

Bibliographic Revision

Diabetes Mellitus

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Diabetes mellitus is impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia. Early symptoms are related to hyperglycemia and include polydipsia, polyphagia, and polyuria. Later complications include vascular disease, peripheral neuropathy, and predisposition to infection. Diagnosis is by measuring plasma glucose. Treatment is diet, exercise, and drugs that reduce glucose levels, including insulin and oral antihyperglycemic drugs. Prognosis varies with degree of glucose control.

There are 2 main categories of diabetes mellitus (DM)—type 1 and type 2, which can be distinguished by a combination of features. Terms that describe the age of onset (juvenile or adult) or type of treatment (insulin- or noninsulin-dependent) are no longer accurate because of overlap in age groups and treatments between disease types.

General Characteristics of Types 1 and 2 Diabetes Mellitus

Characteristic	Type 1	Type 2
Age at onset	Most commonly < 30 yr	Most commonly > 30 yr
Associated obesity	No	Very common
Propensity to ketoacidosis requiring insulin treatment for control	Yes	No
Plasma levels of endogenous insulin	Extremely low to undetectable	Variable; may be low, normal, or elevated depending on degree of insulin resistance and insulin secretory defect
Twin concordance	≤ 50%	> 90%
Associated with specific HLA-D antigens	Yes	No
Islet cell antibodies at diagnosis	Yes	No
Islet pathology	Insulinitis, selective loss of most β cells	Smaller, normal-appearing islets; amyloid (amylin) deposition is common
Prone to develop diabetic complications (retinopathy, nephropathy, neuropathy, atherosclerotic cardiovascular)	Yes	Yes

disease)

Hyperglycemia responds to oral antihyperglycemic drugs

No

Yes, initially in many patients

Impaired glucose regulation (impaired glucose tolerance, or impaired fasting glucose) is an intermediate, possibly transitional, state between normal glucose metabolism and DM that becomes common with age. It is a significant risk factor for DM and may be present for many years before onset of DM. It is associated with an increased risk of cardiovascular disease, but typical diabetic microvascular complications generally do not develop.

Diagnostic Criteria for Diabetes Mellitus and Impaired Glucose Regulation

Test	Normal	Impaired Glucose Regulation	Diabetes
FPG	< 100 (< 5.6)	100–125 (5.6–6.9)	≥ 126 (≥ 7.0)
OGTT	< 140 (< 7.7)	140–199 (7.7–11.0)	≥ 200 (≥ 11.1)

FPG = fasting plasma glucose; OGTT = oral glucose tolerance test, 2 h glucose level.

Note: All values refer to glucose levels in mg/dL [mmol/L].

TYPE 1 DIABETES MELLITUS

In Type 1 Diabetes Mellitus (previously called juvenile-onset or insulin-dependent), insulin production is absent because of autoimmune pancreatic β -cell destruction possibly triggered by an environmental exposure in genetically susceptible people. Destruction progresses subclinically over months or years until β -cell mass decreases to the point that insulin concentrations are no longer adequate to control plasma glucose levels. Type 1 Diabetes Mellitus generally develops in childhood or adolescence and until recently was the most common form diagnosed before age 30; however, it can also develop in adults (latent autoimmune diabetes of adulthood, which often initially appears to be type 2 Diabetes Mellitus). Some cases of type 1 Diabetes Mellitus, particularly in nonwhite populations, do not appear to be autoimmune in nature and are considered idiopathic. Type 1 account for < 10% of all cases of diabetes.

The pathogenesis of the autoimmune β -cell destruction involves incompletely understood interactions between susceptibility genes, autoantigens, and environmental factors. Susceptibility genes include those within the major histocompatibility complex (MHC)—especially HLA-DR3,DQB1*0201 and HLA-DR4,DQB1*0302, which are present in > 90% of patients with type 1 Diabetes Mellitus and those outside the MHC, which seem to regulate insulin production and processing and confer risk for Diabetes Mellitus in concert with MHC genes. Susceptibility genes are more common in some populations than in others and explain the higher prevalence of type 1 Diabetes Mellitus in some ethnic groups (Scandinavians, Sardinians).

Autoantigens include glutamic acid decarboxylase, insulin, insulinoma-associated protein, and other proteins in β cells. It is thought that these proteins are exposed or released during normal β -cell turnover or β -cell injury (eg, from infection), activating a cell-mediated immune response resulting in β -cell destruction (insulinitis). Glucagon-secreting α cells remain unharmed. Antibodies to autoantigens, which can be detected in serum, seem to be a response to (not a cause of) β -cell destruction.

Several viruses (including coxsackievirus, rubella, cytomegalovirus, Epstein-Barr, and retroviruses) have been linked to the onset of type 1 Diabetes Mellitus. Viruses may directly infect and destroy β cells, or they may cause β -cell destruction indirectly by exposing autoantigens, activating autoreactive lymphocytes, mimicking molecular sequences of autoantigens that stimulate an immune response (molecular mimicry), or other mechanisms.

Diet may also be a factor. Exposure of infants to dairy products (especially cow's milk and the milk protein β casein), high nitrates in drinking water, and low vitamin D consumption have been linked to increased risk of type 1 Diabetes Mellitus. Early (< 4 mo) or late (> 7 mo) exposure to gluten and cereals increases islet cell autoantibody production. Mechanisms for these associations are unclear.

TYPE 2 DIABETES MELLITUS

In type 2 Diabetes Mellitus (previously called adult-onset or non-insulin-dependent), insulin secretion is inadequate. Often insulin levels are very high, especially early in the disease, but peripheral insulin resistance and increased hepatic production of glucose make insulin levels inadequate to normalize plasma glucose levels. Insulin production then falls, further exacerbating hyperglycemia. The disease generally develops in adults and becomes more common with age. Plasma glucose levels reach higher levels after eating in older than in younger adults, especially after high carbohydrate loads, and take longer to return to normal, in part because of increased accumulation of visceral and abdominal fat and decreased muscle mass.

Type 2 Diabetes Mellitus is becoming increasingly common in children as childhood obesity has become epidemic: 40 to 50% of new-onset Diabetes Mellitus in children is now type 2. Over 90% of adults with Diabetes Mellitus have type 2 disease. There are clear genetic determinants, as evidenced by the high prevalence of the disease within ethnic groups (especially American Indians, Hispanics, and Asians) and in relatives of people with the disease. No genes responsible for the most common forms of type 2 Diabetes Mellitus have been identified.

Pathogenesis is complex and incompletely understood. Hyperglycemia develops when insulin secretion can no longer compensate for insulin resistance. Although insulin resistance is characteristic in people with type 2 Diabetes Mellitus and those at risk for it, evidence also exists for β -cell dysfunction and impaired insulin secretion, including impaired first-phase insulin secretion in response to IV glucose infusion, a loss of normally pulsatile insulin secretion, an increase in proinsulin secretion signaling impaired insulin processing, and an accumulation of islet amyloid polypeptide (a protein normally secreted with insulin). Hyperglycemia itself may impair insulin secretion, because high glucose levels

desensitize β cells, cause β -cell dysfunction (glucose toxicity), or both. These changes typically take years to develop in the presence of insulin resistance.

Obesity and weight gain are important determinants of insulin resistance in type 2 Diabetes Mellitus. They have some genetic determinants but also reflect diet, exercise, and lifestyle. Adipose tissue increases plasma levels of free fatty acids that may impair insulin-stimulated glucose transport and muscle glycogen synthase activity. Adipose tissue also appears to function as an endocrine organ, releasing multiple factors (adipocytokines) that favorably (adiponectin) and adversely, (tumor necrosis factor- α , IL-6, leptin, resistin) influence glucose metabolism. Intrauterine growth restriction and low birth weight have also been associated with insulin resistance in later life and may reflect prenatal environmental influences on glucose metabolism.

Miscellaneous types: Miscellaneous causes of Diabetes Mellitus that account for a small proportion of cases include genetic defects affecting β -cell function, insulin action, and mitochondrial DNA (eg, maturity-onset diabetes of youth); pancreatic diseases (eg, cystic fibrosis, pancreatitis, hemochromatosis); endocrinopathies (eg, Cushing's syndrome, acromegaly); toxins (eg, the rodenticide pyriminyl [Vacor]); and drug-induced diabetes, most notably from glucocorticoids, β -blockers, protease inhibitors, and therapeutic doses of niacin.

Symptoms and Signs

The most common symptoms of Diabetes Mellitus are those of hyperglycemia: an osmotic diuresis caused by glycosuria leading to urinary frequency, polyuria, and polydipsia that may progress to orthostatic hypotension and dehydration. Severe dehydration causes weakness, fatigue, and mental status changes. Symptoms may come and go as plasma glucose levels fluctuate. Polyphagia may accompany symptoms of hyperglycemia but is not typically a primary patient

concern. Hyperglycemia can also cause weight loss, nausea and vomiting, and blurred vision, and it may predispose to bacterial or fungal infections.

Patients with type 1 Diabetes Mellitus typically present with symptomatic hyperglycemia and sometimes with diabetic ketoacidosis (DKA). Some patients experience a long but transient phase of near-normal glucose levels following acute onset of the disease (honeymoon phase) due to partial recovery of insulin secretion.

Patients with type 2 Diabetes Mellitus may present with symptomatic hyperglycemia but are often asymptomatic, and their condition is detected only on routine testing. In some patients, initial symptoms are those of diabetic complications, suggesting that the disease has been present for some time. In some patients, hyperosmotic coma occurs initially, especially during a period of stress or when glucose metabolism is further impaired by drugs, such as corticosteroids.

Complications

Years of poorly controlled hyperglycemia lead to multiple, primarily vascular complications that affect small (microvascular) large (macrovascular) vessels or both. The mechanisms by which vascular disease develops include glycosylation of serum and tissue proteins with formation of advanced glycation end products; superoxide production; activation of protein kinase C, a signaling molecule that increases vascular permeability and causes endothelial dysfunction; accelerated hexosamine biosynthetic and polyol pathways leading to sorbitol accumulation within tissues; hypertension and dyslipidemias that commonly accompany Diabetes Mellitus; arterial microthromboses; and pro-inflammatory and prothrombotic effects of hyperglycemia and hyperinsulinemia that impair vascular autoregulation. Immune dysfunction is another major complication and develops from the direct effects of hyperglycemia on cellular immunity.

Microvascular disease underlies the 3 most common and devastating manifestations of Diabetes Mellitus: **Retinopathy, Nephropathy, and Neuropathy**. Microvascular disease may also impair skin healing, so that even minor breaks in skin integrity can develop into deeper ulcers and easily become infected. Intensive control of plasma glucose can prevent many of these complications but may not reverse them once established.

Diabetic retinopathy: Diabetic retinopathy is the most common cause of adult blindness in the US. It is characterized initially by retinal capillary microaneurysms and later by macular edema and neovascularization. There are no early symptoms or signs, but focal blurring, vitreous or retinal detachment, and partial or total vision loss eventually develop; rate of progression is highly variable. Diagnosis is by retinal examination. Treatment is argon laser photocoagulation or vitrectomy. Strict glycemic control and early detection and treatment are critical to preventing vision loss.

Diabetic nephropathy: Is a microvascular complication associated with damage to the small blood vessel. The risk of nephropathy is about the same in patients with either type of 1 or type 2 Diabetes Mellitus. Risk factors for the development of this complications include hypertension, genetic predisposition, smoking and chronic hyperglycemia.

Diabetic neuropathy: Is nerve damage that occurs because of the metabolic derangements associated with Diabetes Mellitus. About 60% to 70% of patients with Diabetes have some degree of neuropathy, with neurologic complications occurring equally in type and type 2 Diabetes Mellitus.

GESTACIONAL DIABETES

Pregnancy causes some insulin resistance in all women, but only a few develop Gestational Diabetes.

Gestational diabetes (or gestational diabetes mellitus, GDM) is a condition in which women without previously diagnosed Diabetes exhibit high blood glucose levels during pregnancy. It is estimated that 135,000 pregnant women are diagnosed with Gestational Diabetes each year.

No specific cause has been identified, but it is believed that the hormones produced during pregnancy increase a woman's resistance to insulin, resulting in impaired glucose tolerance.

Diabetes is one of the most prevalent non-communicable diseases, affecting millions of people world-wide. According to a study conducted in America, 3 to 8 in every 100 pregnant women will develop Gestational Diabetes.

Classical risk factors

- ✓ Previous diagnosis of gestational diabetes or pre-diabetes
- ✓ A family history revealing a first degree relative with type 2 diabetes
- ✓ Maternal age
- ✓ Ethnic background
- ✓ Being overweight, obese or severely obese
- ✓ A previous pregnancy which resulted in a child with a high birth
- ✓ Previous poor obstetric history

DIABETIC KETOACIDOSIS (DKA)

Diabetic Ketoacidosis (DKA) is an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. DKA occurs mostly in type 1 diabetes. It causes nausea, vomiting, and abdominal pain and can progress to cerebral edema, coma, and death. DKA is diagnosed by detection of hyperketonemia and anion gap metabolic acidosis in the presence of hyperglycemia. Treatment involves volume expansion, insulin replacement, and prevention of hypokalemia.

DKA is most common in patients with type 1 Diabetes Mellitus and develops when insulin levels are insufficient to meet the body's basic metabolic

requirements. DKA is the first manifestation of type 1 Diabetes Mellitus in a minority of patients. Insulin deficiency can be absolute (e.g. during lapses in the administration of exogenous insulin) or relative (e.g., when usual insulin doses do not meet metabolic needs during physiologic stress). Common physiologic stresses that can trigger DKA include acute infection (particularly pneumonia and UTI), myocardial infarction, stroke, pancreatitis, and trauma. Drugs implicated in causing DKA include corticosteroids, thiazide diuretics, and sympathomimetics. DKA is less common in type 2 Diabetes Mellitus, but it may occur in situations of unusual physiologic stress.

Pathophysiology

Insulin deficiency causes the body to metabolize triglycerides and muscle instead of glucose for energy. Serum levels of glycerol and free fatty acids (FFAs) rise because of unrestrained lipolysis, as does alanine from muscle catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major ketoacids produced, acetoacetic acid and β -hydroxybutyric acid, are strong organic acids that create metabolic acidosis. Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration.

Hyperglycemia caused by insulin deficiency produces an osmotic diuresis that leads to marked urinary losses of water and electrolytes. Urinary excretion of ketones obligates additional losses of Na and K. Serum Na may fall from natriuresis or rise due to excretion of large volumes of free water. K is also lost in large quantities, sometimes > 300 mEq/24 h. Despite a significant total body deficit of K, initial serum K is typically normal or elevated because of the extracellular migration of K in response to acidosis. K levels generally fall further

during treatment as insulin therapy drives K into cells. If serum K is not monitored and replaced as needed, life-threatening hypokalemia may develop.

Symptoms and Signs

Symptoms and signs of Diabetic Ketoacidosis (DKA) include those of hyperglycemia with the addition of nausea, vomiting, and—particularly in children—abdominal pain. Lethargy and somnolence are symptoms of more severe decompensation. Patients may be hypotensive and tachycardic from dehydration and acidosis; they may breathe rapidly and deeply to compensate for acidemia (Kussmaul's respirations). They may also have fruity breath due to exhaled acetone. Fever is not a sign of DKA itself and, if present, signifies underlying infection. In the absence of timely treatment, DKA progresses to coma and death.

Acute cerebral edema, a complication in about 1% of DKA patients, occurs primarily in children and less often in adolescents and young adults. Headache and fluctuating level of consciousness herald this complication in some patients, but respiratory arrest is the initial manifestation in others. The cause is not well understood but may be related to too-rapid reductions in serum osmolality or to brain ischemia. It is most likely to occur in children < 5 yr when DKA is the initial presentation of Diabetes Mellitus. Children with the highest BUN and lowest Paco_2 at presentation appear to be at greatest risk. Delays in correction of hyponatremia and the use of HCO_3 during DKA treatment are additional risk factors.

Diagnosis

In patients suspected of having DKA, serum electrolytes, BUN and creatinine, glucose, ketones, and osmolality should be measured. Urine should be tested for ketones. Those who appear significantly ill and those with positive ketones should have ABG measurement. DKA is diagnosed by an arterial pH < 7.30 with an anion gap > 12 and serum ketones in the presence of hyperglycemia. A

presumptive diagnosis can be made when urine glucose and ketones are strongly positive. Urine test strips and some assays for serum ketones may underestimate the degree of ketosis because they detect acetoacetic and not β -hydroxybutyric acid, which is usually the predominant ketoacid.

Signs and symptoms of a triggering illness should be pursued with appropriate studies (eg, cultures, imaging studies). Adults should have an ECG to screen for acute MI and to help determine the significance of abnormalities in serum K.

Other laboratory abnormalities include hyponatremia, elevated serum creatinine, and elevated serum osmolarity.

Prognosis and Treatment

Mortality rates for DKA are between 1 and 10%. Shock or coma on admission indicates a worse prognosis. Main causes of death are circulatory collapse, hypokalemia, and infection. Among children with cerebral edema, 57% recover completely, 21% survive with neurologic sequelae, and 21% die.

The most urgent goals are rapid intravascular volume repletion, correction of hyperglycemia and acidosis, and prevention of hypokalemia. Identification of precipitating factors is also important. Treatment should occur in intensive care settings because clinical and laboratory assessments are initially needed every hour or every other hour with appropriate adjustments in treatment.

Intravascular volume should be restored rapidly to raise Blood Pressure and ensure glomerular perfusion; adults with DKA typically need a minimum of 3 L of saline over the first 5 h. For children, fluid deficits are estimated at 60 to 100 mL/kg body weight. Maintenance fluids (for ongoing losses) must also be provided.

HYPOGLYCEMIA

Hypoglycemia or low blood glucose occurs when there is too much insulin in proportion to available glucose in the blood, this cause the blood glucose level to drop to less than 70 mg/dl (3,9 mmol/L).

Hypoglycemia unrelated to exogenous insulin therapy is an uncommon clinical syndrome characterized by low plasma glucose level, symptomatic sympathetic nervous system stimulation, and Central Nervous System dysfunction. Many drugs and disorders cause it. Diagnosis requires blood tests performed at the time of symptoms or during a 72-h fast. Treatment is provision of glucose combined with treatment of the underlying disorder.

Symptomatic hypoglycemia unrelated to treatment of Diabetes Mellitus (DM) is relatively rare, in part because the body has extensive counter-regulatory mechanisms to compensate for low blood glucose levels. Glucagon and epinephrine levels surge in response to acute hypoglycemia and appear to be the first line of defense. Cortisol and growth hormone levels also increase acutely and are important in the recovery from prolonged hypoglycemia. The threshold for release of these hormones is usually above that for hypoglycemic symptoms.

Etiology

Causes of physiologic hypoglycemia can be classified as reactive (postprandial) or fasting, insulin-mediated or non-insulin-mediated, and drug-induced or nondrug-induced. Insulin-mediated causes include exogenous administration of insulin or an insulin secretagogue and insulin-secreting tumors (insulinomas). A helpful practical classification is based on clinical status: whether hypoglycemia occurs in patients who appear healthy or ill. Within these categories, causes of hypoglycemia can be divided into drug-induced and other causes. Pseudohypoglycemia occurs when processing of blood specimens in untreated test tubes is delayed and cells, such as RBCs and leukocytes (especially if increased, as in leukemia or polycythemia), consume glucose. Factitious

hypoglycemia is true hypoglycemia induced by nontherapeutic administration of sulfonylureas or insulin.

Symptoms and Signs

The surge in autonomic activity in response to low plasma glucose causes sweating, nausea, warmth, anxiety, tremulousness, palpitations, and possibly hunger and paresthesias. Insufficient glucose supply to the brain causes headache, blurred or double vision, confusion, difficulty speaking, seizures, and coma. In controlled settings, autonomic symptoms begin at or beneath a plasma glucose level of about 60 mg/dL (3.33 mmol/L), whereas CNS symptoms occur at or below a glucose level of about 50 mg/dL (2.78 mmol/L). However, symptoms suggestive of hypoglycemia are far more common than the condition itself. Most people with glucose levels at these thresholds have no symptoms, and most people with symptoms suggestive of hypoglycemia have normal glucose concentrations.

Diagnosis

In principle, diagnosis requires verification that a low plasma glucose level (< 50 mg/dL [< 2.78 mmol/L]) exists at the time hypoglycemic symptoms occur and that the symptoms are responsive to glucose administration. If a practitioner is present when symptoms occur, blood should be sent for glucose testing. If glucose is normal, hypoglycemia is ruled out and no further testing is needed. If glucose is abnormally low, serum insulin, C-peptide, and proinsulin measured from the same tube can distinguish insulin-mediated from non-insulin-mediated and factitious from physiologic hypoglycemia and can obviate the need for further testing. Insulin growth factor 2 (IGF-2) levels may help identify non-islet-cell (IGF-2 secreting) tumors, which are an unusual cause of hypoglycemia.

In practice, however, it is unusual that practitioners are present when patients experience symptoms suggestive of hypoglycemia. Home glucose meters are unreliable for quantifying hypoglycemia, and there are no clear glycosylated

hemoglobin (HbA_{1c}) thresholds that distinguish long-term hypoglycemia from normoglycemia. So the need for more extensive diagnostic testing is based on the probability that an underlying disorder that could cause hypoglycemia exists given a patient's clinical appearance and coexisting illnesses.

Treatment

Immediate treatment of hypoglycemia involves provision of glucose. Patients able to eat or drink can drink juices, sucrose water, or glucose solutions; eat candy or other foods; or chew on glucose tablets when symptoms occur. Infants and younger children may be given 10% dextrose solution 2 to 5 mL/kg IV bolus. Adults and older children unable to eat or drink can be given glucagon 0.5 (< 20 kg) or 1 mg (≥ 20 kg) sc or IM or 50% dextrose 50 to 100 mL IV bolus, with or without a continuous infusion of 5 to 10% dextrose solution sufficient to resolve symptoms. The efficacy of glucagon depends on the size of hepatic glycogen stores; glucagon has little effect on plasma glucose in patients who have been fasting or who are hypoglycemic for long periods.

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