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The Crux

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CONTENTS

Editorial

Type 1 diabetes (T1D), previously known as **juvenile diabetes**, is a form of diabetes in which very little or no insulin is produced by the islets of Langerhans in the pancreas. Insulin is a hormone required for the body to use blood sugar. Before treatment this results in high blood sugar levels in the body. The classic symptoms are frequent urination, increased thirst, increased hunger, and weight loss. Additional symptoms may include blurry vision, tiredness, and poor wound healing. Symptoms typically develop over a short period of time, often a matter of weeks.

The cause of type 1 diabetes is unknown, but it is believed to involve a combination of genetic and environmental factors. Risk factors include having a family member with the condition. The underlying mechanism involves an autoimmune destruction of the insulin producing beta cells in the pancreas. Diabetes is diagnosed by testing the level of sugar or glycated hemoglobin (HbA1C) in the blood. Type 1 diabetes can be distinguished from type 2 by testing for the presence of autoantibodies.

There is no known way to prevent type 1 diabetes. Treatment with insulin is required for survival. Insulin therapy is usually given by injection just under the skin but can also be delivered by an insulin pump. A diabetic diet and exercise are important parts of management. If left untreated, diabetes can cause many complications. Complications of relatively rapid onset include diabetic ketoacidosis and nonketotic hyperosmolar coma. Long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes. Furthermore, complications may arise from low blood sugar caused by excessive dosing of insulin.

Type 1 diabetes makes up an estimated 5–10% of all diabetes cases. The number of people affected globally is unknown, although it is estimated that about 80,000 children develop the disease each year. Rates of disease vary widely, with approximately 1 new case per 100,000 per year in East Asia and Latin America and around 30 new cases per 100,000 per year in Scandinavia and Kuwait. It typically begins in children and young adults. Juvenile Diabetes is the disease considered under **"DISEASE DIAGNOSIS"**. **Not forgotten are aspects as related to COVID 19 too.**

"INTERPRETATION" section highlights understanding of Type2 DIABETES, while **"TROUBLESHOOTING"** segment all diagnostic aspects as related to Diabetes Mellitus. Total focus is on DM.

"BOUQUET" lurks somewhere within the covers!

DISEASE DIAGNOSIS

JUVENILE DIABETES MELLITUS

Background

Type 1 diabetes mellitus (DM) is a multisystem disease with both biochemical and anatomic/structural consequences. It is a chronic disease of carbohydrate, fat, and protein metabolism caused by the lack of insulin, which results from the marked and progressive inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells. (See Pathophysiology.) (See also Glucose Intolerance.) Type 1 DM can occur at any age. Although it frequently arises in juveniles, it can also develop in adults. (See Epidemiology.) Unlike people with type 2 DM, those with type 1 DM usually are not obese and usually present initially with diabetic ketoacidosis (DKA). The distinguishing characteristic of a patient with type 1 DM is that if his or her insulin is withdrawn, ketosis and eventually ketoacidosis develop. Therefore, these patients are dependent on exogenous insulin. (See Presentation.) Treatment of type 1 DM requires lifelong insulin therapy. A multidisciplinary approach by the physician, nurse, and dietitian, with regular specialist consultation, is needed to control glycemia, as well as to limit the development of its devastating complications and manage such complications when they do occur. (See Treatmentand Medication.) Despite the differences between type 1 and type 2 DM, the costs of the 2 conditions are often combined. In a study that focused on type 1 alone, Tao et al estimated that in the United States, type 1 DM is responsible for $14.4 billion in medical costs and lost income each year.

Pathophysiology

Type 1 DM is the culmination of lymphocytic infiltration and destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas. As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed. Patients need exogenous insulin to reverse this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism. Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM. In a genetically susceptible individual, viral infection may stimulate the production of antibodies against a viral protein that trigger an autoimmune response against antigenically similar beta cell molecules. Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majority also have detectable anti-insulin antibodies before receiving insulin therapy. The most commonly found islet cell antibodies are those directed against glutamic acid decarboxylase (GAD), an enzyme found within pancreatic beta cells. The prevalence of type 1 DM is increased in patients with other autoimmune diseases, such as Graves disease, Hashimoto thyroiditis, and Addison disease. Pilia et al found a higher prevalence of islet cell antibodies (IA2) and anti-GAD antibodies in patients with autoimmune thyroiditis. A study by Philippe et al used computed tomography (CT) scans, glucagon stimulation test results, and fecal elastase-1 measurements to confirm reduced pancreatic volume in individuals with DM. This finding, which was equally present in both type 1 and type 2 DM, may also explain the associated exocrine dysfunction that occurs in DM. Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM. Approximately 95% of patients with type 1 DM have either HLA-DR3 or HLA-DR4. Heterozygotes for those haplotypes are at significantly greater risk for DM than homozygotes. HLA-DQs are also considered specific markers of type 1 DM susceptibility. In contrast, some haplotypes (eg, HLA-DR2) confer strong protection against type 1 DM.

Sensory and autonomic neuropathy

Sensory and autonomic neuropathy in people with diabetes are caused by axonal degeneration and segmental demyelination. Many factors are involved, including the accumulation of sorbitol in peripheral sensory nerves from sustained hyperglycemia. Motor neuropathy and cranial mononeuropathy result from vascular disease in blood vessels supplying nerves.

Angiopathy

Using nailfold video capillaroscopy, Barchetta et al detected a high prevalence of capillary changes in patients with diabetes, particularly those with retinal damage. This reflects a generalized microvessel involvement in both type 1 and type 2 DM. Microvascular disease causes multiple pathologic complications in people with diabetes. Hyaline arteriosclerosis, a characteristic pattern of wall thickening of small arterioles and capillaries, is widespread and is responsible for ischemic changes in the kidney, retina, brain, and peripheral nerves. Atherosclerosis of the main renal arteries and their intrarenal branches causes chronic nephron ischemia. It is a significant component of multiple renal lesions in diabetes. Vitamin D deficiency is an important independent predictor of development of coronary artery calcification in individuals with type 1 DM. Joergensen et al determined that vitamin D deficiency in type 1 diabetes may predict all causes of mortality but not development of microvascular complications.

Nephropathy

In the kidneys, the characteristic wall thickening of small arterioles and capillaries leads to diabetic nephropathy, which is characterized by proteinuria, glomerular hyalinization (Kimmelstiel-Wilson), and chronic renal failure. Exacerbated expression of cytokines such as tumor growth factor beta 1 is part of the pathophysiology of glomerulosclerosis, which begins early in the course of diabetic nephropathy. Genetic factors influence the development of diabetic nephropathy. Single-nucleotide polymorphisms affecting the factors involved in its pathogenesis appear to influence the risk for diabetic nephropathy in different people with type 1 DM.

Double diabetes

In areas where rates of type 2 DM and obesity are high, individuals with type 1 DM may share genetic and environmental factors that lead to their exhibiting type 2 features such as reduced insulin sensitivity. This condition is termed double diabetes. In a study that included 207 patients with type 1 DM, Epstein et al used the estimated glucose disposal rate (eGDR) to assess insulin resistance and found that mean eGDR was significantly lower (and, thus, insulin resistance was higher) in black patients (5.66 mg/kg/min) than in either Hispanic patients (6.70 mg/kg/min) or white patients (7.20 mg/kg/min). In addition, low eGDR was associated with an increased risk of vascular complications of diabetes (eg, cardiovascular disease, diabetic retinopathy, or severe chronic kidney disease).

Etiology

Type 1A DM results from autoimmune destruction of the beta cells of the pancreas and involves both genetic predisposition and an environmental component.

Genetic factors

Although the genetic aspect of type 1 DM is complex, with multiple genes involved, there is a high sibling relative risk. Whereas dizygotic twins have a 5-6% concordance rate for type 1 DM, monozygotic twins will share the diagnosis more than 50% of the time by the age of 40 years. For the child of a parent with type 1 DM, the risk varies according to whether the mother or the father has diabetes. Children whose mother has type 1 DM have a 2-3% risk of developing the disease, whereas those whose father has the disease have a 5-6% risk. When both parents are diabetic, the risk rises to almost 30%. In addition, the risk for children of parents with type 1 DM is slightly higher if onset of the disease occurred before age 11 years and slightly lower if the onset occurred after the parent's 11th birthday. The genetic contribution to type 1 DM is also reflected in the significant variance in the frequency of the disease among different ethnic populations. Type 1 DM is most prevalent in European populations, with people from northern Europe more often affected than those from Mediterranean regions. The disease is least prevalent in East Asians. Genome-wide association studies have identified several loci that are associated with type 1 DM, but few causal relations have been established. The genomic region most strongly associated with other autoimmune diseases, the major histocompatibility complex (MHC), is the location of several susceptibility loci for type 1 DM—in particular, class II HLA DR and DQ haplotypes.

A hierarchy of DR-DQ haplotypes associated with increased risk for type 1 DM has been established. The most susceptible haplotypes are as follows :

- DRB1*0301 - DQA1*0501 - DQB1*0201 (odds ratio [OR] 3.64)
- DRB1*0405 - DQA1*0301 - DQB1*0302 (OR 11.37)
- DRB1*0401 - DQA1*0301 - DQB*0302 (OR 8.39)
- DRB1*0402 - DQA1*0301 - DQB1*0302 (OR 3.63)
- DRB1*0404 - DQA1*0301 - DQB1*0302 (OR 1.59)
- DRB1*0801 - DQB1*0401 - DQB1*0402 (OR 1.25)

Other haplotypes appear to offer protection against type 1 DM. These include the following :

- DRB1*1501 - DQA1*0102 - DQB1*0602 (OR 0.03)
- DRB1*1401 - DQA1*0101 - DQB1*0503 (OR 0.02)
- DRB1*0701 - DQA1*0201 - DQB1*0303 (OR 0.02)

From 90% to 95% of young children with type 1 DM carry HLA-DR3 DQB1*0201, HLA-DR4 DQB1*0302, or both. Carriage of both haplotypes (ie, DR3/4 heterozygotes) confers the highest susceptibility. These high-risk haplotypes are found primarily in people of European descent; other ethnic groups are less well studied. In African Americans, the DRB1*07:01 - DQA1*03:01 - DQB1*02:01g haplotype is associated with increased risk (OR 3.96), whereas the DRB1*07:01-DQA1*02:01 - DQB1*02:01g haplotype appears to be protective (OR 0.34). The insulin gene (INS), which encodes for the pre-proinsulin peptide, is adjacent to a variable number of tandem repeats (VNTR) polymorphism at chromosome 11p15.5. Different VNTR alleles may promote either resistance or susceptibility to type 1 DM through their effect on INS transcription in the thymus; for example, protective VNTRs are associated with higher INS expression, which may promote deletion of insulin-specific T cells. Other genes that have been reported to be involved in the mechanism of type 1 DM include CTLA4 (important in T-cell activation), PTPN22 (produces LYP, a negative regulator of T-cell kinase signaling), and IL2RA (encodes for CD25 which is involved with regulating T-cell function). UBASH3A (also known as STS2), may be involved in the increased risk not only of type 1 DM but also of other autoimmune disease and Down syndrome; it is located on locus chromosome 21q22.3.

In addition, genome-wide association studies have implicated numerous other genes, including the following :

- SH2B3
- ERBB3
- CLEC16A
- IL18RAP
- PTPN2
- CCR5

Environmental factors

Extragenetic factors also may contribute. Potential triggers for immunologically mediated destruction of the beta cells include viruses (eg, enterovirus, mumps, rubella, and coxsackievirus B4), toxic chemicals, exposure to cow's milk in infancy, and cytotoxins. Combinations of factors may be involved. Lempainen et al found that signs of an enterovirus infection by 12 months of age were associated with the appearance of type 1 DM–related autoimmunity among children who were exposed to cow's milk before 3 months of age. These results suggest an interaction between the 2 factors and provide a possible explanation for the contradictory findings obtained in studies that examined these factors in isolation. One meta-analysis found a weak but significant linear increase in the risk of childhood type 1 DM with increasing maternal age. However, little evidence supports any substantial increase in childhood type 1 DM risk after pregnancy complicated by preeclampsia. A study by Simpson et al found that neither vitamin D intake nor 25-hydroxyvitamin D levels throughout childhood were associated with islet autoimmunity or progression to type 1 DM. This study was based in Denver, Colorado, and has been following children at increased risk of diabetes since 1993. Early upper respiratory infection may also be a risk factor for type 1 diabetes. In an analysis of data on 148 children considered genetically at risk for diabetes, upper respiratory infections in the first year of life were associated with an increased risk for type 1 diabetes . All children in the study who developed islet autoimmunity had at least 2 upper respiratory infections in the first year of life and at least 1 infection within 6 months before islet autoantibody seroconversion. Children with respiratory infections in the first 6 months of life had the greatest increased hazard ratio (HR) for islet autoantibody seroconversion (HR = 2.27), and the risk was also increased in those with respiratory infections at ages 6 to almost 12 months (HR = 1.32). The rate of islet autoantibody seroconversion was highest among children with more than 5 respiratory infections in the first year of year of life. Respiratory infections in the second year of life were not related to increased risk. Although controversial, some evidence exists that coronavirus disease 2019 (COVID-19) may actually lead to the development of type 1 and type 2 diabetes. It has been theorized, for example, that diabetes arises when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, binds “to angiotensin-converting enzyme 2 (ACE2) receptors in key metabolic organs and tissues, including pancreatic beta cells and kidneys.” The CoviDiab registry was established by an international group of diabetes researchers to gather data on COVID-19–related diabetes.

Epidemiology

International statistics

Internationally, rates of type 1 DM are increasing. In Europe, the Middle East, and Australia, rates of type 1 DM are increasing by 2-5% per year. The prevalence of type 1 DM is highest in Scandinavia (ie, approximately

20% of the total number of people with DM) and lowest in China and Japan (ie, fewer than 1% of all people with diabetes). Some of these differences may relate to definitional issues and the completeness of reporting.

Age-related demographics

Previously referred to as juvenile-onset diabetes, type 1 DM is typically diagnosed in childhood, adolescence, or early adulthood. Although the onset of type 1 DM often occurs early in life, 50% of patients with new-onset type 1 DM are older than 20 years of age. Type 1 DM usually starts in children aged 4 years or older, appearing fairly abruptly, with the peak incidence of onset at age 11-13 years (ie, in early adolescence and puberty). There is also a relatively high incidence in people in their late 30s and early 40s, in whom the disease tends to present less aggressively (ie, with early hyperglycemia without ketoacidosis and gradual onset of ketosis). This slower-onset adult form of type 1 DM is referred to as latent autoimmune diabetes of the adult (LADA). A study by Thomas et al, using data from the UK Biobank, determined that in 42% of type 1 DM cases reviewed, disease onset occurred in patients aged 31 to 60 years. The report also found that because type 2 DM is far more common than type 1 in individuals in the 31- to 60-year age group, with type 1 DM making up only 4% of all diabetes cases in this population, identification of type 1 DM is difficult in patients over age 30 years. The presence of type 1 DM was identified in the study using a genetic risk score that employed 29 common genetic variants. The risk of development of antibodies (anti-islet) in relatives of patients with type 1 DM decreases with increasing age. This finding supports annual screening for antibodies in relatives younger than 10 years and 1 additional screening during adolescence.

Sex- and race-related demographics

Type 1 DM is more common in males than in females. In populations of European origin, the male-to-female ratio is greater than 1.5:1. Type 1 DM is most common among non-Hispanic whites, followed by African Americans and Hispanic Americans. It is comparatively uncommon among Asians.

Prognosis

Type 1 DM is associated with a high morbidity and premature mortality. More than 60% of patients with type 1 DM do not develop serious complications over the long term, but many of the rest experience blindness, end-stage renal disease (ESRD), and, in some cases, early death. The risk of ESRD and proliferative retinopathy is twice as high in men as in women when the onset of diabetes occurred before age 15 years. Patients with type 1 DM who survive the period 10-20 years after disease onset without fulminant complications have a high probability of maintaining reasonably good health. Other factors affecting long-term outcomes are the patient's education, awareness, motivation, and intelligence level. The 2012 American Diabetes Association (ADA) standard of care emphasizes the importance of long-term, coordinated care management for improved outcomes and suggests structural changes to existing systems of long-term care delivery.

The morbidity and mortality associated with diabetes are related to the short- and long-term complications. Such complications include the following:

- Hypoglycemia from management errors
- Increased risk of infections
- Microvascular complications (eg, retinopathy and nephropathy)
- Neuropathic complications
- Macrovascular disease

These complications result in increased risk for ischemic heart disease, cerebral vascular disease, peripheral vascular disease with gangrene of lower limbs, chronic renal disease, reduced visual acuity and blindness, and autonomic and peripheral neuropathy. Diabetes is the major cause of blindness in adults aged 20-74 years, as well as the leading cause of nontraumatic lower-extremity amputation and ESRD. In both diabetic and non-diabetic patients, coronary vasodilator dysfunction is a strong independent predictor of cardiac mortality. In diabetic patients without coronary artery disease, those with impaired coronary flow reserve have event rates similar to those with prior coronary artery disease, while patients with preserved coronary flow reserve have event rates similar to non-diabetic patients. A study by Bode et al indicated that among patients with coronavirus disease 2019 (COVID-19), the US in-hospital death rate for individuals living with diabetes, patients with an HbA1c of 6.5% or higher, and those with hyperglycemia throughout their stay is 29%, a figure over four times greater than that for patients without diabetes or hyperglycemia. Moreover, the in-hospital death rate for patients with no evidence of preadmission diabetes who develop hyperglycemia while admitted was found to be seven times higher (42%). However, a Belgian study, by Vangoitsenhoven et al, indicated that in most people, the presence of type 1 diabetes mellitus is not associated with a greater risk of hospitalization for COVID-19. The investigators found that during the first 3 months of the pandemic in Belgium, the COVID-19 hospitalization rate was similar between individuals with type 1 diabetes and those without (0.21% vs 0.17%, respectively). Among the patients with type 1 diabetes, older persons had a greater tendency toward COVID-19–related hospitalization, although glucose control, comorbidity profile, and angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) therapy did not significantly differ between the hospitalized and non-hospitalized groups. This and other research suggest that in persons with type 1 diabetes, an increased risk of death from COVID-19 is found primarily in particularly vulnerable individuals instead of in such patients overall. Type 1 diabetic patients also have a high prevalence of small-fiber neuropathy. In a prospective study of 27 patients who had type 1 diabetes with a mean disease duration of 40 years, almost 60% of the subjects showed signs or symptoms of neuropathy, including sensory neuropathy symptoms (9 patients), pain (3 patients), and carpal-tunnel symptoms (5 patients). Of the 27 patients, 22 were diagnosed with small-fiber dysfunction by means of quantitative sensory testing. Abnormal results on intraepidermal nerve-fiber density measurement (IENFD) were seen in 19 patients. IENFD was negatively correlated with HbA1c, but this relation was no longer significant after adjustment for age, body mass index, and height. N-ε-(carboxymethyl) lysine (CML), which is linked to painful diabetic neuropathy, remained independently associated with IENFD even after adjustment for these variables. Large-fiber neuropathy was also common, being found in 16 patients. Although ESRD is one of the most severe complications of type 1 DM, its incidence is relatively low: 2.2% at 20 years after diagnosis and 7.8% at 30 years after diagnosis. A greater risk is that mild diabetic nephropathy in type 1 diabetic persons appears to be associated with an increased likelihood of cardiovascular disease. Moreover, the long-term risk of an impaired glomerular filtration rate (GFR) is lower in persons treated with intense insulin therapy early in the course of disease than in those given conventional therapy. Although mortality from early-onset type 1 DM (onset age, 0-14 y) has declined, the same may not be true for late-onset type 1 DM (onset age, 15-29 y). One study suggest that women tend to fare worse in both cohorts and that alcohol and drug use account for more than one third of deaths. Control of blood glucose, hemoglobin A1c (HbA1c), lipids, blood pressure, and weight significantly affects

prognosis. Excess weight gain with intensified diabetes treatment is associated with hypertension, insulin resistance, dyslipidemia and extetnsive atherosclerotic cardiovascular disease. Patients with diabetes face a lifelong challenge to achieve and maintain blood glucose levels as close to the normal range as possible. With appropriate glycemic control, the risk of both microvascular and neuropathic complications is decreased markedly. In addition, aggressive treatment of hypertension and hyperlipidemia decreases the risk of macrovascular complications. The benefits of glycemic control and control of comorbidities must be weighed against the risk of hypoglycemia and the short-term costs of providing high-quality preventive care. However, studies have shown cost savings due to a reduction in acute diabetes-related complications within 1-3 years of starting effective preventive care.

Patient Education

Education is a vital aspect of diabetes management. Patients with new-onset type 1 DM require extensive education if they are to manage their disease safely and effectively and to minimize long-term complications. Such education is best coordinated by the patient's long-term care providers.

At every encounter, the clinician should educate the patient—and, in the case of children, the parents—about the disease process, management, goals, and long-term complications. In particular, clinicians should do the following:

- Make patients aware of the signs and symptoms of hypoglycemia and knowledgeable about ways to manage it
- Help patients understand and acknowledge the course of diabetes (eg, by teaching patients that they have a chronic condition that requires lifestyle modification and that they are likely to have chronic complications if they do not take control of their disease)
- Reassure patients about the prognosis in properly managed type 1 DM

ADA guidelines urge that attention be paid to older adolescent patients who may be leaving their home and their current health care providers. At the transition between pediatric and adult health care, older teens can become detached from the health care system, putting their medical care and their glycemic control at risk. Education about an appropriate treatment plan and encouragement to follow the plan are especially important in patients with diabetes. Physicians must ensure that the care for each patient with diabetes includes all necessary laboratory tests, examinations (eg, foot and neurologic examinations), and referrals to specialists (eg, an ophthalmologist or podiatrist). A dietitian should provide specific diet control education to the patient and family. A nurse should educate the patient about self–insulin injection and performing fingerstick tests for blood glucose level monitoring.

Clinical Presentation

History

The most common symptoms of type 1 diabetes mellitus (DM) are polyuria, polydipsia, and polyphagia, along with lassitude, nausea, and blurred vision, all of which result from the hyperglycemia itself. Polyuria is caused by osmotic diuresis secondary to hyperglycemia. Severe nocturnal enuresis secondary to polyuria can be an indication of onset of diabetes in young children. Thirst is a response to the hyperosmolar state and dehydration. Fatigue and weakness may be caused by muscle wasting from the catabolic state of insulin deficiency, hypovolemia, and hypokalemia. Muscle cramps are caused by electrolyte imbalance. Blurred vision results from the effect of the hyperosmolar state on the lens and vitreous humor. Glucose and its metabolites cause osmotic swelling of the lens, altering its normal focal length. Symptoms at the time of the first clinical presentation can usually be traced back several days to several weeks. However, beta-cell destruction may have started months, or even years, before the onset of clinical symptoms. The onset of symptomatic disease may be sudden. It is not unusual for patients with type 1 DM to present with diabetic ketoacidosis (DKA), which may occur de novo or secondary to the stress of illness or surgery. An explosive onset of symptoms in a young lean patient with ketoacidosis always has been considered diagnostic of type 1 DM. Over time, patients with new-onset type 1 DM will lose weight, despite normal or increased appetite, because of depletion of water and a catabolic state with reduced glycogen, proteins, and triglycerides. Weight loss may not occur if treatment is initiated promptly after the onset of the disease.

Gastrointestinal (GI) symptoms of type 1 DM are as follows:

- Nausea, abdominal discomfort or pain, and change in bowel movements may accompany acute DKA
- Acute fatty liver may lead to distention of the hepatic capsule, causing right upper quadrant pain
- Persistent abdominal pain may indicate another serious abdominal cause of DKA (eg, pancreatitis
- Chronic GI symptoms in the later stage of DM are caused by visceral autonomic neuropathy

Neuropathy affects up to 50% of patients with type 1 DM, but symptomatic neuropathy is typically a late development, developing after many years of chronic prolonged hyperglycemia. Peripheral neuropathy presents as numbness and tingling in both hands and feet, in a glove-and-stocking pattern; it is bilateral, symmetric, and ascending.

History in patients with established diabetes

It is important to inquire about the type and duration of the patient's diabetes and about the care the patient is receiving for diabetes. Determination of the type of diabetes is based on history, therapy, and clinical judgment. The chronic complications of diabetes are related to the length of time the patient has had the disease. Ask about the type of insulin being used, delivery system (pump vs injections), dose, and frequency. Also ask about oral antidiabetic agents, if any. Of course, a full review of all medications and over-the-counter supplements being taken is crucial in the assessment of patients with type 1 DM. Patients using a pump or a multiple-injection regimen have a basal insulin (taken through the pump or with the injection of a long-acting insulin analogue) and a premeal rapid-acting insulin, the dose of which may be determined as a function of the carbohydrate count plus the correction (to adjust for how high the premeal glucose level is). In these patients, ask about the following:

- Basal rates (eg, units per hour by pump, generally 0.4-1.5 U/h, potentially varying on the basis of time of day); the total daily dose as basal insulin is a helpful value to know
- Carbohydrate ratio (ie, units of insulin per grams of carbohydrate, generally 1 unit of rapid-acting insulin per 10-15 g carbohydrate)
- Correction dose (ie, how far the blood glucose level is expected to decrease per unit of rapid-acting insulin, often 1 U of insulin per 50-mg/dL decrease, though individuals with insulin resistance may need 1 U per 25-mg/dL decrease)
- Some patients may be taking premeal pramlintide (an amylin analogue)

A focused diabetes history should also include the following questions:

- Is the patient's diabetes generally well controlled, with near-normal blood glucose levels? (Patients with poorly controlled blood glucose levels heal more slowly and are at increased risk for infection and other complications)

- Does the patient have severe hypoglycemic reactions? (If the patient has episodes of severe hypoglycemia and therefore is at risk for losing consciousness, this possibility must be addressed, especially if the patient drives)
- Does the patient have diabetic nephropathy that might alter the use of medications or intravenous (IV) radiographic contrast material?
- Does the patient have macrovascular disease, such as coronary artery disease (CAD), which should be considered in the emergency department (ED)?
- Does the patient self-monitor his or her blood glucose levels? (Note the frequency and range of values at each time of day; an increasing number of patients monitor with continuous sensors)
- When was the patient's hemoglobin A1c (HbA1c) value (an indicator of long-term glucose control) last measured? What was it?

In assessing glycemic exposure of a patient with established type 1 DM, review of self-monitored blood glucose levels is necessary. Ideally, this done by uploading time- and date-stamped levels from the patient's meter to assure full understanding of the frequency of testing and the actual levels.

Questions regarding hypoglycemia and hyperglycemia

Hypoglycemia and hyperglycemia should be considered. Ask the following questions as needed:

- Has the patient experienced recent polyuria, polydipsia, nocturia, or weight loss?
- Has the patient had episodes of unexplained hypoglycemia? If so, when, how often, and how does the patient treat these episodes?
- Does the patient have hypoglycemia unawareness (ie, does the patient lack the adrenergic warning signs of hypoglycemia)? (Hypoglycemia unawareness indicates an increased risk of subsequent episodes of hypoglycemia)

Questions regarding microvascular complications

Microvascular complications, such as retinopathy and nephropathy, should be considered as well. Ask the following questions as appropriate:

- When was the patient's last dilated eye examination? What were the results?
- Does the patient have known kidney disease?
- What were the dates and results of the last measurements of urine protein and serum creatinine levels?

Questions regarding macrovascular complications

Macrovascular complications should be explored. Questions should include the following:

- Does the patient have hypertension? What medications are taken?
- Does the patient have symptoms of claudication or a history of vascular bypass?
- Has the patient had a stroke or transient ischemic attack?
- What are the patient's most recent lipid levels?
- Is the patient taking lipid-lowering medication?

Questions regarding neuropathy

Potential neuropathy should be taken into account. Ask whether the patient has a history of neuropathy or symptoms of peripheral neuropathy or whether autonomic neuropathy is present (including erectile dysfunction if the patient is a man).

Other questions

The possibility of foot disease should be addressed. Inquire as to whether the patient has a history of foot ulcers or amputations or whether any foot ulcers are present. (See Diabetic Foot and Diabetic Foot Infections.) The possibility of infection also should be considered. Be sure to inquire about whether frequent infections are a problem and, if so, at what sites.

Physical Examination

In new cases of diabetes, physical examination findings are usually normal. Patients with DKA, however, will have Kussmaul respiration, signs of dehydration, hypotension, and, in some cases, altered mental status. In established cases, patients should be examined every 3 months for macrovascular and microvascular complications. They should undergo funduscopic examination for retinopathy and monofilament testing for peripheral neuropathy.

Diabetes-focused examination

A diabetes-focused physical examination includes assessment of vital signs, funduscopic examination, limited vascular and neurologic examinations, and foot examination. Other organ systems should be assessed as indicated by the patient's clinical situation. A comprehensive examination is not necessary at every visit.

Assessment of vital signs

Patients with established diabetes and autonomic neuropathy may have orthostatic hypotension. Orthostatic vital signs may be useful in assessing volume status and in suggesting the presence of an autonomic neuropathy. Measurement of the pulse is important, in that relative tachycardia is a typical finding in autonomic neuropathy, often preceding the development of orthostatic hypotension. If the respiratory rate and pattern suggest Kussmaul respiration, DKA must be considered immediately, and appropriate tests must be ordered.

Funduscopic examination

The funduscopic examination should include a careful view of the retina. Both the optic disc and the macula should be visualized. If hemorrhages or exudates are seen, the patient should be referred to an ophthalmologist as soon as possible. Examiners who are not ophthalmologists tend to underestimate the severity of retinopathy, which cannot be evaluated accurately unless the patients' pupils are dilated.

Foot examination

The dorsalis pedis and posterior tibialis pulses should be palpated and their presence or absence noted. This is particularly important in patients who have foot infections: poor lower-extremity blood flow can delay healing and increase the risk of amputation. Documenting lower-extremity sensory neuropathy is useful in patients who present with foot ulcers because decreased sensation limits the patient's ability to protect the feet and ankles. If peripheral neuropathy is found, the patient should be made aware that foot care (including daily foot examination) is very important for the prevention of foot ulcers and lower-extremity amputation.

Complications

Infections

Infections cause considerable morbidity and mortality in patients with diabetes. Infection may precipitate metabolic derangements, and conversely, the metabolic derangements of diabetes may facilitate infection. Patients with long-standing diabetes tend to have microvascular and macrovascular disease with resultant poor tissue perfusion and increased risk of infection. The ability of the skin to act as a barrier to infection may be compromised when the diminished sensation of diabetic neuropathy results in unnoticed injury. Diabetes increases

susceptibility to various types of infections. The most common sites are the skin and urinary tract. Dermatologic infections that occur with increased frequency in patients with diabetes include staphylococcal follicular skin infections, superficial fungal infections, cellulitis, erysipelas, and oral or genital candidal infections. Both lower urinary tract infections and acute pyelonephritis are seen with greater frequency. A few infections, such as malignant otitis externa, rhinocerebral mucormycosis, and emphysematous pyelonephritis, occur almost exclusively in patients with diabetes, though they are fairly rare even in this population. Infections such as staphylococcal sepsis occur more frequently and are more often fatal in patients with diabetes than in others. Infections such as pneumococcal pneumonia affect patients with diabetes and other patients with the same frequency and severity.

COVID-19

A study reported that out of 178 adult patients hospitalized with coronavirus disease 2019 (COVID-19), at least one underlying condition was found in 89.3%, the most common being hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%). According to a report by Stokes et al, out of 287,320 US cases of COVID-19 in which the patient's underlying health status was known, diabetes was the second most common underlying condition (30%), after cardiovascular disease (32%), which in this study included hypertension. The aforementioned study by Barrera et al found the overall prevalence of diabetes in patients with COVID-19 to be 12%, with the prevalence being 18% in severe COVID-19. In patients with type 1 DM who were diagnosed with COVID-19, a study by Ebekozien et al found that high blood glucose (48.5%), elevated temperature (45.5%), dry cough (39.4%), excess fatigue (33.3%), vomiting (33.3%), shortness of breath (30.3), nausea (30.2%), and body aches/headaches (21.2%) were the most prevalent presenting symptoms reported. Moreover, diabetic ketoacidosis was the most prevalent adverse outcome (45.5%) among these patients. The Centers for Disease Control and Prevention (CDC) includes type 2 DM in the list of conditions that increase the likelihood of severe illness in persons with COVID-19, and type 1 DM in the list of conditions that may increase this likelihood.

Ophthalmologic complications

Diabetes can affect the lens, vitreous, and retina, causing visual symptoms that may prompt the patient to seek emergency care. Visual blurring may develop acutely as the lens changes shape with marked changes in blood glucose concentrations. This effect, which is caused by osmotic fluxes of water into and out of the lens, usually occurs as hyperglycemia increases, but it also may be seen when high glucose levels are lowered rapidly. In either case, recovery to baseline visual acuity can take up to a month, and some patients are almost completely unable to read small print or do close work during this period. Patients with diabetes tend to develop senile cataracts at a younger age than persons without diabetes. Rarely, patients with type 1 DM that is very poorly controlled (eg, those with frequent episodes of DKA) can acutely develop a “snowflake” (or “metabolic”) cataract. Named for their snowflake or flocculent appearance, these cataracts can progress rapidly and create total opacification of the lens within a few days. Whether diabetes increases the risk of glaucoma remains controversial; epidemiologic studies have yielded conflicting results. Glaucoma in diabetes relates to the neovascularization of the iris (ie, rubeosis iridis diabetica). Diabetic retinopathy is the principal ophthalmologic complication of DM.

Diabetic retinopathy is the leading cause of blindness internationally in people younger than 60 years and affects the eyes in the following different ways:

- Background retinopathy involves retinal small vessel abnormality leading to hard exudates, hemorrhages, and microaneurysms; it does not affect acuity
- Proliferative retinopathy involves extensive proliferation of new retinal small blood vessels; a sudden loss of vision can occur because of vitreous hemorrhage from proliferating new vessels or retinal detachment
- Maculopathy involves edema and hard exudate or retinal ischemia; it causes a marked reduction of acuity.

Whether patients develop diabetic retinopathy depends on the duration of their diabetes and on the level of glycemic control. The following are the 5 stages in the progression of diabetic retinopathy:

1. Dilation of the retinal venules and formation of retinal capillary microaneurysms
2. Increased vascular permeability
3. Vascular occlusion and retinal ischemia
4. Proliferation of new blood vessels on the surface of the retina
5. Hemorrhage and contraction of the fibrovascular proliferation and the vitreous

The first 2 stages of diabetic retinopathy are jointly referred to as background or nonproliferative retinopathy. Initially, the retinal venules dilate, then microaneurysms (tiny red dots on the retina that cause no visual impairment) appear. The microaneurysms or retinal capillaries become more permeable, and hard exudates appear, reflecting leakage of plasma. Rupture of intraretinal capillaries results in hemorrhage. If a superficial capillary ruptures, a flame-shaped hemorrhage appears. Hard exudates are often found in partial or complete rings (circinate pattern), which usually include multiple microaneurysms. These rings usually mark an area of edematous retina. The patient may not notice a change in visual acuity unless the center of the macula is involved. Macular edema can cause visual loss; therefore, all patients with suspected macular edema must be referred to an ophthalmologist for evaluation and possible laser therapy. Laser therapy is effective in decreasing macular edema and preserving vision but is less effective in restoring lost vision. (See Macular Edema in Diabetes .) Preproliferative (stage 3) and proliferative diabetic retinopathy (stages 4 and 5) are the next phases in the progression of the disease. Cotton-wool spots can be seen in preproliferative retinopathy. These represent retinal microinfarcts from capillary occlusion and appear as off-white to gray patches with poorly defined margins. Proliferative retinopathy is characterized by neovascularization, or the development of networks of fragile new vessels that often are seen on the optic disc or along the main vascular arcades. The vessels undergo cycles of proliferation and regression. During proliferation, fibrous adhesions develop between the vessels and the vitreous. Subsequent contraction of the adhesions can result in traction on the retina and retinal detachment. Contraction also tears the new vessels, which hemorrhage into the vitreous.

Diabetic nephropathy

About 20–30% of patients with type 1 DM develop evidence of nephropathy, and all patients with diabetes should be considered to have the potential for renal impairment unless proven otherwise. Chronically elevated blood pressure contributes to the decline in renal function. The use of contrast media can precipitate acute renal failure in patients with underlying diabetic nephropathy. Although most recover

from contrast medium–induced renal failure within 10 days, some have irreversible renal failure.

Diabetic neuropathy

In the peripheral nerves, diabetes causes peripheral neuropathy. (See Diabetic Lumbosacral Plexopathy and Diabetic Neuropathy.) The 4 types of diabetic neuropathy are as follows:

- Peripheral distal symmetrical polyneuropathy, predominantly sensory
- Autonomic neuropathy
- Proximal painful motor neuropathy
- Cranial mononeuropathy (ie, cranial nerve III, IV, or VI)

Of these 4 types, distal symmetric sensorimotor polyneuropathy (in a glove-and-stocking distribution) is the most common. Besides causing pain in its early stages, this type of neuropathy eventually results in the loss of peripheral sensation. The combination of decreased sensation and peripheral arterial insufficiency often leads to foot ulceration and eventual amputation. Acute-onset mononeuropathies in diabetes include acute cranial mononeuropathies, mononeuropathy multiplex, focal lesions of the brachial or lumbosacral plexus, and radiculopathies. Of the cranial neuropathies, the third cranial nerve (oculomotor) is most commonly affected, followed by the sixth nerve (abducens) and the fourth nerve (trochlear). Patients can present with diplopia and eye pain. In diabetic third-nerve palsy, the pupil is usually spared, whereas in third-nerve palsy due to intracranial aneurysm or tumor, the pupil is affected in 80-90% of cases. It is important to consider nondiabetic causes of cranial nerve palsies, including intracranial tumors, aneurysms, and brainstem stroke. Therefore, evaluation should include nonenhanced and contrast-enhanced compute4d tomography (CT) or, preferably, magnetic resonance imaging (MRI). Neurologic consultation is recommended. Acute cranial-nerve mononeuropathies usually resolve in 2-9 months. Acute thrombosis or ischemia of the blood vessels supplying the structure involved is thought to cause these neuropathies.

Macrovascular complications

People with diabetes experience accelerated atherosclerosis, affecting the small arteries of the heart, brain, lower extremity, and kidney. Coronary atherosclerosis often occurs at a younger age and is more severe and extensive than in those without diabetes, increasing the risk of ischemic heart disease. Atherosclerosis of the internal carotid and vertebrobasilar arteries and their branches predisposes to cerebral ischemia. Severe atherosclerosis of the iliofemoral and smaller arteries of the lower legs predisposes to gangrene. Ischemia of a single toe or ischemic areas on the heel are characteristic of diabetic peripheral vascular disease; these result from the involvement of much smaller and more peripheral arteries. Atherosclerosis of the main renal arteries and their intrarenal branches causes chronic nephron ischemia, which is a significant component of multiple renal lesions in diabetes. However, not all people with type 1 DM are at risk for nephropathy, because there are some polymorphisms in the various factors involved in its pathogenesis, which can modulate the course of this disease from one person to the other.

Risk factors for macrovascular disease

Macrovascular disease is the leading cause of death in patients with diabetes, causing 65-75% of deaths in this group, compared with approximately 35% of deaths in people without diabetes. Diabetes by itself increases the risk of myocardial infarction (MI) 2-fold in men and 4-fold in women, and many patients have other risk factors for MI as well. The HbA1c value per se, rather than self-reported diabetes status or other established risk factors, robustly predicts MI odds. Each 1% increment in HbA1c independently predicts 19% higher odds for MI. The risk of stroke in people with diabetes is double that of nondiabetic people, and the risk of peripheral vascular disease is 4 times that of people without diabetes. Patients with diabetes may have an increased incidence of silent ischemia. Diastolic dysfunction is common in patients with diabetes and should be considered in patients who have symptoms of congestive heart failure and a normal ejection fraction.

Differential Diagnoses

Diagnostic Considerations

The following conditions and factors should be taken into account in considering a diagnosis of type 1 diabetes mellitus (DM):

- Type 2 DM
- Monogenic DM, previously known as maturity-onset diabetes of youth (MODY), a rare autosomal dominant condition found primarily in whites
- Secondary hyperglycemia
- Disorders of target tissues (liver, muscles, adipose tissue)
- Endocrine disorders - Endocrine tumor causing increased production of growth hormone, glucocorticoids, catecholamines, glucagon, and somatostatin; Addison disease; Graves disease; Hashimoto thyroiditis; acanthosis nigricans (genetic disorders with insulin resistance)
- Drugs - Thiazide diuretics, phenytoin, and glucocorticoids
- Chronic pancreatitis
- Cystic fibrosis
- Prader-Willi syndrome - Mental retardation, muscular hypotonia, obesity, short stature, and hypogonadism associated with DM
- Nondiabetic glycosuria
- Renal glycosuria - Glucose appears in urine despite normal glucose concentration in blood; this may occur because of an autosomal genetic disorder or dysfunction of the proximal renal tubule (eg, Fanconi syndrome or chronic renal failure), or it may occur during pregnancy as a consequence of the increased glucose load placed on tubules by the elevated glucose filtration rate
- Peripheral neuropathy from alcohol abuse or vitamin B-12 deficiency.

Type 1 versus type 2 diabetes

Determining whether a patient has type 1 or type 2 DM is an important diagnostic and therapeutic concern because patients with type 1 DM depend on continuous exogenous insulin for survival. A patient whose diabetes is controlled with diet or an oral antidiabetic agent clearly has type 2 DM. A lean patient who has had diabetes since childhood, who has always been dependent on insulin, or who has a history of diabetic ketoacidosis (DKA) almost certainly has type 1 DM. Distinguishing the type of diabetes can be difficult in (1) patients who are treated with insulin and who are younger but clinically appear to have type 2 DM and (2) older patients with late-onset diabetes who nonetheless take insulin and seem to share characteristics of patients with type 1 DM. (This latter group is now said to have latent autoimmune diabetes of the adult [LADA].) It should be noted that for many patients, it will not be possible to fully distinguish type 1 DM from type 2. When in doubt, treat the patient with insulin and close monitoring of glucose levels. It is not unusual for adolescents or young adults, particularly Hispanic or African-American patients, to present with DKA and subsequently be found to have type 2 DM.

Monogenic diabetes

Although monogenic diabetes syndromes are not very common, representing fewer than 5% of pediatric diabetes cases, it is important to avoid misdiagnosis of monogenic DM as type 1 or type 2 DM. The American Diabetes Association (ADA) advises considering a diagnosis of monogenic diabetes when the following criteria are present :

- Diabetes is diagnosed within 6 months of birth
- A strong family history of diabetes is present, without type 2 features (eg, obesity or higher-risk ethnicity)
- Mild fasting hyperglycemia is observed, especially in young, nonobese children
- Diabetes is present, but islet cell autoantibodies, obesity, and insulin resistance are absent

If a form of monogenic diabetes is suspected, it is increasingly feasible to obtain a true genetic diagnosis through commercially available genetic testing. For further information about the diagnosis and management of monogenic diabetes, the ADA suggests consulting the 2009 clinical practice consensus guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) at the ISPAD website.

Differential Diagnoses

- Diabetic Ketoacidosis (DKA)
- Diabetic Nephropathy
- Diabetic Foot Ulcers
- Insulin Resistance
- Lead Nephropathy
- Type 2 Diabetes Mellitus.

Workup

Laboratory Studies

Plasma glucose

Patients with type 1 diabetes mellitus (DM) typically present with symptoms of uncontrolled hyperglycemia (eg, polyuria, polydipsia, polyphagia). In such cases, the diagnosis of DM can be confirmed with a random (nonfasting) plasma glucoseconcentration of 200 mg/dL or a fasting plasma glucose concentration of 126 mg/dL (6.99 mmol/L) or higher. A fingerstick glucose test is appropriate in the emergency department (ED) for virtually all patients with diabetes. All fingerstick capillary glucose levels must be confirmed in serum or plasma to make the diagnosis. All other laboratory studies should be selected or omitted on the basis of the individual clinical situation. Intravenous (IV) glucose testing may be considered for possible early detection of subclinical diabetes. Individually measured glucose levels may differ considerably from estimated glucose averages calculated from measured hemoglobin A1c (HbA1c) levels. Therefore, caution is urged when the decision is made to estimate rather than actually measure glucose concentration; the difference between the 2 has a potential impact on decision making.

Hemoglobin A

HbA1c is the stable product of nonenzymatic irreversible glycation of the beta chain of hemoglobin by plasma glucose and is formed at rates that increase with increasing plasma glucose levels. HbA1c levels provide an estimate of plasma glucose levels during the preceding 1-3 months. The reference range for nondiabetic people is 6% in most laboratories. Glycated hemoglobin levels also predict the progression of diabetic microvascular complications. American Diabetes Association (ADA) guidelines recommend measuring HbA1c at least every 6 months in patients with diabetes who are meeting treatment goals and who have stable glycemic control. For patients whose therapy has changed or who are not meeting glycemic goals, the guidelines recommend HbA1c testing every 3 months. In the past, HbA1c measurements were not considered useful for the diagnosis of DM. Drawbacks included a lack of international standardization and insensitivity for the detection of milder forms of glucose intolerance. In a 2009 report, however, an international expert committee appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Association recommended the HbA1c assay for diagnosing type 1 and type 2 DM. In the case of type 1 DM, however, the committee recommended using the test only when the condition is suspected but the classic symptoms of type 1 DM—polyuria, polydipsia, polyphagia, a random glucose level of 200 mg/dL, and unexplained weight loss—are absent.

The committee noted the improvement in standardization and cited the following advantages of HbA1c testing over glucose measurement:

- Ability to capture long-term glucose exposure
- Less biologic variability
- No requirement for fasting or timed samples
- Current use in guiding management decisions

Consequently, since 2010 the ADA has included an HbA1c level of 6.5% or higher as a criterion for diabetes diagnosis, with confirmation from repeat testing (unless clinical symptoms are present and the glucose level exceeds 200 mg/dL). HbA1ctesting cannot be used in patients with abnormal red blood cell (RBC) turnover (as in hemolytic or iron-deficiency anemia). In children with rapidly evolving type 1 DM, HbA1c may not be significantly elevated despite frank diabetes. One study found seasonal variability in HbA1c levels of school-age children with higher levels (0.44%) coinciding with colder outdoor temperatures, fewer hours of sunlight, and lower levels of solar irradiance. This effect was seen in school-aged children but not preschoolers and may hold importance for studies using HbA1c as a primary endpoint and HbA1c -based diagnosis of diabetes. HbA1c cannot be used as an indicator of glycemic control in patients with neonatal diabetes mellitus (NDM) because of the high levels of fetal hemoglobin (HbF) remaining in the blood. A study by Suzuki et al found that glycated albumin, which is not affected by HbF levels, more strongly correlated with 1-month average postprandial blood glucose and was therefore a better marker of diabetes in neonates. This finding is important to neonatologist and those caring for newborns. Moreover, the overall efficacy of HbA1c testing in diabetes diagnosis remains uncertain. A study presented in 2019, using data derived from 9000 adults, reported diabetes diagnosis with the HbA1c blood test to be unreliable. The investigators found evidence that in comparison with the oral glucose tolerance test, HbA1c testing would lead to a 42% overdiagnosis of glucose tolerance and a 73% underdiagnosis of diabetes, in adults. ADA guidelines recommend measuring HbA1c at least every 6 months year in patients who are meeting treatment goals and who have stable glycemic control. For patients whose therapy has changed or who are not meeting glycemic goals, the guidelines recommend HbA1c testing every 3 months.

Other laboratory studies

Fructosamine levels also test for glucose levels. Fructosamine is formed by a chemical reaction of glucose with plasma protein and reflects glucose control in the previous 1-3 weeks. This assay, therefore, may show a change in control before HbA1c and often is helpful when applying intensive treatment and in short-term clinical trials. A white blood cell (WBC) count and blood and urine cultures may be performed to rule out infection. Urine ketones are not reliable for diagnosing or monitoring diabetic ketoacidosis (DKA), although they may be useful in screening to see whether a hyperglycemic individual may have some degree of ketonemia. The plasma acetone level—specifically, the beta-

hydroxybutyrate level—is a more reliable indicator of DKA, along with measurement of plasma bicarbonate or arterial pH as clinically required. (See the Medscape Reference Laboratory Medicine article Ketones.) Screening for type 1 DM in asymptomatic low-risk individuals is not recommended. However, in patients at high risk (eg, those who have first-degree relatives with type 1 DM), it may be appropriate to perform annual screening for anti-islet antibodies before the age 10 years, along with 1 additional screening during adolescence.

Tests to Differentiate Type 1 from Type 2 Diabetes

Although the oral glucose tolerance test with insulin levels is usually considered unnecessary for diagnosing type 1 DM, the dramatic increase of type 2 DM in the young suggests that assessment of insulin secretion may become more important. The 2011 American Association of Clinical Endocrinologists (AACE) guidelines note that to help distinguish between the 2 types in children, physicians should measure insulin and C-peptide levels and immune markers (eg, glutamic acid decarboxylase [GAD] autoantibodies), as well as obtain a detailed family history. C-peptide is formed during conversion of proinsulin to insulin. An insulin or C-peptide level below 5 µU/mL (0.6 ng/mL) suggests type 1 DM; a fasting C-peptide level greater than 1 ng/dL in a patient who has had diabetes for more than 1-2 years is suggestive of type 2 (ie, residual beta-cell function). An exception is the individual with type 2 DM who presents with a very high glucose level (eg, >300 mg/dL) and a temporarily low insulin or C-peptide level but who will recover insulin production once normal glucose is restored. Most patients who present with undiagnosed type 1 DM have the classic symptoms of uncontrolled hyperglycemia, including polyuria, polydipsia, nocturia, fatigue, and weight loss. In these patients, a confirmatory random plasma glucose level of greater than 200 mg/dL is adequate to establish the diagnosis of DM. On occasion, a patient who is ultimately found to have type 1 DM presents with subtle symptoms because of residual insulin secretion. Islet-cell (IA2), anti-GAD65, and anti-insulin autoantibodies can be present in early type 1 but not type 2 DM. Measurements of IA2 autoantibodies within 6 months of diagnosis can help differentiate between type 1 and type 2 DM. These titers decrease after 6 months. Anti-GAD65 antibodies can be present at diagnosis of type 1 DM and are persistently positive over time. (See also Type 2 Diabetes Mellitus.) Testing for islet autoantibodies can substitute for expensive genetic testing in those patients suspected of having maturity-onset diabetes of the young (MODY). The prevalence of these antibodies is the same in patients with MODY as in the healthy population. A positive test for positive islet autoantibodies makes MODY highly unlikely.

Treatment & Management

Glycemic control

The ADA recommends using patient age as one consideration in the establishment of glycemic goals, with different targets for preprandial, bedtime/overnight, and hemoglobin A1c (HbA1c) levels in patients aged 0-6, 6-12, and 13-19 years. Benefits of tight glycemic control include not only continued reductions in the rates of microvascular complications but also significant differences in cardiovascular events and overall mortality.

Self-monitoring

Optimal diabetic control requires frequent self-monitoring of blood glucose levels, which allows rational adjustments in insulin doses. All patients with type 1 diabetes should learn how to self-monitor and record their blood glucose levels with home analyzers and adjust their insulin doses accordingly. Real-time continuous monitoring of glucose—using continuous glucose monitors (CGMs)—can help patients improve glycemic control. CGMs contain subcutaneous sensors that measure interstitial glucose levels every 1-5 minutes, providing alarms when glucose levels are too high or too low or are rapidly rising or falling.

Insulin therapy

Patients with type 1 diabetes require lifelong insulin therapy. Most require 2 or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels. Insulin replacement is accomplished by giving a basal insulin and a preprandial (premeal) insulin. The basal insulin is either long-acting (glargine or detemir) or intermediate-acting (NPH). The preprandial insulin is either rapid-acting (lispro, aspart, insulin inhaled, or glulisine) or short-acting (regular).

Common insulin regimens include the following:

- Split or mixed: NPH with rapid-acting (eg, lispro, aspart, or glulisine) or regular insulin before breakfast and supper
- Split or mixed variant: NPH with rapid-acting or regular insulin before breakfast, rapid-acting or regular insulin before supper, and NPH before bedtime (the idea is to reduce fasting hypoglycemia by giving the NPH later in the evening)
- Multiple daily injections (MDI): A long-acting insulin (eg, glargine or detemir) once a day in the morning or evening (or twice a day in about 20% of patients) and a rapid-acting insulin before meals or snacks (with the dose adjusted according to the carbohydrate intake and the blood glucose level)
- Continuous subcutaneous insulin infusion (CSII): Rapid-acting insulin infused continuously 24 hours a day through an insulin pump at 1 or more basal rates, with additional boluses given before each meal and correction doses administered if blood glucose levels exceed target levels

Diet and activity

All patients on insulin should have a comprehensive diet plan, created with the help of a professional dietitian, that includes the following:

- A daily caloric intake prescription
- Recommendations for amounts of dietary carbohydrate, fat, and protein
- Instructions on how to divide calories between meals and snacks

Exercise is also an important aspect of diabetes management. Patients should be encouraged to exercise regularly.

Management of Complications

Infections

Diabetes predisposes patients to a number of infectious diseases. These include the following:

- Malignant otitis externa
- Rhinocerebral mucormycosis
- Bacteriuria
- Pyuria
- Cystitis
- Upper urinary tract infection
- Intrarenal bacterial infection
- Skin and soft tissue infections
- Osteomyelitis

Ophthalmologic complications

Patients with preproliferative or proliferative retinopathy must immediately be referred for ophthalmologic evaluation. Laser therapy is

effective in this condition, especially if it is provided before hemorrhage occurs. Often, the first hemorrhage is small and is noted by the patient as a fleeting dark area (or "floater") in the field of vision. Because subsequent hemorrhages can be larger and more serious, the patient should immediately be referred to an ophthalmologist for possible laser therapy. Patients with retinal hemorrhage should be advised to limit their activity and keep their head upright (even while sleeping), so that the blood settles to the inferior portion of the retina and thus obscures less of the central visual area. Multifactorial intervention is important for slowing the progression of diabetic retinopathy. Metabolic control, smoking cessation, and blood pressure control are all protective. Patients with active proliferative diabetic retinopathy are at increased risk for retinal hemorrhage if they receive thrombolytic therapy; therefore, this condition is a relative contraindication to the use of thrombolytic agents

Diabetic nephropathy

Extreme care should be exercised whenever any nephrotoxic agent is used in a patient with diabetes. Potentially nephrotoxic drugs should be avoided whenever possible. Renally excreted or potentially nephrotoxic drugs should be given at reduced doses appropriate to the patient's serum creatinine level. In particular, caution should be exercised when contrast-enhanced radiologic studies are being considered in patients with diabetes who have a creatinine level higher than 2 mg/dL. Indeed, such studies should absolutely be avoided in patients with a creatinine level higher than 3 mg/dL. Patients with diabetes who must undergo such studies should be well hydrated before, during, and after the study, and their renal function should be carefully monitored. A better solution is to seek equivalent clinical information by using an alternative modality that does not require the use of contrast material (eg, ultrasonography, noncontrast computed tomography [CT], or magnetic resonance imaging [MRI]). Current ADA guidelines recommend annual screening for nephropathy. All adults with diabetes should have serum creatinine measured at least annually. In adults (and children aged 10 years or older) who have had type 1 DM for 5 or more years, annual assessment of urine albumin excretion is appropriate. Microalbuminuria and macroalbuminuria are not permanent features in most diabetic children and adolescents. Regression of microalbuminuria is common; female gender, absence of retinopathy, better glucose control, lower blood pressure, and better lipid control favor this outcome. In patients with persistent microalbuminuria, the use of angiotensin-converting enzyme (ACE) inhibitors and good metabolic control can usually induce remission. Progression and regression of kidney disease are common even after development of persistent microalbuminuria. Tight glycemic control, lower blood pressure, and a favorable lipid profile are associated with improved outcome. When chronic kidney disease is present, reduction of protein intake may improve renal function. If kidney disease is advanced or difficult to manage or its etiology is unclear, consider referral to a physician with experience in kidney disease patient care. Control of blood pressure is a critical element of care. An ACE inhibitor or an angiotensin II receptor blocker (ARB) should be used because these classes of agents decrease proteinuria and slow the decline in renal function independent of the effect on blood pressure. ACE inhibitors and ARBs tend to increase the serum potassium levels and therefore should be used with caution in patients with renal insufficiency or elevated serum potassium levels.

Diabetic neuropathy

Autonomic dysfunction can involve any part of the sympathetic or parasympathetic chains and produce myriad manifestations. Patients likely to seek care in the ED are those with diabetic gastroparesis and vomiting, severe diarrhea, bladder dysfunction and urinary retention, or symptomatic orthostatic hypotension. Treatment of gastroparesis is symptomatic, and symptoms tend to wax and wane. Patients with gastroparesis may benefit from metoclopramide or erythromycin. Before these therapies are started, the degree of dehydration and metabolic imbalance must be assessed, and other serious causes of vomiting must be excluded. In severe cases, gastric pacing has been used. Patients with disabling orthostatic hypotension may be treated with salt tablets, support stockings, or fludrocortisone. Alleviating the functional abnormalities associated with the autonomic neuropathy is often difficult and frustrating for both doctor and patient.

Diabetic foot disease

Patients with diabetes who present with wounds, infections, or ulcers of the foot should be treated intensively. In addition to appropriate use of antibiotics, the use of crutches, wheelchairs, or bed rest is mandatory for preventing further trauma to the healing foot. Patients should be treated by a podiatrist or an orthopedist with experience in the care of diabetic foot disease. If bone or tendon is visible, osteomyelitis is present, and hospitalization for IV antibiotic therapy is often necessary. Many patients need a vascular evaluation in conjunction with local treatment of the foot ulcer because a revascularization procedure may be required to provide adequate blood flow for wound healing. Because ulcers and foot infections are difficult to cure, their prevention is extremely important. At one clinic, the rate of amputation was halved after patients were required to remove their shoes and socks at every visit. The emergency physician can facilitate this practice by briefly inspecting the feet of patients with diabetes and by educating them about the need for proper foot care.
Referral to a podiatrist is indicated for diabetic patients with any of the following:

- Distal sensory neuropathy with inability to feel a pinprick or light touch
- Decreased peripheral pulses
- Moderate-to-severe onychomycosis
- Impending skin breakdown

Charcot joint, a type of arthropathy observed in people with diabetes, is a progressive deterioration of foot joints caused by underlying neuropathy. Tarsometatarsal and midtarsal joints are affected most commonly. Other neuromuscular foot deformities also may be present. Early diagnosis and treatment are important for preventing further joint degeneration.

Macrovascular disease

Hypercholesterolemia and hypertension increase the risk of specific late complications and require special attention and appropriate treatment. Although physicians can safely use beta blockers (eg, propranolol) in most patients, these agents can mask the adrenergic symptoms of insulin-induced hypoglycemia and can impair the normal counterregulatory response. ACE inhibitors are the drugs of choice for hypertension because of their renal protective action, especially early in the course of the disease. The ADA advises that a systolic blood pressure below 130 mm Hg is an appropriate goal for most patients with diabetes and hypertension, but it also recommends modifying systolic blood pressure targets in accordance with individual patient characteristics. Diastolic blood pressure should be less than 80 mm Hg. Subtle differences in the pathophysiology of atherosclerosis in patients with diabetes result in both earlier development and a more malignant course. Therefore, lipid abnormalities must be treated aggressively to reduce the risk of serious atherosclerosis. This is important from an

epidemiologic point of view and has a bearing on the treatment strategies that must be used to mitigate the risk. Prediction of cardiovascular risk in diabetic patients on the basis of the lipid profile is not affected by the timing of blood specimen. Therefore, it may be unnecessary to insist on using fasting blood samples to determine the lipid profile. In a study involving diabetic adolescents and children, nocturnal hypertension was significantly associated with higher daytime blood pressure and carotid intima-media thickness, which could be precursors of atherosclerotic cardiovascular disease later in life; these findings warrant confirmation and longitudinal follow-up. Patients with diabetes may have increased incidence of silent ischemia. However, silent ischemia is common in many patients with CAD, and the apparent increase in its incidence may come about because patients with diabetes are more likely than others to have CAD to begin with. Nevertheless, it is prudent to perform electrocardiography (ECG) in patients who have diabetes and a serious illness or who present with generalized weakness, malaise, or other nonspecific symptoms that are not usually expected to result from myocardial ischemia. Persistent lipid abnormalities remain in patients with diabetes, despite evidence supporting the benefits of lipid-modifying drugs. Up-titration of the statin dose and addition of other lipid-modifying agents are needed. Although metformin is used principally in type 2 DM because of its lipid-lowering effect, a placebo-controlled study by Lund et al found that metformin (1000 mg orally twice daily) significantly reduced total cholesterol and low-density lipoprotein (LDL) cholesterol in patients with type 1 DM. The American Diabetes Association (ADA) provided recommendations on the use of statins in patients with diabetes to align with those of the American College of Cardiology and the American Heart Association.

- The ADA recommends statin use for nearly everyone with diabetes.
- The ADA guidelines divide diabetes patients by 3 age groups:
  - Younger than 40 years: No statins for those with no cardiovascular disease (CVD) risk factors other than diabetes; moderate intensity or high-intensity statin doses for those with additional CVD risk factors (baseline LDL cholesterol 100 or greater, high blood pressure, smoking, and overweight/obesity); and high-intensity statin doses for those with overt CVD (including previous cardiovascular events or acute coronary syndrome).
  - Age 40-75 years: Moderate-intensity statins for those with no additional risk factors, and high-intensity statins for those with either CVD risk factors or overt CVD.
  - Older than 75 years: Moderate-intensity statins for those with CVD risk factors; and high-intensity statins for those with overt CVD.
- Lipid monitoring for adherence is recommended as needed, and annual monitoring is advised for patients younger than 40 years who have not yet started on statins.
- There is a new BMI cut point of 23 kg/m (instead of 25 kg/m) for screening Asian Americans for prediabetes and diabetes, based on evidence that Asian populations are at increased risk at lower BMIs relative to the general population.
- The premeal glucose target of 70-130 mg/dL was changed to 80-130 mg/dL to better reflect new data that compared average glucose levels with HbA 1c targets.
- The goal for diastolic blood pressure was raised to 90 mm Hg from 80 mm Hg to better reflect data from randomized clinical trials. (This follows ADA's 2013 shift from a systolic target of 130 mm Hg to 140 mm Hg.)
- With regard to physical activity, the document now advises limiting the time spent sitting to no longer than 90 min.
- The ADA does not support e-cigarettes as alternatives to smoking or to facilitate smoking cessation.
- Immunization against pneumococcal disease is recommended.
- A new HbA 1c target of less than 7.5% for children is now recommended.

Glycemic Control During Serious Medical Illness and Surgery

Serious medical illness and surgery produce a state of increased insulin resistance and relative insulin deficiency. Hyperglycemia can occur even in patients without diabetes as a consequence of stress-induced insulin resistance coupled with the use of dextrose-containing IV fluids. Increases in glucagon, catecholamines, cortisol, and growth hormone levels antagonize the effects of insulin, and the alpha-adrenergic effect of increased catecholamine levels inhibits insulin secretion. Counterregulatory hormones also directly increase hepatic gluconeogenesis. Much less is known about optimal blood glucose levels in hospitalized patients with preexisting diabetes whose hyperglycemia reflects both their diabetes and a stress response to illness. Nonetheless, it is clear that management of hospitalized patients with preexisting diabetes requires modification of treatment regimens to compensate for both the decreased caloric intake and the increased physiologic stress. Near-normal blood glucose levels should be maintained in medical and surgical patients with diabetes, for the following reasons:

- To prevent the development of ketosis
- To prevent electrolyte abnormalities and volume depletion secondary to osmotic diuresis
- To prevent the impairment of leukocyte function that occurs when blood glucose levels are elevated
- To prevent the impairment of wound healing that occurs when glucose levels are elevated

Patients with type 1 DM must take in insulin and carbohydrate at all times to prevent ketosis. It is strongly recommended that continuous IV infusions of dextrose and insulin be used in patients who are undergoing general anesthesia or who are critically ill. Blood glucose levels must be measured with a glucose meter every hour, and the rates of insulin and dextrose infusion must be adjusted accordingly to prevent hypoglycemia or persistent hyperglycemia. Algorithms are available for insulin infusions, and the use of a preprinted order facilitates administration and reduces dosing errors. For patients who are less seriously ill or are undergoing minor surgery, frequent blood glucose monitoring is not always possible. These patients may do as well with subcutaneously injected insulin. A basal bolus insulin regimen, rather than a sliding-scale regular insulin regimen, should be used in these patients. The same principles of providing a constant source of insulin and carbohydrate apply to patients with type 1 DM who must also take nothing by mouth for medical reasons. Patients should receive a basal insulin (eg, glargine or detemir insulin) with additional correction doses of regular insulin or a rapid-acting insulin. In many localities, regular insulin has been replaced by rapid-acting insulin (eg, lispro, aspart, or glulisine). To prevent hypoglycemia, regular insulin should not be given more often than every 3-4 hours, because a dose is effective for up to 6 hours. Rapid-acting insulins may be given every 3 hours. Once the patient is eating, a preprandial insulin dose can be added. Cardiovascular disease or renal dysfunction increases surgical morbidity and mortality, and diabetic autonomic neuropathy increases the risk of cardiovascular instability.

The emergency physician caring for patients with diabetes who require emergency surgery must notify the surgeon and the anesthesiologist of the patient's condition, consult medical specialists when appropriate, and promptly initiate a thorough medical evaluation. Recent guidelines have trended away from stressing intensive glucose control in ill patients with diabetes. The ADA recommends that in critically ill patients, insulin therapy should be initiated if the glucose level exceeds 180 mg/dL (10 mmol/L), with a target range of 140-180 mg/dL (7.8-10 mmol/L) for the majority of critically ill patients. More stringent goals, such as 110-140 mg/dL (6.1-7.8 mmol/L), may be appropriate for selected patients, provided that significant hypoglycemia can be avoided. In the absence of clear evidence for specific blood glucose goals in non–critically ill patients, the ADA suggests that reasonable targets are premeal blood glucose levels lower than 140 mg/dL (7.8 mmol/L) with random blood glucose levels below 180 mg/dL (10.0 mmol/L), provided that these targets can be safely achieved. It may be appropriate to use more stringent targets in stable patients with previous tight glycemic control and less stringent targets in patients with severe comorbidities. The guidelines on glycemic control in hospitalized patients formulated by the American College of Physicians (ACP) recommend a target blood glucose level of 140-200 mg/dL if insulin therapy is used to manage patients with diabetes in nonsurgical (medical) intensive care units (ICUs). These guidelines were based on a review of 21 trials in intensive care, perioperative care, myocardial infarction, stroke, or brain injury settings. The ACP found no convincing evidence that intensive insulin therapy reduced short-term or long-term mortality, infection rates, length of hospital stay, or the need for renal replacement therapy. In recommending 200 mg/dL as the upper target, the ACP guidelines depart from the 2009 AACE/ADA consensus statement on inpatient glycemic control, which recommended a target range of 140-180 mg/dL in critically ill patients. Nevertheless, in certain circumstances, such as after cardiovascular surgery and during treatment in a surgical ICU, it is very important to maintain near-normal blood glucose levels in patients with acute hyperglycemia of illness. These patients should receive sufficient insulin to maintain glucose levels around 100 mg/dL.

Perioperative blood glucose management

Surgical procedures—including the preoperative emotional stress and the effects of general anesthesia as well as the trauma of the procedure itself—can markedly increase plasma glucose levels and induce DKA in patients with type 1 DM. In patients going to surgery who have not received a dose of intermediate-acting insulin that day, injection of one third to one half of the total daily dose as NPH insulin or 80% of the dose as glargine or detemir insulin before surgery is often effective. At the same time, an IV infusion containing 5% glucose in either 0.9% saline solution or water should be started at a rate of 1 L (50 g glucose) over 6-8 hours (or 125-150 mL/h). Blood glucose levels should be checked every 2 hours during the surgical procedure, and small doses of regular or rapid-acting insulin (eg, lispro, aspart, or glulisine) should be given if values exceed 140 mg/dL. After the operation, check plasma glucose levels and assess for a reaction to ketones. Unless a change in dosage is indicated, repeat the preoperative dose of insulin when the patient recovers from the anesthesia, and continue the glucose infusion. Monitor plasma glucose and ketones at 2- to 4-hour intervals, and administer regular insulin every 4-6 hours as needed to maintain the plasma glucose level in the range of 100-250 mg/dL (ie, 5.55-13.88 mmol/L). Continue until the patient can be switched to oral feedings and a 2- or 3-dose insulin schedule. Some physicians prefer to withhold subcutaneous insulin on the day of the operation and to add 6-10 units of regular insulin to 1 L of 5% glucose in normal saline or water infused at 150 mL/h on the morning of the operation, depending on the plasma glucose level. The infusion is continued through recovery, with insulin adjustments depending on the plasma glucose levels obtained in the recovery room and at 2- to 4-hour intervals thereafter. Postoperative IV insulin infusion after major surgical procedures is currently considered the standard of care in most hospitals.

Glycemic Control During Pregnancy

Because pregnant patients with type 1 DM are at risk for multiple poor maternal and fetal outcomes, it is essential to provide these patients with prepregnancy counseling, good glycemic control before and during pregnancy, and a complete medical evaluation. High-risk possibilities include exacerbation of existing hypertension, renal insufficiency, retinopathy, and more frequent congenital anomalies. These patients should be referred to obstetricians specializing in high-risk pregnancies. Despite advanced age, multiparity, obesity, and social disadvantage, patients with type 2 DM were found to have better glycemic control, fewer large-for-gestational-age infants, fewer preterm deliveries, and fewer neonatal care admissions than patients with type 1 DM. This finding suggests that better tools are needed to improve glycemic control in patients with type 1 DM.

Prevention

Significant improvements in the prediction of type 1 DM have led to several trials of prevention. These include the Diabetes Prevention Trial–Type 1 (DPT-1) in the United States and the European Nicotinamide Diabetes Intervention Trial (ENDIT) in Europe and North America. Both trials have reported disappointing results. In DPT-1, parenteral insulin failed to delay or prevent type 1 DM in subjects at elevated risk (as indicated by family history and the presence of islet cell antibodies). These subjects received low-dose subcutaneous Ultralente insulin twice daily, plus annual 4-day continuous IV infusions of insulin. DPT-1 subjects who received oral insulin experienced considerable delays in the onset of diabetes, but once therapy was stopped, their rate of developing diabetes increased to a rate similar to that seen in the placebo group. In the ENDIT study, nicotinamide (which prevents autoimmune diabetes in animal models) did not prevent or delay the clinical onset of diabetes in people with a first-degree family history of type 1 DM. Subjects in the treatment arm received oral modified-release nicotinamide in a dose of 1.2 g/m.

Slowing progress of recent-onset type 1 DM

In animal models of autoimmunity, treatment with a target antigen can modulate aggressive autoimmunity. However, a trial of antigen-based immunotherapy with 2 or 3 doses of glutamic acid decarboxylase formulated with aluminum hydroxide (GAD-alum) vaccine for 4-12 weeks in patients with newly diagnosed type 1 DM did not alter the course of loss of insulin secretion during the first year. A phase 3 trial using an anti-CD3 monoclonal antibody, teplizumab, found an encouraging trend toward preservation of beta-cell function with reduction in daily insulin requirements in patients with recently diagnosed type 1 DM. However, rash was almost 3 times more common in treated patients than in those receiving placebo. A study by Orban et al found that costimulation modulation of activated T cells with abatacept slowed reduction in beta-cell function over a 2-year period of administration. However, this effect was reduced after 6 months of treatment, suggesting that T-cell activation lessens over time. Further studies are needed.

Type 1 Diabetes Mellitus Guidelines

Guidelines Summary

ADA: Position statement on type 1 diabetes in children and adolescents

In August 2018, the American Diabetes Association released a position statement on type 1 diabetes in children and adolescents, which included the following guidelines :

- Consult a pediatric endocrinologist before diagnosing type 1 diabetes when isolated glycosuria or hyperglycemia is discovered in patients with acute illness in the absence of classic symptoms
- Differentiating type 1 diabetes, type 2 diabetes, monogenic diabetes, and other forms of diabetes is based on patient history and characteristics, as well as on laboratory tests, such as an islet autoantibody panel
- The majority of children with type 1 diabetes should be treated with intensive insulin regimens using multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion
- A 1C should be measured every 3 months
- Blood glucose levels should be monitored up to 6-10 times daily
- Continuous glucose monitors (CGM) should be considered in all children and adolescents with type 1 diabetes; the benefits of CGM correlate with adherence to ongoing use of the device
- Blood or urine ketone levels should be monitored in children with type 1 diabetes in the presence of prolonged/severe hyperglycemia or acute illness
- Individualized medical nutrition therapy is recommended for children and adolescents
- Exercise is recommended, with a goal of 60 minutes a day of moderate to vigorous aerobic activity, along with vigorous muscle-strengthening and bone-strengthening activities at least 3 days a week
- It is important to frequently monitor glucose before, during, and after exercise (with or without CGM use) to prevent, detect, and treat hypoglycemia and hyperglycemia
- All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin; lack of access and insulin omissions are major causes of diabetic ketoacidosis
- Glucagon should be prescribed for all individuals with type 1 diabetes, and caregivers or family members should be instructed regarding administration
- Once the child has had diabetes for 5 years, annual screening for albuminuria, using a random spot urine sample (morning sample preferred to avoid effects of exercise) to assess the albumin-to-creatinine ratio, should be considered at puberty or at age greater than 10 years, whichever occurs earlier
- Once the youth has had diabetes for 3-5 years, an initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, and an annual routine follow-up is generally recommended
- For adolescents who have had type 1 diabetes for 5 years, consider an annual comprehensive foot exam at the start of puberty or at age 10 years, whichever is earlier
- Blood pressure should be measured at each routine visit; children who have high-normal blood pressure (systolic blood pressure [SBP] or diastolic blood pressure [DBP] at 90th percentile for age, sex, and height) or hypertension (SBP or DBP at 95th percentile for age, sex, and height) should have blood pressure confirmed on 3 separate days
- Initial treatment of high-normal blood pressure (SBP or DBP consistently at the 90th percentile for age, sex, and height) includes dietary modification and increased exercise for weight control; if target blood pressure is not reached within 3-6 months after lifestyle intervention, consider pharmacologic treatment
- Because of their potential teratogenic effects, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be considered for initial pharmacologic treatment of hypertension after reproductive counseling
- The blood pressure treatment goal is consistently less than the 90th percentile for age, sex, and height
- If low-density lipoprotein (LDL) cholesterol is within an acceptable risk level (< 100 mg/dL [2.6 mmol/L]), a lipid profile every 3-5 years is reasonable
- If lipid levels are abnormal, initial therapy should consist of optimizing glucose control and initiating a Step 2 American Heart Association diet (restricting saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day)
- After age 10 years, consider adding a statin if, despite 6 months of medical nutrition therapy and lifestyle changes, LDL cholesterol remains greater than 160 mg/dL (4.1 mmol/L) or LDL cholesterol remains greater than 130 mg/dL (3.4 mmol/L) with one or more cardiovascular disease (CVD) risk factors present (after reproductive counseling because of the potential teratogenic effects of statins)
- The LDL therapy goal is less than 100 mg/dL (2.6 mmol/L)
- In children with type 1 diabetes, consider testing for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis
- In children and adolescents with type 1 diabetes, an A 1C target of less than 7.5% should be considered but individualized
- Glucose (15 g) is preferred treatment for conscious individuals with hypoglycemia (blood glucose < 70 mg/dL [3.9 mmol/L]), but any form of carbohydrate may be used; treatment should be repeated if self-monitoring blood glucose (SMBG) 15 minutes after treatment shows hypoglycemia is still present; when blood glucose concentration returns to normal, consider a meal or snack and/or reduce insulin to prevent recurrence of hypoglycemia
- In patients with classic symptoms, blood glucose measurement is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose ≥200 mg/dL [11.1 mmol/L])
- Measure thyroid-stimulating hormone concentrations when the patient is clinically stable or once glycemic control has been established; if normal, suggest rechecking every 1-2 years (or sooner if the patient develops symptoms or signs that suggest thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability)
- Screen children for celiac disease by measuring IgA tissue transglutaminase antibodies
- Criteria for diagnosis of diabetes is fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
- In asymptomatic children and adolescents at high risk for diabetes, if FPG ≥126 mg/dL (7 mmol/L), if 2-hr PG ≥200 mg/dL (11.1 mmol/L), or if A 1C ≥6.5%, testing should be repeated on a separate day to confirm the diagnosis.

ADA: Standards of Medical Care in Diabetes

The American Diabetes Association's Standards of Medical Care in Diabetes-2018 include the following A-grade recommendations, ie, recommendations based on "[c]lear evidence from well-conducted, generalizable randomized controlled trials that are adequately

powered":

- Align approaches to diabetes management with the Chronic Care Model, emphasizing productive interactions between a prepared, proactive care team and an informed, activated patient
- Providers should assess social factors that can affect patients with diabetes, such as potential food insecurity, housing stability, and financial barriers, and apply that information to treatment decisions
- Provide patients with self-management support from lay health coaches, navigators, or community health workers, when available
- Effective diabetes self-management education and support should be patient centered, may be given in group or individual settings or using technology, and should help guide clinical decisions
- Psychosocial care should be integrated with a collaborative, patient-centered approach and provided to all people with diabetes, with the goal of optimizing health outcomes and health-related quality of life
- A reasonable A 1C goal for many nonpregnant adults is below 7% (53 mmol/mol)
- Insulin-treated patients with hypoglycemia unawareness or an episode of clinically significant hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes
- Most people with type 1 diabetes should be treated with a multiple daily injection regimen of prandial insulin and basal insulin or continuous subcutaneous insulin infusion
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk
- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of less than 140 mmHg and a diastolic blood pressure goal of under 90 mmHg
- Patients with a confirmed office-based blood pressure of 140/90 mmHg or above should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals
- Patients with a confirmed office-based blood pressure of 160/100 mmHg or above should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes
- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], thiazide-like diuretics, or dihydropyridine calcium channel blockers)
- Multiple-drug therapy is generally required to achieve blood pressure targets; however, combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs with direct renin inhibitors should not be used
- Lifestyle modifications focusing on weight loss (if indicated); the reduction of saturated fat, trans fat, and cholesterol intake; an increase in dietary omega-3 fatty acids, viscous fiber, and plant stanol/sterol intake; and increased physical activity should be recommended to improve the lipid profile in patients with diabetes
- High-intensity statin therapy should be added to lifestyle therapy for patients of all ages with diabetes and atherosclerotic cardiovascular disease (ASCVD)
- For patients aged 40-75 years who have diabetes but do not have ASCVD, use moderate-intensity statin treatment in addition to lifestyle therapy
- For patients with diabetes and ASCVD, if the low-density lipoprotein (LDL) cholesterol level is 70 mg/dL (3.9 mmol/L) or above on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or a proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor) after evaluating the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences; ezetimibe may be preferred due to lower cost
- Combination therapy (statin/fibrate) has not been shown to improve ASCVD outcomes and is generally not recommended
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended
- Use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in patients with diabetes and a history of ASCVD
- In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as ASCVD risk factors are treated
- Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease
- Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease
- Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m
- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy
- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy
- The traditional standard treatment, panretinal laser photocoagulation therapy, is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy
- Intravitreous injections of the vascular endothelial growth factor inhibitor ranibizumab are not inferior to traditional panretinal laser photocoagulation and are also indicated to reduce the risk of vision loss in patients with proliferative diabetic retinopathy
- Intravitreous injections of vascular endothelial growth factor inhibitor are indicated for central-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage
- Either pregabalin or duloxetine is recommended as initial pharmacologic treatment for neuropathic pain in diabetes.

ADA: hypertension guidelines

Guidelines published in 2017 by the American Diabetes Association on managing hypertension in patients with diabetes state the following :

- Blood pressure should be measured at every routine clinical care visit; patients found to have an elevated blood pressure (≥140/90 mm Hg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension

- All hypertensive patients with diabetes should have home blood pressure monitored to identify white-coat hypertension
- Orthostatic measurement of blood pressure should be performed during initial evaluation of hypertension and periodically at follow-up, or when symptoms of orthostatic hypotension are present, and regularly if orthostatic hypotension has been diagnosed
- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of < 140 mm Hg and a diastolic blood pressure goal of < 90 mm Hg
- Lower systolic and diastolic blood pressure targets, such as < 130/80 mm Hg, may be appropriate for individuals at high risk for cardiovascular disease if they can be achieved without undue treatment burden
- For patients with systolic blood pressure >120 mm Hg or diastolic blood pressure >80 mm Hg, lifestyle intervention consists of weight loss if the patients are overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)–style dietary pattern, including reduced sodium and increased potassium intake, increased fruit and vegetable consumption, moderation of alcohol intake, and increased physical activity
- Patients with confirmed office-based blood pressure ≥140/90 mm Hg should, in addition to lifestyle therapy, have timely titration of pharmacologic therapy to achieve blood pressure goals
- Patients with confirmed office-based blood pressure ≥160/100 mm Hg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes
- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes: angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), thiazide-like diuretics, or dihydropyridine calcium channel blockers; multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and ARBs)
- An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and a urine albumin-to-creatinine ratio of ≥300 mg/g creatinine or 30–299 mg/g creatinine; if one class is not tolerated, the other should be substituted
- For patients treated with an ACE inhibitor, ARB, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored
- Pregnant women with diabetes and preexisting hypertension or mild gestational hypertension with systolic blood pressure < 160 mm Hg, diastolic blood pressure < 105 mm Hg, and no evidence of end-organ damage do not need to be treated with pharmacologic antihypertensive therapy
- In pregnant patients with diabetes and preexisting hypertension who are treated with antihypertensive therapy, systolic or diastolic blood pressure targets of 120-160/80-105 mm Hg are suggested in the interest of optimizing long-term maternal health and fetal growth.

ISPAD: Diabetic vascular complications in children and adolescents

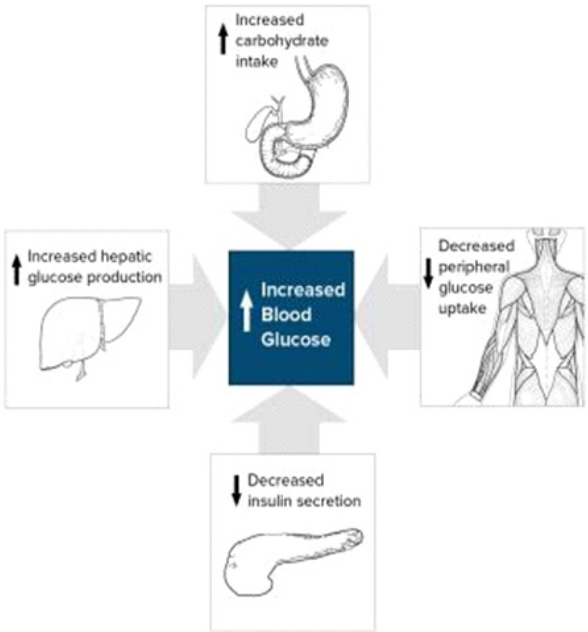
In August 2018, the International Society for Pediatric and Adolescent Diabetes (ISPAD) released clinical practice consensus guidelines on diabetic microvascular and macrovascular complications in children and adolescents. These include the following :

- Commence screening for microvascular complications at age 11 years
- Screening for microvascular disease should be performed preconception and during each trimester of pregnancy
- Intensive education and treatment should be provided to children and adolescents to prevent or delay the onset and progression of vascular complications
- Achievement of target glycemic control will reduce the risk for onset and progression of diabetic vascular complications
- Prevention or cessation of smoking will reduce progression of albuminuria and cardiovascular disease
- Screening for diabetic retinopathy should start at age 11 years with 2 to 5 years' diabetes duration
- Screening for diabetic retinopathy should be performed by an ophthalmologist or optometrist or a trained, experienced observer, through dilated pupils, with assessment carried out via biomicroscopic examination or fundal photography
- Laser treatment and intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents reduce the rate of vision loss for individuals in vision-threatening stages of retinopathy (severe nonproliferative retinopathy or worse and/or diabetic macular edema)
- Screen for renal disease using first morning albumin/ creatinine ratio as the preferred method.
- Blood pressure (BP) should be measured at least annually; hypertension is defined as average systolic BP (SBP) and/or diastolic BP (DBP) that is at or above the 95th percentile for gender, age, and height on three or more occasions
- Angiotensin-converting enzyme (ACE) inhibitors are recommended for use in children with diabetes and hypertension; they have been effective and safe in children in short-term studies but are not safe during pregnancy
- Screen for lipid abnormalities in the nonfasting state
- With regard to macrovascular disease, screening of BP and lipids is recommended, as above; the benefit of routine screening for other markers of macrovascular complications outside the research setting is unclear.

INTERPRETATION

UNDERSTANDING TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. See the image.



Simplified scheme for the pathophysiology of type 2 diabetes mellitus.

Signs and symptoms

Many patients with type 2 diabetes are asymptomatic. Clinical manifestations include the following:

- Classic symptoms: Polyuria, polydipsia, polyphagia, and weight loss
- Blurred vision
- Lower-extremity paresthesias
- Yeast infections (eg, balanitis in men)

Diagnosis

Diagnostic criteria by the American Diabetes Association (ADA) include the following [1]:

- A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, or
- A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or
- A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

Whether a hemoglobin A1c (HbA1c) level of 6.5% or higher should be a primary diagnostic criterion or an optional criterion remains a point of controversy.

Indications for diabetes screening in asymptomatic adults includes the following [2,3]:

- Sustained blood pressure >135/80 mm Hg
- Overweight and 1 or more other risk factors for diabetes (eg, first-degree relative with diabetes, BP >140/90 mm Hg, and HDL < 35 mg/dL and/or triglyceride level >250 mg/dL)
- ADA recommends screening at age 45 years in the absence of the above criteria

Management

Goals of treatment are as follows:

- Microvascular (ie, eye and kidney disease) risk reduction through control of glycemia and blood pressure
- Macrovascular (ie, coronary, cerebrovascular, peripheral vascular) risk reduction through control of lipids and hypertension, smoking cessation
- Metabolic and neurologic risk reduction through control of glycemia

Recommendations for the treatment of type 2 diabetes mellitus from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) place the patient's condition, desires, abilities, and tolerances at the center of the decision-making process. [4,5,6]

The EASD/ADA position statement contains 7 key points:

1. Individualized glycemic targets and glucose-lowering therapies
2. Diet, exercise, and education as the foundation of the treatment program
3. Use of metformin as the optimal first-line drug unless contraindicated
4. After metformin, the use of 1 or 2 additional oral or injectable agents, with a goal of minimizing adverse effects if possible
5. Ultimately, insulin therapy alone or with other agents if needed to maintain blood glucose control
6. Where possible, all treatment decisions should involve the patient, with a focus on patient preferences, needs, and values
7. A major focus on comprehensive cardiovascular risk reduction.

The 2013 ADA guidelines for SMBG frequency focus on an individual's specific situation rather than quantifying the number of tests that should be done. The recommendations include the following [7,8]:

- Patients on intensive insulin regimens – Perform SMBG at least before meals and snacks, as well as occasionally after meals; at bedtime; before exercise and before critical tasks (eg, driving); when hypoglycemia is suspected; and after treating hypoglycemia until normoglycemia is achieved.
- Patients using less frequent insulin injections or noninsulin therapies – Use SMBG results to adjust to food intake, activity, or medications to reach specific treatment goals; clinicians must not only educate these individuals on how to interpret their SMBG data, but they should also reevaluate the ongoing need for and frequency of SMBG at each routine visit.

Approaches to prevention of diabetic complications include the following:

- HbA1c every 3-6 months
- Yearly dilated eye examinations
- Annual microalbumin checks
- Foot examinations at each visit
- Blood pressure < 130/80 mm Hg, lower in diabetic nephropathy
- Statin therapy to reduce low-density lipoprotein cholesterol.

TROUBLESHOOTING

DIABETES MELLITUS DIAGNOSIS

Symptoms of type 1 diabetes often appear suddenly and are often the reason for checking blood sugar levels. Because symptoms of other types of diabetes and prediabetes come on more gradually or may not be evident, the American Diabetes Association (ADA) has recommended screening guidelines. The ADA recommends that the following people be screened for diabetes:

- **Anyone with a body mass index higher than 25 (for whites) (23 for Asians), regardless of age,** who has additional risk factors, such as high blood pressure, abnormal cholesterol levels, a sedentary lifestyle, a history of polycystic ovary syndrome or heart disease, and who has a close relative with diabetes.
- **Anyone older than age 45** is advised to receive an initial blood sugar screening, and then, if the results are normal, to be screened every three years thereafter.
- **Women who have had gestational diabetes** are advised to be screened for diabetes every three years.
- **Anyone who has been diagnosed with prediabetes** is advised to be tested every year.

Tests for type 1 and type 2 diabetes and prediabetes

- **Glycated hemoglobin (A1C) test.** This blood test, which doesn't require fasting, indicates your average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells.

  The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5% or higher on two separate tests indicates that you have diabetes. An A1C between 5.7 and 6.4 % indicates prediabetes. Below 5.7 is considered normal.

  If the A1C test results aren't consistent, the test isn't available, or you have certain conditions that can make the A1C test inaccurate — such as if you are pregnant or have an uncommon form of hemoglobin (known as a hemoglobin variant) — your doctor may use the following tests to diagnose diabetes:
- **Random blood sugar test.** A blood sample will be taken at a random time. Regardless of when you last ate, a blood sugar level of 200 milligrams per deciliter (mg/dL) — 11.1 millimoles per liter (mmol/L) — or higher suggests diabetes.
- **Fasting blood sugar test.** A blood sample will be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.
- **Oral glucose tolerance test.** For this test, you fast overnight, and the fasting blood sugar level is measured. Then you drink a sugary liquid, and blood sugar levels are tested periodically for the next two hours.

  A blood sugar level less than 140 mg/dL (7.8 mmol/L) is normal. A reading of more than 200 mg/dL (11.1 mmol/L) after two hours indicates diabetes. A reading between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes.

If type 1 diabetes is suspected, your urine will be tested to look for the presence of a byproduct produced when muscle and fat tissue are used for energy because the body doesn't have enough insulin to use the available glucose (ketones). Your doctor will also likely run a test to see if you have the destructive immune system cells associated with type 1 diabetes called autoantibodies.

Tests for gestational diabetes

Your doctor will likely evaluate your risk factors for gestational diabetes early in your pregnancy:

- **If you're at high risk of gestational diabetes** — for example, if you were obese at the start of your pregnancy; you had gestational diabetes during a previous pregnancy; or you have a mother, father, sibling or child with diabetes — your doctor may test for diabetes at your first prenatal visit.
- **If you're at average risk of gestational diabetes**, you'll likely have a screening test for gestational diabetes sometime during your second trimester — typically between 24 and 28 weeks of pregnancy.

Your doctor may use the following screening tests:

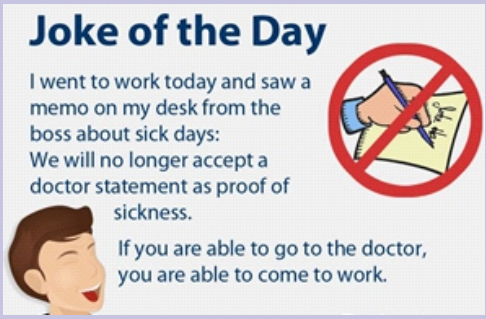
- **Initial glucose challenge test.** You'll begin the glucose challenge test by drinking a syrupy glucose solution. One hour later, you'll have a blood test to measure your blood sugar level. A blood sugar level below 140 mg/dL (7.8 mmol/L) is usually considered normal on a glucose challenge test, although this may vary at specific clinics or labs.

  If your blood sugar level is higher than normal, it only means you have a higher risk of gestational diabetes. Your doctor will order a follow-up test to determine if you have gestational diabetes.
- **Follow-up glucose tolerance testing.** For the follow-up test, you'll be asked to fast overnight and then have your fasting blood sugar level measured. Then you'll drink another sweet solution — this one containing a higher concentration of glucose — and your blood sugar level will be checked every hour for a period of three hours.

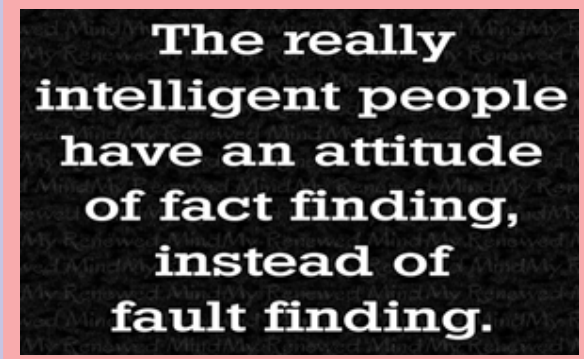
  If at least two of the blood sugar readings are higher than the normal values established for each of the three hours of the test, you'll be diagnosed with gestational diabetes.

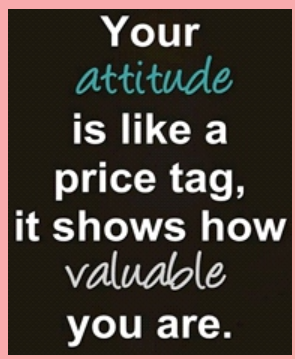
BOUQUET

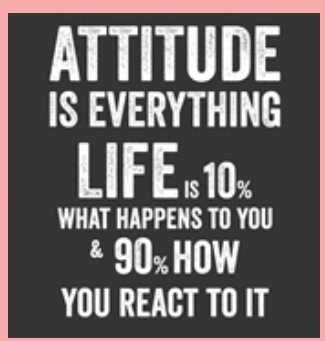
In Lighter Vein

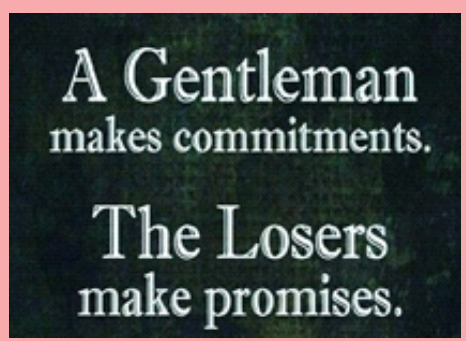


Wisdom Whispers









Brain Teasers

1. **Polyuria, polydipsia, weight loss (and possibly ketoacidosis), hyperglycemia and glycosuria are often associated with:**
   A. Hyperadrenalism
   B. Hyperpituitarism
   C. Diabetes mellitus
   D. Hyperthyroidism

2. **Diabetes mellitus that is characterized by absolute insulin deficiency and acute onset, usually before 25 years of age, should now be referred to as:**
   A. Type 1
   B. Type I
   C. IDDM
   D. Juvenile diabetes mellitus.

3. **What does I stand for in NIDDM?**
   A. Immediate
   B. Insulin
   C. Instantaneous
   D. Independent

4. **Which of the following are indications for starting screening for diabetes at earlier age?**
   A. Persons who are obese (120% of desirable body weight or greater or a body mass index of 27 kg per m2 or greater)
   B. Who havea first-degree relative with diabetes mellitus
   C. Who have delivered a baby weighing more than 4.032 g (9 lb)
   D. All of the above.

ANSWER: 1.C, 2.A, 3. B ,4. D

Tulip Introduces

SafeLyte UV

*UVC rays between 200 and 280 nm is one of the most efficient way of killing microbes, bacteria and viruses. UVC irradiation is an important step in fostering SAFETY from SURFACE TO HUMAN transmission of pathogens like **SARS-CoV-2** virus**

***Tested at CSIO**
(CSIO is a CSIR Testing Centre)

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