care* 17:81–86, 1994
 28. 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
 29. 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
 30. Garg S, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S, Jovanovic L: Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* 29:44–50, 2006
 31. 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
 32. Cagliero E, Levina EV, Nathan DM: Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. *Diabetes Care* 22:1785–1789, 1999
 33. 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
 34. 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
 35. DCCT: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
 36. DCCT-EDIC: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 342:381–389, 2000
 37. Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL: Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 29:340–344, 2006
 38. 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
 39. Ohkubo Y, Kishikawa H, Araki E, Miyata

- T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
40. UKPDS: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:854–865, 1998
 41. 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
 42. Kuusisto J, Mykkanen L, Pyorala K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
 43. 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
 44. 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
 45. American Diabetes Association: Postprandial blood glucose (Consensus Statement). *Diabetes Care* 24:775–778, 2001
 46. Ceriello A, Taboga C, Tonutti L, Quagliaro L, Piconi L, Bais B, Da Ros R, Motz E: Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: effects of short- and long-term simvastatin treatment. *Circulation* 106:1211–1218, 2002
 47. 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
 48. DeWitt DE, Hirsch IB: Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 289: 2254–2264, 2003
 49. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A: Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 28: 950–955, 2005
 50. Mooradian AD, Bernbaum M, Albert SG: Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 145:125–134, 2006
 51. 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
 52. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457–2471, 2007
 53. Singh S, Loke YK, Furberg CD: Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 298:1189–1195, 2007
 54. American Diabetes Association. Nutrition Recommendations and Interventions for Diabetes—2008. *Diabetes Care* 31 (Suppl. 1):S61–S78, 2008
 55. Pastors JG, Warshaw H, Daly A, Franz M, Kulkarni K: The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 25:608–613, 2002
 56. Pastors JG, Franz MJ, Warshaw H, Daly A, Arnold MS: How effective is medical nutrition therapy in diabetes care? *J Am Diet Assoc* 103:827–831, 2003
 57. Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM: Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr* 69:632–646, 1999
 58. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N: A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 336:1117–1124, 1997
 59. Norris SL, Zhang X, Avenell A, Gregg E, Bowman B, Schmid CH, Lau J: Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. *Am J Prev Med* 28:126–139, 2005
 60. Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, Clark NG: Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Diabetes Care* 27:2067–2073, 2004
 61. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Kim C, Lau J: Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 164: 1395–1404, 2004
 62. Wolf AM, Conaway MR, Crowther JQ, Hazen KY, Nadler L, Oneida B, Bobbjerg VE: Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care* 27:1570–1576, 2004
 63. Manning RM, Jung RT, Leese GP, Newton RW: The comparison of four weight reduction strategies aimed at overweight patients with diabetes mellitus: four-year follow-up. *Diabet Med* 15:497–502, 1998
 64. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, Graves K, Haffner SM, Harrison B, Hill JO, Horton ES, Jakicic J, Jeffery RW, Johnson KC, Kahn S, Kelley DE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montgomery B, Nathan DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesche-Thobaben J, Wing RR, Yanovski SZ: Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care* 30:1374–1383, 2007
 65. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S: A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 348: 2082–2090, 2003
 66. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF: The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 140:778–785, 2004
 67. Gardner C, Kiazand A, Alhassan S, Soowon K, Stafford R, Balise R, Kraemer H, and King A: Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women. *JAMA* 297:969–977, 2007
 68. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Jr, Brehm BJ, Bucher HC: Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 166:285–293, 2006
 69. Institute of Medicine: *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. National Academies Press,

- Washington, DC, 2002
70. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 25:148–198, 2002
 71. Piette JD, Glasgow RE: Strategies for improving behavioral and health outcomes among people with diabetes: self-management education. In *Evidence-Based Diabetes Care*. Gerstein HC, Hayes RB, Eds. BC Decker, Ontario, Canada, 2000
 72. 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
 73. 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, 2002
 74. 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
 75. 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
 76. 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
 77. 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
 78. Funnell MM, Brown TL, Childs BP, Haas LB, Hoseney GM, Jensen B, Maryniuk M, Peyrot M, Piette JD, Reader D, Siminerio LM, Weinger K, Weiss MA: National standards for diabetes self-management education. *Diabetes Care* 30:1630–1637, 2007
 79. Mulcahy K, Maryniuk M, Peeples M, Peyrot M, Tomky D, Weaver T, Yarbrough P: Diabetes self-management education core outcomes measures. *Diabetes Educ* 29: 768–84:787, 2003
 80. Barker JM, Goehrig SH, Barriga K, Hoffman M, Slover R, Eisenbarth GS, Norris JM, Klingensmith GJ, Rewers M: Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* 27:1399–1404, 2004
 81. Rickheim PL, Weaver TW, Flader JL, Kendall DM: Assessment of group versus individual diabetes education: a randomized study. *Diabetes Care* 25:269–274, 2002
 82. Trento M, Passera P, Borgo E, Tomalino M, Bajardi M, Cavallo F, Porta M: A 5-year randomized controlled study of learning, problem solving ability, and quality of life modifications in people with type 2 diabetes managed by group care. *Diabetes Care* 27:670–675, 2004
 83. Norris SL, Chowdhury FM, Van Le K, Horsley T, Brownstein JN, Zhang X, Jack L, Jr, Satterfield DW: Effectiveness of community health workers in the care of persons with diabetes. *Diabet Med* 23: 544–556, 2006
 84. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C: Physical activity/exercise and type 2 diabetes. *Diabetes Care* 27:2518–2539, 2004
 85. Wasserman DH, Zimman B: Exercise in individuals with IDDM. *Diabetes Care* 17:924–937, 1994
 86. 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
 87. 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
 88. 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
 89. 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
 90. 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
 91. 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
 92. Sigal RJ, Kenny GP, Boule NG, Wells GA, Prud'homme D, Fortier M, Reid RD, Tulloch H, Coyle D, Phillips P, Jennings A, Jaffey J: Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med* 147:357–369, 2007
 93. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ: Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 30:2729–2736, 2007
 94. 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
 95. American Diabetes Association: Physical activity/exercise and diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1): S58–S62, 2004
 96. Berger M: Adjustment of insulin and oral agent therapy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 365–376
 97. Aiello LP, Wong J, Cavallerano J, Bursell SE, Aiello LM: Retinopathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 401–413
 98. Vinik A, Erbas T: Neuropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 463–496
 99. Levin ME: The diabetic foot. In *Handbook of Exercise in Diabetes*. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 385–399
 100. 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
 101. Valensi P, Sachs RN, Harfouche B, Lormeau B, Paries J, Cossion 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
 102. Mogensen CE: Nephropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 433–449
 103. 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
 104. Jacobson AM: Depression and diabetes.

- Diabetes Care* 16:1621–1623, 1993
105. Rubin RR, Peyrot M: Psychosocial problems and interventions in diabetes: a review of the literature. *Diabetes Care* 15: 1640–1657, 1992
 106. Surwit RS, Schneider MS, Feinglos MN: Stress and diabetes mellitus. *Diabetes Care* 15:1413–1422, 1992
 107. Young-Hyman D: Psychosocial 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
 108. Delahanty LM, Grant RW, Wittenberg E, Bosch JL, Wexler DJ, Cagliero E, Meigs JB: Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. *Diabet Med* 24:48–54, 2007
 109. Anderson BJ, Auslander WF, Jung KC, Miller JP, Santiago JV: Assessing family sharing of diabetes responsibilities. *J Pediatr Psychol* 15:477–492, 1990
 110. 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
 111. Rubin RR, Peyrot M: Psychological issues and treatments for people with diabetes. *J Clin Psychol* 57:457–478, 2001
 112. Peyrot M, Rubin RR: Behavioral and psychosocial interventions in diabetes: a conceptual review. *Diabetes Care* 30: 2433–2440, 2007
 113. 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
 114. 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
 115. Peyrot M, Rubin RR: Behavioral and psychosocial interventions in diabetes: a conceptual review. *Diabetes Care* 30: 2433–2440, 2007
 116. American Diabetes Association: Hyperglycemic crises in diabetes. *Diabetes Care* 27 (Suppl. 1):S94–S102, 2004
 117. Cryer PE: Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937–948, 2002
 118. 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
 119. Cryer PE: Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 350:2272–2279, 2004
 120. Cryer PE, Davis SN, Shamoon H: Hypoglycemia in diabetes. *Diabetes Care* 26: 1902–1912, 2003
 121. Smith SA, Poland GA: Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 23:95–108, 2000
 122. 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
 123. 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
 124. American Diabetes Association: Influenza and pneumococcal immunization in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S111–S113, 2004
 125. Arauz-Pacheco C, Parrott MA, Raskin P: The treatment of hypertension in adult patients with diabetes. *Diabetes Care* 25: 134–147, 2002
 126. Haffner SM: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21:160–178, 1998
 127. Colwell JA: Aspirin therapy in diabetes. *Diabetes Care* 20:1767–1771, 1997
 128. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes. *Diabetes Care* 22: 1887–1898, 1999
 129. Buse JB, Ginsberg HN, Barkis GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone N: J Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 30:162–172, 2007
 130. 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
 131. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM: Cardiovascular prognosis of “masked hypertension” detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 291:1342–1349, 2004
 132. Segal R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G: Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 111:1777–1783, 2005
 133. UKPDS: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317:703–713, 1998
 134. 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
 135. 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
 136. 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
 137. 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
 138. 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
 139. 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
 140. 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
 141. Schrier RW, Estacio RO, Mehler PS, Hiatt WR: Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. *Nat Clin Pract Nephrol* 3:428–438, 2007
 142. ALLHAT: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lower-

- ing Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002
143. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS: Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 289:2534–2544, 2003
 144. HOPE: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355:253–259, 2000
 145. 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
 146. 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
 147. 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
 148. 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
 149. 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
 150. 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
 151. 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
 152. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD: Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA* 277:739–745, 1997
 153. Sibai BM: Treatment of hypertension in pregnant women. *N Engl J Med* 335:257–265, 1996
 154. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267–1278, 2005
 155. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson 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
 156. 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
 157. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* 98:2513–2519, 1998
 158. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D: Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 29:1220–1226, 2006
 159. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 28:1151–1157, 2005
 160. Knopp RH, d'Emden M, Smilde JG, Pocock SJ: Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 29:1478–1485, 2006
 161. 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
 162. Singh IM, Shishehbor MH, Ansell BJ: High-density lipoprotein as a therapeutic target: a systematic review. *JAMA* 298:786–798, 2007
 163. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W: Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 8:1245–1255, 1986
 164. 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
 165. 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
 166. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskiran MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366:1849–1861, 2005
 167. NCEP: 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
168. Hayward RA, Hofer TP, Vijan S: Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med* 145:520–530, 2006
 169. 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
 170. 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
 171. 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
 172. 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
 173. 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
 174. 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
 175. Jones PH, Davidson MH: Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 95:120–122, 2005
 176. American Diabetes Association: Aspirin therapy in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S72–S73, 2004
 177. 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
 178. USPSTF: Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 136:157–160, 2002
 179. Antithrombotic Trialists Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324:71–86, 2002
 180. Smith SC, Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA: AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 113:2363–2372, 2006
 181. Campbell CL, Smyth S, Montalescot G, Steinhubl SR: Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 297:2018–2024, 2007
 182. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A: Primary Prevention of Cardiovascular Events With Low-Dose Aspirin and Vitamin E in Type 2 Diabetic Patients: Results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 26:3264–3272, 2003
 183. 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
 184. American Diabetes Association: Smoking and diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S74–S75, 2004
 185. US Preventive Services Task Force: *Counseling to Prevent Tobacco Use and Tobacco-Related Diseases: Recommendation Statement*. Agency for Healthcare Research and Quality, Rockville, MD, 2003
 186. Ranney L, Melvin C, Lux L, McClain E, Lohr KN: Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med* 145:845–856, 2006
 187. American Diabetes Association: Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. American Diabetes Association. *Diabetes Care* 21:1551–1559, 1998
 188. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A: Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 47:65–71, 2006
 189. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS: Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 356:1503–1516, 2007
 190. Wackers FJ, Chyun DA, Young LH, Heller GV, Iskandrian AE, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE: Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes mellitus in the DIAD Study. *Diabetes Care* 2007
 191. Garg JP, Bakris GL: Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med* 7:35–43, 2002
 192. 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
 193. 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
 194. 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
 195. 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
 196. DCCT: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 47:1703–1720, 1995
 197. 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, 1993
 198. Remuzzi G, Macia M, Ruggenenti P: Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENE-DICT study. *J Am Soc Nephrol* 17:S90–

- S97, 2006
199. 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
 200. 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
 201. 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
 202. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancina 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
 203. Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, Agarwal R, Catanzaro D: ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* 58:2084–2092, 2000
 204. 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
 205. 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
 206. 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
 207. 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
 208. 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
 209. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 139:137–147, 2003
 210. Kramer H, Molitch ME: Screening for kidney disease in adults with diabetes. *Diabetes Care* 28:1813–1816, 2005
 211. 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
 212. 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
 213. 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
 214. Levinsky NG: Specialist evaluation in chronic kidney disease: too little, too late. *Ann Intern Med* 137:542–543, 2002
 215. American Diabetes Association: Nephropathy in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S79–S83, 2004
 216. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995
 217. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW: Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *Am J Kidney Dis* 31:947–953, 1998
 218. Leske MC, Wu SY, Hennis A, Hyman L, Nemesure B, Yang L, Schachat AP: Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology* 112:799–805, 2005
 219. Fong DS, Aiello LP, Ferris FL, III, Klein R: Diabetic retinopathy. *Diabetes Care* 27:2540–2553, 2004
 220. DCCT: Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes Care* 23:1084–1091, 2000
 221. The Diabetic Retinopathy Study (DRS) Research Group. Preliminary report on the effects of photocoagulation therapy: DRS Report #1. *Am J Ophthalmol* 81:383–396, 1976
 222. ETDRS: Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 103:1796–1806, 1985
 223. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 102:520–526, 1984
 224. Harris MI, Klein R, Welborn TA, Knudman MW: Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
 225. 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
 226. Klein R: Screening interval for retinopathy in type 2 diabetes. *Lancet* 361:190–191, 2003
 227. 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
 228. Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA: The sensitivity and specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. *Diabetes Care* 29:2205–2209, 2006
 229. American Diabetes Association: Retinopathy in diabetes. *Diabetes Care* 27 (Suppl. 1):S84–S87, 2004
 230. Ciulla TA, Amador AG, Zinman B: Diabetic Retinopathy and Diabetic Macular Edema: Pathophysiology, screening, and novel therapies. *Diabetes Care* 26:2653–2664, 2003
 231. 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
 232. Vinik AI, Maser RE, Mitchell BD, Freeman R: Diabetic autonomic neuropathy. *Diabetes Care* 26:1553–1579, 2003
 233. American Diabetes Association: Peripheral Arterial Disease in People With Diabetes (Consensus Statement). *Diabetes Care* 26:3333–3341, 2003
 234. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM: Preventive foot care in people with diabetes. *Diabetes Care* 21:2161–2177, 1998
 235. American Diabetes Association: Preventive foot care in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S63–S64, 2004
 236. American Diabetes Association: Consensus Development Conference on Diabetic Foot Wound Care, 7–8 April 1999, Boston, Massachusetts. American Diabetes Association. *Diabetes Care* 22:1354–1360, 1999

237. Silverstein J, Klingensmith G, Copeland KC, Plotnick L, Kaufman F, Laffel L, Deeb LC, Grey M, Anderson BJ, Holzmeister LA, Clark N, 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
238. Northam EA, Anderson PJ, Werther GA, Warne GL, Adler RG, Andrewes D: Neuropsychological complications of IDDM in children 2 years after disease onset. *Diabetes Care* 21:379–384, 1998
239. Rovet J, Alvarez M: Attentional functioning in children and adolescents with IDDM. *Diabetes Care* 20:803–810, 1997
240. Bjorgaas M, Gimse R, Vik T, Sand T: Cognitive function in type 1 diabetic children with and without episodes of severe hypoglycaemia. *Acta Paediatr* 86:148–153, 1997
241. 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
242. 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
243. Krantz JS, Mack WJ, Hodis HN, Liu CR, Liu CH, Kaufman FR: Early onset of subclinical atherosclerosis in young persons with type 1 diabetes. *J Pediatr* 145:452–457, 2004
244. Jarvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Ronnema T, Raitakari OT: Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes* 51:493–498, 2002
245. Haller MJ, Samyn M, Nichols WW, Brusko T, Wasserfall C, Schwartz RF, Atkinson M, Shuster JJ, Pierce GL, Silverstein JH: Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care* 27:2911–2917, 2004
246. Orchard TJ, Forrest KY, Kuller LH, Becker DJ: Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 24:1053–1059, 2001
247. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J: Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 114:2710–2738, 2006
248. Salo P, Viikari J, Hamalainen M, Lapinleimu H, Routi T, Ronnema T, Sepänen R, Jokinen E, Valimäki I, Simell O: Serum cholesterol ester fatty acids in 7- and 13-month-old children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet: the STRIP baby project. Special Turku coronary Risk factor Intervention Project for children. *Acta Paediatr* 88:505–512, 1999
249. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. *JAMA* 273:1429–1435, 1995
250. McCrindle BW, Ose L, Marais AD: Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 143:74–80, 2003
251. de Jongh S, Lilien MR, op't RJ, Stroes ES, Bakker HD, Kastelein JJ: Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 40:2117–2121, 2002
252. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ: Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 292:331–337, 2004
253. Holmes GK: Screening for coeliac disease in type 1 diabetes. *Arch Dis Child* 87:495–498, 2002
254. 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
255. Roldan MB, Alonso M, Barrio R: Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Diabetes Nutr Metab* 12:27–31, 1999
256. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Gruters-Kieslich A: Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with Type 1 diabetes. *Diabet Med* 19:518–521, 2002
257. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F: The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. *Diabet Med* 19:70–73, 2002
258. Chase HP, Garg SK, Cockerham RS, Wilcox WD, Walravens PA: Thyroid hormone replacement and growth of children with subclinical hypothyroidism and diabetes. *Diabet Med* 7:299–303, 1990
259. Eppens MC, Craig ME, Cusumano J, Hing S, Chan AK, Howard NJ, Silink M, Donaghue KC: Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 29:1300–1306, 2006
260. 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
261. 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
262. 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
263. Tchobrousky 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
264. Willhoite MB, Bennert HW, Jr, Palomaki GE, Zarella 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
265. Cooper WO, 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* 354:2443–2451, 2006
266. 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
267. American Diabetes Association: Preconception care of women with diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S76–S78, 2004
268. 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
269. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G,

- Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J: Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA* 276:1886–1892, 1996
270. 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
271. American Association of Clinical Endocrinologists: Inpatient diabetes and metabolic control: conference proceedings. *Endocr Pract* 10 (Suppl. 2):1–108, 2004
272. Garber AJ, Moghissi ES, Bransome ED, Jr, Clark NG, Clement S, Cobin RH, Furnary AP, Hirsch IB, Levy P, Roberts R, van den BG, Zamudio V: American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 10 (Suppl. 2):4–9, 2004
273. ACE/ADA Task Force on Inpatient Diabetes: American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycemic control: a call to action. *Diabetes Care* 29:1955–1962, 2006
274. Centers for Disease Control and Prevention: *Hospitalizations for Diabetes as Any-Listed Diagnosis*. Atlanta, GA, CDC, 2003
275. Pomposelli JJ, Baxter JK, III, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA, Bistrrian BR: Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *J Parenter Enteral Nutr* 22:77–81, 1998
276. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE: Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 87:978–982, 2002
277. 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
278. 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
279. 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
280. 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
281. Malmberg K, Ryden L, Wedel H, Birke-land 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
282. 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
283. Cheung NW, Wong VW, McLean M: The hyperglycemia: intensive insulin infusion in infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care* 29:765–770, 2006
284. 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
285. 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
286. 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
287. 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
288. van den Bergh G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345:1359–1367, 2001
289. van den Bergh 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
290. van den Bergh 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
291. 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
292. Krinsley J: Glycemic control in critically ill patients: Leuven and beyond. *Chest* 132:1–2, 2007
293. Brunkhorst FM, Reinhart K: Intensive insulin therapy in the ICU: benefit versus harm? *Intensive Care Med* 33:1302, 2007
- 293a. Glucontrol Study. Available at www.glucontrol.org. Accessed 6 November 2007.
294. 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
295. Misbin RI, Green L, Stadel BV, Gueriguan JL, Gubbi A, Fleming GA: Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 338:265–266, 1998
296. Misbin RI: The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care* 27:1791–1793, 2004
297. 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
298. 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
299. 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
300. Walts LF, Miller J, Davidson MB, Brown J: Perioperative management of diabetes mellitus. *Anesthesiology* 55:104–109, 1981
301. Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, Puig A, Mejia R: Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 30:2181–2186, 2007
302. Schmeltz LR, DeSantis AJ, Schmidt K, O'Shea-Mahler E, Rhee C, Brandt S, Peterson S, Molitch ME: Conversion of intravenous insulin infusions to subcutaneously administered insulin glargine in patients with hyperglycemia. *Endocr*

- Pract 12:641–650, 2006
303. Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M: Hypoglycemia in hospitalized nondiabetic older patients. *J Am Geriatr Soc* 46:978–982, 1998
 304. Fischer KF, Lees JA, Newman JH: Hypoglycemia in hospitalized patients. Causes and outcomes. *N Engl J Med* 315:1245–1250, 1986
 305. 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
 306. 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
 307. Levetan CS, Passaro MD, Jablonski KA, Ratner RE: Effect of physician specialty on outcomes in diabetic ketoacidosis. *Diabetes Care* 22:1790–1795, 1999
 308. Koproski J, Pretto Z, Poretzky L: Effects of an intervention by a diabetes team in hospitalized patients with diabetes. *Diabetes Care* 20:1553–1555, 1997
 309. 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
 310. American Diabetes Association: Diabetes nutrition recommendations for health care institutions (Position Statement). *Diabetes Care* 27 (Suppl. 1):S55–S57, 2004
 311. Boucher JL, Swift CS, Franz MJ, Kulkarni K, Schafer RG, Pritchett E, Clark NG: Inpatient management of diabetes and hyperglycemia: implications for nutrition practice and the food and nutrition professional. *J Am Diet Assoc* 107:105–111, 2007
 312. 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
 313. American Diabetes Association: Diabetes care in the school and day care setting. *Diabetes Care* 31 (Suppl. 1):S79–S86, 2008
 314. National Diabetes Education Program: *Helping the Student with Diabetes Succeed: A Guide for School Personnel*. Available at <http://www.ndep.nih.gov/diabetes/youth/youth.htm>. Accessed 6 November 2007
 315. American Diabetes Association. *Diabetes Care Tasks at School: What Key Personnel Need to Know*. Available at <http://www.diabetes.org/advocacy-and-legalresources/discrimination/school/schooltraining.jsp>. Accessed 6 November 2007
 316. American Diabetes Association: Diabetes care at diabetes camps. *Diabetes Care* 29 (Suppl. 1):S56–S58, 2006
 317. American Diabetes Association: Diabetes management in correctional institutions. *Diabetes Care* 31 (Suppl. 1):S87–S94, 2008
 318. Cefalu WT, Smith SR, Blonde L, Fonseca V: The Hurricane Katrina aftermath and its impact on diabetes care: observations from “ground zero”: lessons in disaster preparedness of people with diabetes. *Diabetes Care* 29:158–160, 2006
 319. American Diabetes Association Statement on Emergency and Disaster Preparedness: a report of the Disaster Response Task Force. *Diabetes Care* 30:2395–2398, 2007
 320. American Diabetes Association: Hypoglycemia and employment/licensure. *Diabetes Care* 31 (Suppl. 1):S95, 2008
 321. American Diabetes Association: Third-party reimbursement for diabetes care, self-management education, and supplies. *Diabetes Care* 31 (Suppl. 1):S96–S97, 2008
 322. 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
 323. Clark CM, Jr, Snyder JW, Meek RL, Stutz LM, Parkin CG: A systematic approach to risk stratification and intervention within a managed care environment improves diabetes outcomes and patient satisfaction. *Diabetes Care* 24:1079–1086, 2001
 324. Meigs JB, Cagliero E, Dubey A, Murphy-Sheehy P, Gildesgame C, Chueh H, Barry MJ, Singer DE, Nathan DM: A controlled trial of web-based diabetes disease management: the MGH diabetes primary care improvement project. *Diabetes Care* 26:750–757, 2003
 325. O'Connor PJ, Desai J, Solberg LI, Reger LA, Crain AL, Asche SE, Pearson TL, Clark CK, Rush WA, Cherney LM, Sperl-Hillen JM, Bishop DB: Randomized trial of quality improvement intervention to improve diabetes care in primary care settings. *Diabetes Care* 28:1890–1897, 2005
 326. Sperl-Hillen JM, O'Connor PJ: Factors driving diabetes care improvement in a large medical group: ten years of progress. *Am J Manag Care* 11:S177–S185, 2005
 327. Siminerio LM: Implementing diabetes self-management training programs: breaking through the barriers in primary care. *Endocr Pract* 12 (Suppl. 1):124–130, 2006
 328. Mahoney JJ: Reducing patient drug acquisition costs can lower diabetes health claims. *Am J Manag Care* 11:S170–S176, 2005
 329. Maney M, Tseng CL, Safford MM, Miller DR, Pogach LM: Impact of self-reported patient characteristics upon assessment of glycemic control in the Veterans Health Administration. *Diabetes Care* 30:245–251, 2007
 330. Bergenstal RM: Treatment models from the International Diabetes Center: advancing from oral agents to insulin therapy in type 2 diabetes. *Endocr Pract* 12 (Suppl. 1):98–104, 2006
 331. O'Connor PJ: Electronic medical records and diabetes care improvement: are we waiting for Godot? *Diabetes Care* 26:942–943, 2003
 332. Shojania KG, Ranji SR, McDonald KM, Grimshaw JM, Sundaram V, Rushakoff RJ, Owens DK: Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. *JAMA* 296:427–440, 2006