FIRST CONSULT

Diabetes mellitus type 2 in adults

Revised: November 15, 2013

Latest updates: November 14, 2013

On November 12, 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published four related guidelines on the prevention of atherosclerotic cardiovascular disease (ASCVD) events, with a focus on cholesterol, obesity, and lifestyle management tools.

The strongest recommendations from the new guideline on the management of overweight and obesity in adults focus on achieving a 3% to 5% weight loss using any medically recognized, low-calorie diet within a comprehensive, heavily supervised lifestyle change program for at least 6 months.

The new guideline on lifestyle management to reduce cardiovascular risk continues to recommend any medically recognized heart-healthy dietary program, including a reduction in the percentage of calories from saturated and trans fats, aiming for 5% to 6% of calories from saturated fat, and to lower sodium intake and follow a DASH-type diet.

The new guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommends a fundamental change in patient management from the National Heart, Lung, and Blood Institute's (NHLBI) Adult Treatment Panel III (ATP3) recommendations, the acknowledged leading guideline since 2004. In contrast to the ATP3, the ACC/AHA recommends treating all patients who fall into one of four statin benefit groups with either standardized, fixed-dose high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) or moderate-intensity statin therapy (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, or pravastatin 40–80 mg, among other statins).

Two of the four statin benefit groups are relevant to diabetes:

- All individuals with clinical ASCVD should receive high-intensity statin therapy, either atorvastatin (40–80 mg) or rosuvastatin (20–40 mg). Patients older than 75 years should receive moderate-intensity statin therapy, such as atorvastatin (10–20 mg), rosuvastatin (5–10 mg), simvastatin (20–40 mg), or pravastatin (40–80 mg), among others
- Individuals aged 40 to 75 years with diabetes and LDL-C levels between 70 to 189 mg/dL but without clinical ASCVD, should receive at least moderate-intensity statin therapy

Finally, the 2013 ACC/AHA guideline on the assessment of cardiovascular risk introduces a new 10-year and lifetime cardiovascular risk assessment tool based on a pooled cohort to predict first ASVCD-related event in non-Hispanic men and women. Routine measurement of carotid intima-media thickness is not recommended as part of primary prevention.

Key points

- Diabetes mellitus type 2 is a chronic metabolic disorder characterized by relative resistance to insulin and dysfunction of the β-cells in the pancreatic islets of Langerhans
- Onset is slow and insidious; the disease tends to present in middle-aged and elderly adults but may occur at any age
- Patients can present with thirst, polyuria, and lethargy; symptoms due to complications; or incidental findings of glycosuria or elevated blood glucose
- Ketosis can occur but is uncommon in patients with type 2 diabetes; it may occur late in the disease when significant β-cell depletion or exhaustion has occurred

- Management always includes dietary modification and regular exercise, usually in conjunction with oral hypoglycemic drugs; insulin may be required for adequate glucose control
- The natural course of the disease is progressive deterioration of glucose control, which, when uncontrolled over time, is followed by the development of microvascular and macrovascular complications

Urgent action:

- It is rare for any urgent action to be required at the time of diagnosis, unless there is severe metabolic disturbance or complications such as peripheral vascular occlusion or retinal detachment
- Hyperosmolar hyperglycemic state (HHS):
  - Impaired mental state and elevated plasma osmolality in a patient with hyperglycemia
  - Usually includes severe hyperglycemia (*eg*, blood glucose level >400 mg/dL [22.2 mmol/L]) and elevated plasma osmolality (*eg*, ≥315 mOsm/kg [315 mmol/kg])
  - Urgent hospital admission is essential
  - There is often clinical overlap between HHS and diabetic ketoacidosis: patients with HHS can be somewhat acidotic, and patients with diabetic ketoacidosis are often hyperosmolar
- Diabetic ketoacidosis (DKA):
  - Rare in patients with type 2 diabetes, although there is an increased incidence in certain groups (*eg*, young African American patients)
  - Some patients in whom type 2 diabetes is initially diagnosed will later be found to have type 1 diabetes , and, thus, the possibility of ketosis should not be forgotten

- Urgent hospital admission is essential in order to reduce acute morbidity and mortality

Background

Description

- Type 2 diabetes is a chronic metabolic disorder marked by insulin resistance and β-cell dysfunction
- Onset is slow and insidious; the disease tends to present in middle-aged and elderly adults but may occur at any age
- Often occurs in combination with dyslipidemia and hypertension, a combination that represents a clustering of risk factors for cardiovascular disease
- Many newly diagnosed patients are asymptomatic, but polydipsia, polyuria, and polyphagia may be presenting symptoms
- The current definition of diabetes mellitus from the American Diabetes Association (ADA) is a glycosylated hemoglobin (HbA1c) ≥6.5%, a fasting plasma glucose level ≥126 mg/dL (7 mmol/L), a random plasma glucose level ≥200 mg/dL (11 mmol/L) with symptoms of hyperglycemia, or a 2-hour plasma glucose level ≥200 mg/dL (11 mmol/L) following a standard challenge of 75 g of glucose in water. In the absence of unequivocal hyperglycemia where the index of suspicion is high, repeat testing should be done
- Progression of disease leads to significant microvascular and macrovascular complications (*eg*, renal disease, ophthalmic disease, vascular disease)
- Although dramatic in its presentation, diabetic ketosis is generally a manifestation of advanced disease and is relatively uncommon
- Type 2 diabetes accounts for 75% to 90% of all cases of diabetes mellitus

- *Type 2 diabetes*replaces the term*non–insulin-dependent diabetes mellitus*, which is inappropriate because some patients with this type of diabetes do require insulin therapy

Prediabetes

- Includes the categories of impaired glucose tolerance and impaired fasting glucose and identifies persons at relatively high risk of developing diabetes

Impaired glucose tolerance:

- Affects 15% to 20% of persons aged 45 to 74 years in the U.S.
- Diagnosed on the basis of a 2-hour post-load glucose level of 140 to 199 mg/dL (7.8-11.0 mmol/L) on an oral glucose tolerance test
- Fifty percent of patients revert to normal glucose tolerance within 10 years, 25% remain glucose intolerant, and 25% develop type 2 diabetes
- These patients have a higher likelihood of developing type 2 diabetes and may also already be at increased risk for macrovascular complications

Impaired fasting glucose:

- Defined as a fasting plasma glucose level of 100 to 125 mg/dL (5.6-6.9 mmol/L)
- Patients have a higher likelihood of developing type 2 diabetes and may also already be at increased risk for macrovascular complications

HbA1c:

- The range of 5.7% to 6.4% identifies individuals considered at increased risk for future diabetes. Individuals in this range should be advised of their increased risk for diabetes and for cardiovascular disease

- Individuals with HbA1c greater than 6.0% but less than 6.5% are considered a very high risk for future diabetes

Metabolic syndrome

- Metabolic syndrome is also known as dysmetabolic syndrome, insulin resistance syndrome, and syndrome X
- Refers to the clustering together of certain cardiovascular risk factors associated with insulin resistance and hyperinsulinemia
- Characteristics include the following (though not all are included in the different definitions):
  - Insulin resistance (effects of insulin are blunted)
  - Hyperinsulinemia
  - Central obesity
  - Glucose intolerance (impaired glucose tolerance or diabetes mellitus)
  - Hypertension
  - Increased levels of very-low-density lipoprotein (VLDL) cholesterol and triglycerides
  - Decreased high-density lipoprotein (HDL) cholesterol levels
  - Increase in small, dense low-density lipoprotein (LDL) cholesterol particles
  - Increase in plasminogen activator inhibitor 1
  - Increase in markers of inflammation (*eg*, C-reactive protein)
  - Accelerated atherosclerosis

Drug-induced diabetes

- Glucocorticoids
- Thiazides
- Nicotinic acid
- Pentamidine (causes β-cell destruction and, therefore, may cause hypoglycemia in the acute setting)
- Transplant drugs (*eg*, tacrolimus, cyclosporine)
- Human immunodeficiency virus (HIV) treatments (*eg*, indinavir, lopiaovir/ritonavir)
- Statins
- Antipsychotics and antidepressants (*eg*, risperidone, amitriptyline, fluvoxamine, paroxetine, venlafaxine)

Endocrine diseases

- Cushing syndrome
- Acromegaly
- Pheochromocytoma
- Glucagonoma
- Hypothyroidism

Genetic defects associated with β-cell dysfunction

- Mitochondrial diabetes and deafness caused by mitochondrial gene mutations
- Maturity-onset diabetes of the young (MODY)
  - Hepatocyte nuclear factor–4α (MODY 1) gene mutation

- Glucokinase (MODY 2) gene mutation
- Hepatocyte nuclear factor–1α (MODY 3) gene mutation

Rare genetic defects associated with insulin resistance

- Mutations in the insulin receptor gene
- Donohue syndrome (leprechaunism) and Rabson-Mendenhall syndrome
- Some cases of type A insulin resistance
- Mutations affecting postreceptor signal transduction
- Lipoatrophic diabetes
- Some cases of type A insulin resistance

Acquired insulin resistance syndromes

- Type B insulin resistance syndrome (anti-insulin receptor antibodies)
- Some types of lipodystrophy

Other associated genetic syndromes

- Hemochromatosis (common)
- Down syndrome (rare)
- Klinefelter syndrome (rare)
- Turner syndrome (rare)
- Prader-Willi syndrome (rare)
- Laurence-Moon-Biedl syndrome (rare)
- Friedreich ataxia (rare)

- Huntington disease (rare)
- Porphyria (rare)

Epidemiology

Incidence and prevalence

- There are three new cases per 1,000 white persons per year
- Data are thought to underestimate incidence, and the actual figures may be two to four times higher according to some reporting agencies
- Affects 50 to 70 per 1,000 persons in the U.S.
- An additional 27 per 1,000 persons have undiagnosed diabetes on the basis of fasting glucose
- It is estimated that over 25 million Americans have type 2 diabetes, and a much larger number have prediabetes
- The prevalence of diabetes is increasing all over the world, and the number of people affected is estimated to increase to 300 million by 2025; this increase will be mainly due to type 2 diabetes

Demographics

Age:

- The prevalence of type 2 diabetes increases with age
- Type 2 diabetes classically occurs in middle-aged and elderly patients, but the incidence in adolescents and young adults is increasing
- The increase in the number of people over age 65 is an important factor in the increasing prevalence of diabetes worldwide

- There has been an increase in incidence in early adulthood and childhood; the largest and most rapid increase in incidence is among patients aged younger than 25

Gender:

- When compared to persons without diabetes, a greater increase in premature death is seen among women with diabetes than men with diabetes, perhaps because diabetes appears to eliminate the protection against cardiovascular disease conferred by estrogen before menopause

Race:

- Prevalence is increased in African Americans, Native Americans, Asian Americans, Pacific Islanders, and Pima Indians
- The rate is particularly high among groups of North American Indians and Australian Aborigines who have adopted a more 'westernized' lifestyle

Genetics:

- Positive family history in 30% of patients
- Concordance rates of approximately 90% in identical twins
- The existence of one first-degree relative with type 2 diabetes doubles the relative risk, and the existence of two first-degree relatives with the disease increases the risk fourfold
- Type 2 diabetes is not associated with specific human leukocyte antigen genes (unlike type 1 diabetes)
- No single gene that is common to all patients with type 2 diabetes has been identified
- Polymorphisms have been identified within specific ethnic groups

Geography:

- Type 2 diabetes is a major global health problem in developed countries and also in developing countries, where incidence is increasing rapidly, especially in urban populations

Causes and risk factors

- Relative insulin resistance and pancreatic ß-cell dysfunction leading to hyperglycemia and its sequelae constitute the pathophysiology underlying type 2 diabetes mellitus
- Increased prevalence of type 2 diabetes mellitus is found in patients with the following risk factors:
  - Excessive weight (85% of patients)
  - Poor physical fitness
  - Genetic predisposition
- Contributory or predisposing factors:
  - Sedentary lifestyle and physical inactivity
  - Obesity, especially abdominal (centripetal) obesity
  - An association has been shown with food in plentiful supply, a diet high in refined carbohydrates and fats, and a diet with high energy content
  - Increasing age
  - History of gestational diabetes
  - Prediabetes, including impaired glucose tolerance and impaired fasting glucose
  - Presence of coexisting hypertension and dyslipidemia

- Family history of diabetes, particularly one or more first-degree relatives with type 2 diabetes, increases risk
- Certain ethnic groups are predisposed to type 2 diabetes (*ie*, African Americans, Native Americans, Asian Americans, Pacific Islanders, and Pima Indians)

Screening

Summary approach

- There is insufficient evidence to support recommendations for or against routine screening for type 2 diabetes in asymptomatic adults; however, the ADA recommends targeted screening of high-risk individuals. In persons without risk factors, screening for asymptomatic disease is much less likely to be beneficial

Population at risk

- Although there is no evidence suggesting that screening of asymptomatic persons alters outcomes, the ADA has suggested that overweight individuals (body mass index [BMI] >25 kg/m^2) with one or more of the following characteristics may appropriately be screened
- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (*eg*, African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing more than 9 lb or who were diagnosed with gestational diabetes mellitus (GDM)
- Hypertension (blood pressure ≥140/90 mm Hg or being on therapy for hypertension)

- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Women with polycystic ovary syndrome
- HbA1c ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (*eg*, acanthosis nigricans)
- History of cardiovascular disease
- Use of glucocorticoids or antipsychotics

- According to the ADA 2013 guidelines , in the absence of the above factors, testing for diabetes should begin at 45 years of age. If results are normal, testing should be repeated every 3 years or less, with consideration of more-frequent testing depending on initial results (*eg*, those with prediabetes should be tested yearly) and risk factors

Screening modalities

- Fasting plasma glucose or an oral glucose tolerance test (using a 75-g glucose load or a 2-hour glucose measurement), or HbA1c can be used to screen for prediabetes. The results of a glucose tolerance test may better define the risk of diabetes in patients with impaired fasting glucose

Primary prevention

Summary approach

- Facilitate primary prevention through community health promotion efforts, health education, and clinic-based activities
- Encourage patients at high risk of developing diabetes to lose weight and increase physical activity

- Provide interventions to delay and possibly prevent the onset of diabetes in patients with prediabetes (impaired glucose tolerance or impaired fasting glucose). A wide variety of interventions are available; an intensive lifestyle modification program has been shown to be very effective
- Monitor patients with prediabetes for the development of diabetes every 1 to 2 years
- The ADA recommends consideration of metformin therapy for prevention in selected patients: those with impaired glucose tolerance, impaired fasting glucose, or an HbA1c of 5.7% to 6.4%, especially for those in this group who have a BMI over 35 kg/m^2, those aged younger than 60 years, and women with prior GDM

Population at risk

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (*eg*, African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing more than 9 lb or who were diagnosed with GDM
- Hypertension (blood pressure ≥140/90 mm Hg or being on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Women with polycystic ovary syndrome
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- Other clinical conditions associated with insulin resistance (*eg*, Cushing syndrome, acanthosis nigricans)
- History of cardiovascular disease
- Use of glucocorticoids or antipsychotics

Preventive measures

Diet:

- Development of diabetes is associated with consumption of refined carbohydrates and fats and diets with a high energy content
- Foods rich in non-starch polysaccharides and carbohydrates with a low glycemic index appear to protect against the development of type 2 diabetes

Physical activity:

- Exercise has a beneficial effect on insulin sensitivity
- Regular aerobic exercise reduces excess weight and promotes glucose tolerance
- Patients should adopt an active lifestyle and reduce sedentary behavior

Weight management:

- The ADA 2013 guidelines recommend weight loss and exercise in the prevention/delay of type 2 diabetes for patients with prediabetes
- Patients with prediabetes should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 minutes per week of moderate activity such as walking
- The American Association of Clinical Endocrinologists (AACE) 2013 consensus statement also recommends therapeutic lifestyle changes for patients with prediabetes to achieve a goal of weight loss to prevent the development of overt diabetes. When indicated,

some individuals with prediabetes may also benefit from pharmacotherapy or bariatric surgery to achieve clinically meaningful weight loss for diabetes prevention

Evidence

- A systematic review and meta-analysis of randomized, controlled trials (RCTs) involving 8,084 patients studying the effect of pharmacologic or lifestyle interventions on the prevention of type 2 diabetes in patients with impaired glucose tolerance concluded that both pharmacologic (oral antidiabetic agents, orlistat) and lifestyle interventions reduced the rate of progression to type 2 diabetes and that lifestyle interventions were at least as effective as drug therapy. [1] *Level of evidence: 2*

- A systematic review of two RCTs in which dietary advice was the only intervention given, 358 patients showed a 33% reduction in the incidence of diabetes after 6 years in one trial and significant reductions in fasting blood glucose level, BMI, blood pressure, and lipid levels in the other trial. [2] *Level of evidence: 1*

- A systematic review of whole grain foods for the prevention of type 2 diabetes identified one RCT and 11 cohort studies including 2,126 patients, but the quality of the data did not allow any conclusions to be drawn regarding effectiveness. [3] *Level of evidence: 1*

- A systematic review of eight trials with 4,750 patients involving exercise and dietary interventions over 1 to 6 years showed that the combination of exercise and dietary modification reduced the risk of diabetes compared to standard care in patients with prediabetes. [4] *Level of evidence: 1*

- A systematic review of five RCTs involving 2,360 patients with impaired glucose tolerance showed that use of acarbose reduced the incidence of diabetes and may prevent cardiovascular events, but other metabolic and clinical outcomes were not affected. [5] *Level of evidence: 1*

- The Finnish Diabetes Prevention Study randomly assigned 522 overweight or obese subjects with impaired glucose tolerance to an intervention consisting of individualized counseling concerning weight management, diet, and physical activity or to a control group. At 2-year follow-up, the incidence of type 2 diabetes in the intervention group was less than half that in the control group. [6] *Level of evidence: 1*

- Additional follow-up at a median of 4 years showed that the reduced incidence of type 2 diabetes among 522 subjects in the intervention group of the Finnish Diabetes Prevention Study was maintained. [7] *Level of evidence: 2*

- The Diabetes Prevention Program Research Group randomly assigned 3,234 subjects with impaired glucose tolerance to lifestyle modification, metformin, or placebo. Both the lifestyle intervention and metformin therapy had a protective effect on the risk of developing type 2 diabetes and were associated with a return to normal glucose tolerance, but lifestyle modification was associated with greater prevention of type 2 diabetes, especially in older patients, and also was associated with a lower mortality rate compared to metformin. [8] *Level of evidence: 1*

- Follow-up of 2,766 subjects in the U.S. Diabetes Prevention Program Outcome Study for an additional 5.6 years showed that the incidence of diabetes equalized among the lifestyle, metformin, and placebo groups during the extension period. The cumulative incidence of diabetes among subjects in the intervention group was reduced by 34%, however, while the cumulative incidence among subjects in the metformin group was reduced by 18%, compared to the placebo group. [9] *Level of evidence: 2*

- An RCT with over 5,000 patients found that rosiglitazone resulted in a 60% decrease in progression to diabetes among patients with impaired fasting glucose, impaired glucose tolerance, or both, and no previous cardiovascular disease at 3-year follow-up compared to placebo. Cardiovascular event rates were similar between groups,

although there was a small but significant increase in the heart failure rate among patients receiving rosiglitazone. [10] *Level of evidence: 1*

- A subanalysis of the Swedish Obese Subjects study examined the effect of bariatric surgery on the long-term prevention of type 2 diabetes in obese patients. The rate of incident type 2 diabetes among 1,658 obese patients who underwent bariatric surgery was compared to the incidence among 1,771 matched nonsurgical controls. Baseline BMIs for both groups were ≥34 kg/m^{2}or ≥38 kg/m^{2}in men and women, respectively, and none of the subjects from either group had a diagnosis of type 2 diabetes mellitus at study entry. For this study, diabetes was defined as a fasting blood glucose level ≥126 mg/dL or the self-reported use of diabetes medications. Over the 15-year follow-up period, type 2 diabetes developed in 110 patients in the bariatric surgery group (incident rate [IR] 6.8 cases/1,000 person-years; adjusted hazard ratio, 0.17; 95% confidence interval [CI], 0.13-0.21;*P*< .001] compared to 392 patients (IR, 28.4 cases/1,000 person-years) among controls. Thus, bariatric surgery, as compared to conventional care, reduced the long-term incidence of type 2 diabetes by 78% in obese patients. [11] *Level of evidence: 2*

- A prospective single-center study examined the association of Roux-en-Y gastric bypass (RYGB) surgery with weight loss and incidence of diabetes mellitus 6 years after surgery. This nonrandomized study included a total of 1,156 severely obese (BMI >35 kg/m^2) participants with a mean BMI of 45.9 kg/m^2. The incidence of diabetes throughout the course of the study was reduced fivefold to ninefold after RYGB surgery compared with nonsurgical control subjects (2% new diagnoses in RYGB group, 95% CI, 0%-4%; versus 17% new diagnoses for controls, 95% CI, 10%-24% [odds ratio, 0.11; 95% CI, 0.04-0.34;*P*< .001]). Thus, significant weight loss and a reduced risk for the development of type 2 diabetes were evident among obese patients who underwent RYGB surgery compared with severely obese, nonsurgically treated controls. [12] *Level of evidence: 2*

References

Diagnosis

Summary approach

According to the ADA, the presence of any one of the following criteria establishes the diagnosis of diabetes mellitus:

- Random plasma glucose level ≥200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia
- Fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L)
- Plasma glucose level ≥200 mg/dL (11.1 mmol/L) 2 hours after a 75-g anhydrous glucose load in an oral glucose tolerance test
- HbA1c ≥6.5%

Clinical presentation

Symptoms

- It is common for type 2 diabetes to be asymptomatic and diagnosed only following routine blood tests. Onset is often insidious, but symptoms may include lethargy, blurry vision, polyuria, polydipsia, frequent infections, and failure of wounds to heal. Patients may sometimes present with symptoms of complications, such as angina, impotence, and neuropathy

Hyperglycemia:

- Lethargy
- Malaise
- Blurred vision
- Polyuria
- Polydipsia

- Frequent infections (*eg*, candidiasis, balanitis, intertrigo, boils, cellulitis, urinary tract infections, vaginal yeast infections)
- Poor wound healing

Complications:

- Visual deterioration and blurred vision
- Neuropathy: numbness/paresthesias
- Angina
- Intermittent claudication
- Impotence

Other historical information

- Osmotic diuresis and symptoms of dehydration may be caused by high glucose levels
- Blurred vision is due to exposure of the lenses and retina to hyperosmolar fluids as a result of osmotic diuresis
- General fatigue, lethargy, and malaise are symptoms of type 2 diabetes
- High blood glucose levels predispose patients to recurrent fungal and bacterial infections. Poor wound healing is also a problem, and infections are often slow to resolve
- Patient may have experienced numbness or tingling. Nerves are affected as a result of acute glucose toxicity and peripheral neuropathy
- Consider angina if the patient has had chest pain, shortness of breath, pain in the left arm (especially on exertion), or indigestion

- Approximately one third of women with a history of GDM will develop type 2 diabetes later in life
- Recent weight gain may indicate onset of diabetes
- Patients with low levels of physical activity are at increased risk of developing diabetes
- Hypertension or high cholesterol are highly likely to be present in conjunction with diabetes
- Thirty percent of patients with diabetes have a positive family history

Signs

- No abnormalities may be detected on physical examination in the early stages of the disease; however, the following signs of complications may already be present at the time of diagnosis:
  - Ocular signs such as microaneurysms, hemorrhages, hard exudates, soft exudates, new vessel formation, and vitreous hemorrhage
  - Decreased peripheral pulses
  - Skin lesions suggestive of infection (*eg*, foot ulcers)
  - Signs of neuropathy such as decreased vibration or touch sensation, absent ankle-jerk reflex

Other physical examination factors

- Measure height and weight accurately. Patients with type 2 diabetes are often overweight or obese (defined as having a BMI ≥30)

- Measure blood pressure both with the patient lying down and standing up. There is a close association between type 2 diabetes and hypertension ; high blood pressure increases the risk of vascular disease
- Inspect the skin. Acanthosis nigricans (cutaneous hyperpigmented patches with a velvety texture, often in intertriginous areas) is often present and is most frequently seen in dark-skinned, obese patients
- Examine the feet, including both the skin and circulation, and assess for neurologic problems. Patients with diabetes who experience poor lower-extremity blood flow and decreased sensation are at risk for foot ulcers, inflammation, and infection from repeated skin stress and unnoticed minor trauma. A thorough foot inspection should be done, including evaluation for lower-extremity sensory neuropathy, to assess the patient's ability to detect minor trauma to the feet and ankles
- Measure visual acuity. A fundoscopic examination should be done. Blurred vision in a patient with diabetes may arise from fluctuating lenticular changes caused by poor glycemic control. Diabetic retinopathy is linked to duration of diabetes and poor glycemic control. Patients may have some degree of retinopathy at the time of diagnosis, especially if diagnosis is delayed, and patients with poor visual acuity should be referred to an ophthalmologist
- Evaluate the peripheral arterial pulses. Decreased peripheral pulses can indicate vascular disease, although this is more common in patients with longstanding diabetes

Diagnostic testing

Diagnosis:

- Fasting plasma glucose is the most commonly used test for establishing the diagnosis of diabetes mellitus

- Random plasma glucose can also be used for diagnosis in the presence of symptoms of hyperglycemia, although it has poor sensitivity
- Glucose tolerance testing is usually not necessary for the diagnosis of diabetes mellitus, but it can be helpful if the result of fasting plasma glucose is equivocal
- Glycosylated hemoglobin (HbA1c) should be obtained routinely in all patients with diabetes to document the degree of glycemic control at initial assessment and then as part of continuing care. It can also be used to diagnose diabetes
- Blood glucose testing should be repeated on a subsequent day to confirm the diagnosis, unless unequivocal symptoms of hyperglycemia are present

Evaluation:

- Once the diagnosis has been established, a complete medical evaluation should be done to assess for the presence of complications, assist in developing a management plan, and provide a basis for long-term assessment and diabetes care
- Fasting lipid levels can identify the presence of hyperlipidemia , which is a risk factor for cardiovascular disease , especially in patients with diabetes. Lipid levels are adversely affected by hyperglycemia, however, and thus results should not be interpreted until glucose control is improved—unless levels are extremely high and require urgent intervention. Lipid levels should be obtained yearly in patients with type 2 diabetes
- Blood urea nitrogen (BUN), creatinine, glomerular filtration rate, and electrolytes will indicate whether renal function is impaired
- Testing for urinary albumin excretion should be done at baseline and yearly in all patients with diabetes
- Urine glucose testing cannot accurately determine the level of glycemia and, thus, should not be used to monitor glycemic control

Fasting plasma glucose

Description

- Plasma glucose level is measured following an 8-hour fast (no consumption of food or beverages other than water; usually overnight)
- If the result is abnormal, the test must be repeated to establish the diagnosis

Normal result

- Plasma glucose level of 70 to 100 mg/dL (3.9-5.6 mmol/L)

Comments

- The current criteria for diagnosis of diabetes mellitus from the ADA include fasting plasma glucose level ≥126 mg/dL (7 mmol/L)
- In the absence of unequivocal hyperglycemia, where the index of suspicion for diabetes is high, repeat testing should be done
- Hormones such as glucagon, glucocorticoids, growth hormone, epinephrine, estrogen, progesterone (oral contraceptives), and thyroid preparations may cause hyperglycemia, particularly in patients prone to diabetes
- Medications such as corticosteroids can lead to isolated or intermittent hyperglycemia; other drugs and substances that may cause hyperglycemia (particularly in patients prone to diabetes) include thiazide diuretics, furosemide, acetazolamide, diazoxide, β-blockers, α-agonists, calcium-channel blockers, phenytoin, phenobarbital sodium, nicotinic acid, cyclophosphamide,L-asparaginase, epinephrine-like drugs (decongestants and diet pills), nonsteroidal anti-inflammatory drugs (NSAIDs), nicotine, caffeine, sugar-containing syrups, and fish oils

Random plasma glucose

Description

- Plasma glucose level is obtained irrespective of the timing of the patient's last meal or drink

Normal result

- Plasma glucose level <140 mg/dL (7.8 mmol/L)

Comments

- The current criteria for diagnosis of diabetes mellitus from the ADA include random plasma glucose level ≥200 mg/dL (11 mmol/L) with symptoms of hyperglycemia
- Only useful when the patient has symptoms; otherwise cannot be used to make a diagnosis

Oral glucose tolerance test

Description

- In the morning after a 10-hour fast the fasting plasma glucose level is obtained and a 75-g oral glucose load is then administered; periodic serum glucose measurement is then compared to an established nomogram for normal glucose metabolism, generally over a 2-hour period
- During the test, the patient should remain seated and should not smoke
- Should be done only in patients whose diet and physical activity have been unrestricted for 3 days before testing

Normal results

- Fasting plasma glucose level: 60 to 100 mg/dL
- Plasma glucose after 1 hour: <200 mg/dL

- Plasma glucose after 2 hours: <140 mg/dL

Comments

- A plasma glucose level between 140 and 200 mg/dL 2 hours after glucose load is considered impaired glucose tolerance (sometimes called 'prediabetes'); this group is at increased risk for developing diabetes. A level >200 mg/dL 2 hours after glucose load is a sign of diabetes mellitus
- This test is helpful in uncovering overt diabetes in a high-risk patient with impaired glucose tolerance (fasting plasma glucose level of 100-125 mg/dL [5.6-6.9 mmol/L])
- Performing this test in pregnant women using a different glucose load is particularly useful in diagnosing GDM. Initial testing is usually done between 24 and 28 weeks of gestation:
  - In the two-step test, a 1-hour 50-g oral glucose tolerance test is done for screening, and, if the result is abnormal, a 3-hour 100-g glucose tolerance test is done for definitive diagnosis
    - Normal fasting plasma glucose: <95 mg/dL
    - Normal plasma glucose for 50-g load at 1 hour: ≤140 mg/dL
    - Normal plasma glucose for 100-g load: at 1 hour, <180 mg/dL; at 2 hours, <155 mg/dL; at 3 hours, <140 mg/dL
  - A one-step, 3-hour 100-g glucose tolerance test may be done alone for diagnosis in high-risk patients or populations
  - If overtly elevated blood glucose levels are seen repeatedly, no further testing is required

- Glucose tolerance test is not necessary in patients with fasting hyperglycemia (plasma glucose level >125 mg/dL [6.9 mmol/L]) or in hospitalized, acutely ill, or inactive patients
- In the absence of unequivocal hyperglycemia, where the index of suspicion is high, repeat testing should be done
- Test is time consuming

HbA1c

Description

- Serum marker of glycemia
- Should be obtained routinely (every 3-6 months) in all patients with diabetes to document the degree of glycemic control at initial assessment and then as part of continuing care

Normal result

- 4.0% to 5.7%

Comments

- Reflects mean glycemia over the preceding 2 to 3 months
- Each laboratory has its own normal range that may not be calibrated to the reference range
- Range of HbA1c for diagnosis of prediabetes is 5.7% to 6.4%
- Threshold HbA1c for diagnosis of diabetes mellitus is ≥6.5%
- Careful interpretation is required in the setting of anemia, increased erythrocyte turnover, recent blood transfusions, or hemoglobinopathy

Fasting lipid profile

Description

- Assay for determination of serum lipid levels
- To ensure meaningful results, the sample should be obtained after fasting (at least 8 hours of no caloric intake)

Normal ranges

- HDL cholesterol: 50 mg/dL (1.3 mmol/L) in women; >40 mg/dL (1.0 mmol/L) in men
- Triglycerides: 40 to 150 mg/dL (0.45-1.7 mmol/L)
- LDL cholesterol (calculated): 62 to 185 mg/dL (1.6-4.8 mmol/L). For individuals without cardiovascular disease, <100 mg/dL (2.6 mmol/L) is optimal; for those with overt cardiovascular disease, <70 mg/dL (1.8 mmol/L) is optimal
- Total cholesterol: 140 to 250 mg/dL (3.6-6.5 mmol/L)

Comments

- Identifies the presence of hyperlipidemia, a risk factor for cardiovascular disease
- Total cholesterol levels <200 mg/dL (5.2 mmol/L) are recommended

BUN, creatinine, glomerular filtration rate, and electrolytes

Description

- Assay of renal function and serum other chemistry
- Most laboratories now calculate estimated glomerular filtration rate using a formula based on serum creatinine and age, gender, race, height, and weight

Normal ranges

- BUN: 8 to 18 mg/dL (3.0-6.5 mmol/L)
- Creatinine: 0.6 to 1.2 mg/dL (50-110 μmol/L)
- Glomerular filtration rate: >60 mL/min/1.73 m^2
- Sodium: 135 to 147 mEq/L (135-147 mmol/L)
- Potassium: 3.5 to 5.0 mEq/L (3.5-5.0 mmol/L)
- Chloride: 95 to 105 mEq/L (95-105 mmol/L)

Comments

- Serial measurements of BUN, creatinine, and glomerular filtration rate may be used to monitor the patient's progress
- Renal function can decrease to a glomerular filtration rate of 50 mL/min before serum creatinine increases above the normal range
- The calculated glomerular filtration rate may be erroneously high or low in patients at the extremes of body mass, because the formula will underestimate glomerular filtration rate in very muscular patients and overestimate glomerular filtration rate in very small patients
- It is now recommended that estimated glomerular filtration rate be calculated in all patients to better assess renal function and to determine the stage of chronic kidney disease

Urinary albumin excretion

Description

- Measure of albumin in a spot urine collection (milligram albumin per gram creatinine) or 24-hour urine collection (milligram albumin per day)

Normal results

- Spot urine collection: <30 μg/mg creatinine
- 24-hour urine collection: <30 mg albumin/24 hours

Comments

- Can indicate whether there is tubular excretion of albumin, signifying the presence of the earliest signs of diabetic nephropathy
- Moderately increased albuminuria (formerly called 'microalbuminuria') is defined as a urinary albumin excretion of >30 μg/mg creatinine
- Serial measurements may be used to monitor the patient's progress
- 24-hour measurement can be cumbersome and prone to patient collection error

Urine dipstick testing for glucose and ketones

Description

- A clean-catch midstream urine specimen should be used if possible
- Dipstick testing can be used to confirm hyperglycemia in the absence of a glucometer, but results are unreliable
- Testing for ketones may confirm ketoacidosis in an ill patient with diabetes

Normal result

- Absence of glucose
- Absence or traces of ketones in a well patient

Comments

- Glycosuria indicates that the renal threshold for glucose has been exceeded and is highly suggestive of hyperglycemia

- Confirms ketonuria, which is a serious concern in patients with diabetes; however, note that ketonuria can be present in patients who have not eaten for an extended period of time
- Does not quantify blood glucose level

Differential diagnosis

Diabetes mellitus type 1

- Diabetes mellitus type 1 is a chronic metabolic disorder caused by β-cell destruction that leads to absolute insulin deficiency, hyperglycemia, and ketosis
- Features:
  - Sudden, acute onset of symptoms such as polyuria and polydipsia (whereas type 2 diabetes usually has a gradual onset and may present primarily with fatigue and nonspecific malaise)
  - Patients often present with ketoacidosis and dehydration
  - Significant weight loss despite increased appetite (may assist in diagnosis, as patients with type 2 diabetes are often overweight)
  - Fasting serum insulin and C-peptide levels are low or undetectable (whereas these levels are normal or elevated in patients with type 2 diabetes)
  - Circulating antibodies to glutamic acid decarboxylase, islet cells, and insulin are more likely to be present: more than 90% of patients with type 1 diabetes test positive for anti-insulin, anti–islet cell, anti–glutamic acid decarboxylase, anti–tyrosine phosphatase IA-2, and anti–tyrosine phosphatase IA-2β autoantibodies

Diabetes insipidus

- Diabetes insipidus is caused by impaired water resorption by the kidneys because of reduced antidiuretic hormone secretion from the posterior pituitary gland

(neurogenic) or impaired action of antidiuretic hormone on the kidney receptors (nephrogenic)

- Features:
  - Patients classically present with abrupt onset of polyuria, thirst, and compensatory polydipsia, which can be mistaken for diabetes mellitus
  - Plasma osmolality is usually high, and urine osmolality is reduced
  - Serum sodium levels may be high (as in patients with HHS and DKA)

Psychogenic polydipsia

- Psychogenic polydipsia is a functional disorder of compulsive, excessive water drinking
- Features:
  - Compulsive, excessive water drinking
  - Polyuria and polydipsia (may be confused with diabetes mellitus or diabetes insipidus)
  - Most common in middle-aged women with other functional problems
  - Nocturia/nocturnal polyuria is often absent
  - Lower and fluctuating plasma osmolality (265-280 mOsm/kg)
  - Blood glucose is normal
  - Hyponatremia is more likely
  - Can result in acquired nephrogenic diabetes insipidus
  - Prolonged deprivation of water (2-4 days) allows a return to normal

- Treatment involves appropriate management of underlying psychiatric issues

Stress hyperglycemia

- Stress hyperglycemia may be caused by any severe stress to the body (*eg*, severe burns, infection, surgery, myocardial infarction) and may represent underlying diabetes or predilection toward developing diabetes
- Features:
- Usually has a clear precipitating factor
- Often discovered when routine blood chemistry tests in an ill patient show an elevated blood glucose level
- Especially common in patients with hypertonic dehydration and those with elevated catecholamine levels
- Screening tests to rule out underlying diabetes may be done after the patient recovers from the precipitating illness
- Usually resolves spontaneously, requiring no specific treatment
- In the absence of rare hemoglobin abnormalities, HbA1c can be useful to confirm this diagnosis, as it is usually normal or low

Consultation

- Referral to an ophthalmologist is recommended for all patients with diabetes
- A medical nutritional therapist should be consulted to evaluate the patient's diet and make recommendations for achievement of glycemic control through dietary modification
- Patients should be referred to a diabetes educator if diabetes education is not provided by the physician or nursing staff

Treatment

Summary approach

Goals

Overall goals for the treatment of diabetes mellitus:

- Alleviate symptoms
- Enhance quality of life
- Minimize the development of long-term complications
- Reduce early mortality

To reduce the risk of complications and delay the rate of progression of complications, the goals of diabetes care should include:

- Maintenance of strict glycemic control
- Blood pressure control
- LDL lowering
- Prevention and treatment of complications of diabetes
- Lifestyle changes, such as smoking cessation, weight control, and dietary modification

According to the 2013 ADA guidelines, individualized goals are appropriate in management of patients with type 2 diabetes. These goals are based on factors that include:

- Duration of diabetes
- Age and life expectancy

- Comorbid conditions
- Known cardiovascular disease or advanced microvascular complications
- Hypoglycemia unawareness
- Individual patient considerations

Immediate action

- In patients with severely elevated serum glucose levels or impending DKA or HHS, initiate urgent insulin and fluid therapy in an inpatient setting
- In patients with hypoglycemia who are receiving insulin or sulfonylurea therapy:
  - Administer rapidly absorbed carbohydrate (*eg*, glucose tablets, glucose drink, orange juice, or cola) if the patient is alert and able to swallow without the risk of aspiration
  - Administer glucagon, 1 mg subcutaneously, if the patient is obtunded or unresponsive. This requires administration by a friend, relative, or emergency personnel. It is important to note that glucagon will only increase blood glucose for approximately 45 minutes, so additional treatment is needed
  - Consider administering 50% dextrose, 25 to 50 mL intravenously, for severe hypoglycemia when the patient is under medical care and venous access can be obtained
  - Monitor glucose level and patient status carefully following treatment in order to prevent further hypoglycemia, and change the patient's diabetes treatment regimen if warranted
  - Determine the cause of the hypoglycemic episode
  - Urgent admission to the hospital may be required

Summary of therapies

- Lifestyle modifications, including patient education , dietary modification , and a physical activity program , should be initiated immediately and continued and/or intensified throughout therapy
- Current guidelines now recommend that drug therapy be initiated in all patients as soon as the diagnosis of diabetes is established to prevent the deterioration of glycemic control
- Several classes of medications are available for the treatment of type 2 diabetes. The selection of an initial agent, and of subsequent additional or alternative medications thereafter, should depend on several factors, including the patient's HbA1c, age, weight, comorbidities, and risk for hypoglycemia
- Guidelines of the AACE aim for an HbA1c of up to 6.5%. The ADA, in concert with the European Association for the Study of Diabetes, has published guidelines that aim for an HbA1c of up to 7.0%. Both guidelines include the roles of newer therapies and address data from recent trials

ADA guidelines :

- In addition to lifestyle modification, initiate metformin in all patients immediately, provided there are no contraindications, to achieve (in most patients) a target HbA1c lower than 7.0%
- If the HbA1c target is not achieved within 3 months, consider two-drug therapy by adding one of the following with metformin: a sulfonylurea , a thiazolidinedione, a dipeptidyl peptidase–4 (DPP-4) inhibitor , a glucagon-like peptide-1 (GLP-1) receptor agonist , or an insulin (usually basal)
- If the HbA1c target is not achieved within an additional 3 months, consider three-drug therapy by adding one of the following to the regimen: a sulfonylurea, a thiazolidinedione , a DPP-4 inhibitor, a GLP-1 receptor agonist, or an insulin (usually basal)

- If combination therapy that includes basal insulin fails to achieve target levels of HbA1c after 3 to 6 months, proceed to more complex insulin therapy (*eg*, multiple daily doses) with one or two non-insulin agents
- Insulin is likely to be more effective than other agents as a third-line therapy when HbA1c is >9%
- Progression to complex insulin therapy from a two-drug regimen may be justified in patients with HbA1c >10%

AACE guidelines :

- Lifestyle modifications (*ie*, patient education, diet, and exercise) should be initiated at time of diagnosis and continued throughout therapy
- The target HbA1c goal should be ≤6.5% in healthy individuals without concurrent illness who are at low risk for hypoglycemia
- The target HbA1c goal should be >6.5% for patients with concurrent illness at high risk for hypoglycemia

The initial medication regimen depends on the patient's HbA1c. A suggested hierarchy of medication use is as follows:

- In patients with an HbA1c of 6.5% to 7.5%, initiate treatment with metformin
  - If metformin cannot be used, acceptable first-line alternatives include a GLP-1 receptor agonist, a DPP-4 inhibitor, or an α-glucosidase inhibitor (*eg,* acarbose)
  - Thiazolidinediones, sulfonylureas, and meglitinides may also be used, but these agents should be used with caution owing to the potential for weight gain, hypoglycemia, or other risks

- A sodium-glucose co-transporter 2 (SGLT2) inhibitor may also be used in monotherapy as an alternative to metformin, with the awareness that these agents do not have an extensive safety record

- If the HbA1c target is not achieved within 3 months, consider two-drug therapy with metformin plus one of the following: a GLP-1 receptor agonist; a DPP-4 inhibitor; colesevalam; an α-glucosidase inhibitor; or bromocriptine

- Alternative dual therapy could include metformin plus one of the following: a sulfonylurea/meglitinide, thiazolidinedione, or SGLT2 inhibitor

- Alternative dual therapy, if metformin is contraindicated or not well tolerated, could include any of the first-line alternatives to metformin (GLP-1 receptor agonist, a DPP-4 inhibitor, or an α-glucosidase inhibitor) in combination with a sulfonylurea/meglitinide, thiazolidinedione, or SGLT2 inhibitor

- If two-drug combination therapy fails to achieve target levels of HbA1c after another 3 months, a third drug may be safely added to enhance treatment efficiency if the HbA1C is <8.0%. If the HbA1C is >9% with two-drug combination therapy, the addition of insulin should be considered. In such cases, a single daily dose of basal insulin should be added to the drug regimen

- In patients with an HbA1c of 7.6% to 9.0%, initiate treatment with a dual therapy combination of metformin (or other first-line agent) plus a GLP-1 receptor agonist, DPP-4 inhibitor, colesevelam, α-glucosidase inhibitor, or bromocriptine

- Alternative dual therapy is metformin plus a sulfonylurea/meglitinide, thiazolidinedione, or SGLT2 inhibitor

- If two-drug combination therapy fails to achieve target levels of HbA1c after another 3 months, a third drug may be safely added to enhance treatment efficiency if the HbA1C is <8%. If the HbA1C is >8% with two-drug combination therapy, the

addition of insulin should be considered. In such cases, a single daily dose of basal insulin should be added to the drug regimen

- In patients with an entry HbA1c of >9%, asymptomatic patients not currently undergoing treatment for diabetes may be managed with dual or triple non-insulin medications
- Symptomatic patients not currently undergoing treatment for diabetes with an entry HbA1c of >9% should be managed with insulin plus other agents (such as pramlintide) as necessary

Efficacy of therapies

- Type 2 diabetes is characterized by progressive β-cell failure; consequently, in the absence of major lifestyle changes, increasing doses of oral agents and eventually insulin therapy are often required
- Most patients cannot be sufficiently managed with lifestyle modification alone and will require oral hypoglycemic medication or insulin

Medications

Metformin

Indication

- Metformin is used for initial treatment of diabetes mellitus type 2

Dose information

- Immediate-release formulation: 500 mg orally, twice a day initially; increase by 500 mg/d at weekly intervals
- Maintenance: 500 to 850 mg orally two or three times a day
- Maximum: 2,000 mg/d

- Slow-release formulation can be given once daily

Major contraindications

- Diabetic ketoacidosis
- Metabolic acidosis
- Radiographic contrast administration
- Renal failure

Comments

- Metformin is the initial drug of choice for most patients with type 2 diabetes provided that renal function is satisfactory
- Dose selection in the elderly should be cautious, usually starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function and concomitant diseases and medications

Evidence

- A systematic review of 29 trials involving over 5,000 patients compared metformin monotherapy versus placebo and a variety of other agents and found that metformin improved glycemic control, weight, dyslipidemia, and diastolic blood pressure. [13] *Level of evidence: 1*
- Metformin has the clinical benefit of being weight neutral, but it is associated with some harms, including the rare but serious effect of lactic acidosis. A systematic review of 347 RCTs incorporating the experience of about 120,000 patients, however, found no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis as compared to other oral hypoglycemic agents evaluated in RCTs. [14] *Level of evidence: 1*

- An RCT of 451 patients found that patients with type 2 diabetes taking metformin regularly experienced reductions in HbA1c versus those receiving placebo. [15] *Level of evidence: 1*
- Another RCT, this one including 96 patients, found both acarbose and metformin equally effective in comparison to placebo with respect to a reduction in HbA1c. [16] *Level of evidence: 3*

References

Sulfonylureas

Indication

- Sulfonylureas are an alternative first-line (ADA) or second-line (AACE) treatment agent in most patients with diabetes mellitus type 2

Dose information

- Note that the glucose-lowering effect of sulfonylureas tends to be maximal at roughly half of the maximum recommended dose; higher doses increase the risk of adverse effects

Glimepiride :

- 1 to 2 mg/d orally, initially; increase to a maintenance dose of 1 to 4 mg/d
- Maximum: 8 mg/d

Glipizide :

- 2.5 to 5.0 mg orally, initially; increase by 2.5- to 5-mg increments every 2 to 3 days
- Maximum: 40 mg/d

Glyburide :

- 2.5 to 5.0 mg/d orally, initially
- Maximum: 20 mg/d

Major contraindications

- DKA
- Type 1 diabetes mellitus (glyburide)

Comments

- Sulfonylureas are effective in lowering HbA1c but lack durability, are associated with modest weight gain, and have a high risk of serious hypoglycemia
- Dose selection in the elderly should be cautious, usually starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function and concomitant diseases and medications
- Glyburide in particular has been associated with an increased risk of severe hypoglycemia in elderly patients. Glipizide has a shorter duration of action than either glyburide or glimepiride and is generally a safer choice for elderly patients
- Adverse effects include skin rashes and respiratory infections
- The ability of these agents to effectively lower blood sugar may decrease over time (secondary failure)

Evidence

- A systematic review found glyburide was among several oral anti-glycemic agents effective at reducing serum HbA1c. An average reduction of 1% to 2% for the serum marker was noted. Studies (63) were included in the analysis if they had a study period of at least 3 months, if each group contained at least 10 subjects at the study's conclusion, and if HbA1c was reported. When multiple dosages of a drug were tested, the results of the highest approved dosage were used. In placebo-controlled

trials, HbA1c data are presented as the difference between the change in treated versus placebo subjects. [17] *Level of evidence: 1*

- In the UK Prospective Diabetes Study, 3,867 patients with newly diagnosed type 2 diabetes were randomly assigned to either intensive glycemic control with a sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin or to conventional glycemic control using diet. Among patients assigned to dietary modification, drug therapy was added only if hyperglycemic symptoms were present or if the fasting plasma glucose level increased to higher than 270 mg/dL (15 mmol/L). No significant differences in the rates of myocardial infarction or stroke over 5 years were found between groups, but intensive glycemic control was associated with a significant reduction in microvascular complications, including the need for retinal photocoagulation, compared to conventional glycemic control. In addition, treatment with sulfonylurea significantly reduced HbA1c over 10 years compared to dietary modification alone. Patients assigned to intensive therapy, however, experienced more hypoglycemic episodes and more weight gain compared to those assigned to conventional therapy. [18] *Level of evidence: 1*

- An RCT of 70 patients found that once-daily glimepiride plus diet/exercise was effective in Mexican Americans with type 2 diabetes whose disease was inadequately controlled with diet and exercise alone. [19] *Level of evidence: 3*

- Another RCT involving 569 patients with type 2 diabetes mellitus reported a similar reduction in HbA1c as well as a significant improvement in quality of life after 12 weeks of treatment with glipizide versus placebo. [20] *Level of evidence: 1*

References

Dipeptidyl peptidase–4 inhibitors

Indication

- DPP-4 inhibitors are used as monotherapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes; they may be used in

combination with metformin or athiazolidinedioneswhen monotherapy with any of these agents is inadequate

Dose information

Sitagliptin :

- 100 mg orally, once a day

Saxagliptin :

- 2.5 to 5.0 mg orally, once a day

Linagliptin :

- 5 mg orally, once daily

Alogliptin :

- 25 mg orally, once daily

Major contraindications

- Angioedema

Comments

- DPP-4 inhibitors have moderate HbA1c-lowering effects, are weight neutral, and are relatively well tolerated
- Hypersensitivity reactions including urticaria, angioedema, exfoliative dermatitis, or bronchospasm have been observed with these medications
- Dosages of sitagliptin, saxagliptin, and alogliptin should be reduced for patients with moderate renal impairment. Linagliptin does not require dosage adjustment for renal dysfunction

- Case reports of acute pancreatitis have arisen in a set of individuals treated with GLP-1 receptor agonists or DPP-4 inhibitors. The exact nature of the association is uncertain and currently under investigation by the U.S. Food and Drug Administration (FDA)

Sodium-glucose co-transporter 2 inhibitor

Indication

- SGLT2 inhibitors are indicated as monotherapy for the treatment of type 2 diabetes as an adjunct to diet and exercise

Dose information

- Canagliflozin : 100 to 300 mg orally, once daily

Major contraindications

- Dialysis
- Renal failure

Comments

- Inhibition of SGLT2 reduces resorption of glucose in the kidney, resulting in increased urinary glucose excretion, with a consequent lowering of serum glucose levels
- Data available from clinical trials indicate that canagliflozin has moderate HbA1c-lowering effects, promotes weight loss, and reduces systolic blood pressure, but it also slightly increases LDL cholesterol levels
- Most common side effects are vaginal yeast infection (vulvovaginal candidiasis) and urinary tract infection. Orthostatic hypotension may occur due to the medication's effect on intravascular volume

Evidence

- A randomized, double-blind, placebo-controlled trial of 584 adult subjects with type 2 diabetes who were inadequately controlled with diet and exercise received canagliflozin 100 or 300 mg or placebo once daily. At 26 weeks, patients who received canagliflozin 100 and 300 mg had significantly reduced HbA1c as compared to those who received placebo (−0.77%, −1.03%, and 0.14%, respectively;*P*< .001 for both). Both doses of canagliflozin significantly decreased body weight (*P*< .001 for both). The overall incidences of adverse events were modestly higher with canagliflozin versus placebo. The incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related effects were higher with canagliflozin, although these led to few discontinuations. The incidence of hypoglycemia across all groups was low. The authors concluded that treatment with canagliflozin improves glycemic control, reduces body weight, and is generally well tolerated in adults with type 2 diabetes whose glycemic control is suboptimal with diet and exercise alone. [21] *Level of evidence: 1*

References

Glucagon-like peptide-1 receptor agonists

Indication

- Liraglutide is used in the treatment of type 2 diabetes in combination with diet and exercise but is not recommended as first-line therapy
- Exenatide is similarly used as a second-line therapy in combination with diet and exercise and can be given as monotherapy or in combination with other drugs used to treat type 2 diabetes

Dose information

- Liraglutide : 1.2 to 1.8 mg/d subcutaneously after initial titration of 0.6 mg/d over 1 week

- Exenatide : 5 µg subcutaneously twice a day, initially; increase to 10 µg twice a day after 1 month
- Exenatide XR : 2 mg subcutaneously once weekly

Major contraindications

- Angioedema (liraglutide)
- Medullary thyroid carcinoma
- Multiple endocrine neoplasia syndrome type 2
- Thyroid cancer

Comments

- GLP-1 agonists are an injectable therapy that have potent HbA1c-lowering effects, promote weight loss, and have low risk for hypoglycemia
- Drugs of this class act in a glucose-dependent manner, meaning they will stimulate insulin secretion only when blood glucose levels are higher than normal; consequently there is a low risk for hypoglycemia unless used with other hypoglycemic agents. Under those circumstances, it may be necessary to adjust the dose of concurrent medications to avoid hypoglycemia, especially in elderly patients
- Case reports of acute pancreatitis have arisen in a set of individuals treated with GLP-1 receptor agonists or DPP-4 inhibitors. The exact nature of the association is uncertain and currently under investigation by the FDA
- History of pancreatitis is an additional contraindication, due to recent reports showing an association between GLP-1–based agents and pancreatitis

Evidence

- A multicenter open-label RCT compared the efficacy and safety of the addition of once-daily liraglutide versus twice-daily exenatide in 464 adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulfonylurea, or both. After 26 weeks, the group assigned to receive liraglutide experienced a greater reduction in HbA1c as compared to exenatide (–1.12%*vs*–0.79%; estimated treatment difference –0.33; 95% CI, –0.47 to –0.18;*P*< .0001), primarily as a result of improvements in fasting blood glucose levels. Both drugs promoted similar weight losses and were generally well tolerated, but nausea was less persistent and minor hypoglycemia less frequent with liraglutide than with exenatide. Thus, liraglutide once a day provided significantly greater improvements in glycemic control than did exenatide twice a day and was generally better tolerated. [22] *Level of evidence: 2*

- An open-label noninferiority study comparing once-weekly administration of exenatide versus twice-daily administration of exenatide in 295 patients with type 2 diabetes showed that once-weekly administration of a long-acting preparation resulted in better glycemic control and similar reduction in weight with no increased risk of hypoglycemia. [23] *Level of evidence: 2*

- A multicenter randomized open-label trial compared the efficacy and safety of exenatide once weekly with liraglutide once daily in patients with type 2 diabetes. In the trial, 911 patients with uncontrolled type 2 diabetes treated with lifestyle modification and oral diabetes drugs were randomly assigned to receive once-daily liraglutide or once-weekly exenatide. Patients treated with liraglutide experienced a greater reduction in HbA1c compared to those treated with weekly exenatide (–1.48%*vs*–1.28% for a treatment difference 0.21%; 95% CI, 0.08–0.33). Gastrointestinal adverse events were the most common, and these occurred less frequently in the exenatide group and with decreasing incidence over time in both groups. [24] *Level of evidence: 2*

- An RCT examined the efficacy of twice-daily exenatide injections in 261 adults with type 2 diabetes who were already receiving insulin glargine alone or in combination with metformin or pioglitazone. After 30 weeks of therapy, the group treated with

exenatide showed a greater decrease in HbA1c (–1.74%*vs*–1.04%; between-group difference –0.69%; 95% CI, –0.93% to –0.46%;*P*< .001). Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo (between-group difference –2.7 kg; 95% CI, –3.7 to –1.7). Average increases in insulin dosage with exenatide and placebo were 13 U/d and 20 U/d. The estimated rate of minor hypoglycemia was similar between groups. Adverse gastrointestinal effects were higher with exenatide than with placebo. Thus, the addition of twice-daily exenatide injections improved glycemic control without increasing hypoglycemia or weight gain in participants with uncontrolled type 2 diabetes who were already receiving insulin glargine. [25] *Level of evidence: 2*

- A population-based case-control study was conducted to determine whether GLP-1–based medications such as exenatide and sitagliptin are associated with an increased risk of acute pancreatitis. A large U.S. administrative database identified 1,269 adults with type 2 diabetes who were hospitalized with acute pancreatitis. These cases were matched against 1,269 control subjects for patient characteristics such as age, sex, enrollment pattern, and diabetes complications. After adjusting for available confounders and metformin use, current use of GLP-1–based therapies within 30 days (adjusted odds ratio, 2.24 [95% CI, 1.36-3.68]) and recent use past 30 days and less than 2 years (2.01 [95% CI, 1.37-3.18]) were associated with significantly increased odds of acute pancreatitis relative to the odds in nonusers. [26] *Level of evidence: 2*

References

Pramlintide

Indication

- Pramlintide is to be used as an adjunct to mealtime insulin therapy in patients who have not achieved optimal glucose control

Dose information

- 60 μg subcutaneously initially, three times a day or before each major meal; increase to 120 μg before each major meal after 3 to 7 days

Major contraindications

- Cresol hypersensitivity
- Gastroparesis
- Hypoglycemia

Comments

- Pramlintide is a synthetic analog of human amylin, a naturally occurring hormone synthesized by pancreatic β-cells that contributes to glucose control during the postprandial period
- Coadministration with insulin may cause severe hypoglycemia; when pramlintide is initiated insulin doses should be reduced and blood glucose levels monitored closely
- The addition of pramlintide as a therapeutic option for type 2 diabetes is most useful as a means to avert weight gain in patients using insulin

Evidence

- An open-label multicenter study was performed to compare the efficacy and safety of adding mealtime pramlintide or rapid-acting insulin analogs to basal insulin for patients with inadequately controlled type 2 diabetes. In the study, 113 patients with uncontrolled type 2 diabetes who were already using basal insulin and other oral diabetes medications were randomized to receive prandial pramlintide or rapid-acting insulin analogs. The primary end point was the proportion of patients achieving HbA1c ≤7.0% without weight gain or severe hypoglycemia. After 24 weeks, more patients treated with pramlintide than with rapid-acting insulin analogs achieved an HbA1c without hypoglycemia (30%*vs*11%,*P*= .018) with a similar dose of basal insulin. Addition of pramlintide did not increase body weight, whereas the

addition of rapid-acting insulin analogs did yield weight gain (0 ± 0.7 kg*vs*+4.7 ± 0.7 kg,*P*< .0001). [27] *Level of evidence: 2*

References

Insulins

Indication

- Insulins are indicated for management of diabetes mellitus as an adjunct to oral or injectable glucose-lowering agents or, as in cases of refractory disease, as monotherapy for glycemic control

Dose information

- All weight-based dosing recommendations and other insulin calculations listed below should be considered as approximations only and require adjustments based on patient-specific characteristics

Basal and basal/bolus dosing regimen:

- By body weight: 0.1 to 0.2 U/kg body weight of basal insulin (NPH insulin , insulin glargine , or insulin detemir) subcutaneously is a typical initial single-dose therapy; greater degrees of hyperglycemia may require amounts of 0.3 to 0.4 U/kg body weight
- A long-acting basal insulin, such as insulin glargine or insulin detemir, is often effective as a single daily dose; some patients may require two doses per day
- Basal insulin can also be administered as a continuous subcutaneous infusion using an insulin pump
- Pre-meal bolus doses of rapid-acting insulin (insulin lispro , insulin aspart , insulin glulisine) or regular insulin are added to provide postprandial glucose control if necessary; rapid-acting insulins are generally preferred

Twice-daily regimen using premixed insulin:

- 0.2 to 1.5 U/kg/d subcutaneously, given in two equally divided doses
- Soluble insulin and NPH insulin are administered twice daily (before breakfast and before dinner) as a premixed dose of 25% soluble insulin and 75% NPH insulin, 30% soluble insulin and 70% NPH insulin, or 50% soluble insulin and 50% NPH insulin
- Generally not recommended because of limited efficacy and flexibility; however, it is convenient, may be less expensive than more complex regimens, and can be effective in some patients (*ie*, patients with HbA1c of ≥9%)
- Similar regimens using intermediate- and short-acting insulin that is not premixed can be used

Alternative three-injection regimen:

- Usual starting dose is 0.2 to 0.4 U/kg/d subcutaneously
- Administration of doses of 40% to 45% NPH insulin and 15% to 20% soluble insulin before breakfast, a dose of 15% to 20% soluble insulin before dinner, and a dose of 20% NPH insulin at bedtime
- Premixed insulins are not recommended, except when simplicity or cost issues are paramount

Major contraindications

- Hypoglycemia (insulin lispro, insulin aspart, insulin glulisine, regular insulin, isophane insulin [NPH])

Comments

- Insulin can be initiated in patients with type 2 diabetes using a single dose of long-acting insulin of 0.1 to 0.2 U/kg per day. Basal insulin, with or without oral agents,

can be effective for some time. If or when postprandial hyperglycemia becomes uncontrolled, prandial insulin may be added at that time

- Dose selection in the elderly should be cautious, usually starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function and concomitant diseases and medications
- Available in rapid-, intermediate-, and long-acting formulations or a combination of these; supplied in a variety of forms in solution or suspension
- The newer long-acting insulins glargine and detemir are equally effective to NPH as basal insulins for their glucose-lowering abilities. Their main advantage is a reduced risk of symptomatic overall and nocturnal hypoglycemia, at the disadvantage of increased cost
- A possible association between treatment with insulin glargine and an increased risk of cancer has been raised based upon data from a few retrospective population-based studies. The results of the ORIGIN trial, a randomized trial comparing the addition of insulin glargine to standard care in patients with cardiovascular disease and either type 2 diabetes or prediabetes, however, found that there was no increase in cancer risk after 6 years
- Insulin degludec is a long-acting, once-daily basal insulin with a long (>40 hours) duration of action that has been approved for use in Europe. Its main advantage appears to be a reduced risk of nocturnal hypoglycemia but maintains similar efficacy to that of insulin glargine. The FDA denied approval of insulin degludec due to lack of acceptable cardiovascular safety data; studies are now ongoing to address the risk of adverse cardiovascular events

Evidence

Efficacy of insulin in lieu of oral hypoglycemic agents in patients with moderately or poorly controlled type 2 diabetes:

- An RCT of 172 patients who were poorly controlled on an oral hypoglycemic agent (maximum dose of glyburide) established that mean HbA1c and fasting glucose levels were consistently reduced to target therapeutic levels with insulin treatment. Furthermore, treatment satisfaction was greater in the insulin group, despite a higher rate of hypoglycemia compared to oral therapy. [28] *Level of evidence: 2*

- Another RCT in 38 patients, most of whom were switched from an oral hypoglycemic agent to insulin, found similar reductions in HbA1c, but at the cost of weight gain and occasional hypoglycemic episodes during therapy. [29] *Level of evidence: 3*

- An RCT comparing intensive insulin therapy versus oral hypoglycemic agents in 382 patients with newly diagnosed type 2 diabetes showed that patients receiving early intensive insulin therapy experience more frequent recovery of β-cell function and higher remission rates than those on oral hypoglycemic agents. [30] *Level of evidence: 1*

  Glycemic control in patients on insulin or a sulfonylurea versus dietary modification alone:

- In the UK Prospective Diabetes Study, 3,867 patients with newly diagnosed type 2 diabetes were randomly assigned to either intensive glycemic control with a sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin or to conventional glycemic control using diet. No significant differences in HbA1c were found between patients receiving insulin and those receiving a sulfonylurea; however, both insulin and the sulfonylurea resulted in a significant reduction in HbA1c as compared to dietary modification alone. No significant differences in the rates of myocardial infarction or stroke over 5 years were found between groups, but intensive glycemic control was associated with a significant reduction in microvascular complications, including the need for retinal photocoagulation, compared to conventional glycemic control. Patients assigned to intensive therapy, however, experienced more

hypoglycemic episodes and more weight gain compared to those assigned to conventional therapy. [18] *Level of evidence: 1*

- A longitudinal study conducted over 6 years of 5,535 patients was unable to find any difference in quality-of-life scores between the patients receiving treatment with insulin, a sulfonylurea, or dietary modification alone in the UK Prospective Diabetes Study. [31] *Level of evidence: 2*

Effect of combination therapy with insulin and oral hypoglycemic agents:

- A systematic review of 20 RCTs and 1,811 patients found that bedtime administration of NPH insulin in combination with oral hypoglycemic agents as a daily regimen in patients with type 2 diabetes resulted in glycemic control comparable to that of insulin monotherapy (twice-daily or multiple daily injections) and was also associated with less weight gain if metformin was used. [32] *Level of evidence: 1*

Newer long-acting insulin analogs versus NPH insulin:

- A systematic review of 8 RCTs including 2,293 patients compared long-acting insulin analogs (glargine or detemir) versus NPH insulin in patients with type 2 diabetes and concluded that the only benefit of long-acting insulins over NPH insulin was a significant reduction in the incidence of nocturnal hypoglycemia. There were no differences in mortality, morbidity, or quality-of-life scores. [33] *Level of evidence: 1*

Long-acting insulin analogs versus multiple-dose short-acting insulin analogs:

- An open RCT comparing once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in 418 patients with type 2 diabetes already on oral hypoglycemic agents found that although prandial insulin lispro resulted in better postprandial blood glucose levels, once-daily basal insulin glargine was equally

effective in lowering HbA1c and resulted in less hypoglycemia. [34] *Level of evidence: 1*

- An open-label multicenter RCT was performed to assess the risks and benefits of the addition of specific insulin regimens to oral therapy in patients with type 2 diabetes mellitus. In the study, 708 patients with type 2 diabetes and suboptimal glycemic control on metformin/sulfonylurea combination therapy were randomly assigned to receive one of three insulin regimens: (1) biphasic insulin aspart twice daily, (2) prandial insulin aspart three times daily, or (3) basal insulin detemir once daily. After 1 year, HbA1c levels were similar among all the groups; however, fewer patients had a level of 6.5% or less in the biphasic group (31.9%) than in the prandial group (44.7%,*P*= .006) or in the basal group (43.2%,*P*= .03). Median rates of hypoglycemia per patient per year were lowest in the basal group, higher in the biphasic group, and highest in the prandial group (*P*< .001 for the overall comparison). Weight gain was greatest in the prandial group. [35] *Level of evidence: 2*

Long-acting insulin analogs glargine versus detemir:

- A multicenter RCT was performed to compare the efficacy and safety of once-daily insulin initiation using insulin detemir versus insulin glargine when added to existing metformin therapy in patients with type 2 diabetes. The trial involved 457 insulin-naïve adults with type 2 diabetes with starting HbA1c 7% to 9%, to which either detemir or glargine was added to current metformin therapy and titrated to a target fasting plasma glucose ≤90 mg/dL. After 26 weeks, the HbA1c decreased with detemir and glargine by 0.48 and 0.74 percentage points, respectively (estimated between-treatment difference, 0.30; 95% CI, 0.14-0.46). The proportions of patients reaching HbA1c ≤ 7% at 26 weeks were 38% and 53% (*P* = .026) with detemir and glargine, respectively. Hypoglycemia, which was uncommon in both groups, was observed less frequently with detemir than glargine. Weight decreased with detemir (−0.49 kg) and increased with glargine (+1.0 kg, 95% CI for difference, −2.17 to −0.89 kg). Thus, both detemir and glargine, when added to metformin therapy,

improved glycemic control, with glargine providing greater reductions in HbA1c and detemir promoting less weight gain and hypoglycemia. [36] *Level of evidence: 2*

Effect of basal insulin glargine on cardiovascular outcomes and cancer:

- An RCT was performed to determine whether the use of sufficient basal insulin to normalize fasting plasma glucose levels reduces cardiovascular events. The trial randomized 12,537 people with cardiovascular risk factors plus prediabetes or type 2 diabetes to receive insulin glargine or standard care and to receive omega-3 fatty acids or placebo, using a two-by-two factorial design. The two coprimary outcomes were: (1) nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes; and (2) a composite of these events plus revascularization or hospitalization for heart failure. After a median follow-up of 6.2 years, there was no difference in the rates of incident cardiovascular outcomes in the insulin-glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first coprimary outcome (hazard ratio, 1.02; 95% CI, 0.94-1.11;*P*= .63) and 5.52 and 5.28 per 100 person-years, respectively, for the second coprimary outcome (hazard ratio, 1.04; 95% CI, 0.97-1.11;*P*= .27). Thus, therapy with basal insulin glargine for more than 6 years had a neutral effect on cardiovascular outcomes and cancers, maintained near-normal glycemic control, and slowed progression of dysglycemia but also increased hypoglycemia and modestly increased weight. [37] *Level of evidence: 1*

Subcutaneous continuous insulin infusion versus multiple insulin injections:

- An RCT comparing continuous infusion of insulin aspart versus multiple injections of basal NPH insulin and bolus insulin aspart was unable to find any significant difference in HbA1c after 24 weeks of therapy in 132 patients; quality of life was not assessed. [38] *Level of evidence: 1*

References

Thiazolidinediones

Indication

- Thiazolidinediones can be used as adjunctive treatment of diabetes mellitus, often in combination with metformin or other hypoglycemic agents

Dose information

Pioglitazone :

- 15 to 30 mg/d orally, initially
- Maximum: 45 mg/d

Major contraindications

- Acute heart failure
- Heart failure

Comments

- The ADA currently considers thiazolidinediones as a tier 2 option, with pioglitazone the preferred drug. Rosiglitazone is not recommended because of inconclusive evidence regarding cardiovascular risk. It is only available to patients by prescription through physicians enrolled in a limited access program
- Dose selection in the elderly should be cautious, usually starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function and concomitant diseases and medications
- An increased risk of bladder cancer has been observed among patients with the longest duration and highest cumulative dose exposure to pioglitazone. The increased risk reached statistical significance after 24 months of exposure to pioglitazone

- The rate of bone fractures in women taking pioglitazone is increased compared to women taking a control (placebo or other antidiabetic agent)
- Patients with class III or IV heart failure should not be prescribed thiazolidinediones as this class of medication is associated with worsening the condition

Evidence

Pioglitazone may not share the adverse cardiovascular effects associated with rosiglitazone.

- A systematic review of 22 RCTs and 6,200 patients concluded that there was no evidence that treatment with pioglitazone resulted in improved mortality, morbidity, adverse effects, and health-related quality of life in patients with type 2 diabetes. [39] *Level of evidence: 1*

  Rosiglitazone appears to delay the progression to type 2 diabetes in high-risk patients compared to placebo but has uncertain long-term cardiovascular effects, which has generated widespread controversy over the safety of its use.

- A meta-analysis of 42 RCTs and 28,000 patients published in 2007 found that patients with type 2 diabetes receiving rosiglitazone had a significantly increased risk of myocardial infarction compared to control subjects. [40] *Level of evidence: 2*
- A systematic review of 18 RCTs involving 3,888 patients showed no difference in lowering of HbA1c with rosiglitazone compared to other drugs, and use of rosiglitazone was associated with increased edema, increased cardiovascular risk, and increased fracture rates among women. [41] *Level of evidence: 1*
- An RCT with over 5,000 patients found that rosiglitazone resulted in a 60% decrease in progression to diabetes among patients with impaired fasting glucose, impaired glucose tolerance, or both, and no previous cardiovascular disease at 3-year follow-up compared to placebo. Cardiovascular event rates were similar between groups,

although there was a small but significant increase in the heart failure rate among patients receiving rosiglitazone. [42] *Level of evidence: 1*

- A subsequent RCT with 4,447 patients confirmed that the addition of rosiglitazone to metformin or a sulfonylurea in patients with type 2 diabetes increased the risk of heart failure and the rate of fractures among women. There was no increase, however, in the risk of overall cardiovascular morbidity or mortality compared with other antidiabetic drugs. [43] *Level of evidence: 1*

Thiazolidinediones can be used in combination with other oral therapies:

- A multicenter, double-blind RCT of 639 patients comparing the addition of pioglitazone to a sulfonylurea versus metformin plus a sulfonylurea in patients with poorly controlled type 2 diabetes found that both regimens resulted in equivalent improvements in glycemic control over 1 year. The pioglitazone-containing regimen reduced the urinary albumin-to-creatinine ratio more than the metformin-containing regimen and also resulted in a significantly greater improvement in triglyceride and HDL cholesterol levels. The pioglitazone combination resulted in a small increase in LDL cholesterol levels, however, whereas the metformin combination resulted in a significant reduction in LDL cholesterol levels. [44] *Level of evidence: 2*

References

Acarbose

Indication

- Acarbose is used for the treatment of type 2 diabetes mellitus in patients not controlled by diet alone; it may be used as monotherapy or in combination with a sulfonylurea, metformin, or insulin

Dose information

- 25 mg orally three times a day; increase after 6 to 8 weeks to 50 to 100 mg three times a day

Major contraindications

- DKA
- Gastrointestinal disease
- Gastrointestinal obstruction
- Ileus
- Inflammatory bowel disease

Comments

- Dose selection in the elderly should be cautious, usually starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function and concomitant diseases and medications

Evidence

- A systematic review of 5 RCTs including 2,036 patients evaluated α-glucosidase inhibitors for type 2 diabetes and found that acarbose had a clear effect on glycemic control compared to placebo, but there were not enough data to establish its effect on morbidity or mortality. The review also found that patients with type 2 diabetes receiving acarbose experienced more adverse effects than those receiving a sulfonylurea. [5] *Level of evidence: 1*

References

Meglitinides

Indication

- Meglitinides are an alternative first-line treatment agent in most patients with diabetes mellitus type 2

Dose information

Nateglinide :

- 120 mg orally, three times a day

Repaglinide :

- 0.5 mg orally, three times a day initially; increase up to 4 mg three to four times a day
- Maximum: 16 mg/d

Major contraindications

- DKA
- Type 1 diabetes mellitus

Comments

- Dose selection in the elderly should be cautious, usually starting at the low end of the dosing range. This reflects the greater frequency of decreased hepatic, renal, or cardiac function and concomitant diseases and medications

Evidence

- A systematic review of 11 RCTs and 3,781 patients comparing meglitinides versus placebo found that repaglinide resulted in reductions in HbA1c of 0.1% to 2.1%, an effect similar to that of metformin, and nateglinide resulted in reductions in HbA1c of between 0.2% and 0.6%, an effect similar or slightly less marked than that of metformin. Meglitinides were associated with greater weight gain and frequency of hypoglycemic episodes than metformin, but diarrhea was less likely. Evidence for

long-term outcomes, including mortality, is limited at present. [45] *Level of evidence: 1*

- An RCT of 9,306 patients examined the impact of treatment with nateglinide on cardiovascular events over a period of 6.5 years and found no significant difference in patients treated with the medication and those receiving placebo controls. The study also failed to show any benefit in preventing diabetes among the participants who received nateglinide versus those in the control arm. Nateglinide did, however, increase the chance of hypoglycemia. [46] *Level of evidence: 1*

References

Non-drug treatments

Patient education

- Diabetes education is beneficial in initiating and continuing effective self-care, helps to maintain effective self-management in the presence of new challenges and changes in treatment, facilitates improvement of glycemic control, and aids in the prevention and management of diabetes-associated complications
- Education regarding treatment, self-management, and potential complications of type 2 diabetes is vital; the ADA's National Standards for Diabetes Self-Management Education should be followed
- All patients with type 2 diabetes should receive comprehensive self-management education at or shortly after diagnosis. It is essential that patients with diabetes assume an active role in their care within a collaborative and integrated team approach. An individualized management plan should be formulated in collaboration with the patient and family, the physician, and other members of the health care team. This plan should include diabetes self-management education as an integral component of care
- Diabetes self-management education programs usually involve a diabetes nurse and a dietitian specially trained in diabetes education and should include training in self-

monitoring of blood glucose (SMBG), ensuring that the patient understands the technique and interpretation of results

- Patients should be taught how to use blood glucose data to adjust food intake, exercise, or drug therapy to achieve specific glycemic goals
- Frequency and timing of SMBG should address the needs of the patient and be sufficient to facilitate achievement of glycemic goals
- SMBG should occur regularly during periods of acute illness or when symptoms of hyperglycemia or hypoglycemia occur in all patients with type 2 diabetes, regardless of their therapy
- Most patients on multiple-dose insulin or insulin pump therapy may need to perform SMBG several times per day, including before meals, occasionally postprandially, at bedtime, before exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and before critical tasks such as driving
- The optimal frequency of SMBG for patients on nonintensive regimens, such as those with type 2 diabetes on basal insulin, is not known. When prescribed as part of a broader educational context, SMBG results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or non-insulin therapies
- Psychosocial issues also should be addressed, as emotional well-being is associated with positive diabetes outcomes

Evidence

- A systematic review of 14 trials assessing the effect of group-based education programs for 1,532 patients with type 2 diabetes found that group-based education was associated with improved fasting blood glucose levels and HbA1c; improved

diabetes knowledge; and reduced systolic blood pressure, body weight, and need for diabetes medication. [47] *Level of evidence: 1*

- A systematic review including nine studies and the experiences of 1,359 patients showed that individual education on glycemic control is better than usual care in patients with an HbA1c higher than 8%, but there was no difference in outcomes such as weight or blood pressure between patients receiving individual education versus those receiving group education after 12 to 18 months. [48] *Level of evidence: 1*

- A systematic review of 11 trials in 1,603 patients showed that culturally appropriate diabetes education improved knowledge at 3, 6, and 12 months compared to usual care. Other outcome measures, including lipid levels, blood pressure, quality of life, and behavioral indices, did not differ between the intervention and control groups. [49] *Level of evidence: 1*

- A systematic review of 21 studies (4,135 patients) of interventions to improve adherence to treatment recommendations in patients with diabetes mellitus showed that interventions by nurses and pharmacists, home aids, and diabetes education had a small beneficial effect on a variety of outcomes, including HbA1c. There were no data on mortality, morbidity, or quality of life. [50] *Level of evidence: 1*

- An RCT inclusive of 453 patients compared a self-monitoring program alone or combined with instruction versus usual care and found little difference in HbA1c as measured at 12 months. [51] *Level of evidence: 1*

- An RCT evaluating the impact of a structured group education program on a variety of medical and lifestyle measures in 827 patients with type 2 diabetes found that the intervention led to greater improvements in weight loss and smoking cessation but no difference in HbA1c after 12 months. [52] *Level of evidence: 1*

- An RCT showed that an individualized electronic decision support and reminder system had a beneficial effect on both process outcomes and clinical outcomes, such

as blood pressure and HbA1c, in 511 patients with type 2 diabetes after 6 months. [53] *Level of evidence: 1*

- A meta-analysis was performed to assess the effectiveness of SMBG levels in people with non-insulin–treated type 2 diabetes compared with clinical management without self monitoring and to explore the effects in specific patient groups. The analysis included 6 randomized trials with a total of 2,552 patients with type 2 diabetes. A mean reduction in HbA1c level of 0.25% or –2.7 mmol/mol (95% CI, –3.9 to –1.6) was observed for those using SMBG levels compared with no self-monitoring at 6 months. The difference in HbA1c levels between groups was consistent across age, baseline HbA1c level, sex, and duration of diabetes. [54] *Level of evidence: 1*

- A systematic review and meta-analysis was performed to examine the effectiveness of SMBG as a tool in the self-management for patients with type 2 diabetes who are not using insulin. The review identified 12 RCTs with a total of 3,259 patients with type 2 diabetes. Meta-analysis of studies including patients with a diabetes duration of 1 year or more showed a statistically significant SMBG decrease in HbA1c at up to 6 months follow-up (–0.3; 95% CI, –0.4 to –0.1), yet an overall statistically non-significant SMBG–induced decrease was seen at 12-month follow-up (–0.1; 95% CI, –0.3 to 0.04). Examination of the effect of SMBG on well-being and quality of life showed no effect on patient satisfaction, general well-being, or general health-related quality of life. The authors concluded that when diabetes duration is over 1 year, the overall effect of SMBG on glycemic control in patients with type 2 diabetes who are not using insulin is small up to 6 months after initiation and subsides after 12 months. [55] *Level of evidence: 1*

References

Dietary modification

Description

General ADA recommendations for patients with type 2 diabetes:

- A nutritionally adequate, healthy diet with a reduction in total fat, especially saturated fat, should be the aim
- Spacing of meals should be considered so as to spread the intake of nutrients, particularly carbohydrates, throughout the day
- Total fat:
  - Less than 7% of caloric content should be from saturated fats
  - Intake of trans fat should be minimized
  - The distribution of calories from monounsaturated fats and carbohydrates can vary and can be individualized on the basis of the nutritional assessment and treatment goals
  - If obesity and weight loss are the primary concerns, a reduction in dietary fat should be considered
- Carbohydrates:
  - Monitoring carbohydrate intake is vital to glycemic control
  - The percentage of calories from carbohydrates will vary and is individualized on the basis of the patient's eating habits and glucose and lipid goals
  - Use of the glycemic index and glycemic load may be beneficial
  - Foods that are rich in nonstarch polysaccharides and carbohydrate-containing foods with a low glycemic index should be encouraged
  - Sucrose and sucrose-containing foods must be substituted for other carbohydrates gram for gram and not simply added to the meal plan

- Low-carbohydrate diets (restricting total carbohydrate intake to <130 g/d) are not recommended

- Fiber:

- Recommendations are the same as for the general population

- Protein:

- With the onset of overt nephropathy, lower intake of protein should be considered; the general consensus is to prescribe a protein intake of approximately the recommended daily allowance for adults of 0.8 g/kg/d (approximately 10% of daily caloric intake) in patients with overt nephropathy

- Protein-restricted meal plans should be designed by a registered dietitian who is familiar with all components of nutrition therapy for diabetes

- Sodium:

- Recommendations are the same as for the general population

- In patients with mild to moderate hypertension, <1,500 mg/d of sodium is recommended

- Alcohol:

- Precautions are the same as for the general population

- Daily alcohol intake should be moderate (*ie*, one drink per day or less for women and two drinks per day or less for men)

Recommendations for obese patients with type 2 diabetes:

- Modest weight loss has been shown to reduce insulin resistance and, therefore, is recommended for all overweight or obese patients with diabetes

- Either a low-carbohydrate diet or a low-fat diet may be helpful in the short term
- Patients should be referred to a nutritionist and exercise therapist to commence a weight-loss regimen
- Lifestyle changes, including education, reduced caloric and fat intake, and regular physical activity, should be the primary approach to weight loss
- The AACE guidelines state that pharmacotherapy for weight loss in patients with type 2 diabetes mellitus may be considered when lifestyle modification fails to achieve desired weight goals and BMI is greater than 27. The guidelines do not make recommendations concerning specific therapeutic agents for this purpose
- In patients with a BMI higher than 35 who fail to lose weight with dietary modification and increased physical activity, bariatric surgery may be indicated; if so, patients should be referred to an experienced surgeon

Indication

- All patients with type 2 diabetes should receive individualized medical nutritional therapy from a dietitian familiar with the management of diabetes to help achieve treatment goals
- Weight reduction is a priority in patients who are overweight or obese

Comments

- Dietary modification and adherence to a medical nutritional therapy plan are beneficial in maintaining glycemic control and reducing the risk of complications, as well as for weight loss and improving general health and well-being
- Patients must recognize the benefits of an appropriate diet; understand that carbohydrate counting, exchange, or experience-based estimation form the basis of nutritional glycemic control; and adhere to the individualized diet plan and follow medical advice on healthy eating in the setting of diabetes

Evidence

- A systematic review of 22 studies including about 3,400 patients on a variety of medications used for weight loss in adults with type 2 diabetes showed that drug therapy led to modest reductions in weight, with little or no difference among agents. There was a modest but significant decrease in HbA1c. Use is limited by side effects, especially with sibutramine. [56] *Level of evidence: 1*

- A systematic review of 12 studies including 585 patients suggested that protein restriction slightly slowed the progression of diabetic renal disease, but the results were not statistically significant. [57] *Level of evidence: 1*

- A systematic review of 36 trials and 1,467 patients on various diets used in the treatment of type 2 diabetes found no high-quality data on efficacy. [58] *Level of evidence: 1*

- An RCT comparing a low–glycemic index diet versus a high-fiber diet found that the low–glycemic index diet was more effective in reducing HbA1c compared to the high-fiber diet. [59] *Level of evidence: 1*

- An RCT comparing a low-carbohydrate Mediterranean diet versus a low-fat diet in 215 overweight patients with newly diagnosed type 2 diabetes showed that the Mediterranean-style diet resulted in better glycemic control and control of coronary risk factors than the low-fat diet. [60] *Level of evidence: 1*

- A multicenter RCT was performed to determine whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among patients with type 2 diabetes. In the study, 5,145 overweight or obese patients with type 2 diabetes were randomly assigned to one of two groups: (1) participation in an intensive lifestyle intervention that promoted weight loss through limiting caloric intake and increasing physical activity or (2) participation in diabetes support and education, which constituted the control group. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction,

nonfatal stroke, or hospitalization for angina. After a median follow-up of 9.6 years, the trial was terminated early on the basis of a futility analysis. Weight loss was greater in the intervention group than in the control group throughout the study (8.6%*vs*0.7% at 1 year; 6.0%*vs*3.5% at study end). The intensive lifestyle intervention also produced greater reductions in HbA1c and greater initial improvements in fitness and most cardiovascular risk factors. The rate of the primary outcome, however, was similar for the intervention group and the control group (hazard ratio in the intervention group, 0.95; 95% CI, 0.83-1.09;*P*= .51). Thus, although intensive lifestyle intervention in overweight or obese adults with type 2 diabetes improved glycemia and cardiovascular risk factors, there was no evidence for a reduction in the rate of cardiovascular events. [61] *Level of evidence: 1*

References

Physical activity

Description

- At least 150 minutes of moderate-intensity aerobic physical activity (50%-70% of maximum heart rate) spread out over at least 3 days per week, with no more than 2 consecutive days without exercise
- Adults with type 2 diabetes should be encouraged to additionally perform resistance training at least twice per week
- Alternatively, a regimen of 75 minutes of vigorous aerobic physical activity per week, or a structured exercise plan with a combination of aerobic exercise (*eg*, brisk walking, cycling, jogging, and swimming) and resistance exercise (*eg*, weight lifting and using weight machines) at least twice per week, unless contraindicated
- Exercise should always include proper warm-up and cool-down periods

Indications

- Increased physical activity should be encouraged to improve glycemic control, assist with weight maintenance, and reduce cardiovascular risk

Complications

- In patients taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if the medication dose or carbohydrate consumption is not altered. Supplementary carbohydrate may be required

Comments

- Before beginning an exercise program, patients should be carefully screened for the presence of macrovascular and microvascular complications that may be worsened by the program
- Exercise testing with electrocardiographic monitoring should be considered in sedentary patients
- Regular physical activity improves glycemic control, reduces cardiovascular risk, contributes to weight loss, and improves general health and well-being
- Programs designed to improved fitness in overweight adults with type 2 diabetes slows the decline in mobility that otherwise is likely to occur
- Blood glucose levels should be monitored by the patient, and the overall exercise program should be monitored by medical personnel
- Proper footwear is essential and must be emphasized for patients with peripheral neuropathy. Patients must be taught to monitor closely for blisters and other potential damage to their feet, both before and after exercise
- Proper hydration is also essential, as dehydration can have an adverse effect on blood glucose levels and heart function. Special attention to maintaining hydration is required when exercising in hot weather

Evidence

- A systematic review of 14 RCTs comparing exercise versus no exercise in 377 patients with type 2 diabetes found that exercise resulted in a significant improvement in glycemic control, with a reduction in HbA1c levels by 0.6%. Other findings from the study included a reduction in visceral and subcutaneous fat as well as plasma triglycerides in the exercise group. [62] *Level of evidence: 1*

- An RCT was performed to determine whether intensive lifestyle intervention that produces weight loss and improves fitness could slow the loss of mobility in overweight patients with type 2 diabetes. In the study, 5,145 overweight or obese adults within the age range of 45 to 74 years were randomized to either an intensive lifestyle intervention or a diabetes support-and-education program. The primary outcome was self-reported limitation in mobility. After 4 years the lifestyle-intervention group had a relative reduction of 48% in the risk of loss of mobility, as compared with the support group (odds ratio, 0.52; 95% CI, 0.44-0.63;*P*< .001). Both weight loss and improved fitness were significant mediators of this effect (*P*< .001 for both). Adverse events associated with the lifestyle intervention included a minor increase in musculoskeletal symptoms at year 1. Thus, weight loss and improved fitness slows the decline in mobility in overweight adults with type 2 diabetes. [63] *Level of evidence: 1*

- A multicenter RCT was performed to determine whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among patients with type 2 diabetes. In the study, 5,145 overweight or obese patients with type 2 diabetes were randomly assigned to one of two groups: (1) participation in an intensive lifestyle intervention that promoted weight loss through limiting caloric intake and increasing physical activity or (2) participation in diabetes support and education, which constituted the control group. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. After a median follow-up of 9.6 years, the trial was terminated early on the basis of a futility analysis. Weight loss was

greater in the intervention group than in the control group throughout the study (8.6%*vs*0.7% at 1 year; 6.0%*vs*3.5% at study end). The intensive lifestyle intervention also produced greater reductions in HbA1c and greater initial improvements in fitness and most cardiovascular risk factors. The rate of the primary outcome, however, was similar for the intervention group and the control group (hazard ratio in the intervention group, 0.95; 95% CI, 0.83-1.09;*P*= .51). Thus, although intensive lifestyle intervention in overweight or obese adults with type 2 diabetes improved glycemia and cardiovascular risk factors, there was no evidence for a reduction in the rate of cardiovascular events. [61] *Level of evidence: 1*

References

Special circumstances

Comorbidities

Coexisting disease

Coronary heart disease :

- Aggressive glycemic control does not increase, and may decrease, the risk of cardiovascular disease
- Treatment with an angiotensin-converting enzyme inhibitor can reduce the risk of subsequent cardiovascular events and overall mortality rates in patients with diabetes aged older than 55 who have additional cardiovascular risk factors and/or previously diagnosed cardiovascular disease
- Aspirin is effective for primary and secondary prevention of cardiovascular disease in patients with diabetes
- Coronary artery bypass grafting reduces the mortality rate more than percutaneous transluminal coronary angioplasty (without stents) in patients with diabetes and multivessel coronary artery disease

- The combination of stenting and glycoprotein IIb/IIIa inhibition in patients undergoing percutaneous coronary revascularization reduces the rates of restenosis and serious morbidities

Dyslipidemia :

- A common abnormal lipid pattern is an elevation of VLDL cholesterol; a reduction in HDL cholesterol; and a greater proportion of small, dense, atherogenic LDL particles
- Maximal nutrition therapy typically reduces LDL cholesterol levels to 15 to 25 mg/dL (0.39-0.65 mmol/L)
- The first priority of dyslipidemia therapy is to lower LDL cholesterol to a target goal of <100 mg/dL (2.60 mmol/L) in individuals without overt cardiovascular disease and <70 mg/dL (1.8 mmol/L) in those with overt cardiovascular disease. Lifestyle intervention, 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 and increases in omega-3 fatty acids, viscous fiber (such as in oats, legumes, citrus), and plant stanols/sterols
- Optimal triglyceride levels are <150 mg/dL (1.70 mmol/L)

Dyslipidemia in the presence of established coronary artery disease:

- Presence of type 2 diabetes is considered to be equivalent to coronary artery disease and, therefore, requires aggressive lipid-lowering therapy
- In those with clinical cardiovascular disease or who are over age 40 years and have cardiovascular 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

- Statins reduce cardiovascular morbidity and mortality rates in patients with diabetes after myocardial infarction , with or without elevated LDL cholesterol levels
- Statins and fibrates are effective for primary and secondary prevention of cardiovascular events in patients with diabetes and dyslipidemia

Hypertension :

- The addition of hypertension to diabetes greatly increases the risk of cardiovascular disease
- Aggressive control of hypertension, with a target blood pressure of 130/80 mm Hg or lower, reduces cardiovascular morbidity and mortality rates compared to less tight control

Special patient groups

Pregnant patients:

- Insulin is preferred to oral hypoglycemic agents for the management of diabetes in pregnancy
- Close supervision of glycemic control, insulin therapy, and fetal well-being is essential and requires the care of a specialist
- Women with pre-existing diabetes who plan to conceive should have a comprehensive eye examination and should be counseled on the risk of development and/or progression of diabetic retinopathy
- Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout the pregnancy

Elderly patients:

- Elderly patients taking insulin or a sulfonylurea are at particular risk for hypoglycemia; a nonhypoglycemic alternative, such as metformin, may be used
- Administration of insulin may be difficult if the patient has associated or concomitant disorders, such as visual impairment or arthritis

Patient satisfaction/lifestyle priorities

- Extreme care is required in balancing the need for optimal glycemic control with the harm of hypoglycemic episodes and their effect on patients' ability to drive, continue certain work-related tasks, and participate in sports and other leisure activities
- Elderly, isolated, or housebound patients are at particular risk for falls resulting from severe hypoglycemic episodes and reduced mental capacity resulting from recurrent, prolonged, minor degrees of hypoglycemia

Consultation

Acute hospital admission is appropriate for the following:

- DKA
- HHS
- Hypoglycemia with coma, seizures, or altered behavior or in a patient failing to respond to initial treatment, especially if the agent is a long-acting sulfonylurea (hypoglycemia may recur after initial treatment)

Referral for assistance in management of diabetes is appropriate for the following:

- Persistent refractory hyperglycemia
- Recurring episodes of severe hypoglycemia
- Metabolic instability manifested by frequent swings between hypoglycemia and fasting hyperglycemia

- Repeated absence from work as a result of severe psychosocial problems

Referral for assistance in management of comorbid conditions is appropriate for the following:

- Other medical conditions (*eg*, infections) and therapies (*eg*, surgery, chemotherapy) in which diabetes is a confounding factor
- Situations in which rapid initiation of rigorous control of diabetes can improve outcome (*eg*, pregnancy)
- Situations in which a primary medical problem or the therapeutic intervention (*eg*, large glucocorticoid doses) can cause a major deterioration in diabetes control

Follow-up

Monitoring

- Guidelines for follow-up of patients with diabetes are outlined in the ADA's Standards of Medical Care in Diabetes—2013

Self-management training:

- Diabetic patients should receive self-management education (*eg*, knowledge of diabetes, medications, self-monitoring, acute/chronic complications, and problem-solving skills) at the time of diagnosis and as needed thereafter
- These efforts should be monitored and measured as part of the treatment plan
- The educational effort should include assessment of psychosocial well-being
- Screen for problems with and barriers to self-care and assist the patient in identifying achievable self-care goals at each visit
- Encourage SMBG as needed to meet treatment goals (routine use may not be of great value in patients on oral agents)

Physical examination:

- Check the patient's blood pressure (target of <130/80 mm Hg) at every visit. Blood pressure can also be checked at home by the patient, and antihypertensives can be titrated by the physician every 2 to 3 weeks to achieve a goal blood pressure
- Titrate lipid-lowering agents every 6 to 8 weeks to achieve goals of LDL cholesterol (<100 mg/dL [2.6 mmol/L] in patients without cardiovascular disease and <70 mg/dL [1.80 mmol/L] in those with overt cardiovascular disease), HDL cholesterol (>40 mg/dL [1.0 mmol/L] for men and >50 mg/dL [1.3 mmol/L] for women), and triglycerides (<150 mg/dL [1.7 mmol/L])

Foot evaluation:

- Examine the patient's legs and feet, including between the toes and the posterior aspect of the heels, at every regular visit to assess for diabetic foot
- Do a comprehensive vascular evaluation; neurologic examination, including sensorimotor examination; musculoskeletal examination, including foot and ankle joint range of motion and inspection for bone abnormalities; and skin and soft tissue evaluation at least annually
- Modalities to assess the distal extremities include pinprick, vibration, and 10-g monofilament pressure sensation. Loss of 10-g monofilament sensation and reduced vibration perception are predictive of foot ulcers in the future
- Observe the patient's gait or stance (with and without shoes), and check the patient's shoes for abnormal wear patterns
- Ascertain the cause of any observed abnormalities, and provide appropriate therapy or obtain a consultation

Eye examination:

- A trained expert should examine the patient for diabetic retinopathy shortly after diagnosis and then every year thereafter
- If dilated ophthalmoscopy is used, eye examination should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in the management of diabetic retinopathy
- If skilled reading of seven-field stereo photographs is available and shows no retinopathy at the initial screening, then the next screening examination does not need to be done for 4 years
- Patients with persistently elevated glucose levels or proteinuria should have yearly eye examinations
- Counsel women with pre-existing diabetes who are planning to conceive on the risk of development and/or progression of diabetic retinopathy
- Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout the pregnancy

Laboratory tests:

- ObtainHbA1cevery 2 to 3 months if there are changes in treatment or if the patient is not meeting goals (target of <6.5%-7%) and then once or twice a year if stable
- Begintesting for urinary albumin excretionat the time of diagnosis and then continue every year thereafter
- Obtain alipid profileat the initial visit and then annually

Interventions:

- Unless contraindicated, prescribe aspirin therapy in all patients with type 2 diabetes and a history of cardiovascular disease and all patients over age 40 with type 2 diabetes

and an increased risk of cardiovascular disease (smoking, family history of cardiovascular disease, dyslipidemia)

- Provide advice, support, and counseling on smoking cessation
- Administer influenza and pneumococcal vaccinations as per recommendations for all adults
- Hepatitis B vaccine should be given to adults aged 19 through 59 years who have diabetes mellitus as recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices
- Patients should have dental examinations at least twice yearly

Prognosis

- The mortality rate in patients with diabetes is increased, and life expectancy is reduced
- Macrovascular disease is the major cause of death in patients with type 2 diabetes
- Life expectancy has improved dramatically with improved treatment, but this has also led to an enormous increase in the incidence of chronic complications
- Good glycemic control can prevent or delay the progress of microvascular complications
- Reduction of cardiovascular disease requires good control of blood pressure, hyperlipidemia , urinary albumin excretion, and blood glucose, as well as smoking cessation
- Early detection and treatment of retinopathy , nephropathy , and neuropathy can reduce the incidence of blindness, kidney failure, and amputation

Therapeutic failure:

- Patients will ultimately progress from needing lifestyle advice and oral hypoglycemic agents to requiring insulin therapy

Deterioration:

- Type 2 diabetes is a progressive disorder, requiring increased therapy over time
- Optimal treatment may be limited by the threat of hypoglycemia
- Inadequate control of blood glucose and other cardiovascular risk factors results in an increase in complications
- Referral may be needed for inadequate glycemic control or the onset of complications to ensure appropriate management

Complications

Acute complications

Infections:

- Patients with diabetes are predisposed to infections, which can cause increased morbidity and mortality
- Acute bacterial, viral, and fungal infections are common in patients with diabetes
- Respiratory tract infections, urinary tract infections, and soft tissue infections are particularly common in patients with diabetes, and invasive otitis externa, rhinocerebral mucormycosis, and emphysematous infections (cholecystitis and pyelonephritis) occur almost exclusively in patients with diabetes
- Some infections occur with increased severity and may be associated with an increased risk of complications in patients with diabetes

HHS:

- Requires urgent hospital admission
- Most commonly seen in older patients with type 2 diabetes
- Often seen in patients with previously unrecognized diabetes; after recovery, control can be achieved without insulin in 50% of such patients
- Precipitating factors include infection, especially pneumonia; use of thiazide or loop diuretics; consumption of excessive sugary drinks to quench thirst; and impaired renal function
- Characterized by severe hyperglycemia (plasma glucose level >600 mg/dL), drowsiness or loss of consciousness, severe dehydration, and hyperosmolality but no hyperventilation or ketoacidosis
- Impaired cerebral perfusion may give rise to focal neurologic signs, often leading to suspicion of a cerebrovascular accident
- Principles of treatment and complications (apart from cerebral edema, which is extremely rare) are similar to those for ketoacidosis

DKA :

- Medical emergency requiring urgent hospital admission
- Occasionally occurs in patients with type 2 diabetes but is much more common in patients with type 1 diabetes

Treatment-related hypoglycemia :

- May occur in patients with type 2 diabetes receiving sulfonylurea or insulin therapy
- Clinical features are related to adrenergic symptoms, including tachycardia, palpitations, tremor, anxiety, and sweating, and neuroglycopenic symptoms,

including faintness, hunger, headache, abnormal behavior, altered consciousness, and eventually coma

- Elderly patients may present with impaired consciousness or abnormal behavior, leading to a mistaken diagnosis of cerebrovascular accident
- Patients who are awake and alert may be treated with oral glucose 15 to 20 g (*eg*, glucose tablets) followed by a meal to prevent recurrence of hypoglycemia
- Patients who are unconscious should be given 20 to 50 mL of 50% intravenous dextrose followed by an infusion of 10% to 20% dextrose to maintain blood glucose between 108 mg/dL (6 mmol/L) and 180 mg/dL (10 mmol/L)
- Intravenous or intramuscular glucagon 1 mg is also effective and is convenient in the outpatient setting, but excess alcohol may block its action of breaking down glycogen to glucose
- May recur in patients taking a sulfonylurea due to the long half-life of these agents
- Patients with diabetic autonomic neuropathy or recurrent episodes of hypoglycemia may be particularly unaware of impending hypoglycemia and, therefore, are at particular risk

Chronic complications

Retinopathy :

- In western countries, diabetes mellitus is the most common cause of blindness in persons aged 20 to 60 years
- Diabetes accounts for 8% of all legal blindness in the U.S.
- Tight glycemic control delays the onset and progression of retinopathy
- Proteinuria, elevated BUN, and elevated serum creatinine are all good predictors

- Incidence is related to the duration of diabetes and the degree of glycemic control achieved
- Present in 10% to 20% of patients at the time of diagnosis and will be present in some form in 80% to 90% of patients 20 years after diagnosis
- Early detection and treatment is essential for a favorable outcome

Cataract :

- Five times more common among patients with diabetes

Glaucoma :

- Occurs with increased frequency in patients with diabetes

Nephropathy :

- Occurs in 20% of patients with type 2 diabetes
- Single most common cause of end-stage renal failure; in the U.S., 35% of patients requiring dialysis have diabetes
- Develops slowly (over 15-25 years), but the development period may appear to be shorter in patients with type 2 diabetes
- A moderate increase in urinary albumin excretion (albumin excretion of 30-299 mg/24 hours) is the first evidence of nephropathy; by the time an increase in serum creatinine has occurred, over 50% of renal function has been lost
- Management includes tight control of blood glucose and blood pressure and reduction of protein intake
- Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers delay the progression of the state of moderately increased urinary albumin excretion into overt diabetic nephropathy

- Reducing protein intake in patients with chronic renal failure has been shown to reduce the rate of renal disease–related death by approximately 40% compared to higher or unrestricted protein intake

Neuropathy:

- Occurs in 70% to 80% of patients with diabetes
- Development is linked to the duration of diabetes and the degree of glycemic control
- May affect any part of the nervous system (cranial, peripheral, and autonomic), but peripheral neuropathy is most common
- Mainly affects the lower limbs
- Often causes paresthesias of the extremities
- Symptoms are symmetric and associated with intense burning
- Mononeuropathies of cranial nerves III, IV, and VI (causing diplopia and abnormality of visual fields); the intercostal nerves; and the femoral nerves are common
- Autonomic neuropathy may cause gastrointestinal disturbances, leading to esophageal motility problems, abnormal gastroparesis, diarrhea (usually nocturnal), or genitourinary disturbances, leading to neurogenic bladder (urinary hesitancy, weak urine stream, dribbling) and impotence

Diabetic foot ulcers :

- Prompt and proper care is essential
- Systemic infection must be excluded, and a vascular evaluation should be done
- Bacterial infections of foot lesions are commonly polymicrobial, primarily consisting of anaerobes

- Infection and/or inflammation may result in widely fluctuating blood glucose levels
- Surgical and antibiotic treatment of abscesses or deep infection may control the infection and also improve glycemic control
- Patients with severe hyperglycemia may have decreased ability to fight infection; therefore, good glycemic control should be a primary goal of overall patient care
- Poor nutritional status may hinder the healing process and must be corrected promptly
- The annual incidence of foot ulcers among patients with diabetes is 2.5% to 10.7%, and the annual incidence of amputation is 0.25% to 1.80%
- Monofilament testing has been found to be a more sensitive screening modality than vibration perception threshold measurement for peripheral neuropathy and, therefore, for patients at risk for foot ulceration
- Screening and referral of patients at high risk of developing foot problems to a foot care clinic reduces the risk of foot ulcers and major amputation

Charcot foot :

- An acutely swollen foot with no radiographic changes in a patient with diabetes may represent the early stage of Charcot foot
- Requires careful observation, appropriate rest, elevation and immobilization, and referral to a professional experienced in the treatment of Charcot joint
- Differentiation from infection or monarticular arthritis may be difficult, and careful follow-up is required

Erectile dysfunction :

- Prevalence in men with diabetes ranges from 50% to 60%

Cardiovascular disease :

- Diabetes mellitus is a major risk factor for cardiovascular disease in the U.S., and 60% to 75% of patients with diabetes die from cardiovascular causes
- Annual incidence of cardiovascular disease is increased twofold or threefold in men with diabetes and threefold or fourfold in women with diabetes after adjusting for age and other cardiac risk factors
- Diabetes-specific risk factors for cardiovascular disease include elevated urinary protein excretion, poor glycemic control, overweight or obesity, abdominal adiposity, and blood clotting activity
- In patients with type 2 diabetes, there is an additional increased risk of obesity and lipid abnormalities independent of the level of glycemic control
- Monitoring of lipid levels and management of hyperlipidemia are essential in the prevention of macrovascular complications
- According to the ADA guidelines the first priority of dyslipidemia therapy in patients with diabetes who do not have overt cardiovascular disease is to lower LDL cholesterol to a target goal of <100 mg/dL (2.60 mmol/L) and in patients with known cardiovascular disease to aim for a target of <70 mg/dL (1.80 mmol/L). Lifestyle intervention, 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 and increases in omega-3 fatty acids, viscous fiber (such as in oats, legumes, citrus), and plant stanols/sterols
- Recent trials investigating the impact of intensive diabetes management on macrovascular disease have shown that, in the populations studied, intensive glycemic control did not reduce macrovascular events. In one study, therapy to

achieve very aggressive goals was associated with increased mortality. Post hoc analyses suggest that younger patients with type 2 diabetes, a shorter duration of disease, and less vasculopathy may experience macrovascular benefits with strict glycemic control

Cerebrovascular disease:

- Incidence is two to four times greater in patients with diabetes than in those without diabetes

Peripheral vascular disease :

- Incidence is six times greater in patients with diabetes than in those without diabetes

Skin problems:

- Bacterial and fungal infections of the skin and mucus membranes are more common in patients with diabetes than in the general population

Patient education

General recommendations on diet:

- Eat regular meals
- Eat more complex carbohydrates rather than simple carbohydrates
- Eat less sugar and sugary foods
- Reduce fat, particularly saturated fat, intake
- Avoid special diabetic products (*ie*, items specifically manufactured or marketed for diabetes patients that are likely expensive and not more helpful than following simple dietary guidelines)
- Reduce salt intake

- Keep alcohol intake moderately low

Exercise:

- At least 150 minutes of moderate-intensity aerobic physical activity (50%-70% of maximum heart rate) spread over at least 3 days per week is recommended, with no more than 2 consecutive days without exercise
- A regimen of 75 minutes of vigorous aerobic physical activity per week is recommended as an alternative
- A structured exercise plan, with a combination of aerobic exercise (*eg*, brisk walking, cycling, jogging, and swimming) plus resistance exercise (*eg*, weight lifting and using weight machines) at least twice per week, unless contraindicated, is also recommended
- Include proper warm-up and cool-down periods
- Take precautionary measures for exercises involving the feet
- Maintain proper hydration, especially in hot weather, as dehydration can adversely affect blood glucose levels and heart function

SMBG:

- Attempt to achieve and maintain blood glucose levels as close to normal as is safely possible
- Recognize the importance of daily testing to monitor for and prevent asymptomatic hypoglycemia, especially if on insulin
- Be aware that the accuracy of testing is instrument and user dependent, and the monitoring technique must be evaluated by the health care provider both initially and at regular intervals thereafter

Avoidance of foot complications:

- Understand proper foot care, including foot hygiene, proper footwear, avoidance of foot trauma, the need to stop smoking, actions to take if problems develop, and when to see a health care professional
- If at high risk, perform daily foot inspections
- Be aware of the potential for neuropathic and vascular complications and their relationship to foot problems

Questions patients ask

- *Do I have to adhere to a very strict diet?*Patients may have misconceptions regarding dietary requirements and may not be aware of the relative flexibility of modern guidelines
- *Is type 2 diabetes a serious disease?*Patients may regard type 2 diabetes as the 'mild' form of diabetes and may not appreciate the potential severity of complications and importance of avoiding or reducing them
- *Will I need to inject insulin?*Patients may think that all types of diabetes are associated with the need for insulin treatment

Online information for patients

- Mayo Clinic: Type 2 diabetes
- National Diabetes Education Program: More than 50 ways to prevent diabetes
- Agency for Healthcare Research and Quality: Medicines for type 2 diabetes: a review of the research for adults
- ADA: Taking care of type 2 diabetes

Resources

Summary of evidence

Evidence

Prevention

- A systematic review and meta-analysis of RCTs involving 8,084 patients studying the effect of pharmacologic or lifestyle interventions on the prevention of type 2 diabetes in patients with impaired glucose tolerance concluded that both pharmacologic (oral antidiabetic agents, orlistat) and lifestyle interventions reduced the rate of progression to type 2 diabetes and that lifestyle interventions were at least as effective as drug therapy. [1] *Level of evidence: 2*

- A systematic review of two RCTs in which dietary advice was the only intervention given, 358 patients showed a 33% reduction in the incidence of diabetes after 6 years in one trial and significant reductions in fasting blood glucose level, BMI, blood pressure, and lipid levels in the other trial. [2] *Level of evidence: 1*

- A systematic review of whole grain foods for the prevention of type 2 diabetes identified one RCT and 11 cohort studies including 2,126 patients, but the quality of the data did not allow any conclusions to be drawn regarding effectiveness. [3] *Level of evidence: 1*

- A systematic review of eight trials with 4,750 patients involving exercise and dietary interventions over 1 to 6 years showed that the combination of exercise and dietary modification reduced the risk of diabetes compared to standard care in patients with prediabetes. [4] *Level of evidence: 1*

- A systematic review of five RCTs involving 2,360 patients with impaired glucose tolerance showed that use of acarbose reduced the incidence of diabetes and may prevent cardiovascular events, but other metabolic and clinical outcomes were not affected. [5] *Level of evidence: 1*

- The Finnish Diabetes Prevention Study randomly assigned 522 overweight or obese subjects with impaired glucose tolerance to an intervention consisting of individualized counseling concerning weight management, diet, and physical activity or to a control group. At 2-year follow-up, the incidence of type 2 diabetes in the intervention group was less than half that in the control group. [6] *Level of evidence: 1*

- Additional follow-up at a median of 4 years showed that the reduced incidence of type 2 diabetes among 522 subjects in the intervention group of the Finnish Diabetes Prevention Study was maintained. [7] *Level of evidence: 2*

- The Diabetes Prevention Program Research Group randomly assigned 3,234 subjects with impaired glucose tolerance to lifestyle modification, metformin, or placebo. Both the lifestyle intervention and metformin therapy had a protective effect on the risk of developing type 2 diabetes and were associated with a return to normal glucose tolerance, but lifestyle modification was associated with greater prevention of type 2 diabetes, especially in older patients, and also was associated with a lower mortality rate compared to metformin. [8] *Level of evidence: 1*

- Follow-up of 2,766 subjects in the U.S. Diabetes Prevention Program Outcome Study for an additional 5.6 years showed that the incidence of diabetes equalized among the lifestyle, metformin, and placebo groups during the extension period. The cumulative incidence of diabetes among subjects in the intervention group was reduced by 34%, however, while the cumulative incidence among subjects in the metformin group was reduced by 18%, compared to the placebo group. [9] *Level of evidence: 2*

- An RCT with over 5,000 patients found that rosiglitazone resulted in a 60% decrease in progression to diabetes among patients with impaired fasting glucose, impaired glucose tolerance, or both, and no previous cardiovascular disease at 3-year follow-up compared to placebo. Cardiovascular event rates were similar between groups,

although there was a small but significant increase in the heart failure rate among patients receiving rosiglitazone. [10] *Level of evidence: 1*

- A subanalysis of the Swedish Obese Subjects study examined the effect of bariatric surgery on the long-term prevention of type 2 diabetes in obese patients. The rate of incident type 2 diabetes among 1,658 obese patients who underwent bariatric surgery was compared to the incidence among 1,771 matched nonsurgical controls. Baseline BMIs for both groups were ≥34 kg/m^{2}or ≥38 kg/m^{2}in men and women, respectively, and none of the subjects from either group had a diagnosis of type 2 diabetes mellitus at study entry. For this study, diabetes was defined as a fasting blood glucose level ≥126 mg/dL or the self-reported use of diabetes medications. Over the 15-year follow-up period, type 2 diabetes developed in 110 patients in the bariatric surgery group (IR, 6.8 cases/1,000 person-years; adjusted hazard ratio, 0.17; 95% CI, 0.13-0.21;*P*< .001] compared to 392 patients (IR, 28.4 cases/1,000 person-years) among controls. Thus, bariatric surgery, as compared to conventional care, reduced the long-term incidence of type 2 diabetes by 78% in obese patients. [11] *Level of evidence: 2*

- A prospective single-center study examined the association of RYGB surgery with weight loss and incidence of diabetes mellitus 6 years after surgery. This nonrandomized study included a total of 1,156 severely obese (BMI >35 kg/m^2) participants with a mean BMI of 45.9 kg/m^2. The incidence of diabetes throughout the course of the study was reduced fivefold to ninefold after RYGB surgery compared with nonsurgical control subjects (2% new diagnoses in RYGB group, 95% CI, 0%-4%; versus 17% new diagnoses for controls, 95% CI, 10%-24% [odds ratio, 0.11; 95% CI, 0.04-0.34;*P*< .001]). Thus, significant weight loss and a reduced risk for the development of type 2 diabetes were evident among obese patients who underwent RYGB surgery compared with severely obese, nonsurgically treated controls. [12] *Level of evidence: 2*

Treatments

Metformin

- A systematic review of 29 trials involving over 5,000 patients compared metformin monotherapy versus placebo and a variety of other agents and found that metformin improved glycemic control, weight, dyslipidemia, and diastolic blood pressure. [13] *Level of evidence: 1*
- Metformin has the clinical benefit of being weight neutral, but it is associated with some harms, including the rare but serious effect of lactic acidosis. A systematic review of 347 RCTs incorporating the experience of about 120,000 patients, however, found no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis as compared to other oral hypoglycemic agents evaluated in RCTs. [14] *Level of evidence: 1*
- An RCT of 451 patients found that patients with type 2 diabetes taking metformin regularly experienced reductions in HbA1c versus those receiving placebo. [15] *Level of evidence: 1*
- Another RCT, this one including 96 patients, found both acarbose and metformin equally effective in comparison to placebo with respect to a reduction in HbA1c. [16] *Level of evidence: 3*

Sulfonylureas

- A systematic review found glyburide was among several oral anti-glycemic agents effective at reducing serum HbA1c. An average reduction of 1% to 2% for the serum marker was noted. Studies (63) were included in the analysis if they had a study period of at least 3 months, if each group contained at least 10 subjects at the study's conclusion, and if HbA1c was reported. When multiple dosages of a drug were tested, the results of the highest approved dosage were used. In placebo-controlled trials, HbA1c data are presented as the difference between the change in treated versus placebo subjects. [17] *Level of evidence: 1*

- In the UK Prospective Diabetes Study, 3,867 patients with newly diagnosed type 2 diabetes were randomly assigned to either intensive glycemic control with a sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin or to conventional glycemic control using diet. Among patients assigned to dietary modification, drug therapy was added only if hyperglycemic symptoms were present or if the fasting plasma glucose level increased to higher than 270 mg/dL (15 mmol/L). No significant differences in the rates of myocardial infarction or stroke over 5 years were found between groups, but intensive glycemic control was associated with a significant reduction in microvascular complications, including the need for retinal photocoagulation, compared to conventional glycemic control. In addition, treatment with sulfonylurea significantly reduced HbA1c over 10 years compared to dietary modification alone. Patients assigned to intensive therapy, however, experienced more hypoglycemic episodes and more weight gain compared to those assigned to conventional therapy. [18] *Level of evidence: 1*

- An RCT of 70 patients found that once-daily glimepiride plus diet/exercise was effective in Mexican Americans with type 2 diabetes whose disease was inadequately controlled with diet and exercise alone. [19] *Level of evidence: 3*

- Another RCT involving 569 patients with type 2 diabetes mellitus reported a similar reduction in HbA1c as well as a significant improvement in quality of life after 12 weeks of treatment with glipizide versus placebo. [20] *Level of evidence: 1*

SGLT2 inhibitors

- A randomized, double-blind, placebo-controlled trial of 584 adult subjects with type 2 diabetes who were inadequately controlled with diet and exercise received canagliflozin 100 or 300 mg or placebo once daily. At 26 weeks, patients who received canagliflozin 100 and 300 mg had significantly reduced HbA1c as compared to those who received placebo (−0.77%, −1.03%, and 0.14%, respectively;$P < .001$ for both). Both doses of canagliflozin significantly decreased body weight ($P < .001$ for both). The overall incidences of adverse events were modestly higher with

canagliflozin versus placebo. The incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related effects were higher with canagliflozin, although these led to few discontinuations. The incidence of hypoglycemia across all groups was low. The authors concluded that treatment with canagliflozin improves glycemic control, reduces body weight, and is generally well tolerated in adults with type 2 diabetes whose glycemic control is suboptimal with diet and exercise alone. [21] *Level of evidence: 1*

GLP-1 receptor agonists

- A multicenter open-label RCT compared the efficacy and safety of the addition of once-daily liraglutide versus twice-daily exenatide in 464 adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulfonylurea, or both. After 26 weeks, the group assigned to receive liraglutide experienced a greater reduction in HbA1c as compared to exenatide (–1.12%*vs*–0.79%; estimated treatment difference –0.33; 95% CI, –0.47 to –0.18;*P*< .0001), primarily as a result of improvements in fasting blood glucose levels. Both drugs promoted similar weight losses and were generally well tolerated, but nausea was less persistent and minor hypoglycemia less frequent with liraglutide than with exenatide. Thus, liraglutide once a day provided significantly greater improvements in glycemic control than did exenatide twice a day and was generally better tolerated. [22] *Level of evidence: 2*
- An open-label noninferiority study comparing once-weekly administration of exenatide versus twice-daily administration of exenatide in 295 patients with type 2 diabetes showed that once-weekly administration of a long-acting preparation resulted in better glycemic control and similar reduction in weight with no increased risk of hypoglycemia. [23] *Level of evidence: 2*
- A multicenter randomized open-label trial compared the efficacy and safety of exenatide once weekly with liraglutide once daily in patients with type 2 diabetes. In the trial, 911 patients with uncontrolled type 2 diabetes treated with lifestyle modification and oral diabetes drugs were randomly assigned to receive once-daily

liraglutide or once-weekly exenatide. Patients treated with liraglutide experienced a greater reduction in HbA1c compared to those treated with weekly exenatide (–1.48%*vs*–1.28% for a treatment difference 0.21%; 95% CI, 0.08–0.33). Gastrointestinal adverse events were the most common, and these occurred less frequently in the exenatide group and with decreasing incidence over time in both groups. [24] *Level of evidence: 2*

- An RCT examined the efficacy of twice-daily exenatide injections in 261 adults with type 2 diabetes who were already receiving insulin glargine alone or in combination with metformin or pioglitazone. After 30 weeks of therapy, the group treated with exenatide showed a greater decrease in HbA1c (–1.74%*vs*–1.04%; between-group difference –0.69%; 95% CI, –0.93% to –0.46%;*P*< .001). Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo (between-group difference –2.7 kg; 95% CI, –3.7 to –1.7). Average increases in insulin dosage with exenatide and placebo were 13 U/d and 20 U/d. The estimated rate of minor hypoglycemia was similar between groups. Adverse gastrointestinal effects were higher with exenatide than with placebo. Thus, the addition of twice-daily exenatide injections improved glycemic control without increasing hypoglycemia or weight gain in participants with uncontrolled type 2 diabetes who were already receiving insulin glargine. [25] *Level of evidence: 2*

- A population-based case-control study was conducted to determine whether GLP-1–based medications such as exenatide and sitagliptin are associated with an increased risk of acute pancreatitis. A large U.S. administrative database identified 1,269 adults with type 2 diabetes who were hospitalized with acute pancreatitis. These cases were matched against 1,269 control subjects for patient characteristics such as age, sex, enrollment pattern, and diabetes complications. After adjusting for available confounders and metformin use, current use of GLP-1–based therapies within 30 days (adjusted odds ratio, 2.24 [95% CI, 1.36-3.68]) and recent use past 30 days and less than 2 years (2.01 [95% CI, 1.37-3.18]) were associated with

significantly increased odds of acute pancreatitis relative to the odds in nonusers. [26] *Level of evidence: 2*

Pramlintide

- An open-label multicenter study was performed to compare the efficacy and safety of adding mealtime pramlintide or rapid-acting insulin analogs to basal insulin for patients with inadequately controlled type 2 diabetes. In the study, 113 patients with uncontrolled type 2 diabetes who were already using basal insulin and other oral diabetes medications were randomized to receive prandial pramlintide or rapid-acting insulin analogs. The primary end point was the proportion of patients achieving HbA1c ≤7.0% without weight gain or severe hypoglycemia. After 24 weeks, more patients treated with pramlintide than with rapid-acting insulin analogs achieved an HbA1c without hypoglycemia (30%*vs*11%,*P*= .018) with a similar dose of basal insulin. Addition of pramlintide did not increase body weight, whereas the addition of rapid-acting insulin analogs did yield weight gain (0 ± 0.7 kg*vs*+4.7 ± 0.7 kg,*P*< .0001). [27] *Level of evidence: 2*

Insulins

Efficacy of insulin in lieu of oral hypoglycemic agents in patients with moderately or poorly controlled type 2 diabetes:

- An RCT of 172 patients who were poorly controlled on an oral hypoglycemic agent (maximum dose of glyburide) established that mean HbA1c and fasting glucose levels were consistently reduced to target therapeutic levels with insulin treatment. Furthermore, treatment satisfaction was greater in the insulin group, despite a higher rate of hypoglycemia compared to oral therapy. [28] *Level of evidence: 2*
- Another RCT in 38 patients, most of whom were switched from an oral hypoglycemic agent to insulin, found similar reductions in HbA1c, but at the cost of weight gain and occasional hypoglycemic episodes during therapy. [29] *Level of evidence: 3*

- An RCT comparing intensive insulin therapy versus oral hypoglycemic agents in 382 patients with newly diagnosed type 2 diabetes showed that patients receiving early intensive insulin therapy experience more frequent recovery of β-cell function and higher remission rates than those on oral hypoglycemic agents. [30] *Level of evidence: 1*

  Glycemic control in patients on insulin or a sulfonylurea versus dietary modification alone:

- In the UK Prospective Diabetes Study, 3,867 patients with newly diagnosed type 2 diabetes were randomly assigned to either intensive glycemic control with a sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin or to conventional glycemic control using diet. No significant differences in HbA1c were found between patients receiving insulin and those receiving a sulfonylurea; however, both insulin and the sulfonylurea resulted in a significant reduction in HbA1c as compared to dietary modification alone. No significant differences in the rates of myocardial infarction or stroke over 5 years were found between groups, but intensive glycemic control was associated with a significant reduction in microvascular complications, including the need for retinal photocoagulation, compared to conventional glycemic control. Patients assigned to intensive therapy, however, experienced more hypoglycemic episodes and more weight gain compared to those assigned to conventional therapy. [18] *Level of evidence: 1*

- A longitudinal study conducted over 6 years of 5,535 patients was unable to find any difference in quality-of-life scores between the patients receiving treatment with insulin, a sulfonylurea, or dietary modification alone in the UK Prospective Diabetes Study. [31] *Level of evidence: 2*

  Effect of combination therapy with insulin and oral hypoglycemic agents:

- A systematic review of 20 RCTs and 1,811 patients found that bedtime administration of NPH insulin in combination with oral hypoglycemic agents as a

daily regimen in patients with type 2 diabetes resulted in glycemic control comparable to that of insulin monotherapy (twice-daily or multiple daily injections) and was also associated with less weight gain if metformin was used. [32] *Level of evidence: 1*

Newer long-acting insulin analogs versus NPH insulin:

- A systematic review of 8 RCTs including 2,293 patients compared long-acting insulin analogs (glargine or detemir) versus NPH insulin in patients with type 2 diabetes and concluded that the only benefit of long-acting insulins over NPH insulin was a significant reduction in the incidence of nocturnal hypoglycemia. There were no differences in mortality, morbidity, or quality-of-life scores. [33] *Level of evidence: 1*

Long-acting insulin analogs versus multiple-dose short-acting insulin analogs:

- An open RCT comparing once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in 418 patients with type 2 diabetes already on oral hypoglycemic agents found that although prandial insulin lispro resulted in better postprandial blood glucose levels, once-daily basal insulin glargine was equally effective in lowering HbA1c and resulted in less hypoglycemia. [34] *Level of evidence: 1*

- An open-label multicenter RCT was performed to assess the risks and benefits of the addition of specific insulin regimens to oral therapy in patients with type 2 diabetes mellitus. In the study, 708 patients with type 2 diabetes and suboptimal glycemic control on metformin/sulfonylurea combination therapy were randomly assigned to receive one of three insulin regimens: (1) biphasic insulin aspart twice daily, (2) prandial insulin aspart three times daily, or (3) basal insulin detemir once daily. After 1 year, HbA1c levels were similar among all the groups; however, fewer patients had a level of 6.5% or less in the biphasic group (31.9%) than in the prandial group (44.7%,*P*= .006) or in the basal group (43.2%,*P*= .03). Median rates of

hypoglycemia per patient per year were lowest in the basal group, higher in the biphasic group, and highest in the prandial group ($P < .001$ for the overall comparison). Weight gain was greatest in the prandial group. [35] *Level of evidence: 2*

Long-acting insulin analogs glargine versus detemir:

- A multicenter RCT was performed to compare the efficacy and safety of once-daily insulin initiation using insulin detemir versus insulin glargine when added to existing metformin therapy in patients with type 2 diabetes. The trial involved 457 insulin-naïve adults with type 2 diabetes with starting HbA1c 7% to 9%, to which either detemir or glargine was added to current metformin therapy and titrated to a target fasting plasma glucose ≤90 mg/dL. After 26 weeks, the HbA1c decreased with detemir and glargine by 0.48 and 0.74 percentage points, respectively (estimated between-treatment difference, 0.30; 95% CI, 0.14-0.46). The proportions of patients reaching HbA1c ≤ 7% at 26 weeks were 38% and 53% ($P = .026$) with detemir and glargine, respectively. Hypoglycemia, which was uncommon in both groups, was observed less frequently with detemir than glargine. Weight decreased with detemir (−0.49 kg) and increased with glargine (+1.0 kg, 95% CI for difference, −2.17 to −0.89 kg). Thus, both detemir and glargine, when added to metformin therapy, improved glycemic control, with glargine providing greater reductions in HbA1c and detemir promoting less weight gain and hypoglycemia. [36] *Level of evidence: 2*

Effect of basal insulin glargine on cardiovascular outcomes and cancer:

- An RCT was performed to determine whether the use of sufficient basal insulin to normalize fasting plasma glucose levels reduces cardiovascular events. The trial randomized 12,537 people with cardiovascular risk factors plus prediabetes or type 2 diabetes to receive insulin glargine or standard care and to receive omega-3 fatty acids or placebo, using a two-by-two factorial design. The two coprimary outcomes were: (1) nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes; and (2) a composite of these events plus revascularization or

hospitalization for heart failure. After a median follow-up of 6.2 years, there was no difference in the rates of incident cardiovascular outcomes in the insulin-glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first coprimary outcome (hazard ratio, 1.02; 95% CI, 0.94-1.11;*P*= .63) and 5.52 and 5.28 per 100 person-years, respectively, for the second coprimary outcome (hazard ratio, 1.04; 95% CI, 0.97-1.11;*P*= .27). Thus, therapy with basal insulin glargine for more than 6 years had a neutral effect on cardiovascular outcomes and cancers, maintained near-normal glycemic control, and slowed progression of dysglycemia but also increased hypoglycemia and modestly increased weight. [37] *Level of evidence: 1*

Subcutaneous continuous insulin infusion versus multiple insulin injections:

- An RCT comparing continuous infusion of insulin aspart versus multiple injections of basal NPH insulin and bolus insulin aspart was unable to find any significant difference in HbA1c after 24 weeks of therapy in 132 patients; quality of life was not assessed. [38] *Level of evidence: 1*

Thiazolidinediones

Pioglitazone may not share the adverse cardiovascular effects associated with rosiglitazone.

- A systematic review of 22 RCTs and 6,200 patients concluded that there was no evidence that treatment with pioglitazone resulted in improved mortality, morbidity, adverse effects, and health-related quality of life in patients with type 2 diabetes. [39] *Level of evidence: 1*

Rosiglitazone appears to delay the progression to type 2 diabetes in high-risk patients compared to placebo but has uncertain long-term cardiovascular effects, which has generated widespread controversy over the safety of its use.

- A meta-analysis of 42 RCTs and 28,000 patients published in 2007 found that patients with type 2 diabetes receiving rosiglitazone had a significantly increased risk of myocardial infarction compared to control subjects. [40] *Level of evidence: 2*

- A systematic review of 18 RCTs involving 3,888 patients showed no difference in lowering of HbA1c with rosiglitazone compared to other drugs, and use of rosiglitazone was associated with increased edema, increased cardiovascular risk, and increased fracture rates among women. [41] *Level of evidence: 1*

- An RCT with over 5,000 patients found that rosiglitazone resulted in a 60% decrease in progression to diabetes among patients with impaired fasting glucose, impaired glucose tolerance, or both, and no previous cardiovascular disease at 3-year follow-up compared to placebo. Cardiovascular event rates were similar between groups, although there was a small but significant increase in the heart failure rate among patients receiving rosiglitazone. [42] *Level of evidence: 1*

- A subsequent RCT with 4,447 patients confirmed that the addition of rosiglitazone to metformin or a sulfonylurea in patients with type 2 diabetes increased the risk of heart failure and the rate of fractures among women. There was no increase, however, in the risk of overall cardiovascular morbidity or mortality compared with other antidiabetic drugs. [43] *Level of evidence: 1*

Thiazolidinediones can be used in combination with other oral therapies:

- A multicenter, double-blind RCT of 639 patients comparing the addition of pioglitazone to a sulfonylurea versus metformin plus a sulfonylurea in patients with poorly controlled type 2 diabetes found that both regimens resulted in equivalent improvements in glycemic control over 1 year. The pioglitazone-containing regimen reduced the urinary albumin-to-creatinine ratio more than the metformin-containing regimen and also resulted in a significantly greater improvement in triglyceride and HDL cholesterol levels. The pioglitazone combination resulted in a small increase in LDL cholesterol levels, however, whereas the metformin

combination resulted in a significant reduction in LDL cholesterol levels. [44] *Level of evidence: 2*

Acarbose

- A systematic review of 5 RCTs including 2,036 patients evaluated α-glucosidase inhibitors for type 2 diabetes and found that acarbose had a clear effect on glycemic control compared to placebo, but there were not enough data to establish its effect on morbidity or mortality. The review also found that patients with type 2 diabetes receiving acarbose experienced more adverse effects than those receiving a sulfonylurea. [5] *Level of evidence: 1*

Meglitinides

- A systematic review of 11 RCTs and 3,781 patients comparing meglitinides versus placebo found that repaglinide resulted in reductions in HbA1c of 0.1% to 2.1%, an effect similar to that of metformin, and nateglinide resulted in reductions in HbA1c of between 0.2% and 0.6%, an effect similar or slightly less marked than that of metformin. Meglitinides were associated with greater weight gain and frequency of hypoglycemic episodes than metformin, but diarrhea was less likely. Evidence for long-term outcomes, including mortality, is limited at present. [45] *Level of evidence: 1*

- An RCT of 9,306 patients examined the impact of treatment with nateglinide on cardiovascular events over a period of 6.5 years and found no significant difference in patients treated with the medication and those receiving placebo controls. The study also failed to show any benefit in preventing diabetes among the participants who received nateglinide versus those in the control arm. Nateglinide did, however, increase the chance of hypoglycemia. [46] *Level of evidence: 1*

Patient education

- A systematic review of 14 trials assessing the effect of group-based education programs for 1,532 patients with type 2 diabetes found that group-based education was associated with improved fasting blood glucose levels and HbA1c; improved diabetes knowledge; and reduced systolic blood pressure, body weight, and need for diabetes medication. [47] *Level of evidence: 1*

- A systematic review including nine studies and the experiences of 1,359 patients showed that individual education on glycemic control is better than usual care in patients with an HbA1c higher than 8%, but there was no difference in outcomes such as weight or blood pressure between patients receiving individual education versus those receiving group education after 12 to 18 months. [48] *Level of evidence: 1*

- A systematic review of 11 trials in 1,603 patients showed that culturally appropriate diabetes education improved knowledge at 3, 6, and 12 months compared to usual care. Other outcome measures, including lipid levels, blood pressure, quality of life, and behavioral indices, did not differ between the intervention and control groups. [49] *Level of evidence: 1*

- A systematic review of 21 studies (4,135 patients) of interventions to improve adherence to treatment recommendations in patients with diabetes mellitus showed that interventions by nurses and pharmacists, home aids, and diabetes education had a small beneficial effect on a variety of outcomes, including HbA1c. There were no data on mortality, morbidity, or quality of life. [50] *Level of evidence: 1*

- An RCT inclusive of 453 patients compared a self-monitoring program alone or combined with instruction versus usual care and found little difference in HbA1c as measured at 12 months. [51] *Level of evidence: 1*

- An RCT evaluating the impact of a structured group education program on a variety of medical and lifestyle measures in 827 patients with type 2 diabetes found that the

intervention led to greater improvements in weight loss and smoking cessation but no difference in HbA1c after 12 months. [52] *Level of evidence: 1*

- An RCT showed that an individualized electronic decision support and reminder system had a beneficial effect on both process outcomes and clinical outcomes, such as blood pressure and HbA1c, in 511 patients with type 2 diabetes after 6 months. [53] *Level of evidence: 1*

- A meta-analysis was performed to assess the effectiveness of SMBG levels in people with non-insulin–treated type 2 diabetes compared with clinical management without self monitoring and to explore the effects in specific patient groups. The analysis included 6 randomized trials with a total of 2,552 patients with type 2 diabetes. A mean reduction in HbA1c level of 0.25% or −2.7 mmol/mol (95% CI, −3.9 to −1.6) was observed for those using SMBG levels compared with no self-monitoring at 6 months. The difference in HbA1c levels between groups was consistent across age, baseline HbA1c level, sex, and duration of diabetes. [54] *Level of evidence: 1*

- A systematic review and meta-analysis was performed to examine the effectiveness of SMBG as a tool in the self-management for patients with type 2 diabetes who are not using insulin. The review identified 12 RCTs with a total of 3,259 patients with type 2 diabetes. Meta-analysis of studies including patients with a diabetes duration of 1 year or more showed a statistically significant SMBG decrease in HbA1c at up to 6 months follow-up (−0.3; 95% CI, −0.4 to −0.1), yet an overall statistically non-significant SMBG–induced decrease was seen at 12-month follow-up (−0.1; 95% CI, −0.3 to 0.04). Examination of the effect of SMBG on well-being and quality of life showed no effect on patient satisfaction, general well-being, or general health-related quality of life. The authors concluded that when diabetes duration is over 1 year, the overall effect of SMBG on glycemic control in patients with type 2 diabetes who are not using insulin is small up to 6 months after initiation and subsides after 12 months. [55] *Level of evidence: 1*

Dietary modification

- A systematic review of 22 studies including about 3,400 patients on a variety of medications used for weight loss in adults with type 2 diabetes showed that drug therapy led to modest reductions in weight, with little or no difference among agents. There was a modest but significant decrease in HbA1c. Use is limited by side effects, especially with sibutramine. [56] *Level of evidence: 1*

- A systematic review of 12 studies including 585 patients suggested that protein restriction slightly slowed the progression of diabetic renal disease, but the results were not statistically significant. [57] *Level of evidence: 1*

- A systematic review of 36 trials and 1,467 patients on various diets used in the treatment of type 2 diabetes found no high-quality data on efficacy. [58] *Level of evidence: 1*

- An RCT comparing a low–glycemic index diet versus a high-fiber diet found that the low–glycemic index diet was more effective in reducing HbA1c compared to the high-fiber diet. [59] *Level of evidence: 1*

- An RCT comparing a low-carbohydrate Mediterranean diet versus a low-fat diet in 215 overweight patients with newly diagnosed type 2 diabetes showed that the Mediterranean-style diet resulted in better glycemic control and control of coronary risk factors than the low-fat diet. [60] *Level of evidence: 1*

- A multicenter RCT was performed to determine whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among patients with type 2 diabetes. In the study, 5,145 overweight or obese patients with type 2 diabetes were randomly assigned to one of two groups: (1) participation in an intensive lifestyle intervention that promoted weight loss through limiting caloric intake and increasing physical activity or (2) participation in diabetes support and education, which constituted the control group. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction,

nonfatal stroke, or hospitalization for angina. After a median follow-up of 9.6 years, the trial was terminated early on the basis of a futility analysis. Weight loss was greater in the intervention group than in the control group throughout the study (8.6%*vs*0.7% at 1 year; 6.0%*vs*3.5% at study end). The intensive lifestyle intervention also produced greater reductions in HbA1c and greater initial improvements in fitness and most cardiovascular risk factors. The rate of the primary outcome, however, was similar for the intervention group and the control group (hazard ratio in the intervention group, 0.95; 95% CI, 0.83-1.09;*P*= .51). Thus, although intensive lifestyle intervention in overweight or obese adults with type 2 diabetes improved glycemia and cardiovascular risk factors, there was no evidence for a reduction in the rate of cardiovascular events. [61] *Level of evidence: 1*

Physical activity

- A systematic review of 14 RCTs comparing exercise versus no exercise in 377 patients with type 2 diabetes found that exercise resulted in a significant improvement in glycemic control, with a reduction in HbA1c levels by 0.6%. Other findings from the study included a reduction in visceral and subcutaneous fat as well as plasma triglycerides in the exercise group. [62] *Level of evidence: 1*

- An RCT was performed to determine whether intensive lifestyle intervention that produces weight loss and improves fitness could slow the loss of mobility in overweight patients with type 2 diabetes. In the study, 5,145 overweight or obese adults within the age range of 45 to 74 years were randomized to either an intensive lifestyle intervention or a diabetes support-and-education program. The primary outcome was self-reported limitation in mobility. After 4 years the lifestyle-intervention group had a relative reduction of 48% in the risk of loss of mobility, as compared with the support group (odds ratio, 0.52; 95% CI, 0.44-0.63;*P*< .001). Both weight loss and improved fitness were significant mediators of this effect (*P*< .001 for both). Adverse events associated with the lifestyle intervention included a minor increase in musculoskeletal symptoms at year 1. Thus, weight loss and

improved fitness slows the decline in mobility in overweight adults with type 2 diabetes. [63] *Level of evidence: 1*

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Codes

ICD-9 code

- 250.00 Diabetes mellitus without mention of complication, type 2 or unspecified type, not stated as uncontrolled

- 250.02 Diabetes mellitus without mention of complication, type 2 or unspecified type, uncontrolled

FAQ

- **Who should be screened for diabetes?**The ADA guidelines state that all persons aged 45 years or older should be screened for diabetes; if results are normal, then screening should be repeated every 3 years. Screening also should be considered for younger persons with risk factors, including obesity (BMI ≥27); first-degree relatives with diabetes; African American, Asian, Hispanic, or Native American ethnicity; history of GDM; hypertension (blood pressure >140/90 mm Hg); HDL cholesterol level <35 mg/dL (0.9 mmol/L) or triglyceride level >250 mg/dL (2.8 mmol/L); and impaired glucose tolerance or impaired fasting glucose on previous glucose testing. Despite these recommendations, however, there is no evidence that implementing such a screening process will affect outcomes in asymptomatic persons

- **What are the current criteria for the diagnosis of diabetes?**A fasting plasma glucose level of 126 mg/dL (7 mmol/L) or higher, a random plasma glucose level of 200 mg/dL (11 mmol/L) or higher with symptoms of hyperglycemia, or a 2-hour plasma glucose level of 200 mg/dL (11 mmol/L) or higher following a standard glucose challenge or HbA1c >6.5%

- **How is HbA1c used to guide patient care?**The ADA states that the goal of therapy should be an HbA1c <7%, but the AACE recommends a goal of <6.5%. The treatment regimen should be re-evaluated in patients with an HbA1c consistently >6.5%

- **When adequate glycemic control cannot be achieved with oral medications, how is insulin initiated?**Metformin, either alone or in combination with other agents, can be combined with a single dose of basal insulin. If this treatment regimen is not successful, a multiple daily injection regimen should be used, often in combination with one or two non-insulin agents

- **What does 70/30 insulin contain, and when is it useful?**70/30 insulin contains a combination of 70% intermediate-acting insulin and 30% short-acting insulin and is typically used in twice-daily dosing. Because the ratio of intermediate-acting insulin to short-acting insulin is fixed, ideal glycemic control may be difficult to achieve in some patients with diabetes, in which case a regimen of separate intermediate-acting insulin and slow-acting insulin should be used instead. Other combinations, including 60/40 insulin, 50/50 insulin, and 75% intermediate-acting insulin plus 25% insulin lispro, are also available. Fixed-combination insulin is generally only useful in patients who cannot mix their own insulin reliably (*eg*, elderly patients, patients with impaired vision) or when tight glycemic control is not needed

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