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Type 2 Diabetes Mellitus

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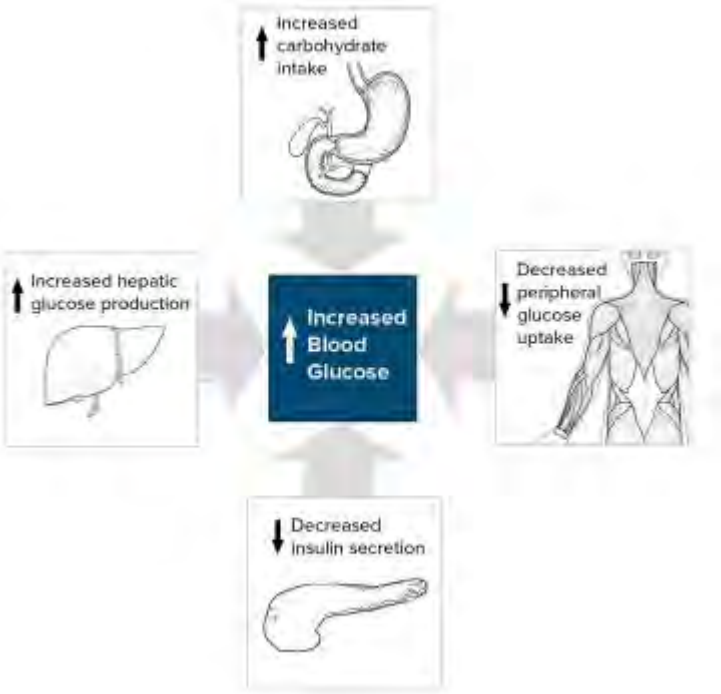
Overview

Practice Essentials

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 below.



Simplified scheme for the pathophysiology of type 2 diabetes mellitus.

See Clinical Findings in Diabetes Mellitus, a Critical Images slideshow, to help identify various cutaneous, ophthalmologic, vascular, and neurologic manifestations of DM.

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)

See Presentation for more detail.

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, 4, 5] :

- 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)
- The ADA recommends screening at age 35 years in the absence of the above criteria

See Workup for more detail.

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.[6, 7, 8]

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

SMBG= Self-Monitored Blood Glucose

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[9, 10] :

- 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

See Treatment and Medication for more detail.

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Background

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. Poorly controlled type 2 diabetes is associated with an array of microvascular, macrovascular, and neuropathic complications.

Microvascular complications of diabetes include retinal, renal, and possibly neuropathic disease. Macrovascular complications include coronary artery and peripheral vascular disease. Diabetic neuropathy affects autonomic and peripheral nerves. (See Pathophysiology and Presentation.)

Unlike patients with type 1 diabetes mellitus, patients with type 2 are not absolutely dependent on insulin for life. This distinction was the basis for the older terms for types 1 and 2, insulin dependent and non–insulin dependent diabetes.

However, many patients with type 2 diabetes are ultimately treated with insulin. Because they retain the ability to secrete some endogenous insulin, they are considered to require insulin but not to depend on insulin. Nevertheless, given the potential for confusion due to classification based on treatment rather than etiology, the older terms have been abandoned.[11] Another older term for type 2 diabetes mellitus was adult-onset diabetes. Currently, because of the epidemic of obesity and inactivity in children, type 2 diabetes mellitus is occurring at younger and younger ages. Although type 2 diabetes mellitus typically affects individuals older than 40 years, it has been diagnosed in children as young as 2 years of age who have a family history of diabetes. In many communities, type 2 diabetes now outnumbers type 1 among children with newly diagnosed diabetes. (See Epidemiology.)

Diabetes mellitus is a chronic disease that requires long-term medical attention to limit the development of its devastating complications and to manage them when they do occur. It is a disproportionately expensive disease; in the United States in 2012, the direct and indirect costs of diagnosed diabetes were estimated to be $245 billion; people with diagnosed diabetes had average medical expenditures 2.3 times those of people without diabetes.[12, 13]

This article focuses on the diagnosis and treatment of type 2 diabetes and its acute and chronic complications, other than those directly associated with hypoglycemia and severe metabolic disturbances, such as hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA). For more information on those topics, see Hyperosmolar Hyperglycemic State and Diabetic Ketoacidosis.

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Pathophysiology

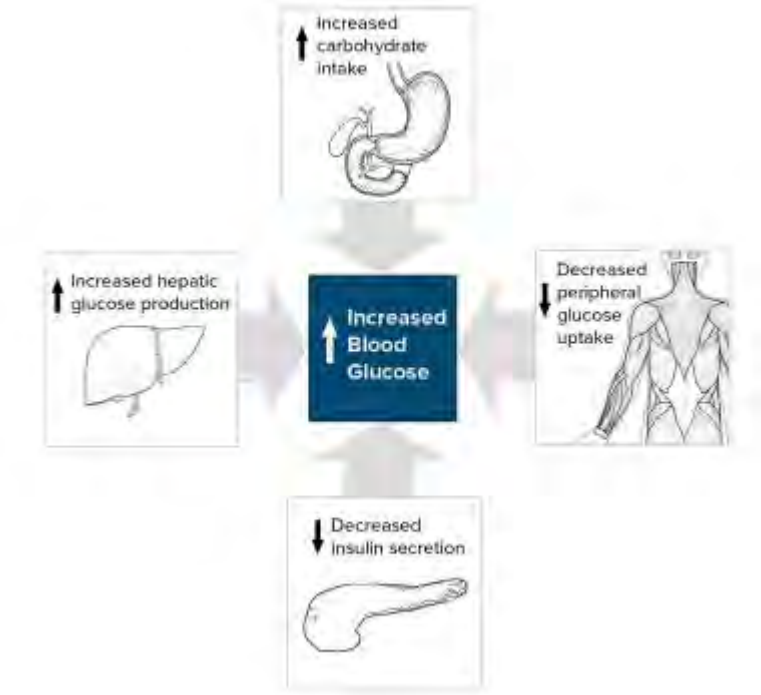
Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia.[14]

For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion

sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for the level of glycemia.

A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.



Simplified scheme for the pathophysiology of type 2 diabetes mellitus.

With prolonged diabetes, atrophy of the pancreas may occur. A study by Philippe et al used computed tomography (CT) scan findings, glucagon stimulation test results, and fecal elastase-1 measurements to confirm reduced pancreatic volume in individuals with a median 15-year history of diabetes mellitus (range, 5-26 years).[15] This may also explain the associated exocrine deficiency seen in prolonged diabetes.

Beta-cell dysfunction

Beta-cell dysfunction is a major factor across the spectrum of prediabetes to diabetes. A study of obese adolescents by Bacha et al confirms what is increasingly being stressed in adults as well: Beta-cell dysfunction develops early in the pathologic process and does not necessarily follow the stage of insulin resistance.[16] Singular focus on insulin resistance as the "be all and end all" is gradually shifting, and hopefully better treatment options that address the beta-cell pathology will emerge for early therapy.

Insulin resistance

In the progression from normal to abnormal glucose tolerance, postprandial blood glucose levels increase first. Eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails.

During the induction of insulin resistance (such as occurs with a high-calorie diet, steroid administration, or physical inactivity), increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance. However, the postprandial glucagonlike peptide-1 (GLP-1) response is unaltered.[17]

Genomic factors

Genome-wide association studies of single-nucleotide polymorphisms (SNPs) have identified a number of genetic variants that are associated with beta-cell function and insulin resistance. Some of these SNPs appear to increase the risk for type 2 diabetes. Over 40 independent loci demonstrating an association with an increased risk for type 2 diabetes have been shown.[18] A subset of the most potent are shared below[19] :

- Decreased beta-cell responsiveness, leading to impaired insulin processing and decreased insulin secretion (TCF7L2)
- Lowered early glucose-stimulated insulin release (MTNR1B, FADS1, DGKB, GCK)

- Altered metabolism of unsaturated fatty acids (FSADS1)
- Dysregulation of fat metabolism (PPARG)
- Inhibition of serum glucose release (KCNJ11)[20]
- Increased adiposity and insulin resistance (FTO and IGF2BP2)[21, 22]
- Control of the development of pancreatic structures, including beta-islet cells (HHEX)[23]
- Transport of zinc into the beta-islet cells, which influences the production and secretion of insulin (SLC30A8)[23]
- Survival and function of beta-islet cells (WFS1)[24]

Susceptibility to type 2 diabetes may also be affected by genetic variants involving incretin hormones, which are released from endocrine cells in the gut and stimulate insulin secretion in response to digestion of food. For example, reduced beta-cell function has been associated with a variant in the gene that codes for the receptor of gastric inhibitory polypeptide (GIPR).[25]

The high mobility group A1 (HMGA1) protein is a key regulator of the insulin receptor gene (INSR).[26] Functional variants of the HMGA1 gene are associated with an increased risk of diabetes.

Amino acid metabolism

Amino acid metabolism may play a key role early in the development of type 2 diabetes. Wang et al reported that the risk of future diabetes was at least 4-fold higher in normoglycemic individuals with high fasting plasma concentrations of 3 amino acids (isoleucine, phenylalanine, and tyrosine). Concentrations of these amino acids were elevated up to 12 years prior to the onset of diabetes.[27] In this study, amino acids, amines, and other polar metabolites were profiled using liquid chromatography tandem mass spectrometry.

Diabetes complications

Although the pathophysiology of the disease differs between the types of diabetes, most of the complications, including microvascular, macrovascular, and neuropathic, are similar regardless of the type of diabetes. Hyperglycemia appears to be the determinant of microvascular and metabolic complications. Macrovascular disease may be less related to glycemia.

Telomere attrition may be a marker associated with presence and the number of diabetic complications. Whether it is a cause or a consequence of diabetes remains to be seen.[28]

Cardiovascular risk

Cardiovascular risk in people with diabetes is related in part to insulin resistance, with the following concomitant lipid abnormalities:

- Elevated levels of small, dense low-density lipoprotein (LDL) cholesterol particles
- Low levels of high-density lipoprotein (HDL) cholesterol
- Elevated levels of triglyceride-rich remnant lipoproteins

Thrombotic abnormalities (ie, elevated type-1 plasminogen activator inhibitor [PAI-1], elevated fibrinogen) and hypertension are also involved. Other conventional atherosclerotic risk factors (eg, family history, smoking, elevated LDL cholesterol) also affect cardiovascular risk.

Insulin resistance is associated with increased lipid accumulation in liver and smooth muscle, but not with increased myocardial lipid accumulation.[29] Persistent lipid abnormalities remain in patients with diabetes despite the use of lipid-modifying drugs, although evidence supports the benefits of these drugs. Statin dose up-titration and the addition of other lipid-modifying agents are needed.[30]

Increased cardiovascular risk appears to begin prior to the development of frank hyperglycemia, presumably because of the effects of insulin resistance. Stern in 1996[31] and Haffner and D'Agostino in 1999[32] developed the "ticking clock" hypothesis of complications, asserting that the clock starts ticking for microvascular risk at the onset of hyperglycemia, while the clock starts ticking for macrovascular risk at some antecedent point, presumably with the onset of insulin resistance.

The question of when diabetes becomes a cardiovascular risk equivalent has not yet been settled. Debate has moved beyond automatically considering diabetes a cardiovascular risk equivalent. Perhaps it would be prudent to assume the equivalency with diabetes that is more than 5-10 years in duration.

Cognitive decline

In a cross-sectional study of 350 patients aged 55 years and older with type 2 diabetes and 363 control participants aged 60 years and older without diabetes, diabetic individuals were more likely to have brain atrophy than cerebrovascular lesions, with patterns resembling those of preclinical Alzheimer disease.[33, 34] Type 2 diabetes was associated with hippocampal atrophy; temporal, frontal, and limbic gray-matter atrophy; and, to a lesser extent, frontal and temporal white-matter atrophy.

Type 2 diabetes was also linked with poorer performance on certain cognitive tests. The strength of these associations dropped by almost 50% when adjusted for hippocampal and total gray-matter volumes but was unchanged when adjusted for cerebrovascular lesions or white-matter volume.[33, 34] Patients with type 2 diabetes were more likely to have gray-matter atrophy in several bilateral regions of the cortices, especially in the left hemisphere, similar to the distribution of cortical atrophy described in early Alzheimer disease.[33]

In a 40-month study of 2977 middle-aged and older adults with long-standing type 2 diabetes, depression at baseline was associated with accelerated cognitive decline.[35, 36] The 531 subjects with scores of 10 or higher on the Patient Health Questionnaire Depression Scale at baseline had significantly lower scores on the Digit Symbol Substitution Test (DSST), the Rey Auditory Verbal Learning Test (RAVLT), and the modified Stroop test. Adjustment for other risk factors did not affect the association.

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%).[37]

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.[38, 39]

A report by Barrera et al looking at 65 observational studies (15,794 participants) found the overall prevalence of diabetes in patients with COVID-19 to be 12%, with the prevalence being 18% in severe COVID-19.[40, 41]

Results from a study by Guo et al suggested that in patients with COVID-19 infection, the increase in inflammatory and coagulation markers is greater in those with type 2 diabetes mellitus than in individuals without diabetes. This may help to indicate why the risk of more severe disease and death from COVID-19 infection is higher in patients with diabetes.[42, 43]

Secondary diabetes

Various other types of diabetes, previously called secondary diabetes, are caused by other illnesses or medications. Depending on the primary process involved (eg, destruction of pancreatic beta cells or development of peripheral insulin resistance), these types of diabetes behave similarly to type 1 or type 2 diabetes.

The most common causes of secondary diabetes are as follows:

- Diseases of the pancreas that destroy the pancreatic beta cells (eg, hemochromatosis, pancreatitis, cystic fibrosis, pancreatic cancer)
- Hormonal syndromes that interfere with insulin secretion (eg, pheochromocytoma)
- Hormonal syndromes that cause peripheral insulin resistance (eg, acromegaly, Cushing syndrome, pheochromocytoma)
- Drugs (eg, phenytoin, glucocorticoids, estrogens)

Gestational diabetes

Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (see Diabetes Mellitus and Pregnancy). Gestational diabetes mellitus is a complication of approximately 4% of all pregnancies in the United States. A steady decline in insulin sensitivity as gestation progresses is a normal feature of pregnancy; gestational diabetes mellitus results when maternal insulin secretion cannot increase sufficiently to counteract the decrease in insulin sensitivity.

Subtypes

A study by Ahlqvist et al suggested that type 1 and type 2 diabetes mellitus can actually be divided into five separate types, or clusters, of diabetes. Using six variables to analyze almost 15,000 patients in Sweden and Finland, the investigators came up

with the following clusters, the first of which corresponds to type 1 diabetes and the rest of which are subtypes of type 2 diabetes[44, 45] :

- Severe autoimmune diabetes (SAID) - Essentially corresponding with type 1 diabetes and latent autoimmune diabetes in adults (LADA), this form is characterized by onset at a young age and patients with a relatively low body mass index (BMI), poor metabolic control, and impaired insulin production; in addition, this cluster is positive for glutamic acid decarboxylase antibodies (GADA)
- Severe insulin-deficient diabetes (SIDD) - This cluster is similar to SAID but is GADA-negative and is characterized by high HbA1c and the greatest risk for diabetic retinopathy among all the clusters
- Severe insulin-resistant diabetes (SIRD) - This cluster is characterized by insulin resistance and patients with a high BMI and the greatest risk for diabetic nephropathy
- Mild obesity-related diabetes (MOD) - Patients in this cluster are younger, have obesity, and are not insulin resistant
- Mild age-related diabetes (MARD) - Patients in this cluster are older, and their metabolic alterations are modest

The investigators maintained that studies in less homogeneous populations are needed to confirm their results but see their report as a “first step towards a more precise, clinically useful stratification” of diabetes.[45]

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Etiology

The etiology of type 2 diabetes mellitus appears to involve complex interactions between environmental and genetic factors. Presumably, the disease develops when a diabetogenic lifestyle (ie, excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed on a susceptible genotype.

The body mass index (BMI) at which excess weight increases risk for diabetes varies with different racial groups. For example, compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight.[46] Hypertension and prehypertension are associated with a greater risk of developing diabetes in whites than in African Americans.[47]

In addition, an in utero environment resulting in low birth weight may predispose some individuals to develop type 2 diabetes mellitus.[48, 49, 50] Infant weight velocity has a small, indirect effect on adult insulin resistance, and this is primarily mediated through its effect on BMI and waist circumference.[51]

Approximately 90% of individuals with type 2 diabetes mellitus are overweight or have obesity.[52] However, a large, population-based, prospective study has shown that an energy-dense diet may be a risk factor for the development of diabetes that is independent of baseline obesity.[53]

A study by Cameron et al indicated that in the United States between 2013 and 2016, obesity was responsible for the development of new-onset diabetes in 41% of adults. The highest attributable rate of obesity-related diabetes was among non-Hispanic White women (53%); non-Hispanic Black men demonstrated the lowest rate, with the attributable fraction being 30%.[54, 55]

Some studies suggest that environmental pollutants may play a role in the development and progression of type 2 diabetes mellitus.[56] A structured and planned platform is needed to fully explore the diabetes-inducing potential of environmental pollutants.

Secondary diabetes may occur in patients taking glucocorticoids or when patients have conditions that antagonize the actions of insulin (eg, Cushing syndrome, acromegaly, pheochromocytoma).

A study by Pauza et al suggested that glucagonlike peptide–1 (GLP-1) is associated with the link between diabetes and hypertension. The investigators found that GLP-1 receptors are expressed on the carotid body and, working with rats, determined that reduced expression of these receptors “is linked to sympathetic hyperactivity in rats with cardiometabolic disease.” Thus, the research indicates that GLP-1 not only plays its known part in glucose control (by stimulating insulin release) but is associated with blood pressure control as well.[57, 58]

Major risk factors

The major risk factors for type 2 diabetes mellitus are the following:

- Age greater than 45 years (though, as noted above, type 2 diabetes mellitus is occurring with increasing frequency in young individuals)
- Weight greater than 120% of desirable body weight
- Family history of type 2 diabetes in a first-degree relative (eg, parent or sibling)

- Hispanic, Native American, African American, Asian American, or Pacific Islander descent
- History of previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Hypertension (>140/90 mm Hg) or dyslipidemia (HDL cholesterol level < 40 mg/dL or triglyceride level >150 mg/dL)
- History of gestational diabetes mellitus or of delivering a baby with a birth weight of over 9 lb
- Polycystic ovarian syndrome (which results in insulin resistance)

Genetic influences

The genetics of type 2 diabetes are complex and not completely understood. Evidence supports the involvement of multiple genes in pancreatic beta-cell failure and insulin resistance.

Genome-wide association studies have identified dozens of common genetic variants associated with increased risk for type 2 diabetes.[19] Of the variants thus far discovered, the one with the strongest effect on susceptibility is the transcription factor 7–like 2 (TCF7L2) gene. (For more information, see Type 2 Diabetes and TCF7L2.)

Identified genetic variants account for only about 10% of the heritable component of most type 2 diabetes.[19] An international research consortium found that use of a 40-SNP genetic risk score improves the ability to make an approximate 8-year risk prediction for diabetes beyond that which is achievable when only common clinical diabetes risk factors are used. Moreover, the predictive ability is better in younger persons (in whom early preventive strategies could delay diabetes onset) than in those older than 50 years.[59]

Some forms of diabetes have a clear association with genetic defects. The syndrome historically known as maturity onset diabetes of youth (MODY), which is now understood to be a variety of defects in beta-cell function, accounts for 2-5% of individuals with type 2 diabetes who present at a young age and have mild disease. The trait is autosomal dominant and can be screened for through commercial laboratories.

To date, 11 MODY subtypes have been identified, involving mutations in the following genes[60, 61] :

- HNF-4-alpha
- Glucokinase gene
- HNF-1-alpha
- IPF-1
- HNF-1-beta
- NEUROD1
- KLF11[62]
- CEL[63]
- PAX4[64]
- INS
- BLK[65]

Most of the MODY subtypes are associated with diabetes only; however, MODY type 5 is known to be associated with renal cysts,[66] and MODY type 8 is associated with exocrine pancreatic dysfunction.[63]

A number of variants in mitochondrial deoxyribonucleic acid (DNA) have been proposed as an etiologic factor for a small percentage of patients with type 2 diabetes. Two specific point mutations and some deletions and duplications in the mitochondrial genome can cause type 2 diabetes and sensorineural hearing loss.[67]

Diabetes can also be a finding in more severe mitochondrial disorders such as Kearns-Sayre syndrome and mitochondrial encephalomyopathy, lactic acidosis, and strokelike episode (MELAS). Mitochondrial forms of diabetes mellitus should be considered when diabetes occurs in conjunction with hearing loss, myopathy, seizure disorder, strokelike episodes, retinitis pigmentosa, external ophthalmoplegia, or cataracts. These findings are of particular significance if there is evidence of maternal inheritance.

A meta-analysis of two studies indicated that a genetically associated low birth weight increases an individual's risk for developing type 2 diabetes. The report found that for each one-point increase in an individual's genetic risk score for low birth weight, the type 2 diabetes risk rose by 6%.[68, 69]

Depression

Accumulating evidence suggests that depression is a significant risk factor for developing type 2 diabetes. Pan et al found that the relative risk was 1.17 in women with depressed mood and 1.25 in women using antidepressants.[70] Antidepressant use may be a marker of more severe, chronic, or recurrent depression, or antidepressant use itself may increase diabetes risk, possibly by altering glucose homeostasis or promoting weight gain.

In turn, type 2 diabetes has been identified as a risk factor for the development of depression. Depressive symptoms and major depressive disorder are twice as prevalent in patients with type 2 diabetes as in the general population.[71]

Schizophrenia

Schizophrenia has been linked to the risk for type 2 diabetes. Dysfunctional signaling involving protein kinase B (Akt) is a possible mechanism for schizophrenia; moreover, acquired Akt defects are associated with impaired regulation of blood glucose and diabetes, which is overrepresented in first-episode, medication-naive patients with schizophrenia.[72] In addition, second-generation antipsychotics are associated with greater risk for type-2 diabetes.

Preeclampsia and gestational hypertension

A population-based, retrospective cohort study of 1,010,068 pregnant women examined the association between preeclampsia and gestational hypertension during pregnancy and the risk of developing diabetes post partum. Results showed the incidence rate of diabetes per 1000 person-years was 6.47 for women with preeclampsia and 5.26 for those with gestational hypertension, compared with 2.81 in women with neither condition. Risk was further elevated in women with preeclampsia or gestational hypertension comorbid with gestational diabetes.[73]

COVID-19

Evidence exists that coronavirus disease 2019 (COVID-19) may actually lead to the development of type 1 and type 2 diabetes. One theory is 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.[74]

A report by Xie and Al-Aly found that among study patients who had survived the first 30 days of COVID-19, the risk for diabetes at 1 year was increased by about 40%. More specifically, the hazard ratios (HRs) for diabetes at 1 year among patients who, during the acute infection, were not hospitalized, were hospitalized, or were admitted to intensive care were 1.25, 2.73, and 3.76, respectively. The investigators stated that diabetes "should be considered as a facet of the multifaceted long COVID syndrome."[75, 76]

A study by Tang et al detected SARS-CoV-2 antigen in pancreatic beta cells, as taken from autopsy samples from individuals who had had COVID-19. The research indicated that insulin expression decreases in SARS-CoV-2–infected beta cells, with these cells possibly undergoing transdifferentiation.[77] A study by Wu et al also indicated that infected beta cells secrete less insulin, with the investigators finding evidence that SARS-CoV-2 can induce beta-cell apoptosis.[78]

A study from the US Centers for Disease Control and Prevention (CDC) indicates that SARS-CoV-2 infection increases the likelihood of diabetes developing in children under age 18 years, more than 30 days post infection. The investigators, using two US health claims databases, reported that pediatric patients with COVID-19 in the HealthVerity database were 31% percent more likely than other youth to receive a new diabetes diagnosis, while those in the IQVIA database were 166% more likely. The study could not specify the type or types of diabetes specifically related to COVID-19, with the report saying that the disease could be causing both type 1 and type 2 diabetes but through differing mechanisms. The researchers suggested, however, that COVID-19 may induce diabetes by directly attacking pancreatic cells that express ACE2 receptors, that it may give rise to diabetes "through stress hyperglycemia resulting from the cytokine storm and alterations in glucose metabolism caused by infection," or that COVID-19 may cause diabetes via the conversion of prediabetes to diabetes. Whether the diabetes is transient or chronic was also unknown.[79, 80]

However, a study by Cromer et al looked at adult patients with newly diagnosed diabetes mellitus at the time of hospital admission for COVID-19, finding that a number of them subsequently regressed to a state of normoglycemia or prediabetes. The investigators reported that out of 64 survivors in the study with newly diagnosed diabetes (62 of whom had type 2 diabetes), 26 (40.6%) were known to undergo such regression (median 323-day follow-up).[81]

Epidemiology

Occurrence in the United States

According to the CDC's National Diabetes Statistics Report, the crude prevalence of diabetes in the adult US population is 14.7%. It was estimated that 11.3% of the adult population have actually been diagnosed, while 3.4% of adults have undiagnosed diabetes. The prevalence of diabetes rises with age, reaching 29.2% in persons aged 65 years or older. Data employed in the report were drawn from 2017-2020.[82, 83]

Prediabetes, as defined by the American Diabetes Association, is that state in which blood glucose levels are higher than normal but not high enough to be diagnosed as diabetes. It is presumed that most persons with prediabetes will subsequently progress to diabetes. The above-mentioned CDC report found the age-adjusted estimate for the prevalence of prediabetes in the adult US population to be 10.8%.[82, 83]

A study by Andes et al using a cross-sectional analysis of the National Health and Nutrition Examination Survey (2005-2016) indicated that in the United States, prediabetes exists in approximately 1 out of 5 adolescents and 1 out of 4 young adults.[84, 85]

However, a study by Liu et al reported a higher incidence of prediabetes in young people, revealing that in the United States by 2018, approximately 28% of individuals between ages 12 and 19 years had the condition; this was up from less than 12% in 1999. A greater prevalence of prediabetes was found in males in this group and in youth with overweight or obesity.[86, 87]

In 2014, the CDC reported that about 40% of US adults will develop diabetes, primarily type 2, in their lifetime, and that more than 50% of ethnic minorities will be affected. This is substantially higher than previous estimates. The central reason for the increase is obesity.[88, 89]

A study by Ludwig et al found that neighborhoods with high levels of poverty are associated with increases in the incidence of extreme obesity and diabetes. Although the mechanisms behind this association is unclear, further investigation is warranted.[90]

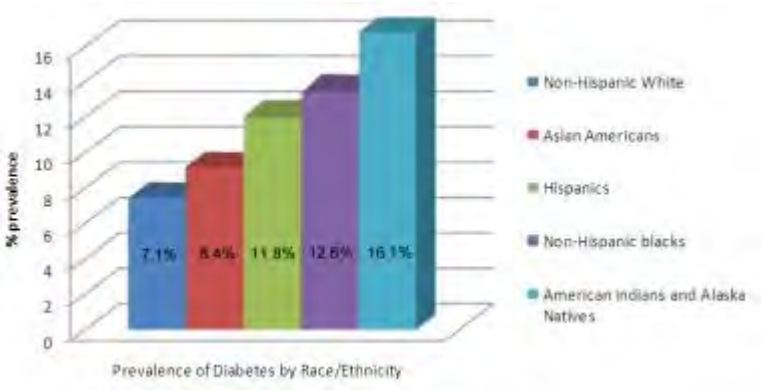
International occurrence

Type 2 diabetes mellitus is less common in non-Western countries where the diet contains fewer calories and daily caloric expenditure is higher. However, as people in these countries adopt Western lifestyles, weight gain and type 2 diabetes mellitus are becoming virtually epidemic.

The 10th edition of the International Diabetes Federation Diabetes Atlas, published in December 2021, reported that worldwide, 1 in 10 adults has diabetes. The data predicted that there would be a global increase in the number of adults with diabetes from 537 million in 2021 to 786 million by 2045, a 46% rise. Although increases are expected throughout the world, Africa, the Middle East, and Southeast Asia are predicted to have the greatest expansion.[91]

Race-related demographics

The prevalence of type 2 diabetes mellitus varies widely among various racial and ethnic groups. The image below shows data for various populations. Type 2 diabetes mellitus is more prevalent among Hispanics, Native Americans, African Americans, and Asians/Pacific Islanders than in non-Hispanic whites. Indeed, the disease is becoming virtually pandemic in some groups of Native Americans and Hispanic people. The risk of retinopathy and nephropathy appears to be greater in blacks, Native Americans, and Hispanics.



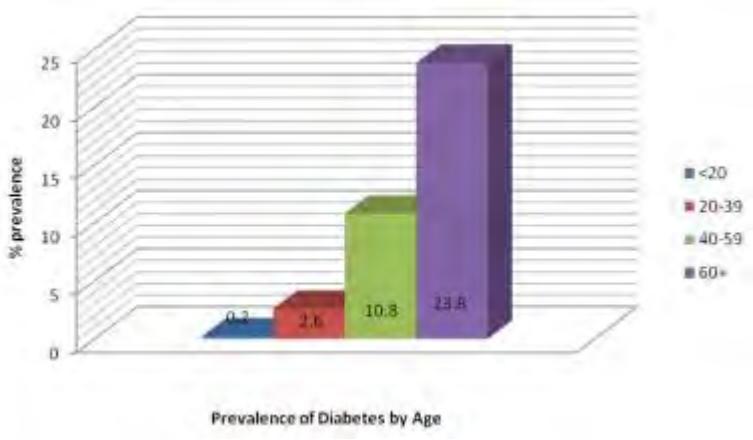
Prevalence of type 2 diabetes mellitus in various racial and ethnic groups in the United States (2007-2009 data).

In a study by Selvin et al, differences between blacks and whites were noted in many glycemic markers and not just the hemoglobin A1c (HbA1c) level.[92] This suggests real differences in glycemia, rather than in the hemoglobin glycation process or erythrocyte turnover, between blacks and whites.

Age-related demographics

Type 2 diabetes mellitus occurs most commonly in adults aged 40 years or older, and the prevalence of the disease increases with advancing age. Indeed, the aging of the population is one reason that type 2 diabetes mellitus is becoming increasingly common. Virtually all cases of diabetes mellitus in older individuals are type 2.

In addition, however, the incidence of type 2 diabetes is increasing more rapidly in adolescents and young adults than in other age groups. The disease is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and the obese. In some areas, more type 2 than type 1 diabetes mellitus is being diagnosed in prepubertal children, teenagers, and young adults. The prevalence of diabetes mellitus by age is shown in the image below.



Prevalence of diabetes mellitus type 2 by age in the United States (2007 estimates).

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Prognosis

The prognosis in patients with diabetes mellitus is strongly influenced by the degree of control of their disease. Chronic hyperglycemia is associated with an increased risk of microvascular complications, as shown in the Diabetes Control and Complications Trial (DCCT) in individuals with type 1 diabetes[93, 94] and the United Kingdom Prospective Diabetes Study (UKPDS) in people with type 2 diabetes.[95]

Reversion to normal glucose regulation during attempts to prevent progression of pre-diabetes to frank diabetes is a good indicator of slowing disease progression, and it is associated with a better prognosis.[96]

Prognosis in intensive therapy

In the UKPDS, more than 5000 patients with type 2 diabetes were followed up for up to 15 years. Those in the intensely treated group had a significantly lower rate of progression of microvascular complications than did patients receiving standard care. Rates of macrovascular disease were not altered except in the metformin-monotherapy arm in obese individuals, in which the risk of myocardial infarction was significantly decreased.

In the 10-year follow-up to the UKPDS, patients in the previously intensively treated group demonstrated a continued reduction in microvascular and all-cause mortality, as well as in cardiovascular events, despite early loss of differences in glycated hemoglobin levels between the intensive-therapy and conventional-therapy groups.[97] The total follow-up was 20 years, half while in the study and half after the study ended.

Other, shorter studies, such as Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), showed no improvement in cardiovascular disease and death with tight control (lower targets than in the UKPDS).[98, 99, 100]

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, increased mortality was noted among the poorly-controlled patients in the intensive glycemic arm; indeed there was a 66% increase in mortality for each 1% increase in HbA1c; the best outcome occurred among patients who achieved the target of an HbA1c of less than 6%. The excess mortality between the intensive and conventional glycemic arms occurred for A1c above 7%.

Differences between the patient populations in these studies and the UKPDS may account for some of the differences in outcome. The patients in these 3 studies had established diabetes and had a prior cardiovascular disease event or were at high risk for a cardiovascular disease event, whereas patients in the UKPDS study were younger, with new-onset diabetes and low rates of cardiovascular disease.

Early, intensive, multifactorial (blood pressure, cholesterol) management in patients with type 2 diabetes mellitus was associated with a small, nonsignificant reduction in the incidence of cardiovascular disease events and death in a multinational European study.[101] The 3057 patients in this study had diabetes detected by screening and were randomized to receive either standard diabetes care or intensive management of hyperglycemia (target HbA1c < 7.0%), blood pressure, and cholesterol levels.

The benefits of intensive intervention were demonstrated in the Steno-2 study in Denmark, which included 160 patients with type 2 diabetes and persistent microalbuminuria; the mean treatment period was 7.8 years, followed by an observational period for a mean of 5.5 years. Intensive therapy was associated with a lower risk of cardiovascular events, death from cardiovascular causes, progression to end-stage renal disease, and need for retinal photocoagulation.[102]

A British study indicated that the HbA1c level achieved 3 months after the initial diagnosis of type 2 diabetes mellitus predicts subsequent mortality. In other words, according to the report, aggressive lowering of glucose after diagnosis bodes well for long-term survival. (Intensified diabetes control must be introduced gradually in newly diagnosed patients.)[103]

Another study, a review of randomized clinical trials, showed that intensive glycemic control reduces the risk of microvascular complications, but at the expense of increased risk of hypoglycemia. All-cause mortality and cardiovascular mortality in the study did not differ significantly with intensive versus conventional glycemic control; however, trials conducted in usual-care settings showed a reduction in the risk of nonfatal myocardial infarction.[104]

Overall, these studies suggest that tight glycemic control (HbA1c < 7% or lower) is valuable for microvascular and macrovascular disease risk reduction in patients with recent-onset disease, no known cardiovascular diseases, and a longer life expectancy. In patients with known cardiovascular disease, a longer duration of diabetes (15 or more years), and a shorter life expectancy, however, tighter glycemic control is not as beneficial, particularly with regard to cardiovascular disease risk. Episodes of severe hypoglycemia may be particularly harmful in older individuals with poorer glycemic control and existing cardiovascular disease.

A study by Zheng et al indicated that HbA1c levels in persons with diabetes are longitudinally associated with long-term cognitive decline, as found using a mean 4.9 cognitive assessments of diabetes patients over a mean 8.1-year follow-up period. The investigators saw a significant link between each 1 mmol/mol rise in HbA1c and an increased rate of decline in z scores for global cognition, memory, and executive function. Patients in the study had a mean age of 65.6 years. The report cited a need for research into whether optimal glucose control in people with diabetes can affect their cognitive decline rate.[105, 106]

Vascular disease considerations

One prospective study with a long follow-up challenges the concept of coronary disease risk equivalency between nondiabetic patients with a first myocardial infarction and patients with type 2 diabetes but without any cardiovascular disease. The study found that patients with type 2 diabetes had lower long-term cardiovascular risk compared with patients with first myocardial infarction. Other studies have similarly questioned this risk equivalency.[107]

Patients with diabetes have a lifelong challenge to achieve and maintain blood glucose levels as close to the reference range as possible. With appropriate glycemic control, the risk of microvascular and neuropathic complications is decreased markedly. In addition, if hypertension and hyperlipidemia are treated aggressively, the risk of macrovascular complications decreases as well.

These benefits are weighed against the risk of hypoglycemia and the short-term costs of providing high-quality preventive care. Studies have shown cost savings due to a reduction in acute diabetes-related complications within 1-3 years after starting effective preventive care. Some studies suggest that broad-based focus on treatment (eg, glycemia, nutrition, exercise, lipids, hypertension, smoking cessation) is much more likely to reduce the burden of excess microvascular and macrovascular events.

Yamasaki et al found that abnormal results on single-photon CT myocardial perfusion imaging in asymptomatic patients with type 2 diabetes indicated a higher risk for cardiovascular events (13%), including cardiac death. Smoking and low glomerular filtration rate were significant contributing factors.[108] However, an earlier study questioned the merit of routine screening with adenosine-stress radionuclide myocardial perfusion imaging (MPI) in otherwise asymptomatic type 2 diabetic patients (the Detection of Ischemia in Asymptomatic Diabetics [DIAD] study).[109]

In both diabetic and nondiabetic 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 nondiabetic patients.[110]

Diabetes-associated mortality and morbidity

In 2015, diabetes mellitus was the seventh leading cause of death in the United States.[12] In addition, diabetes is a contributing cause of death in many cases, and it is probably underreported as a cause of death. Overall, the death rate among people with diabetes is about twice that of people of similar age but without diabetes.[111]

Diabetes mellitus causes morbidity and mortality because of its role in the development of cardiovascular, renal, neuropathic, and retinal disease. These complications, particularly cardiovascular disease (approximately 50-75% of medical expenditures), are the major sources of expenses for patients with diabetes mellitus.

Diabetic retinopathy

Diabetes mellitus is the major cause of blindness in adults aged 20-74 years in the United States; diabetic retinopathy accounts for 12,000-24,000 newly blind persons every year.[112] The National Eye Institute estimates that laser surgery and appropriate follow-up care can reduce the risk of blindness from diabetic retinopathy by 90%.[112]

End-stage renal disease

Diabetes mellitus, and particularly type 2 diabetes mellitus, is the leading contributor to end-stage renal disease (ESRD) in the United States.[112] According to the CDC, diabetes accounts for 44% of new cases of ESRD.[111] In 2008, 48,374 people with diabetes in the United States and Puerto Rico began renal replacement therapy, and 202,290 people with diabetes were on dialysis or had received a kidney transplant.[112]

Neuropathy and vasculopathy

Diabetes mellitus is the leading cause of nontraumatic lower limb amputations in the United States, with a 15- to 40-fold increase in risk over that of the nondiabetic population. In 2006, about 65,700 nontraumatic lower limb amputations were performed related to neuropathy and vasculopathy.[112]

Cardiovascular disease

The risk for coronary heart disease (CHD) is 2-4 times greater in patients with diabetes than in individuals without diabetes. Cardiovascular disease is the major source of mortality in patients with type 2 diabetes mellitus. Approximately two thirds of people with diabetes die of heart disease or stroke. Men with diabetes face a 2-fold increased risk for CHD, and women have a 3- to 4-fold increased risk.

Although type 2 diabetes mellitus, both early onset (< 60 y) and late onset (>60 y), is associated with an increased risk of major CHD and mortality, only the early onset type (duration >10 y) appears to be a CHD risk equivalent.[113]

In patients with type 2 diabetes mellitus, a fasting glucose level of more than 100 mg/dL significantly contributes to the risk of cardiovascular disease and death, independent of other known risk factors.[114] This is based on a review of 97 prospective studies involving 820,900 patients.

Data from a large population-based study affirms that worsening glycemic control appears to increase the risk of heart failure.[115]

Adolescents with obesity and obesity-related type 2 diabetes mellitus demonstrate a decrease in diastolic dysfunction.[116] This suggests that they may be at increased risk of progressing to early heart failure compared with adolescents who are either lean or obese but do not have type 2 diabetes mellitus.

Cancer

A 2010 Consensus Report from a panel of experts chosen jointly by the American Diabetes Association and the American Cancer Society suggested that people with type 2 diabetes are at an increased risk for many types of cancer.[117] Patients with diabetes have a higher risk for bladder cancer, particularly those patients who use pioglitazone.[118, 119] Age, male gender, neuropathy, and urinary tract infections were associated with this risk.

In a meta-analysis of 20 publications comprising 13,008 cancer patients with concurrent type 2 diabetes, researchers found that patients treated with metformin had better overall and cancer-specific survival than those treated with other types of glucose-lowering agents.[120, 121] These improvements were observed across cancer subtypes and geographic locations. Risk reduction was significant among patients with prostate, pancreatic, breast, colorectal and other cancers, but not for those with lung cancer. However, it remains unclear whether metformin can modulate clinical outcomes in cancer patients with diabetes.

Pneumonia

A study by López-de-Andrés et al found the incidence of postoperative pneumonia in patients with type 2 diabetes to be 21% higher than in nondiabetic patients, although the risk of inhospital mortality following the development of postoperative pneumonia was no greater in the presence of type 2 diabetes.[122]

COVID-19

A retrospective study by Chen et al of 136 COVID-19 patients with diabetes (primarily type 2 diabetes) found that older age, elevated C-reactive protein, and insulin use were risk factors for mortality. The adjusted odds ratio (OR) for mortality in insulin use was 3.58. It has been questioned, however, whether insulin itself is a risk factor or if the increased mortality reflected the characteristics of the patients taking it.[123, 124]

A study by Bode et al indicated that among patients with 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%).[125, 126]

A whole-population study from the United Kingdom reported that the risk of in-hospital death for patients with COVID-19 was 2.0 times greater for those with type 2 diabetes and 3.5 times higher for individuals with type 1 diabetes. However, patients under age 40 years with either type of diabetes were at extremely low risk for death.[127, 128]

A retrospective study by Zhu et al found that among individuals with COVID-19, those who also had type 2 diabetes mellitus had a mortality rate of 7.8% (versus 2.7% for those without diabetes), as well as a higher rate of multiple organ injury. However, the investigators also reported that among the patients with type 2 diabetes, the mortality rate was lower in those who, during hospitalization, had well-controlled blood glucose, that is, patients with a glycemic variability within 3.9 to 10.0 mmol/L, than in those with poorly controlled blood glucose, in which the upper limit of glycemic variability extended beyond 10.0 mmol/L.[129, 130]

The aforementioned study by Barrera et al indicated that among COVID-19 patients with diabetes, the unadjusted relative risk for admission to an intensive care unit (ICU) is 1.96, and for mortality, 2.78.[40, 41]

Another study from the United Kingdom found that risk factors for mortality in COVID-19 patients with type 1 or type 2 diabetes include male sex, older age, renal impairment, non-White ethnicity, socioeconomic deprivation, and previous stroke and heart failure. Moreover, patients with type 1 or type 2 diabetes had a significantly greater mortality risk with an HbA1c level of 86 mmol/mol or above, compared with persons with an HbA1c level of 48-53 mmol/mol. In addition, an HbA1c of 59 mmol/mol or higher in patients with type 2 diabetes increased the risk as well. The study also found that in both types of diabetes, BMI had a U-shaped relationship with death, the mortality risk being increased in lower BMI and higher BMI but being reduced between these (25.0-29.9 kg/m2).[131, 128]

A literature review by Schlesinger et al strengthened the association between severe diabetes and COVID-19–related mortality, finding that among study patients with diabetes, the likelihood of death from COVID-19 was 75% greater in chronic insulin users. The study also indicated that the chance of death from COVID-19 is 50% less in individuals undergoing metformin therapy than in other patients with diabetes. The investigators suggested that the medications themselves did not impact survival but were indicators of the severity of diabetes in each group, with the prognosis being poorer among those with more severe diabetes.[132, 133]

A retrospective study by Wang et al indicated that hyperglycemia, even in the absence of diabetes, is an independent predictor of 28-day mortality in patients with COVID-19. The investigators reported that on admission to two hospitals in Wuhan, China, 29.1% of study patients with COVID-19 and no prior diagnosis of diabetes had a fasting blood glucose of at least 7.0 mmol/L. It was believed that the individuals with hyperglycemia included not only persons with undiagnosed diabetes, but also nondiabetic patients with acute stress hyperglycemia. With regard to 28-day mortality, it was determined that the hazard ratio in patients with a fasting blood glucose of 7.0 mmol/L or higher was 2.30.[134, 135]

Similarly, another report found that in study patients with COVID-19 who had a blood glucose level of over 6.1 mmol/L, the risk of disease progression was 58% greater, with the mortality risk being 3.22-fold higher.[136]

A retrospective, multicenter study by Carrasco-Sánchez et al supported these results, indicating that among noncritical patients with COVID-19, the presence of hyperglycemia on hospital admission independently predicts progression to critical status, as well as death, whether or not the patient has diabetes. The in-hospital mortality rate in persons with a blood glucose level of higher than 180 mg/dL was 41.1%, compared with 15.7% for those with a level below 140 mg/dL. Moreover, the need for ventilation and intensive care unit admission were also greater in the presence of hyperglycemia. The report involved over 11,000 patients with confirmed COVID-19, only about 19% of whom had diabetes.[137, 138]

In contrast to the above research, a report by Klonoff et al on over 1500 US patients with COVID-19 found no association between hyperglycemia on hospital admission and mortality, in non-ICU patients. However, the in-hospital mortality rate was significantly greater in such patients if they had a blood glucose level above 13.88 mmol/L on the second or third hospital day, compared with those with a level below 7.77 mmol/L. Findings for patients admitted directly to the ICU differed from these, with the investigators determining that mortality was associated with the presence of hyperglycemia on admission but was not significantly linked with a high glucose level on the second hospital day.[139, 140]

A study by Sardu et al indicated that in hospitalized patients with COVID-19 and moderately severe pneumonia, those with diabetes and those who are hyperglycemic are at higher risk of severe disease than are normoglycemic patients without

diabetes. Moreover, among the patients in the study with hyperglycemia, the risk of severe disease was lower in those who were treated with insulin infusion, providing further evidence of the importance of in-hospital glucose control.[124, 141]

A study by Cariou et al reported that in patients with diabetes hospitalized for COVID-19, a positive, independent association was found between higher body mass index (BMI) and risk of tracheal intubation and/or death within 7 days. The median BMI in patients who suffered this outcome was 29.1 kg/m2, compared with 28.1 kg/m2 in those who did not. However, an association was not found between long-term glucose control and 7-day tracheal intubation and/or death. Regarding specific outcome rates, the study, in which 88.5% of the diabetes cases were type 2 diabetes, reported that 20.3% of the patients with diabetes who were hospitalized with COVID-19 underwent tracheal intubation within 7 days, while 10.6% died within this time.[142, 143]

A French study, by Wargny et al, indicated that among patients with diabetes who are hospitalized with COVID-19, approximately 20% will die within 28 days. Individuals particularly at risk for mortality over this 4-week period include patients of advanced age, as well as those with a history of microvascular complications (especially those who have had kidney or eye damage), who have dyspnea on admission or inflammatory markers (increased white blood cell [WBC] count, raised C-reactive protein, elevated aspartate transaminase), or who have undergone routine insulin and statin treatment. It should be kept in mind, however, that the data was gathered between March 10 and April 10, 2020, with a statement from Diabetes UK explaining that in people with diabetes, COVID-19–associated mortality has decreased over time as treatment has improved.[144, 145]

The Centers for Disease Control and Prevention (CDC) includes type 2 diabetes in the list of conditions that increase the likelihood of severe illness in persons with COVID-19, and type 1 diabetes in the list of conditions that may increase this likelihood.[146]

Pregnancy outcome

Untreated gestational diabetes mellitus can lead to fetal macrosomia, hypoglycemia, hypocalcemia, and hyperbilirubinemia. In addition, mothers with gestational diabetes mellitus have increased rates of cesarean delivery and chronic hypertension.

Despite advanced age, multiparity, obesity, and social disadvantage, patients with type 2 diabetes were found to have better glycemic control, fewer large-for-gestational-age infants, fewer preterm deliveries, and fewer neonatal care admissions compared with patients with type 1 diabetes. This suggests that better tools are needed to improve glycemic control in patients with type 1 diabetes.[147] (For more information, see Diabetes Mellitus and Pregnancy.)

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Patient Education

No longer is it satisfactory to provide patients who have diabetes with brief instructions and a few pamphlets and expect them to manage their disease adequately. Instead, education of these patients should be an active and concerted effort involving the physician, nutritionist, diabetes educator, and other health professionals. Moreover, diabetes education needs to be a lifetime exercise; believing that it can be accomplished in 1 or 2 encounters is misguided.

A randomized, controlled trial found that for patients with poorly controlled diabetes, individual attention and education is superior to group education.[148] Similarly, a diabetes education and self-management group program in the UK for newly diagnosed patients failed to yield significant benefits.[149] Nonphysician health professionals are usually much more proficient at diabetes education and have much more time for this very important activity.

A systematic review suggested that patients with type 2 diabetes who have a baseline HbA1c of greater than 8% may achieve better glycemic control when given individual education rather than usual care. Outside that subgroup, however, the report found no significant difference between usual care and individual education. In addition, comparison of individual education with group education showed equal impact on HbA1c at 12-18 months.[150]

Patient education is an immensely complex topic, however. The clinical impression of most experts in the field is that there is merit in the provision of careful diabetes education at all stages of the disease.

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Presentation

History

The diagnosis of diabetes mellitus is readily entertained when a patient presents with classic symptoms (ie, polyuria, polydipsia, polyphagia, weight loss). Other symptoms that may suggest hyperglycemia include blurred vision, lower extremity paresthesias,

or yeast infections, particularly balanitis in men. However, many patients with type 2 diabetes are asymptomatic, and their disease remains undiagnosed for many years.

In older studies, the typical patient with type 2 diabetes had diabetes for at least 4-7 years at the time of diagnosis.[151] Among patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study, 25% had retinopathy; 9%, neuropathy; and 8%, nephropathy at the time of diagnosis. (For more information, see Diabetic Neuropathy.)

Patients with established diabetes

In patients with known type 2 diabetes, inquire about the duration of the patient's diabetes and about the care the patient is currently receiving for the disease. The duration of diabetes is significant because the chronic complications of diabetes are related to the length of time the patient has had the disease.

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 of losing consciousness, this possibility must be addressed, especially if the patient drives or has significant underlying neuropathy or cardiovascular disease
- 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) that should be considered as a source of acute symptoms
- Does the patient self-monitor his or her blood glucose levels - If so, note the frequency and range of values at each time of day
- When was the patient's hemoglobin A1c (HbA1c; an indicator of long-term glucose control) last measured, and what was it
- What is the patient’s immunization history - Eg, influenza, pneumococcal, hepatitis B, tetanus, herpes zoster

As circumstances dictate, additional questions may be warranted, as follows:

- Does the patient give a history of recent polyuria, polydipsia, nocturia, or weight loss - These are symptoms of hyperglycemia
- 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
- Regarding retinopathy, when was the patient's last dilated eye examination, and what were the results
- Regarding nephropathy, does the patient have known kidney disease; what were the dates and results of the last measurements of urine protein and serum creatinine levels
- Does the patient have hypertension (defined as a blood pressure of >130/80); what medications are taken
- Does the patient have CAD
- Regarding peripheral vascular disease, does the patient have 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
- Does the patient have a history of neuropathy or are symptoms of peripheral neuropathy or autonomic neuropathy present (including impotence if the patient is male)
- Does the patient have a history of foot ulcers or amputations; are any foot ulcers present
- Are frequent infections a problem; at what site

Dawn phenomenon

The Dawn phenomenon, defined as a blood glucose increase of over 20 mg/dL occurring at the end of the night, appears to be common in type 2 diabetes. In a study of 248 noninsulin-treated patients with type 2 diabetes who underwent continuous glucose monitoring for 2 consecutive days, approximately half were found to have the dawn phenomenon.[152, 153] Patients with the dawn phenomenon had HbA1c levels and 24-hour mean glucose values that were significantly higher than in other patients, the mean differences being 4.3 mmol/mol for HbA1c (0.39%) and 12.4 mg/dL for average 24-hour glucose concentrations. Mean 24-hour glucose did not significantly differ between patients treated with diet alone and those treated with oral antihyperglycemic agents (ie, oral antidiabetic drugs did not eliminate the dawn phenomenon).[152, 153]

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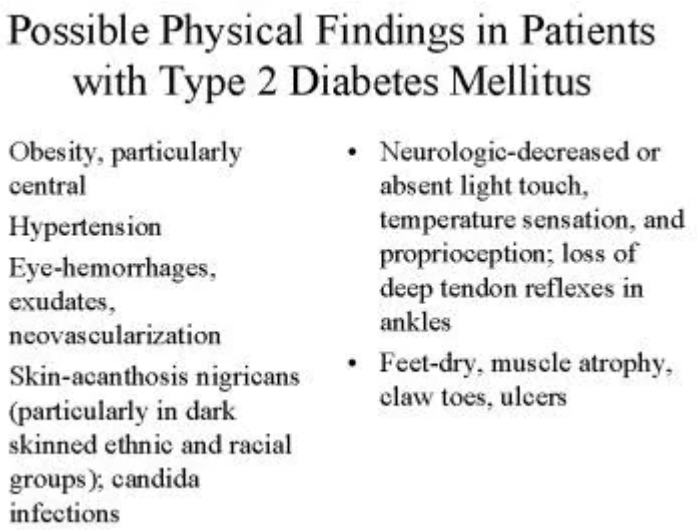
Physical Examination

Early in the course of diabetes mellitus, the physical examination findings are likely to be unrevealing. Ultimately, however, end-organ damage may be observed. Potential findings are listed in the image below.



Possible physical examination findings in patients with type 2 diabetes mellitus.

A diabetes-focused examination includes vital signs, funduscopic examination, limited vascular and neurologic examinations, and a foot assessment. Other organ systems should be examined as indicated by the patient's clinical situation.

Assessment of vital signs

Baseline and continuing measurement of vital signs is an important part of diabetes management. In addition to vital signs, measure height, weight, and waist and hip circumferences.

In many cases, blood pressure measurement will disclose hypertension, which is particularly common in patients with diabetes. 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.

If the respiratory rate and pattern suggest Kussmaul respiration, diabetic ketoacidosis (DKA) must be considered immediately, and appropriate tests ordered. DKA is more typical of type 1 diabetes, but it can occur in type 2.

Funduscopic examination

The funduscopic examination should include a careful view of the retina. 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, especially if the patients' pupils are not dilated.

Whether patients develop diabetic retinopathy depends on the duration of their diabetes and on the level of glycemic control maintained.[154, 155] Because the diagnosis of type 2 diabetes often is delayed, 20% of these patients have some degree of retinopathy at diagnosis. The following are the 5 stages in the progression of diabetic retinopathy:

- Dilation of the retinal venules and formation of retinal capillary microaneurysms

- Increased vascular permeability
- Vascular occlusion and retinal ischemia
- Proliferation of new blood vessels on the surface of the retina
- Hemorrhage and contraction of the fibrovascular proliferation and the vitreous

The first 2 stages of diabetic retinopathy are known as background or nonproliferative retinopathy. Initially, the retinal venules dilate, then microaneurysms (tiny red dots on the retina that cause no visual impairment) appear. As the microaneurysms or retinal capillaries become more permeable, hard exudates appear, reflecting the leakage of plasma.

Larger retinal arteriolar and venular calibres have been associated with lower scores on memory tests but not with lower scores on other cognitive tests.[156] This association was strong in men. Impaired arteriolar autoregulation may be an underlying mechanism of memory decrements.

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. (For more information, see Macular Edema in Diabetes.)

Preproliferative and proliferative diabetic retinopathy are the next stages in the progression of the disease. Cotton-wool spots can be seen in preproliferative retinopathy. These represent retinal microinfarcts caused by capillary occlusion; they appear as patches that range from off-white to gray, and they have 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.

Patients with preproliferative or proliferative retinopathy must immediately be referred for ophthalmologic evaluation because laser therapy is effective in this condition, especially before actual 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 be referred immediately 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, thus obscuring less central vision.

Patients with active proliferative diabetic retinopathy are at increased risk of retinal hemorrhage if they receive thrombolytic therapy; therefore, this condition is a relative contraindication to the use of thrombolytic agents.

One study has shown that individuals with gingival hemorrhaging have a high prevalence of retinal hemorrhage.[157] Much of this association is driven by hyperglycemia, making it possible to use gingival tissue to study the natural course of microvascular disease in patients with diabetes.

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, because poor lower-extremity blood flow can slow 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. This can be assessed with the Semmes Weinstein monofilament or by assessment of reflexes, position, and/or vibration sensation.

If peripheral neuropathy is found, the patient should be made aware that foot care (including daily foot examination) is very important for preventing foot ulcers and avoiding lower-extremity amputation. (For more information, see Diabetic Foot and Diabetic Foot Infections.)

Differentiation of type 2 from type 1 diabetes

Type 2 diabetes mellitus can usually be differentiated from type 1 diabetes mellitus on the basis of history and physical examination findings and simple laboratory tests (see Workup: Tests to Differentiate Type 2 and Type 1 Diabetes). Patients with type 2 diabetes are generally obese, and may have acanthosis nigricans and/or hirsutism in conjunction with thick necks and chubby cheeks.

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Diagnostic Considerations

Correctly determining whether a patient has type 1 or type 2 diabetes is important because patients with type 1 diabetes require continuous exogenous insulin for survival. In contrast, treatment of type 2 diabetes consists of lifestyle measures and a variety of other medications, with insulin introduced if those prove inadequate.

As previously stated, patients with type 2 diabetes mellitus can usually be differentiated from those with type 1 disease on the basis of history and physical examination findings and through simple laboratory tests. Patients with type 2 diabetes are generally obese, and may have acanthosis nigricans and/or hirsutism in conjunction with thick necks and chubby cheeks.

A patient whose diabetes has been controlled with diet or an oral antidiabetic agent for longer than several months generally has type 2 diabetes. 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 diabetes.

When dealing with patients with known diabetes in the emergency department, distinguishing the type of diabetes can be difficult in 2 groups: (1) patients who are treated with insulin and are young but clinically appear to have type 2 diabetes, and (2) older patients with late-onset of diabetes who nonetheless take insulin and seem to share characteristics of patients with type 1 diabetes. (This latter group is now said to have latent autoimmune diabetes of the adult [LADA]).

When in doubt, the emergency department patient should be treated with insulin and his or her glucose levels should be closely monitored. Some adolescents or young adults, mostly Hispanic or African American patients, who present with classic DKA are subsequently found to have type 2 diabetes.

Prediabetes

Prediabetes often precedes overt type 2 diabetes. Prediabetes is defined by a fasting blood glucose level of 100-125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level of 140-200 mg/dL. Persons with prediabetes are at increased risk for macrovascular disease, as well as diabetes.[1]

Often confused with prediabetes is the metabolic syndrome (also called syndrome X or the insulin-resistance syndrome). Metabolic syndrome, thought to be due to insulin resistance, can occur in patients with overtly normal glucose tolerance, prediabetes, or diabetes. It is diagnosed when a patient has at least 3 of the following 5 conditions:

- Abdominal obesity
- Elevated triglyceride level
- Low level of high-density lipoprotein (HDL) cholesterol
- Elevated blood pressure
- Fasting glucose value of 100 mg/dL or higher

Eventually, clinically apparent insulin resistance develops. Unfortunately, insulin resistance is not possible to measure clinically, except in research settings. An elevated fasting blood glucose or triglyceride level may be the first indication of insulin resistance. Fasting insulin levels are generally increased at an earlier stage, but they are more directly related to insulin clearance than to insulin resistance. An effort to standardize insulin assays is under way and may allow for the use of fasting insulin levels to diagnose insulin resistance in the future.

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Workup

Workup

Approach Considerations

The American Diabetes Association (ADA) criteria for the diagnosis of diabetes are any of the following[1] :

- An HbA1c level of 6.5% or higher; the test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay, or
- A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher; fasting is defined as no caloric intake for at least 8 hours, 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 (ie, polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis

The American Association of Clinical Endocrinologists, however, recommends that HbA1c be considered an additional optional diagnostic criterion, rather than a primary criterion for diagnosis of diabetes.[158]

If unequivocal hyperglycemia is absent, then HbA1c, FPG, and OGTT results should be confirmed by repeat testing. The ADA recommends repeating the same test for confirmation, since there will be a greater likelihood of concurrence. However, the diagnosis of diabetes is also confirmed if the results of 2 different tests are above the diagnostic thresholds.[2]

If a patient has had 2 different tests and the results are discordant, the test that has a result above the diagnostic threshold should be repeated. A second abnormal result on this test will confirm the diagnosis.[159]

In asymptomatic patients whose random serum glucose level suggests diabetes (>140 mg/dL), an FPG or HbA1c level should be measured. An FPG level of 100-125 mg/dL is considered an impaired fasting glucose (IFG), and an FPG level of less than 100 mg/dL is considered a normal fasting glucose. However, an FPG of 91-99 mg/dL is a strong independent predictor of future type 2 diabetes.[160]

An HbA1c below 6%is considered normal glucose tolerance (using an assay that has been standardized to the DCCT normal range of 4-6%). An HbA1C of 6-6.4% is neither normal glucose tolerance nor diabetes. With current assays, an HbA1c of less than 5.7% is considered normal and an HbA1c of greater than 6.4% is considered diagnostic for diabetes mellitus (DM). A value between 5.7% and 6.4% is considered diagnostic of prediabetes.

In the emergency department, a fingerstick glucose test is appropriate for virtually all patients with diabetes. All other laboratory studies should be individualized to the clinical situation.[161]

Glucose Studies

Plasma glucose is determined using blood drawn into a gray-top (sodium fluoride) tube, which inhibits red blood cell glycolysis immediately. A serum glucose measurement (commonly obtained on chemistry panels, using a red- or speckled-top tube) may be significantly lower than a plasma glucose measurement. Capillary whole blood measurements are not recommended for the diagnosis of diabetes mellitus, but they are valuable for assessment of patients in acute care situations.

The noted values for fasting glucose measurements are based on the level of glycemia at which retinopathy, a fairly pathognomonic diabetic complication, appears. (However, evidence suggests that retinopathy may occur even in prediabetes.) Fasting glucose measurements are not as predictive for indicating macrovascular risk as are post–glucose load values. However, there are no formal recommendations for using glucose tolerance tests for this purpose.

Impaired glucose tolerance

The World Health Organization (WHO) criteria for impaired glucose tolerance (IGT) are an FPG of less than 126 mg/dL (7 mmol/L), if measured, and a venous plasma glucose of 140 mg/dL to just below 200 mg/dL (≥7.8 to < 11.1mmol/L) 2 hours after a 75-g glucose load with one intervening plasma glucose value at or above 200 mg/dL.[159] The WHO notes that IGT is not a clinical entity but a risk factor for future diabetes and/or adverse outcomes and that the risk of future diabetes, premature death, and cardiovascular disease begins to increase at 2-hour plasma glucose levels below the IGT range.

These criteria are a better predictor of increased macrovascular risk than the ADA's current intermediate category of IFG or prediabetes. Presumably, patients with IFG are at increased risk for development of diabetes mellitus, but their risk for macrovascular disease does not appear to be the same as for patients with IGT (which is about the same as for patients with frank type 2 diabetes mellitus).

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Glycated Hemoglobin Studies

Binding of glucose to hemoglobin A is a nonenzymatic process that occurs over the lifespan of a red blood cell, which averages 120 days. Measurement of glycated hemoglobin thus reflects plasma glucose levels over the preceding 2-3 months.

HbA1c measurements are the criterion standard for monitoring long-term glycemic control. In the past, HbA1c measurements were not considered useful for the diagnosis of diabetes mellitus, because of 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 diabetes mellitus.[162] The committee noted the improvement in standardization and cited the following advantages of HbA1c testing over glucose measurement:

- Captures long-term glucose exposure
- Has less biologic variability
- Does not require fasting or timed samples
- Is currently used to guide 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 is >200 mg/dL). A target HbA1c level of less than 8% is supported for older patients (>60 y). levels below 6% are associated with increased mortality.[163] HbA1c testing cannot be used in patients with abnormal red cell turnover (eg, hemolytic or iron-deficiency anemia).[1]

The American Association of Clinical Endocrinologists recommends that HbA1C be considered an additional, optional diagnostic criterion, rather than the primary criterion for diagnosis of diabetes.[158] Using HbA1c alone in initial diabetes screening identifies approximately 20% fewer cases of diabetes than diagnosis based on fasting and 2-hour postload plasma glucose levels.[164]

Moreover, 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 OGTT, HbA1c testing would lead to a 42% overdiagnosis of glucose tolerance and a 73% underdiagnosis of diabetes, in adults.[165]

Glucose measurement should remain the choice for diagnosing pregnant women or if HbA1c assay is unavailable. In addition, a study by Nowicka et al stated that used on its own, HbA1c is not effective in detecting prediabetes and diabetes in obese children and adolescents.[166]

However, a study by Vijayakumar et al suggested, in contrast, that the evaluation of HbA1c levels is as effective as FPG and 2-hour postload plasma glucose tests in predicting the development of type 2 diabetes in children and adolescents. The study determined that among the report's subjects, the incidence of diabetes at follow-up was fourfold higher in male children and adolescents belonging to the highest HbA1c category (5.7-6.4%) at baseline than in those in the lowest category (5.3% or lower), while the incidence of diabetes in female children and adolescents in the highest category was sevenfold greater than in those belonging to the lowest category.[167, 168]

Lu et al found evidence that a screening HbA1c of 5.5% or below predicts the absence of type 2 diabetes, while an HbA1c of 7% or greater predicts its presence, and levels of 6.5-6.9% indicate a high probability that diabetes is present. The investigators derived these cutoffs from a clinical group of 2494 patients, 34.6% of whom had undiagnosed diabetes, and then evaluated the cutoffs in a population-based sample of 6015 patients, 4.6% of whom had undiagnosed diabetes.

In the population-based group, HbA1c at 5.5% had a sensitivity of 83.5%, while HbA1c at 7% had a specificity of 100%. In both groups, many (61.9-69.3%) individuals with HbA1c levels of 5.6-6.9% had an abnormal glucose status.[169]

A community-based study by Lerner et al of 10,201 patients not previously diagnosed with diabetes found that patients whose baseline HbA1c levels were at 5.5% or higher but less than 6.5% had an increased risk of developing diabetes over the subsequent 5-8 years. Moreover, the risk of developing diabetes doubled with every increase of 0.5% in HbA1c level. The risk of diabetes was not associated with age or low socioeconomic status in this study.[170, 171]

An analysis of 15,780 patients from the INTERHEART study determined that HbA1c levels were more suggestive of myocardial infarction risk than were self-reported diabetes status or many other established risk factors.[172] Each 1% increase independently predicts a 19% increase in odds of experiencing a myocardial infarction after accounting for other risk factors, including diabetes.

HbA1c cannot be used as an indicator of glycemic control in patients with neonatal diabetes mellitus 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, 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.[173]

A study by Wilson et al (in patients with type 1 diabetes) found persistent individual variations in the rate at which individuals glycate hemoglobin. These variations may contribute to inaccuracy in estimating mean glucose concentration from the HbA1c level.[174]

Hemoglobin A1c versus total glycated hemoglobin

Glycated hemoglobin can be measured as HbA1c, HbA1 (HbA1a, b, and c), or total glycated hemoglobin (GHb). HbA1c constitutes approximately 80% of GHb.

Whether HbA1c or GHb assays are superior for measuring glycemic control is debatable. Hemoglobinopathies can affect both measurements. Because the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), as well as the ADA Standards of Care, use HbA1c measurements, this article refers to HbA1c as the standard for glycemic control.

Using GHb measurements is acceptable, but these values are 1-2% higher than HbA1c concentrations. When using GHb, a conversion factor to HbA1c for the assay utilized is helpful.

International Federation of Clinical Chemistry standardization

The International Federation of Clinical Chemistry (IFCC) has developed a reference method for measurement of HbA1c. The IFCC method produces values lower than the HbA1c methods in current clinical use; conversion requires a complex formula. Although more accurate, the IFCC method is complicated, time consuming, and expensive. Consequently, there are no immediate plans for its adoption into clinical practice.

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Urinary Albumin Studies

Annual screening for microalbuminuria (see Microalbumin) is recommended in all patients with diabetes. Measuring the albumin-to-creatinine ratio in a spot urine sample is probably the easiest method; the ratio, expressed in mg/g, is equivalent to albumin excretion in milligrams daily. A result greater than 30 mg/g indicates albuminuria, in which case a quantitation on a timed urine specimen (ie, overnight, 10 h, or 24 h) should be performed.

Normal urine albumin excretion is defined as less than 30 mg daily. Microalbuminuria is defined as 30-300 mg daily (20-200 mcg/min). Because of wide variability among patients, microalbuminuria should be found on at least 2 of 3 samples over 3-6 months. Higher values can be detected by standard protein dipstick screening and are considered macroproteinuria.

Unlike type 1 diabetes mellitus, in which microalbuminuria is a good indicator of early kidney damage, microalbuminuria is a common finding (even at diagnosis) in type 2 diabetes mellitus and is a risk factor for macrovascular (especially coronary heart) disease. It is a weaker predictor of future kidney disease in type 2 diabetes mellitus.

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Diabetes Testing in Asymptomatic Patients

The U.S. Preventive Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg (grade B recommendation).[3]

The ADA recommends considering testing for prediabetes and diabetes in asymptomatic adults who are overweight (body mass index [BMI] ≥25 kg/m2; may be lower in at-risk ethnic groups) and have 1 or more of the following additional risk factors[2] :

- Physical inactivity
- First-degree relative with diabetes
- Member of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- Delivered a baby weighing over 9 lb or diagnosed with gestational diabetes mellitus

- Hypertension (≥140/90 mm Hg or on therapy for hypertension)
- HDL cholesterol level under 35 mg/dL (0.90 mmol/L) and/or a triglyceride level above 250 mg/dL (2.82 mmol/L)
- Polycystic ovary disease
- IGT or IFG on previous testing
- Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)
- History of cardiovascular disease

In the absence of the above criteria, the ADA recommends testing for prediabetes and diabetes beginning at age 35 years.[4, 5]

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Tests to Differentiate Type 2 and Type 1 Diabetes

Measuring concentrations of insulin or C-peptide (a fragment of proinsulin that serves as a marker for insulin secretion) rarely is necessary to diagnose type 2 diabetes mellitus or differentiate type 2 diabetes from type 1 diabetes mellitus. Insulin levels generally are high early in the course of type 2 diabetes mellitus and gradually wane over time.

A fasting C-peptide level of more than 1 ng/dL in a patient who has had diabetes for more than 1-2 years is suggestive of type 2 diabetes (ie, residual beta-cell function). Stimulated C-peptide concentrations (after a standard meal challenge such as Sustacal or after glucagon) are somewhat preserved until late in the course of type 2 diabetes mellitus. Absence of a C-peptide response to carbohydrate ingestion may indicate total beta-cell failure.

Latent autoimmune diabetes of adults (LADA) is a form of slow-onset type 1 diabetes that occurs in middle-aged (usually white) adults. It can be differentiated from type 2 diabetes by confirming the presence of antibodies against the 65-kd isoform of glutamic acid decarboxylase (GAD65), an enzyme found in pancreatic beta cells. Such patients may respond to insulin secretagogues for a brief period (months).

Autoantibodies can be useful in differentiating between type 1 and type 2 diabetes. Islet-cell (IA2), anti-GAD65, and anti-insulin autoantibodies can be present in early type 1 diabetes, but not in type 2 disease. IA2 autoantibodies titers typically decrease after 6 months. Anti-GAD65 antibodies can be present at diagnosis of type 1 diabetes and are more likely to be persistently positive over time.

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Treatment

Approach Considerations

The goals in caring for patients with diabetes mellitus are to eliminate symptoms and to prevent, or at least slow, the development of complications. Microvascular (ie, eye and kidney disease) risk reduction is accomplished through control of glycemia and blood pressure; macrovascular (ie, coronary, cerebrovascular, peripheral vascular) risk reduction, through control of lipids and hypertension, smoking cessation, and aspirin therapy; and metabolic and neurologic risk reduction, through control of glycemia.

New abridged recommendations for primary care providers

The American Diabetes Association has released condensed recommendations for Standards of Medical Care in Diabetes: Abridged for Primary Care Providers, highlighting recommendations most relevant to primary care. The abridged version focusses particularly on the following aspects:

- Prediabetes
- Self-management education
- Nutrition
- Physical activity
- Smoking cessation

- Psychosocial care
- Immunizations
- Glycemic treatment
- Therapeutic targets
- Diagnosis and treatment of vascular complications
- Intensification of insulin therapy in type 2 diabetes

The recommendations can be accessed at American Diabetes Association DiabetesPro Professional Resources Online, Clinical Practice Recommendations – 2015.[175]

Type 2 diabetes care is best provided by a multidisciplinary team of health professionals with expertise in diabetes, working in collaboration with the patient and family.[2] Management includes the following:

- Appropriate goal setting
- Dietary and exercise modifications
- Medications
- Appropriate self-monitoring of blood glucose (SMBG)
- Regular monitoring for complications
- Laboratory assessment

Ideally, blood glucose should be maintained at near-normal levels (preprandial levels of 90-130 mg/dL and hemoglobin A1C [HbA1c] levels < 7%). However, focus on glucose alone does not provide adequate treatment for patients with diabetes mellitus. Treatment involves multiple goals (ie, glycemia, lipids, blood pressure).

Aggressive glucose lowering may not be the best strategy in all patients. Individual risk stratification is highly recommended. In patients with advanced type 2 diabetes who are at high risk for cardiovascular disease, lowering HbA1c to 6% or lower may increase the risk of cardiovascular events.[176]

A study from the ACCORD Study Group found that setting the treatment target for HbA1c below 6% in high-risk patients resulted in reduced 5-year nonfatal myocardial infarctions. However, patients who did not achieve the treatment target experienced increased 5-year mortality.[177]

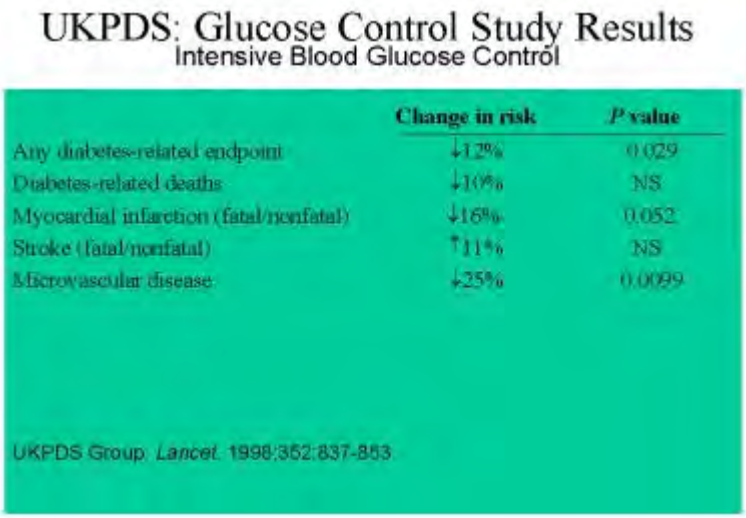
Review of blood glucose logs must be part of any diabetes management plan. Both iron and erythropoietin treatments commonly prescribed in patients with chronic kidney disease cause a significant decrease in HbA1c without affecting blood glucose levels.[178]

With each health-care system encounter, patients with diabetes should be educated about and encouraged to follow an appropriate treatment plan. Adherence to diet and exercise should continue to be stressed throughout treatment, because these lifestyle measures can have a large effect on the degree of diabetic control that patients can achieve.

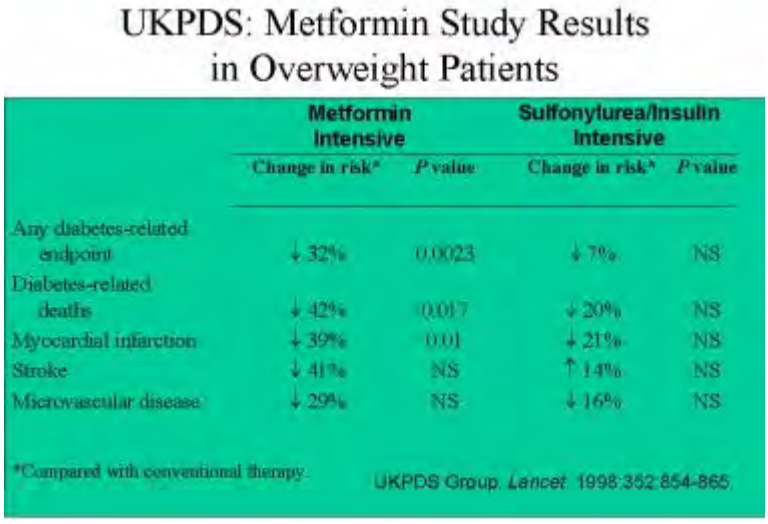
A study by Morrison et al found that more frequent visits with a primary care provider (every 2 wk) led to markedly rapid reductions in serum glucose, HbA1c, and low-density lipoprotein (LDL) cholesterol levels. However, how such a strategy can work globally remains a challenge due to available resources and economic restrictions.[179]

The United Kingdom Prospective Diabetes Study

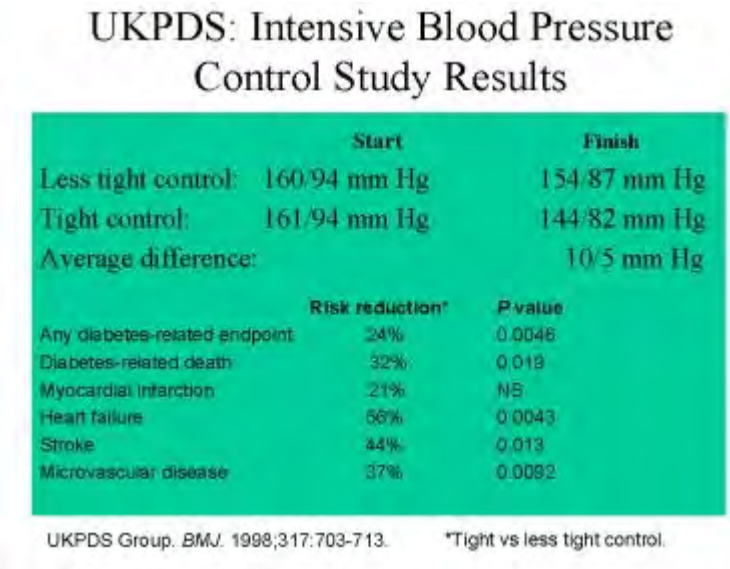
The care of patients with type 2 diabetes mellitus has been profoundly shaped by the results of the United Kingdom Prospective Diabetes Study (UKPDS). This landmark study confirmed the importance of glycemic control in reducing the risk for microvascular complications and refuted previous data suggesting that treatment with sulfonylureas or insulin increased the risk of macrovascular disease. Major findings of the UKPDS are displayed in the images below.



Major findings from the primary glucose study in the United Kingdom Prospective Diabetes Study (UKPDS).



Results from metformin substudy in the United Kingdom Prospective Diabetes Study (UKPDS).



Findings from the blood pressure substudy in the United Kingdom Prospective Diabetes Study (UKPDS).

Significant implications of the UKPDS findings include the following:

- Microvascular complications (predominantly indicated by the need for laser photocoagulation of retinal lesions) are reduced by 25% when mean HbA1c is 7%, compared with 7.9%
- A continuous relationship exists between glycemia and microvascular complications, with a 35% reduction in risk for each 1% decrement in HbA1c; a glycemic threshold (above the upper limit of normal for HbA1c) below which risk for microvascular disease is eliminated does not appear to exist
- Glycemic control has minimal effect on macrovascular disease risk; excess macrovascular risk appears to be related to conventional risk factors such as dyslipidemia and hypertension
- Sulfonylureas and insulin therapy do not increase macrovascular disease risk[95]
- Metformin reduces macrovascular risk in patients who are obese[180]
- Vigorous blood pressure control reduces microvascular and macrovascular events; beta blockers and angiotensin-converting enzyme (ACE) inhibitors appear to be equally effective in this regard

American College of Physicians guidance statement

According to a 2018 guidance statement by the American College of Physicians (ACP), “Clinicians should aim to achieve an HbA1c level between 7% and 8% in most patients with type 2 diabetes.” The ACP said that this higher target is aimed at helping patients benefit from glycemic control while avoiding the adverse effects—associated with low blood sugar, medication burden, and costs—of stricter targets. The ACP stated that evidence does not indicate that medication therapy to reduce the HbA1c level to 7% or less results in reduced mortality or in decreased macrovascular complications, such as heart attack or stroke, compared with a reduction to about 8%.[181, 182]

However, experts from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have expressed skepticism about the higher target, noting that the guidance statement does not take into account the cardiovascular disease benefits of newer drugs, which themselves frequently reduce HbA1c levels. In response, a coauthor of the ACP statement observed that other guidelines have also not specifically accounted for these newer medications in their recommended HbA1c levels and that research on such drugs has primarily been in patients either with cardiovascular disease or at high risk of developing it.[181]

Joint consensus statement on remission

In a 2021 joint consensus statement from the American Diabetes Association, the Endocrine Society, the European Association for the Study of Diabetes, and Diabetes UK, the term “remission,” as it applies to type 2 diabetes, is defined as the presence of an HbA1c level below 6.5% (< 48 mmol/mol) at least 3 months after glucose-lowering pharmacotherapy has been halted. This applies whether the remission has been achieved by way of lifestyle, bariatric surgery, or other means.[183, 184]

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Pharmacologic Therapy

Early initiation of pharmacologic therapy is associated with improved glycemic control and reduced long-term complications in type 2 diabetes. Drug classes used for the treatment of type 2 diabetes include the following:

- Biguanides
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Glucagonlike peptide–1 (GLP-1) agonists
- GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonists
- Dipeptidyl peptidase IV (DPP-4) inhibitors
- Selective sodium-glucose transporter–2 (SGLT-2) inhibitors

- Nonsteroidal mineralocorticoid receptor (MR) antagonists
- Insulins
- Amylinomimetics
- Bile acid sequestrants
- Dopamine agonists

A literature review by Alfayez et al indicated that GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors put patients with type 2 diabetes at no additional cardiovascular risk. Moreover, patients taking GLP-1 agonists actually showed significant reduction in such risk, while those on SGLT-2 inhibitors demonstrated a significant decrease in hospitalization for heart failure events.[185]

A position statement from Primary Care Diabetes Europe (PCDE) provides a clinical decision–making model that primary care clinicians can use in the pharmacologic management of patients with type 2 diabetes, including when addressing cardiovascular disease and its risk.

Biguanides

Metformin is the only biguanide in clinical use. Another biguanide, phenformin, was taken off the market in the United States in the 1970s because of its risk of causing lactic acidosis and associated mortality (rate of approximately 50%). Metformin has proved effective and safe.[186] A nested case-control analysis found that, as with other oral antidiabetic drugs, lactic acidosis during metformin use is very rare and is associated with concurrent comorbidity.[187]

Metformin lowers basal and postprandial plasma glucose levels. Its mechanisms of action differ from those of other classes of oral antidiabetic agents; metformin works by decreasing hepatic gluconeogenesis. It also decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

A study by Sun et al suggested that metformin also exercises glucose control by reducing levels of Bacteroides fragilis in the gut. The research indicated that reduction of the microbe, which has bile salt hydrolase activity, leads to an increase in the bile acid glycoursodeoxycholic acid (GUDCA), which in turn inhibits signaling of the intestinal farnesoid X receptor (FXR), a nuclear receptor that plays a role in regulating hepatic bile acid.[188, 189] Unlike oral sulfonylureas, metformin rarely causes hypoglycemia.

Patients on metformin have shown significant improvements in hemoglobin A1c and their lipid profile, especially when baseline values are abnormally elevated. In addition, metformin is the only oral diabetes drug that reliably facilitates modest weight loss. In the UKPDS, it was found to be successful at reducing macrovascular disease endpoints in obese patients.[190] The results with concomitant sulfonylureas in a heterogeneous population were conflicting,[191] but overall, this drug probably improves macrovascular risk.

In January 2017, the American College of Physicians (ACP) released a guideline update recommending the use of metformin as a first-line treatment for type 2 diabetes. The update also recommended consideration of the addition of a drug from one of the following classes—sulfonylureas, thiazolidinediones, dipeptidyl peptidase IV (DPP-4) inhibitors, or selective sodium-glucose transporter–2 (SGLT-2) inhibitors—to metformin when a second oral therapy is thought to be needed to aid glycemic control. However, the second recommendation was graded as "weak," with the evidence of moderate quality, by the ACP.[192, 193]

A study by Vashisht et al that examined data from more than 246.5 million patients found that when used along with metformin therapy for type 2 diabetes, treatment with sulfonylureas, DPP-4 inhibitors, or thiazolidinediones was equally effective in reducing the HbA1c level to 7% or below that of total hemoglobin. However, compared with DPP-4 inhibitors, there was a slightly increased risk of myocardial infarction and eye disorders associated with sulfonylureas.[194, 195]

Kooy et al found improvements in body weight, glycemic control, and insulin requirements when metformin was added to insulin in patients with type 2 diabetes mellitus. No improvement of an aggregate of microvascular and macrovascular morbidity and mortality was observed; however, reduced risk of macrovascular disease was evident after a follow-up period of 4.3 years. These results support continuing metformin treatment after the introduction of insulin in patients with type 2 diabetes mellitus.[196]

Pradhan et al did not find an association between improvement of glycemic control with metformin or insulin and reduction of inflammatory biomarker levels in patients with recent-onset type 2 diabetes.[197] Patients were randomized to 1 of 4 groups: placebo, placebo plus insulin glargine, metformin only, and metformin and insulin glargine. No difference in levels of the inflammatory biomarker high-sensitivity C-reactive protein was shown between study participants who received insulin or metformin and those who did not.

A retrospective, nationwide cohort study found that metformin is associated with a low risk of mortality in patients who have diabetes and experience heart failure compared with treatment that includes a sulfonylurea or insulin.[198] Roussel et al studied

the expanded use of metformin in groups of patients with diabetes previously considered high risk for possible drug-related adverse outcome and found a decrease in mortality in these patients.[199]

A study by Gross et al found no difference in benefit between drug classes in patients already on metformin and sulfonylurea. The patient's clinical circumstances must guide selection.[200]

In a meta-analysis of 20 publications comprising 13,008 cancer patients with concurrent type 2 diabetes, Yin et al found that patients treated with metformin had better overall and cancer-specific survival than those treated with other types of glucose-lowering agents.[120, 121] These improvements were observed across cancer subtypes and geographic locations.

Risk reduction was significant among patients with prostate, pancreatic, breast, colorectal and other cancers, but not for lung cancer.[121] However, it remains unclear whether metformin can modulate clinical outcomes in cancer patients with diabetes.

Sulfonylureas

Sulfonylureas (eg, glyburide, glipizide, glimepiride) are insulin secretagogues that stimulate insulin release from pancreatic beta cells and probably have the greatest efficacy for glycemic lowering of any of the oral agents. However, that effect is only short-term and quickly dissipates. Sulfonylureas may also enhance peripheral sensitivity to insulin secondary to an increase in insulin receptors or to changes in the events following insulin-receptor binding.

Sulfonylureas are indicated for use as adjuncts to diet and exercise in adult patients with type 2 diabetes mellitus. They are generally well-tolerated, with hypoglycemia the most common side effect. The first-generation sulfonylureas are acetohexamide, chlorpropamide, tolazamide, and tolbutamide; the second-generation agents are glipizide, glyburide, and glimepiride. The structural characteristics of the second-generation sulfonylureas allow them to be given at lower doses and as once-daily regimens.

One study exonerated the sulfonylurea group of oral agents as the chief cause of cardiovascular death in diabetic patients admitted with acute myocardial infarction. However, even though sulfonylureas were safer in general, within the group, the use of glyburide was associated with highest mortality (7.5%) compared with other sulfonylureas, such as gliclazide and glimepiride (2.7%).[201] This raises an important concern about whether the use of glyburide should be avoided.

Meglitinide derivatives

Meglitinides (eg, repaglinide, nateglinide) are much shorter-acting insulin secretagogues than the sulfonylureas are, with preprandial dosing potentially achieving more physiologic insulin release and less risk for hypoglycemia.[202] Although meglitinides are considerably more expensive than sulfonylureas, they are similar in their glycemic clinical efficacy.

Meglitinides can be used as monotherapy; however, if adequate glycemic control is not achieved, then metformin or a thiazolidinedione may be added. Meglitinides may be used in patients who have allergy to sulfonylurea medications. They have a similar risk for inducing weight gain as sulfonylureas do but possibly carry less risk for hypoglycemia.

Alpha-glucosidase inhibitors

These agents delay sugar absorption and help to prevent postprandial glucose surges. Alpha-glucosidase inhibitors prolong the absorption of carbohydrates, but their induction of flatulence greatly limits their use. They should be titrated slowly to reduce gastrointestinal (GI) intolerance.

Thiazolidinediones

TZDs (eg, pioglitazone [Actos], rosiglitazone [Avandia]) act as insulin sensitizers; thus, they require the presence of insulin to work. They must be taken for 12-16 weeks to achieve maximal effect.

These agents are used as monotherapy or in combination with sulfonylurea, metformin, meglitinide, DPP-4 inhibitors, GLP-1 receptor agonists, or insulin. They are the only antidiabetic agents that have been shown to slow the progression of diabetes (particularly in early disease).

In the Canadian Normoglycemia Outcome and Evaluation (CANOE) trial, glycemic parameters and insulin sensitivity improved in patients taking rosiglitazone and metformin in year 1 but deteriorated in the years thereafter, as in the placebo arm. Beta-cell function remained relatively stable in both groups for the first 2 years but then deteriorated progressively in subsequent years. The investigators attributed the lower rate of incident diabetes in the rosiglitazone/metformin group to the early effect of treatment.[203]

In a study by DeFronzo et al, pioglitazone was found to reduce the progression to frank diabetes by 72% in patients with IGT.[204] However, the drug was associated with significant edema and weight gain.

In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone reduced the incidence of diabetes by 62%. It also improved the achievement of normoglycemia by 70% in patients with IFG and by 64% in patients with both IFG and IGT.[205]

A study by Phung et al investigated oral agents used for prevention of type 2 diabetes and found that TZDs resulted in a greater risk reduction than biguanides. Sulfonylureas and glinides had no benefit.[206]

TZDs generally decrease triglyceride levels and increase HDL cholesterol levels. They increase LDL cholesterol, but this increase may involve large, buoyant LDL, which may be less atherogenic.

Pioglitazone in patients unresponsive to combination therapy

Charpentier et al concluded that the early addition of pioglitazone in patients who are not responding to dual therapy is beneficial, decreasing HbA1c, as well as improving FPG levels and other surrogate markers.[207] In this study, patients (n=299) with type 2 diabetes mellitus uncontrolled by combination therapy with metformin and a sulfonylurea or a glinide were randomly assigned to receive add-on therapy with either pioglitazone 30 mg daily or a placebo.

Among patients with a baseline HbA1c level of less than 8.5%, 44.4% of patients in the pioglitazone group achieved an HbA1c level of less than 7% after 7 months, compared with only 4.9% of patients in the placebo group. In patients with a baseline HbA1c level of 8.5% or greater, 13% of those in the pioglitazone group achieved an HbA1c level of less than 7%, while no patients in the placebo group saw the same reduction.[207]

Adverse effects

While TZDs have many desirable effects on inflammation and the vasculature, edema (including macular edema) and weight gain may be problematic adverse effects, especially when TZDs are administered with insulin or insulin secretagogues.[208] These effects may induce or worsen heart failure in patients with left ventricular compromise and occasionally in patients with normal left ventricular function. TZDs have not been tested in patients with New York Heart Association class III or IV heart failure.

Fluid retention from TZDs has been considered resistant to treatment with loop diuretics, because of upregulation of renal epithelial sodium channels. However, a randomized, double-blind, placebo-controlled, crossover study by Rennings et al found that response to the loop diuretics furosemide and amiloride were preserved in rosiglitazone-treated subjects with insulin resistance.[209]

The use of pioglitazone for more than 2 years is weakly associated with an increased bladder cancer risk, with the highest risk among patients who took pioglitazone the longest and at the highest cumulative doses.[210, 211, 212] Constant surveillance and vigilance is needed. Ninety-five percent of these cases were detected in early stage. The US Food and Drug Administration (FDA) currently recommends not prescribing pioglitazone for patients with active bladder cancer and using it with caution in patients with a history of bladder cancer.

A meta-analysis indicated that in women with type 2 diabetes, long-term (ie, 1 y or longer) use of TZDs doubles the risk of fracture.[213] Although in this study, TZDs were not found to have significantly increased fracture risk among men with type 2 diabetes, risk of fracture in males has since been reported.

Rosiglitazone restrictions

In response to data suggesting an elevated risk of myocardial infarction in patients treated with rosiglitazone, the FDA has restricted access to this drug.[214] The use of rosiglitazone is limited to patients already being successfully treated with this agent and to patients whose blood sugar cannot be controlled with other antidiabetic medicines and who do not wish to use pioglitazone, the only other TZD currently available.

Health-care providers and patients must be enrolled in the Avandia-Rosiglitazone Medicines Access Program in order to prescribe and receive rosiglitazone. Patients who are enrolled in the access program receive their medicine by mail order through certified pharmacies that participate in the program.

Glucagonlike peptide–1 agonists

GLP-1 agonists (ie, exenatide, liraglutide, albiglutide, dulaglutide) mimic the endogenous incretin GLP-1; they stimulate glucose-dependent insulin release, reduce glucagon, and slow gastric emptying. The use of a GLP-1 in addition to metformin and/or a sulfonylurea may result in modest weight loss. Animal data suggest that these drugs prevent beta-cell apoptosis and may in time restore beta-cell mass. The latter property, if proven in humans, would have tremendous therapeutic potential.

Exenatide

A comparison by Bunck et al of 1 year's therapy with either exenatide or insulin glargine in metformin-treated patients with type 2 diabetes found that exenatide provided significantly greater improvement in beta-cell function. Reduction in HbA1c was similar

with the 2 drugs. Beta-cell function and glycemic control returned to pretreatment values following discontinuation of exenatide or insulin glargine, suggesting that long-term treatment is required to maintain the beneficial effects of these drugs.[215]

The addition of exenatide in patients receiving insulin glargine as basal insulin helps to improve glycemic control without the risk of increased hypoglycemia or weight gain. This benefit, however, is accompanied by a significant increase in adverse events such as nausea, diarrhea, vomiting, and headache.[216]

Exenatide has greater ease of titration (only 2 possible doses, with most patients progressing to the higher dose) than does insulin. Although the original product requires twice-daily injections, a long-acting exenatide formulation that is given once weekly (Bydureon) has been developed and has been found to provide significantly greater improvement in glycemic control than does the twice-daily formulation.[217] Once-weekly exenatide injections result in improvements in glycemic control and body weight regardless of age, gender, race, duration of diabetes or BMI.[218] Bydureon was approved by the FDA in January 2012.

In the DURATION-5 (Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once Weekly) study, the exenatide once-weekly formulation provided significantly greater improvement in HbA1c and FPG levels than did the twice-daily preparation. Additionally, less nausea was observed with the once-weekly exenatide formulation.[219]

For patients with type 2 diabetes inadequately controlled with metformin, the injectable agent exenatide was found, in one clinical trial, to be more effective than insulin detemir.[220, 221] A clinical trial involving 216 patients with A1c baseline levels >7.1% despite treatment with metformin found that once-daily injections of exenatide resulted in a significantly greater number of patients achieving target A1c than treatment with detemir. At 26 weeks, 44.1% of the exenatide group had achieved an A1c of 7% or less compared to 11.4% of the detemir group.

Liraglutide

Indicated as an adjunct to diet and exercise, liraglutide therapy is aimed at improving glycemic control in adults with type 2 diabetes. In addition, results from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) clinical trial led to liraglutide's approval for risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. With a median follow-up of 3.8 years, risk for the trial's composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke was 13.0% for patients treated with liraglutide, compared with 14.9% for those given placebo therapy.[222]

In June 2019, liraglutide was approved by the FDA for use in children aged 10 years or older with type 2 diabetes. Approval was based on the ELLIPSE clinical trial, in which patients aged 10 years to less than 17 years received up to 1.8 mg/day of subcutaneous liraglutide or placebo. After 26 weeks, the mean HbA1c level was 0.64% lower in the liraglutide patients and 0.42% higher in the placebo patients.[223]

Albiglutide

The glucagonlike peptide-1 (GLP-1) receptor agonist albiglutide (Tanzeum) was approved by the FDA in April 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[224, 225] GLP-1 agonists augment glucose-dependent insulin secretion. Approval of albiglutide was based on a series of individual phase III trials (Harmony 1-8) that included approximately 5,000 individuals.

In an open-label 32-week study in 805 patients with type 2 diabetes inadequately controlled with oral drugs, Pratley and colleagues found that reductions in HbA1c with once-weekly albiglutide injections were clinically meaningful but less than those seen with daily liraglutide injections (0.78% vs 0.99%, respectively). Patients who received albiglutide had fewer gastrointestinal events than those who received liraglutide (35.9% vs 49.9%) but had more injection-site reactions (12.9% vs 5.4%) and less weight loss (0.64 vs 2.19 kg).[226, 227]

The dosage of albiglutide in the study was 30 mg once weekly titrated to 50 mg at week 6. The dosage of liraglutide was 0.6 mg once daily titrated to 1.2 mg at week 1 and 1.8 mg at week 2.[226, 227]

Dulaglutide

Dulaglutide (Trulicity) was approved by the FDA in September 2014 as adjunctive therapy to diet and exercise to improve glycemic control in type 2 diabetes mellitus.[228] It is administered as a once-weekly subcutaneous injection.[228, 229] Approval was based on six clinical trials (AWARD studies) involving a total of 3342 patients who received dulaglutide as monotherapy or as part of combination therapy.[228] Dulaglutide was noninferior to daily liraglutide in one study and superior to the oral dipeptidyl peptidase–4 (DPP-4) inhibitor sitagliptin in another. Adverse effects included nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.[228]

AWARD-1 compared dulaglutide weekly doses of 0.75 mg or 1.5 mg compared with exenatide injectable solution BID. The mean A1C reductions were dulaglutide, 1.5 mg, 1.5%; 0.75 mg, 1.3%; exenatide solution, 1.0%; placebo, 0.5%.[229]

In September 2020, the FDA approved higher doses (ie, 3 mg or 4.5 mg weekly) of dulaglutide for patients requiring additional glycemic control. This approval was based on results from the AWARD-11 clinical trial.[230]

AWARD-3 compared dulaglutide with insulin glargine titrated to target. Mean A1C reductions were dulaglutide 1.5 mg, 1.1-1.6%; 0.75 mg, 0.8-1.6%; and insulin glargine 0.6-1.4%. Dulaglutide was shown to be noninferior as monotherapy compared with metformin in the AWARD-3 trial. Mean A1C reductions were dulaglutide 1.5 mg, 0.8%; dulaglutide 0.75 mg, 0.7%; compared with metformin 0.6%.[231]

AWARD-5 compared dulaglutide with sitagliptin in patients taking metformin. At the 52-week primary endpoint, mean A1C reductions were dulaglutide 1.5 mg, 1.1%; 0.75 mg, 0.9%; compared with sitagliptin 0.4%.[232]

In February 2020, the FDA approved dulaglutide for major adverse cardiovascular (CV) event reduction (with regard to CV death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus in whom established CV disease or multiple CV risk factors are present. Approval stemmed from the REWIND (Researching cardiovascular Events with a Weekly INcretin in Diabetes) study, a multicenter, randomized, double-blind, placebo-controlled trial that found that the incidence of primary composite outcomes (nonfatal myocardial infarction, nonfatal stroke, or CV-related death) was 2.4 per 100 person-years in the dulaglutide group, versus 2.7 per 100 person-years in the placebo group.[233]

Dulaglutide is not recommended for use as first-line pharmacologic treatment for type 2 diabetes, and it is contraindicated in patients with personal or family history of medullary thyroid carcinoma or in those with multiple endocrine neoplasia syndrome type 2.[228] The label will include a boxed warning that thyroid C-cell tumors have been observed in animal studies. Required postmarketing studies will include studies in children, a medullary thyroid carcinoma case registry, and a cardiovascular outcomes study in high-risk patients.[228]

Lixisenatide

Lixisenatide (Adlyxin) was approved by the FDA in July 2016 as adjunctive therapy to diet and exercise to improve glycemic control in type 2 diabetes mellitus. It is administered by subcutaneous injection once daily within 1 hour before the first meal of the day. The starting dose is 10 mcg/day SC for 14 days and is then increased on day 15 to 20 mcg once daily.

The FDA approved lixisenatide based on results from the GetGoal worldwide clinical program and from the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trials.[234, 235, 236]

The drug's safety and efficacy was assessed by the GetGoal program, which included 13 clinical trials of adults with type 2 diabetes mellitus (n >5000). The primary efficacy endpoint, HbA1c reduction, was achieved by all of the GetGoal studies.[234, 235]

The ELIXA study demonstrated that in patients with type 2 diabetes who had had a recent acute coronary syndrome, cardiovascular adverse events did not increase in those taking lixisenatide compared with patients taking placebo. The study included 6068 adults with type 2 diabetes, 39% of whom had a recent non–ST-segment-elevation myocardial infarction, 43% of whom had ST-segment-elevation myocardial infarction, and 17% of whom had unstable angina. At a median of 25 months, the investigators found that cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina had occurred in 13.4% of the lixisenatide patients and 13.2% of the control patients.[236]

A study to assess efficacy and safety of lixisenatide monotherapy in type 2 diabetes found a once-daily dose of the drug improved glycemic control. Once-daily monotherapy significantly lowered postprandial glucose and was well tolerated by patients with type 2 diabetes.[237]

Semaglutide

In December 2017, the FDA approved once-weekly semaglutide SC (Ozempic), a GLP-1 receptor agonist, as a glycemic control–improvement agent in adults with type 2 diabetes. It is administered as a subcutaneous injection once weekly. Meant as an adjunct to diet and exercise, semaglutide was approved following eight phase 3a studies (the SUSTAIN trials).

Semaglutide SC gained FDA approval in January 2020 for risk reduction of major adverse cardiovascular events (MACE) in adults with type 2 diabetes and heart disease. Results from the 2-year randomized study SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) led to approval for the new indication. In the trial, 3297 adults with type 2 diabetes and established cardiovascular disease (CVD) received either injectable semaglutide or placebo, in addition to stand-of-care therapy.[238, 239]

Risk for the primary composite outcome—first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke—for patients treated with semaglutide SC was a significant 26% below that for placebo patients. However, cardiovascular risk reduction primarily resulted from declines in nonfatal stroke (39%) and nonfatal myocardial infarction (26%), with cardiovascular death rates being similar between the semaglutide and placebo patients.[238, 239, 240]

In September 2019, the FDA approved the first oral GLP-1 receptor agonist, a form of semaglutide available under the brand name Rybelsus. It is administered as a once-daily oral tablet. Approval of the oral tablet was based on results from the phase 3

PIONEER trials (n=9543). The trials included head-to-head studies of oral semaglutide compared with sitagliptin (DP4 inhibitor), empagliflozin (sodium-glucose cotransporter-2 [SGLT2] inhibitor), and liraglutide 1.8 mg (GLP-1 agonist). A1c reduction was found with oral semaglutide, as well as, via a secondary endpoint, body weight reduction.[241, 242, 243]

In January 2020, the FDA updated the clinical studies section of Rybelsus's prescribing information, with results added from the randomized, placebo-controlled study PIONEER 6 (Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes), which were released in June 2019. The report found oral semaglutide to be associated with a nonsignificant 21% reduction in three-component MACE. The information added to Rybelsus's label related to cardiovascular safety, not benefit.[244, 239]

Dual glucagonlike peptide-1 and glucose-dependent insulinotropic polypeptide agonist

Tirzepatide

A dual agonist of glucagon-like peptide-1 (GLP-1) receptors and glucose-dependent insulinotropic polypeptide (GIP), tirzepatide was approved by the FDA in May 2022 for improvement of glycemic control in adults with type 2 diabetes mellitus, serving as an adjunct to lifestyle modifications. Insulin secretion is stimulated, glucagon secretion is suppressed, and gastric emptying is delayed by GLP-1 agonists, while, depending on conditions of hypoglycemia or hyperglycemia, GIP agonists may raise or lower glucagon levels, respectively. However, as a dual agonist, tirzepatide may more greatly impact glucose lowering and weight control than will a selective GLP-1 agonist.

In a phase-3 trial comparing tirzepatide with semaglutide in patients with type 2 diabetes, Frias et al found that, in terms of lowering HbA1c, tirzepatide at all doses was noninferior and superior to semaglutide. With regard to body weight reduction, tirzepatide was again determined to be superior to semaglutide.[245]

Dipeptidyl peptidase IV inhibitors

DPP-4 inhibitors (eg, sitagliptin, saxagliptin, linagliptin) are a class of drugs that prolong the action of incretin hormones. DPP-4 degrades numerous biologically active peptides, including the endogenous incretins GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). DPP-4 inhibitors can be used as a monotherapy or in combination with metformin or a TZD. They are given once daily and are weight neutral.

A study comparing the efficacy and safety of monotherapy with sitagliptin or metformin in treatment-naive patients with type 2 diabetes found no statistical differences between the 2 drugs in terms of decreases in HbA1c and fasting glucose levels. The 1050 participants in the study had baseline HbA1c levels of 6.5-9% and received sitagliptin (100 mg qd) or metformin (1000 mg bid) for 24 weeks.[246]

In this study, the incidence of adverse GI effects was lower with sitagliptin than with metformin (11.6% vs 20.7%). Specifically, diarrhea (3.6% vs 10.9%) and nausea (1.1% vs 3.1%) were significantly less common with sitagliptin.[246]

A study by Vilsboll et al in patients receiving stable-dose insulin therapy (with or without concomitant metformin) found that the addition of sitagliptin produced a greater reduction in FPG (by 15 mg/dL [0.8 mmol/L]) and 2-hour postprandial glucose (by 36.1 mg/dL [2 mmol/L]) than did placebo. Sitagliptin reduced HbA1c by 0.6%, while no reduction was seen with placebo. In addition, 13% of patients attained an HbA1c level of less than 7% with sitagliptin, compared with 5% with placebo.[247]

A study by Pérez-Monteverde et al found that a combination of sitagliptin and metformin was associated with improved glycemic control and less weight gain when compared with pioglitazone in the treatment of patients with type 2 diabetes mellitus.[248]

Adding linagliptin to treatment in patients with type 2 diabetes mellitus that has been inadequately controlled with a metformin and sulfonylurea combination improves glycemic control. Because it has predominantly nonrenal excretion and is a clinically nonrelevant substrate for cytochrome-450 isoenzymes, this drug possesses the benefits of having a low risk of drug-drug interaction and of being safe to use in patients with renal insufficiency.[249]

Upper respiratory tract infections have been increasingly reported among users of DPP-4 inhibitors compared with users of other antidiabetic drugs.[250] However, further research is needed to evaluate the scope and underlying mechanisms of this phenomenon. On the other hand, a meta-analysis suggested that treatment with DPP-4 inhibitors could reduce the risk of bone fractures.[251]

A case-control, retrospective, observational study by Solerte et al suggested that in patients with type 2 diabetes mellitus who are hospitalized with COVID-19, glucose lowering with sitagliptin rather than treatment with insulin reduces the likelihood of 30-day death by 77%. The investigators also indicated that the rate at which intensive care or mechanical ventilation is needed in these patients is significantly reduced as well.[252, 253]

Selective sodium-glucose transporter-2 inhibitors

Canagliflozin is the first SGLT-2 inhibitor approved in the United States.[254, 255] SGLT-2 inhibition lowers the renal glucose threshold (ie, the plasma glucose concentration that exceeds the maximum glucose reabsorption capacity of the kidney). Lowering the renal glucose threshold results in increased urinary glucose excretion. A second SGLT-2 inhibitor, dapagliflozin (Farxiga), was approved by the FDA in January 2014,[256, 257] and another, empagliflozin, approved in August, 2014.[258, 259]

Dosage adjustments are required for canagliflozin in patients who have renal impairment (ie, estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m2). Dapagliflozin should not be used if eGFR is < 60 mL/min/1.73 m2. Also consider lowering the dose of insulin or insulin secretagogues to reduce the risk of hypoglycemia when coadministered with SGLT-2 inhibitors.

FDA approval of canagliflozin was based on global phase 3 clinical trials that included over 10,000 patients.[254, 255] In a trial evaluating canagliflozin monotherapy efficacy and safety in 584 adults with type 2 diabetes mellitus inadequately controlled with diet and exercise, treatment for 26 weeks with canagliflozin 100 or 300 mg daily resulted in a statistically significant improvement in HbA1C with both doses compared with placebo.[260]

Canagliflozin add-on combination therapy to metformin and/or sulfonylureas showed a reduction in fasting glucose and a greater proportion of patients achieving an HbA1C level less than 7%.[261] Add-on therapy to insulin and comparative data to thiazolidinediones and to dipeptidyl peptidase-IV inhibitors have also shown improved postprandial glucose levels and HbA1C levels.[261]

In October 2019, canagliflozin received FDA approval for the treatment of diabetic kidney disease (DKD) and, in patients with type 2 diabetes and DKD, reduction in the risk of hospitalization for heart failure. Approval stemmed from the outcome of the phase 3 CREDENCE study, which found that at median 2.62-year follow-up, the risk of renal failure and cardiovascular events was lower in patients with type 2 diabetes and kidney disease who were treated with canagliflozin than in patients on placebo.[262]

Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[256, 257] It can be employed as monotherapy, as initial therapy with metformin, or as an add-on to other oral glucose-lowering agents, including metformin, pioglitazone, glimepiride, sitagliptin, and insulin.[263, 264, 265, 266]

In October 2019, dapagliflozin gained an indication to reduce hospitalization for heart failure in adults with type 2 diabetes and cardiovascular risk. FDA approval was based on the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) study, in which 17,160 patients were evaluated (median 4.2-year follow-up). The investigators found that in patients on dapagliflozin, the rate of cardiovascular death or hospitalization for heart failure was 4.9%, compared with 5.8% for patients on placebo.[267]

Like dapagliflozin, empagliflozin is also approved as an adjunct to diet and exercise to improve glycemic control. The drug's safety and effectiveness were evaluated in 7 clinical trials with 4480 patients with type 2 diabetes. The pivotal trials showed that empagliflozin improved hemoglobin A1c levels compared with placebo.[258, 259] In late 2016, the FDA also approved empagliflozin for a new indiction, specifically, the prevention of cardiovascular disease–related death in adults with type 2 diabetes who also have cardiovascular disease.[268, 269] The new approval was based on results from the (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), which included more than 7000 patients.[270]

Indicated as an adjunct to diet and exercise, ertugliflozin therapy is aimed at improving glycemic control in adults with type 2 diabetes. Ertugliflozin's approval stemmed from a series of nine phase-3 clinical trials in which statistically significant improvements were seen in HbA1c, fasting plasma glucose, body weight, and systolic and diastolic blood pressures, in adult patients with type 2 diabetes.[271, 272, 273]

Nonsteroidal mineralocorticoid receptor antagonists

In July 2021, the FDA approved finerenone (Kerendia) for inhibition of the effects in adults of chronic kidney disease associated with type 2 diabetes, including sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure. It is the first nonsteroidal mineralocorticoid receptor (MR) antagonist to be approved for this purpose. Approval was based on the FIDELIO-DKD trial, a placebo-controlled study that involved over 5700 patients with type 2 diabetes to whom the maximum-tolerated dose of renin-angiotensin system inhibitor (RASI) was already being administered. However, until more data on finerenone is gathered, RASIs and SGLT-2 inhibitors will be the preferred agents for slowing chronic kidney disease in type 2 diabetes.[274, 275, 276]

Insulins

Ultimately, many patients with type 2 diabetes mellitus become markedly insulinopenic. The only therapy that corrects this defect is insulin. Because most patients are insulin resistant, small changes in insulin dosage may make no difference in glycemia in some patients. Furthermore, because insulin resistance is variable from patient to patient, therapy must be individualized in each patient.

A study by de la Pena et al found that although the overall insulin exposure and effects of 500 U/mL of insulin were similar to those of 100 U/mL of insulin, peak concentration was significantly lower at 500 U/mL, and the effect after the peak was prolonged; areas under the curve were similar for both doses. This observation should help guide therapy.[277]

A range of insulin preparations, individual and premixed, is currently available. The Agency for Healthcare Research and Quality (AHRQ) has reviewed the use of premixed insulin analogues in patients with type 2 diabetes mellitus. Conclusions for which the strength of evidence was high are as follows[278] :

- For lowering postprandial glucose, premixed insulin analogues are more effective than either long-acting insulin analogues alone or premixed neutral protamine Hagedorn (NPH)/regular human insulin 70/30
- For lowering HbA1c, premixed insulin analogues are as effective as premixed NPH/regular human insulin 70/30 and more effective than long-acting insulin analogues
- The frequency of hypoglycemia reported with premixed insulin analogues is similar to that with premixed human insulin and higher than that with oral antidiabetic agents

Long-acting insulins used in the United States include insulin glargine (Lantus, Toujeo) and insulin detemir (Levemir). Insulin glargine has no peak and produces a relatively stable level lasting more than 24 hours. In some cases, it can produce a stable basal serum insulin concentration with a single daily injection, though patients requiring lower doses typically are given twice-daily injections. Insulin detemir has a duration of action that may be substantially shorter than that of insulin glargine but longer than those of intermediate-acting insulins.

Toujeo 300 U/mL is a newer dosage strength and form of insulin glargine than Lantus 100 U/mL, having been approved by the US Food and Drug Administration (FDA) in February 2016. Compared with those of Lantus 100 U/mL, the pharmacokinetic and pharmacodynamic profiles of Toujeo are more stable and prolonged; the duration of action exceeds 24 hours. Clinical trials showed comparable glycemic control between Lantus and Toujeo, although the trials noted the need for higher daily basal insulin doses (ie, 12-17.5%) with Toujeo. The risk for nocturnal hypoglycemia was lower with Toujeo in insulin-experienced patients with type 2 diabetes, but this was not the case for insulin-naïve patients with type 1 DM or for patients with type 2 DM.[279]

With its March 2018 approval by the FDA, Toujeo Max SoloStar became the highest capacity long-acting insulin pen on the market. Toujeo Max necessitates fewer refills and, for some diabetes patients, fewer injections to deliver the required Toujeo dosage.[280]

A new ultralong-acting basal insulin, insulin degludec (Tresiba), which has a duration of action of up to beyond 42 hours, has been approved by the US Food and Drug Administration (FDA). This new basal insulin forms a soluble multihexamer after subcutaneous injection to provide a depot effect that is long lasting. It is indicated for diabetes mellitus types 1 and 2. A combination product of insulin degludec and the rapid-acting insulin aspart was also approved (Ryzodeg 70/30). Approval was based on results from the BEGIN trial[281, 282] that showed noninferiority to comparator productions. The cardiovascular outcomes trial (DEVOTE) comparing cardiovascular safety of insulin degludec to that of insulin glargine in patients with type 2 DM is ongoing. A combination product (Ryzodeg) was also approved that contains insulin degludec plus a rapid-acting insulin (insulin aspart).

A study by Zinman et al found that insulin degludec provides comparable glycemic control to insulin glargine without additional adverse effects.[283] A reduced dosing frequency may be possible because of its ultralong-action profile. Careful study is needed when making a decision regarding reduced dosing frequency.

A rapid-acting inhaled insulin powder (Afrezza) for types 1 and 2 diabetes mellitus was approved by the FDA in June 2014. Approval was based on a study involving over 3,000 patients over a 24-week period. In persons with type 1 diabetes, the inhaled insulin was found to be noninferior to standard injectable insulin when used in conjunction with basal insulin at reducing hemoglobin A1c. In persons with type 2 diabetes, the inhaled insulin was compared to placebo inhalation in combination with oral diabetic agents and showed a statistically significant lower hemoglobin A1c.[284]

The first inhaled insulin (Exubera) was approved by the FDA in January 2006 as a rapid-acting prandial insulin. It did not produce better glycemic control than did conventionally injected insulins, and it required a mildly cumbersome device and skill to deliver an accurate dose (up to a few minutes to deliver 1 dose) and pulmonary function monitoring due to concerns about lung toxicity over time. Exubera was withdrawn from the market in October 2007, not because of safety concerns but because too few patients were using the product for its continued sale to be economically feasible.

In September 2017, the FDA approved the rapid-acting insulin aspart Fiasp for the treatment of adults with diabetes. This human insulin analog is formulated with niacinamide, which aids in speeding the initial absorption of insulin. Dosing can occur at the beginning of a meal or within 20 minutes after the meal commences. In a study of adult patients with type 1 DM, Fiasp could be detected in the circulation about 2.5 minutes after it was administered. Maximum insulin levels occurred approximately 63 minutes after the drug’s administration.[285, 286]

Insulin and cancer

On July 1, 2009, the FDA issued an early communication regarding a possible increased risk of cancer in patients using insulin glargine (Lantus).[287] The FDA communication was based on 4 observational studies that evaluated large patient databases and found some association between insulin glargine (and other insulin products) and various types of cancer.

Further evaluation is warranted, however, before the link between insulin use and cancer is confirmed. The duration of these observational studies was shorter than that considered to be necessary to evaluate for drug-related cancers. Additionally, findings were inconsistent within and across the studies, and patient characteristics differed across treatment groups.

In a study by Suissa et al, insulin glargine use was not associated with an increased risk of breast cancer during the first 5 years of use. The risk tended to increase after 5 years, however, and significantly so for the women who had taken other forms of insulin before starting insulin glargine.[288]

A study by Johnson et al found the same incidence rate for all cancers in patients receiving insulin glargine as in patients not receiving the drug. Overall, no increase in breast cancer rates was associated with insulin glargine use, although patients who used only insulin glargine had a higher rate of cancer than did those who used another type of insulin. This finding was attributed to allocation bias and differences in baseline characteristics.[289]

A study by Steansdottir showed that different drug regimens used to accomplish intensified glycemic control did not alter the risk of cancer in patients with diabetes.[290] This study differs from previous studies, in which metformin use was associated with lower cancer risk.

The FDA states that patients should not stop taking insulin without consulting their physician. An ongoing review by the FDA will continue to update the medical community and consumers with additional information as it emerges. Statements from the ADA and the European Association for the Study of Diabetes called the findings conflicting and inconclusive and cautioned against overreaction.

Amylinomimetics

Pramlintide acetate is an amylin analog that mimics the effects of endogenous amylin, which is secreted by pancreatic beta cells. This agent delays gastric emptying, decreases postprandial glucagon release, and modulates appetite.[291]

Bile acid sequestrants

Bile acid sequestrants were developed as lipid-lowering agents for the treatment of hypercholesterolemia but were subsequently found to have a glucose-lowering effect. The bile acid sequestrant colesevelam is FDA-approved as an adjunctive therapy to improve glycemic control. It has a favorable, but insignificant, impact on FPG and HbA1c levels.[292]

A study in patients with early type 2 diabetes who were receiving metformin found that the addition of colesevelam reduced HbA1c levels to a degree that was statistically significant but that may have been clinically irrelevant, as no data show that a 0.3% reduction of HbA1c produces a better outcome than a 0.2% reduction of HbA1c. Achievement of LDL cholesterol goals was also improved with the use of colesevelam, but it is not known whether that result correlates with significantly different outcomes in these patients.[293]

Colesevelam is a relatively safe addition to the menu of choices available to reduce LDL cholesterol in patients with prediabetes. It should be avoided in patients with hypertriglyceridemia (a rule that applies to bile acid sequestrants in general).

Dopamine agonists

In 2009, the FDA approved a quick-release formulation of bromocriptine mesylate (Cycloset) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Bromocriptine is a centrally acting dopamine D2 receptor agonist. When given in a single timed morning dose, it is thought to act on circadian neuronal activities within the hypothalamus to reset the abnormally elevated drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients.[294]

Quick-release bromocriptine may be considered for obese patients who do not tolerate other diabetes medications or who need only a minimal reduction in HbA1c to reach their glycemic goal. This agent has the benefits of not causing hypoglycemia and weight gain. In addition, a randomized trial of bromocriptine in 3095 patients found that cardiovascular events were less frequent in the treatment arm than in the placebo arm.[295]

Adverse events most commonly reported in clinical trials of bromocriptine included nausea, fatigue, vomiting, headache, and dizziness. These events were more likely to occur during initial titration of the drug and lasted a median of 14 days. Nausea and vomiting were not described as serious.

Bromocriptine can cause orthostatic hypotension and syncope, particularly on initiation of therapy and dose escalation. Caution is advised when treating patients who are receiving antihypertensive therapy; orthostatic vital signs should be evaluated at baseline and periodically thereafter.

Comparison of oral antidiabetic agents

In 2007, the AHRQ compared the effectiveness and safety of oral diabetes medications for adults with type 2 diabetes, with a 2011 update.[296, 297] The AHRQ found little evidence to support predictions as to whether a particular medication is more likely to be effective in a given patient subgroup or to cause adverse effects in a particular patient.

The AHRQ concluded that although the long-term benefits and harms of diabetes medications remain unclear, the evidence supports the use of metformin as a first-line agent. On average, monotherapy with many of the oral diabetes drugs reduces HbA1c levels by 1 percentage point (although metformin has been found to be more efficacious than the DPP-4 inhibitors), and 2-drug combination therapies reduce HbA1c about 1 percentage point more than do monotherapies.

Other AHRQ findings included the following:

- Metformin decreased LDL cholesterol levels relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors
- Unfavorable effects on weight were greater with TZDs and sulfonylureas than with metformin (mean difference of +2.6 kg)
- Risk of mild or moderate hypoglycemia was 4-fold higher with sulfonylureas than with metformin alone; this risk was more than 5-fold higher with sulfonylureas plus metformin than with a TZD plus metformin
- Risk of heart failure was higher with TZDs than with sulfonylureas
- Risk of bone fractures was higher with TZDs than with metformin

Diarrhea was more common with metformin than with glitazones.

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Management of Glycemia

In 2013, the American Association of Clinical Endocrinologists (AACE) issued a comprehensive new type 2 diabetes treatment algorithm--the first to incorporate obesity, prediabetes, and cardiovascular risk factor management.[298, 299]

Obesity management was incorporated into the algorithm because it is now clear that weight loss also reduces blood glucose. The authors suggest that obesity management can be considered first-line treatment for people with prediabetes. The prediabetes section of the algorithm considers cardiovascular risk factors and the options of antihyperglycemic or antiobesity therapy, though without making a recommendation regarding which form of treatment is better.

As in the AACE's earlier glycemic-control algorithm, the level of treatment depends on the initial hemoglobin A1c (HbA1c). (Lifestyle modification, including weight loss, is a component of all treatments.) Whereas the earlier algorithm recommended an HbA1c of 6.5% or lower as the goal for most patients, the current algorithm refines this advice, recommending an HbA1c of 6.5% or lower for healthy patients without concurrent illness and at low risk for hypoglycemia but individualized target HbA1c values greater than 6.5% for patients with concurrent illness and those who are at risk for hypoglycemia.

Metformin

Metformin is the preferred initial agent for monotherapy and is a standard part of combination treatments. Advantages of metformin include the following:

- Efficacy
- Absence of weight gain or hypoglycemia
- Generally low level of side effects
- High level of patient acceptance
- Relatively low cost

The dose of metformin is titrated over 1-2 months to at least 2000 mg daily, administered in divided doses (during or after meals to reduce gastrointestinal [GI] side effects). Exercise increases metformin levels and interferes with its glucose-lowering effect. [300]

Metformin may also decrease the risk of dementia associated with type 2 diabetes. In a 2013 observational study of 14,891 patients aged 55 years and older with type 2 diabetes, treatment with metformin signlificantly lowered the risk of developing

dementia.[301] Only patients who initiated therapy with a single drug (metformin, sulfonylureas [SU], thiazolidinediones [TZDs], or insulin) during the study period were included.

During 5 years of followup, dementia was diagnosed in 1487 (9.9%) patients.[301] Compared with patients starting SU, those starting metformin had about a 20% reduced risk for dementia. Compared with patients starting TZD, those starting metformin had a 23% lower risk.[301]

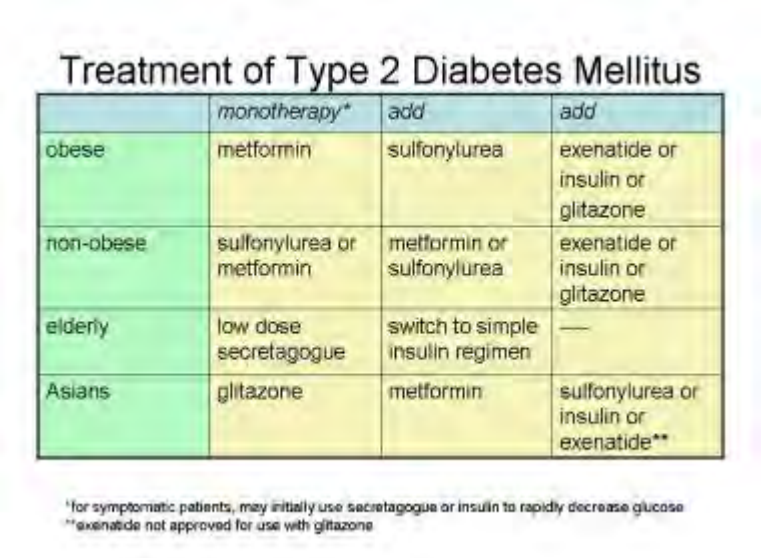
Conversely, starting SU treatment (compared with metformin) was associated with a 24% increased risk for dementia; starting TZD treatment was associated with an 18% increased risk; and starting insulin treatment was associated with a 28% increased risk.[301]

Dual-drug therapy

If the patient fails to safely achieve or sustain glycemic goals within 2-3 months, another medication should be added. The choice should be guided by patient characteristics (eg, a DPP-4 inhibitor if both postprandial and fasting glucose levels are elevated; a GLP-1 agonist if postprandial glucose levels are strongly elevated; a TZD if the patient has metabolic syndrome and/or nonalcoholic fatty liver disease).[302]

Failure of initial therapy usually should result in addition of another class of drug rather than substitution. Reserve the use of substitution for cases in which patients experience intolerance to a drug because of adverse effects.

Considerable debate exists regarding which second agent to add to (or use initially in conjunction with) metformin. An outline of the therapeutic approach generally used by the author is presented in the first 2 images below. An idealized scheme for glucose and insulin patterns is presented in the third image below. The author finds that keeping such an idealized scheme in mind is helpful when treating and educating patients, even if the patient is trying to replicate it with less intensive insulin therapy.

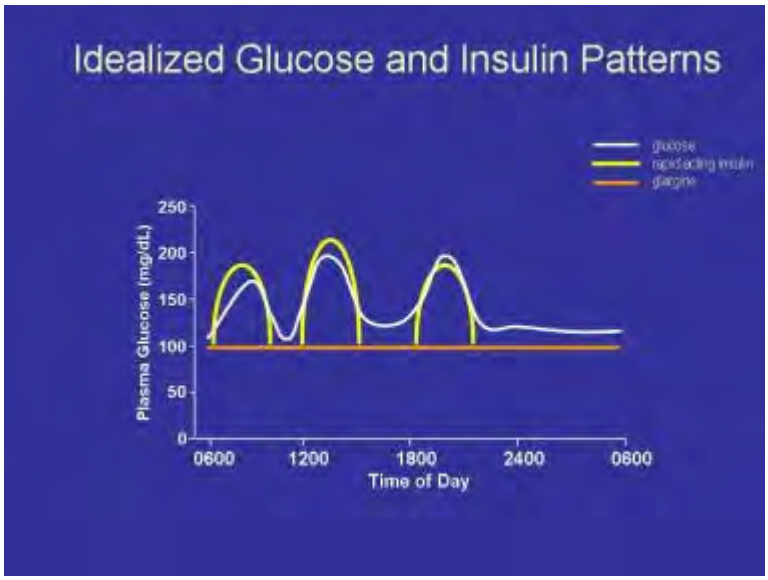


Treatment of type 2 diabetes mellitus.

Simplified Scheme for Insulin Therapy

- Bedtime NPH or glargine with pills, start 10-15 units and titrate to fasting glucose <120 mg/dL
- For twice daily insulin, start ~0.5 U/kg with 2/3 in morning and 2/3 as NPH; titrated by SMBG results (meals and insulin administration must be consistent from day to day—give insulin about 20-30 min pre-meal
- For mulitple daily injections, start with 50% basal (glargine or ultralente) and pre-prandial rapid acting (20% pre-breakfast, 15% pre-lunch, 15% pre-supper; titrate by SMBG results
- For 2 or more injections daily, add metformin (titrate to 2 g daily) or glitazone (4 mg rosiglitazone or 30 mg pioglitazone) if total insulin dose >1-2 U/kg

Simplified scheme for using insulin in treating patients with type 2 diabetes mellitus.



Simplified scheme of idealized blood glucose values and multiple dose insulin therapy in type 2 diabetes mellitus.

Because TZDs not infrequently cause weight gain and edema, the author usually reserves these agents for patients who cannot use metformin, as a result of intolerance or contraindications. Exceptions to this practice may include patients of relatively normal weight who have marked insulin resistance, such as patients of Asian heritage.

Before adding a second agent for a patient who is taking an insulin secretagogue, the clinician should warn the patient about the possibility that the second agent will induce hypoglycemia. If hypoglycemia occurs, the dose of the insulin secretagogue, not the newly added agent, should be reduced.

Triple-drug therapy

If 2 drugs prove unsuccessful after 2-3 months, the next step is triple therapy. The third drug may be an oral agent from a third class of antidiabetic drugs, basal insulin (typically at bedtime), or the injectable drug exenatide. The expense and adverse effect profile of TZDs make their use in an oral triple therapy approach less desirable.

The addition of exenatide to 1 or 2 oral agents (eg, metformin and/or a sulfonylurea) is attractive because of its simplicity (ie, only 2 possible doses of exenatide, with easy titration compared with insulin); although expensive, it avoids hypoglycemia. If basal insulin is used, the insulin dose is titrated to the fasting glucose concentration, which the patient can measure at home.

Glucose values

Some patients need reduction of their oral antidiabetic agent to prevent daytime hypoglycemia as the bedtime insulin is initiated or increased and the fasting glucose concentration decreases. If a GLP-1 agonist is used, the author monitors fasting and postprandial sugars, expecting a marked flattening of the postprandial rise in glucose concentrations.

Measurement of glucose patterns in patients with type 2 diabetes, particularly those who have central obesity and hepatic steatosis, often reveals that the highest preprandial glucose level of the day is before breakfast (because of disordered hepatic glucose production overnight), with a "stair-step" decrease during the day (after the usual postmeal rise). These higher-than-desired morning glucose values do not necessarily dictate abandonment of the current therapeutic regimen, provided that the HbA1c level is at target.

For patients trying to achieve near euglycemia, premeal glucose values of 80-120 mg/dL are the goal, with the patient going to sleep at night with a value at least 100 mg/dL. In patients with less stringent glycemic goals (eg, because of advanced age, advanced complications, or severe concomitant disease), preprandial glucose values of 100-140 mg/dL are desired. Because of the limitations of therapies, essentially no patient is able to achieve these goals all the time if, in fact, insulin is needed to treat their disease.

For patients who primarily have fasting hyperglycemia, basal insulin is the easiest way to correct this abnormality. Basal insulin is typically scheduled at bedtime but can be given at suppertime if that is more convenient for the patient.

The goal of a combined daytime oral agent plus once-a-day insulin is to lower the fasting glucose level to 100 mg/dL by titrating the insulin. When this target is achieved, the oral agents can be effective in maintaining preprandial and postprandial blood glucose levels throughout the day. If a regimen combining oral agents and insulin fails to lower glucose levels into the normal range, patients should be switched to a daily multiple-injection schedule with a premeal rapid-acting insulin and a longer-acting basal insulin.

Insulin regimens

A necessary condition for twice-daily insulin to succeed is a regimented lifestyle, with mealtimes regularly spaced and insulin injections taken at essentially the same time every day, including weekends and holidays. Lack of regularity in the schedule is self-defeating for this approach to therapy.

The author limits the use of premixed insulin to patients who may have trouble mixing their insulins. The author prefers premixes containing regular insulin if the premix is administered to maintain better midday coverage. Premixes with rapid-acting medications can be used if the midday meal is small. A systematic review found that glycemic control with premixed insulin analogues (ie, mixtures of rapid-acting and intermediate-acting insulin analogues) is similar to that with premixed human insulin.[303]

Multiple daily dosing

Conventional multiple daily dosing of insulin gives the patient the greatest flexibility. In this approach, long-acting insulin (eg, glargine, detemir) is generally given once daily as the basal insulin, and rapid-acting insulin (eg, aspart, glulisine, lispro) is administered just before each meal.

The basal component can be administered at any time of day as long as it is given at the same time each day. However, interpreting glucose patterns is probably easiest if the basal insulin is administered at or near bedtime. The basal insulin can then be titrated to the morning sugar, and the bolus premeal insulin can be titrated to the next premeal sugar and, in some cases, a postprandial (2 h) value.

All insulin injections should preferably be administered in the abdomen, although they can also be given in the thigh, hip, or buttock regions. Adiposity blunts the pharmacodynamics of the basal insulins NPH, glargine, and, especially, detemir.[304]

Insulin dosing can be safely reduced in patients with renal insufficiency without compromising glycemic control.[305] Dosing based solely on weight is not advisable in these patients, who have reduced lean body mass and water retention.

Continuous subcutaneous insulin infusion

The American Association of Clinical Endocrinologists and American College of Endocrinology released a consensus statement on insulin pump management:[306]

- Based on currently available data, continuous subcutaneous insulin infusion (CSII) is justified for basal-bolus insulin therapy in patients with type 1 diabetes mellitus.
- Only providers whose practice can assume full responsibility for a comprehensive pump management program should offer this technology.
- The ideal CSII candidate is a patient with type 1 diabetes mellitus or intensively management insulin-dependent type 2 diabetes mellitus who is currently performing 4 or more insulin injections and 4 or more self-monitored blood glucose

measurements daily; is motivated to achieve optima blood glucose control; is willing and able to carry out the tasks that are required to use this complex and time-consuming therapy safely and effectively; and is willing to maintain frequent contact with their health care team.

- Adult patients
    - At CSII initiation, the patient should have daily contact with the pump trainer. a return visit with the endocrinologist/diabetologist/advanced practice nurse is advised within 3-7 days after CSII initiation.
    - Educational consults should be scheduled weekly or biweekly at first, then periodically as needed.
    - Specialist follow-up visits should be scheduled at least monthly until the pump regimen is stabilized, then at least once every 3 mo.
- Pediatric patients
    - CSII is indicated for pediatric patients with elevated hemoglobin A1C (HbA1C) levels on injection therapy; frequent, severe hypoglycemia; widely fluctuating glucose levels; a treatment regimen that compromises lifestyle; and microvascular complications and/or risk factors for macrovascular complications.
    - Ideal pediatric candidates are those with motivated families who are committed to monitoring blood glucose 4 or more times per day and have a working understanding of basic diabetes management.
    - Patient age and duration of diabetes should not be factors in determining the transition from injections to CSII.

Intensified basal-bolus regimen

An intensified basal-bolus regimen of insulin glargine and insulin glulisine provides better glycemic control than does a standard, premixed insulin regimen, in patients with long-standing, insulin-treated type 2 diabetes mellitus, according to a study by Fritsche et al. In this open-label, randomized, multinational trial, an intensified insulin regimen combining insulin glargine (once daily) with premeal insulin glulisine (basal-bolus group; n=153) was compared with twice-daily conventional therapy with premixed insulin (n=157).

The mean decrease from baseline HbA1c was -1.31% for the basal-bolus group, versus -0.80% for the premix patients, with more patients in the basal-bolus group attaining HbA1c of 7% or less. Moreover, significantly lower blood glucose levels were observed in the basal-bolus group than in the premix group.[307]

Postprandial glycemic control

Glycemic control is a function not only of fasting and preprandial glucose values but also of postprandial glycemic excursions. Emphasis on postprandial glucose measurements has been fueled to some degree by the availability of short-acting insulin secretagogues, very-short-acting insulin, and alpha-glucosidase inhibitors, all of which target postprandial glycemia.

While postprandial glucose levels are a better predictor of macrovascular disease risk early in the course of loss of glucose tolerance, it remains to be seen whether targeting after-meal glucose excursions has a greater effect on the risk of complications than do more conventional strategies. A study by Siegelaar et al seriously questions the notion that targeting postprandial glucose variability favorably affects cardiovascular outcomes in patients after myocardial infarction.[308] Clearly, more studies are needed.

Intuitively, one would assume that therapies that normalize preprandial and postprandial glycemia (or that come close to normalizing them) would be optimal. Whether such a strategy can be achieved without untoward adverse effects and with further reductions in microvascular and macrovascular disease risk (compared with regimens used in the UKPDS) using newly available therapies is open to question. Practically speaking, most patients are fully occupied trying to handle conventional glucose monitoring and insulin dose adjustment.

Eating a high-protein prebreakfast snack, such as one with soy yogurt, is a simple way to achieve better postbreakfast glycemic control, according to a study by Chen et al; this study confirms a phenomenon observed in healthy humans nearly a century ago (Staub, 1921).[309]

Glycemic monitoring

Decisions about glycemic management are generally made on the basis of HbA1c measurements and the results of self-monitoring of blood glucose (SMBG). HbA1c is measured at least twice yearly in patients with stable glycemic control who are meeting treatment goals and quarterly in patients whose therapy has changed or who are not meeting treatment goals.[2]

If a total glycated hemoglobin (GHb) measurement is used, the number is 1-2% higher. However, the laboratory should provide a correlation of GHb values with HbA1c values.[3, 95, 169]

Glycemic targets

A guideline from the American College of Physicians (ACP) recommends that an HbA1c target of less than 7% is appropriate for many patients.[310] Some organizations (eg, the American Association of Clinical Endocrinologists,[158] the International Diabetes Federation) recommend a glycemic target of less than 6.5% for HbA1c, although this is a general target that always has to be individualized according to patient characteristics and health conditions

The ACP advises, however, that an HbA1c of 7% may not be an appropriate target for all patients.[310] Goals should be tailored to the individual patient and should take the following considerations into account:

- The patient's preferences
- Risk for complications from diabetes
- Comorbidity
- Life expectancy

In a meta-analysis of 13 studies, intensive glucose lowering had no significant effect on all-cause mortality or cardiovascular deaths. A reduction in nonfatal myocardial infarction and microalbuminuria was noted. However, patients experienced a 2-fold increased risk of hypoglycemia.[311]

Risks of and considerations in intensive treatment

Risk for hypoglycemia is almost always the limiting factor in achieving the lowest possible HbA1c that does not cause undue harm. Unfortunately, some practitioners and their patients pursue a particular HbA1c value despite uncertain benefit or unacceptable risk, with significant risk for side effects.

Factors that can produce an unfavorable risk-benefit ratio for intensive blood glucose lowering include advanced age, other major systemic disease, and advanced microvascular and neuropathic complications. For example, in an elderly patient, risk considerations may include the possibility of falling and breaking a hip during a hypoglycemic episode. (Such considerations are addressed in Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty. A national collaborative stakeholder initiative, from Diabetes UK.)

In elderly patients who have a life expectancy of less than 5 years or in any patient with a terminal disease, tight control may be unnecessary. Patients with cardiovascular or cerebrovascular disease may also need higher preprandial blood glucose targets (eg, 100-150 mg/dL) to prevent severe hypoglycemia.

For patients older than 65 years, a recent consensus statement from the American Diabetes Association and the American Geriatrics Society recommends adjusting treatment goals for glycemia, blood pressure, and dyslipidemia according to life expectancy and the presence of comorbidities. The statement suggests 3 broad groupings[312, 313] :

- Healthy: Patients with few coexisting chronic conditions and intact cognitive and functional status
- Complex/intermediate: Patients with multiple coexisting chronic illnesses or 2 or more impairments in activities of daily living (ADL) or mild to moderate cognitive impairment
- Very complex/poor health: Patients in long-term care or with end-stage chronic illnesses or moderate to severe cognitive impairment or with 2 or more ADL dependencies

Corresponding HbA1c targets might be less than 7.5%, less than 8%, and less than 8.5%, respectively, for the 3 groups above.

Additionally, patients with alcoholism or other serious substance abuse problems and patients with severe, uncontrolled mental illness may be unable to effectively participate in the care of their diabetes. Consequently, they are at high risk for severe hypoglycemic reactions if near-normal glucose levels are targeted.

Finally, patients with hypoglycemia unawareness (ie, lack adrenergic warning signs of hypoglycemia) or those with recurrent episodes of severe hypoglycemia (ie, hypoglycemia requiring treatment by another person) should also have high target levels, at least temporarily. Fortunately, patients with type 2 diabetes mellitus (unlike those with long-standing type 1 disease) usually maintain adequate hypoglycemia awareness. This greatly facilitates hypoglycemic therapy (ie, insulin secretagogues, insulin) in patients with type 2 diabetes.

Self-monitoring of blood glucose

Daily SMBG is important for patients treated with insulin or insulin secretagogues to monitor for and prevent hypoglycemia, as well as to optimize the treatment regimen. The optimal frequency of SMBG for patients with type 2 diabetes is unresolved, but it should be sufficient to facilitate reaching glucose goals.

The author often utilizes no or minimal SMBG in patients using lifestyle changes alone or agents that do not cause hypoglycemia (eg, metformin, TZDs, glucosidase inhibitors). Patients using multiple insulin injections should use SMBG at least 3 times a day.[2]

A task force from the Endocrine Society evaluated the following potential uses for continuous glucose monitoring:

- Real-time, continuous glucose monitoring in adults in hospital settings
- Real-time outpatient monitoring in children and adolescents
- Real-time outpatient monitoring in adults

The Task Force developed recommendations regarding benefits in maintaining target levels of glycemia and limiting the risk of hypoglycemia.[314]

Although the use of continuous glucose monitors (CGMs) has primarily been aimed at persons with type 1 diabetes, the devices have come to increasingly be employed in type 2 diabetes.[315] For example, the CGM device sugarBEAT (Nemaura Medical; Loughborough, UK) was developed specifically for individuals with type 2 diabetes, being produced for such patients who are not at high risk for hypoglycemia; it can also be utilized in persons with prediabetes. The sugarBeat CGM uses an adhesive patch and sensor, drawing glucose molecules from the interstitial fluid just beneath the skin's surface for measurement. A Bluetooth connection is employed to transmit data every 5 minutes to a smartphone app. The device is worn for 14 hours at a time during the day and for just 2-4 days monthly (in contrast to CGMs for patients with type 2 diabetes, which are utilized every day). Although sugarBEAT is noninvasive, a once-daily fingerstick is still needed for calibration. In May 2019, it received a CE (Conformité Européenne) Mark in Europe for use as a Class IIb medical device. Although still awaiting FDA approval in the United States, permission has in the meantime been granted for this CGM to be marketed as a “wellness” device, with sugarBEAT in this capacity producing retroactive reports for the physician and patient rather than real-time values.[316]

Dietary Modifications

For most patients, the best diet is one consisting of the foods that they are currently eating. Attempts to calibrate a precise macronutrient composition of the diet to control diabetes, while time-honored, are generally not supported by the research. Caloric restriction is of first importance. After that, individual preference is reasonable.

Modest restriction of saturated fats and simple sugars is also reasonable. However, some patients have remarkable short-term success with high-fat, low-carbohydrate diets of various sorts. Therefore, the author always stresses weight management in general and is flexible regarding the precise diet that the patient consumes. Also, the practitioner should advocate a diet composed of foods that are within the financial reach and cultural milieu of the patient. For example, patients who participate in Ramadan may be at higher risk of acute diabetic complications. Although these patients do not eat during the annual observance, they should be encouraged to actively monitor their glucose, alter the dosage and timing of their medication, and seek dietary counseling and patient education to counteract any complications.[317]

Weight loss

Modest weight losses of 5-10% have been associated with significant improvements in cardiovascular disease risk factors (ie, decreased HbA1c levels, reduced blood pressure, increase in HDL cholesterol, decreased plasma triglycerides) in patients with type 2 diabetes mellitus. Risk factor reduction was even greater with losses of 10-15% of body weight.[318, 319]

A study by Lazo et al attested to the benefits of lifestyle intervention, which aimed at a minimum weight loss of 7%, on hepatic steatosis in patients with type 2 diabetes.[320] Since there is no known treatment for nonalcoholic fatty liver disease, a weight loss strategy may help to prevent progression to serious liver damage.

One-year results from the open-label, randomized Diabetes Remission Clinical Trial (DiRECT) demonstrated a type 2 diabetes remission rate of 46% in participants who underwent intervention with a very low–calorie liquid diet. The regimen included gradual reintroduction of food after 3-5 months and ongoing weight-loss maintenance support. The remission rate reached 73% in just those patients in the intervention group who at 12 months had maintained a weight loss of at least 10 kg.[321, 322]

Mediterranean-style diet

Esposito et al reported greater benefit from a low-carbohydrate, Mediterranean-style diet than from a low-fat diet in patients with newly diagnosed type 2 diabetes mellitus.[323] In a single-center, randomized trial, 215 overweight patients with newly diagnosed type 2 diabetes mellitus who had never been treated with antihyperglycemic drugs and whose HbA1c levels were less than 11% were assigned to either a Mediterranean-style diet (< 50% of daily calories from carbohydrates) or a low-fat diet (< 30% of daily calories from fat).

After 4 years, participants assigned to the Mediterranean-style diet had lost more weight and had demonstrated more improvement in some measures of glycemic control and coronary risk than had participants consuming the low-fat diet; 44% of patients in the Mediterranean-style diet group required antihyperglycemic drug therapy, compared with 70% of those in the low-fat diet group.

High-protein versus high-carbohydrate diet

A study by Larsen et al concluded that the long-term therapeutic effect of a high-protein diet is not superior to that of a high-carbohydrate diet in the treatment of type 2 diabetes mellitus. In this 12-month trial, 99 overweight or obese diabetic patients followed a low-fat diet (30% total energy) that was either high in protein (30% total energy) or high in carbohydrate (55% total energy); both groups benefited equally.[324]

It should also be noted that already-attenuated glucose disposal is not worsened by postprandial circulating amino acid concentration. Therefore, recommendations to restrict dietary proteins in patients with type 2 diabetes seem unwarranted.[325]

Trans-palmitoleate

In the Cardiovascular Health Study, phospholipid trans -palmitoleate levels were found to be associated with lower metabolic risk.[326] Trans -palmitoleate is principally derived from naturally occurring dairy and other ruminant trans -fats. Circulating trans -palmitoleate is associated with lower insulin resistance, incidence of diabetes, and atherogenic dyslipidemia. Potential health benefits, therefore, need to be explored.

Advanced glycation end products

Food-derived, pro-oxidant, advanced glycation end products may contribute to insulin resistance in clinical type 2 diabetes mellitus and may suppress protective mechanisms. Advanced glycation end-product restriction may preserve native defenses and insulin sensitivity by maintaining a lower basal oxidative state.[327]

Other considerations

Oral ginseng (or ginsenoside) does not improve pancreatic beta-cell function. Routine use is not recommended.[328]

Pasta enriched with biologically active isoflavone aglycons improves endothelial function in patients with type 2 diabetes mellitus and favorably affects cardiovascular disease risk markers.[329]

In patents with type 2 diabetes mellitus, impaired fasting glucose or impaired glucose tolerance at high risk for cardiovascular disease, addition of n-3 fatty acids does not reduce risk of cardiovascular events, including death from cardiovascular causes.[330]

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Activity Modifications

Most patients with type 2 diabetes mellitus can benefit from increased activity. Aerobic exercise improves insulin sensitivity and may improve glycemia markedly in some patients.

Structured exercise training of more than 150 minutes per week is associated with greater HbA1c reduction; however, physical activity helps lower HbA1c only when combined with dietary modifications.[331]

The patient should choose an activity that she or he is likely to continue. Walking is accessible to most patients in terms of time and financial expenditure.

A previously sedentary patient should start activities slowly. Older patients, patients with long-standing disease, patients with multiple risk factors, and patients with previous evidence of atherosclerotic disease should have a cardiovascular evaluation, probably including an imaging study, prior to beginning a significant exercise regimen.

Balducci et al showed that a supervised, facility-based exercise training program, when added to standard treatments for type 2 diabetes mellitus, yields better results than does simply counseling patients to exercise.[332]

A randomized, controlled trial by Church et al emphasized the need to incorporate both aerobic and resistance training to achieve better lowering of HbA1c levels.[333] Aerobic exercise alone or in combination with resistance training improves glycemic control, circulating triglycerides, systolic blood pressure, and waist circumference.[334] The impact of resistance exercise alone, however, remains unclear.

Loimaala et al found that long-term endurance and strength training resulted in improved metabolic control of diabetes mellitus and significant cardiovascular risk reduction, compared with standard treatment. However, exercise training did not improve conduit arterial elasticity.[335]

In a 3-month trial, Hegde et al found that yoga can be effective in reducing oxidative metabolic stress in patients with type 2 diabetes mellitus. However, yoga did not impact waist-to-hip ratio, blood pressure, vitamin E, or superoxide dismutase.[336]

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Bariatric Surgery

In morbidly obese patients, bariatric surgery has been shown to improve diabetes control and, in some situations, normalize glucose tolerance. It is certainly a reasonable alternative in carefully selected patients if an experienced team (providing appropriate preoperative evaluation, as well as technical surgical expertise) is available.

In 2011, the International Diabetes Federation Taskforce on Epidemiology and Prevention of Diabetes released a position statement on bariatric surgery. The task force recommended bariatric surgery as an appropriate treatment for people with type 2 diabetes mellitus and obesity who have been unable to achieve recommended treatment targets using medical therapies, particularly if other major comorbidities exist.[337, 338]

According to guidelines released in 2016 by the 2nd Diabetes Surgery Summit (DSS-II), an international consensus conference, bariatric surgery should be considered even for type 2 diabetes patients with mild, class 1 obesity (BMI 30.0-34.9 kg/m2) if their hyperglycemia is inadequately controlled with optimal treatment. In addition, the guidelines state that bariatric surgery should be a “recommended option” for type 2 diabetes patients with class 3 obesity (BMI 40 kg/m2 or above) no matter what level of glycemic control has been achieved. The guidelines also say that of the different forms of bariatric surgery, Roux-en-Y gastric bypass seems to have the best risk/benefit profile for the majority of patients with type 2 diabetes.[339, 340]

Kashyap and colleagues demonstrated that bariatric surgery improved glycemic control in patients with type 2 diabetes.[341] The study compared the metabolic effects of 2 types of bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy) combined with intensive medical therapy with intensive medical therapy alone in 60 patients with uncontrolled type 2 diabetes and moderate obesity. At 24-month follow-up, glycemic control improved in all 3 groups. Body fat reduction was similar in the 2 surgery groups, with patients in the gastric bypass group showing a greater absolute reduction in truncal fat.[341] Insulin sensitivity increased significantly only in the gastric bypass group, and pancreatic β-cell function increased significantly more in these patients compared with those in the other 2 groups.[341]

A retrospective study of 252 patients with type 2 diabetes mellitus who underwent bariatric surgery found that 44% of the patients were able to do without insulin treatment by median 7-year follow-up. The patients had a mean preoperative BMI of 46 kg/m2, with those who underwent the Roux-en-Y procedure showing a 1.4 percentage-point reduction in HbA1c at 7 years, and those who underwent sleeve gastrectomy showing a 1.6 percentage-point reduction.[342]

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Laboratory Monitoring

Because diabetes mellitus is a multisystem disease, focusing solely on blood glucose is inadequate. The image below lists appropriate laboratory parameters in the global assessment of patients with type 2 diabetes mellitus. Obviously, patients with abnormalities need more frequent monitoring to guide therapeutic interventions. Drug-specific monitoring is also necessary (eg, serum creatinine and vitamin B12 in patients taking metformin, serum transaminases for patients taking a TZD).

Laboratory Monitoring of Patients with Type 2 Diabetes Mellitus

Test	HbA1c	FLP	Scr	Umab	ECG
Type 2 DM-insulin treated	Every 3 months	Yearly	Yearly	Yearly	Baseline
Type 2 DM-no insulin	Every 3-6 months	Yearly	Yearly	Yearly	Baseline

Laboratory monitoring guidelines for patients with type 2 diabetes mellitus.

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Monitoring for Diabetic Complications

The ADA recommends initiation of complications monitoring at the time of diagnosis of diabetes mellitus.[2] This regimen should include yearly dilated eye examinations, annual microalbumin checks, and foot examinations at each visit.

A study by Cigolle et al found that middle-aged and older adults with diabetes have an increased risk for the development of geriatric conditions (eg, cognitive, vision, and hearing impairments; falls).[343] These conditions substantially contribute to morbidity and functional impairment. The authors concluded that adults with diabetes should be monitored for the development of geriatric conditions at a younger age than was previously considered.

The risk for early development of Parkinson disease is 36% higher in patients with diabetes mellitus.[344] However, a systematic review from Cereda et al found no conclusive evidence of this association.[345]

A high overall risk for pancreatic neoplasm is noted in individuals with diabetes mellitus, particularly in those aged 45-65 years.[346]

The incidence of complications widely vary among the Asian subgroups, suggesting the need for an ethnic stratified nuanced approach in evaluation and surveillance.[347] One size does not fit all.

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Management of Hypertension

Blood pressure goals

The role of hypertension in increasing microvascular and macrovascular risk in patients with diabetes mellitus has been confirmed in the UKPDS and Hypertension Optimal Treatment (HOT) trials.[348, 349]

In a 2017 update to its recommendations for hypertension management in diabetes, the ADA states that the goal in most patients with diabetes and hypertension should be a systolic blood pressure (SBP) of below 140 mm Hg and a diastolic blood pressure (DBP) of under 90 mm Hg. For patients with a high risk of cardiovascular disease, however, the recommendations say that it may be appropriate to target a lower SBP/DBP, such as below 130/80 mm Hg, if the goal can be met “without undue treatment burden.”[350, 351]

In patients with greater than 1 g/day proteinuria and renal insufficiency, a more aggressive therapeutic goal (ie, 125/75 mm Hg) has been advocated. According to the Veterans Affairs Diabetes Trial, however, a diastolic blood pressure of less than 70 mm Hg increases the risk of cardiovascular disease in patients with diabetes, even when systolic blood pressure is within the current guidelines (recommended range, < 140 mm Hg).[352]

The ADA recommendations endorse blood pressure measurement “at every routine clinical care visit” and state that patients whose blood pressure is found to be elevated (at or above 140/90 mm Hg) should undergo multiple readings to confirm hypertension, including blood pressure assessment on a separate day.[350, 351]

Cardiovascular risk and hypertension medications

In a safety review, the FDA found no clear evidence of increased cardiovascular risk with the hypertension drug olmesartan in diabetic patients.[353] This review addressed data from the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, which found an increased risk of cardiovascular mortality in patients taking olmesartan, as well as data from an epidemiologic study of Medicare patients, which suggested a similarly increased risk.

Because of discrepant survival results in diabetics and nondiabetics in the Medicare study, the FDA concluded that the evidence for the increased cardiovascular risk was not conclusive and did not support recommending that olmesartan not be used in patients with diabetes.[353, 354]

Pharmacologic therapy

While angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), diuretics, beta blockers, and calcium channel blockers are all considered acceptable initial therapy, the author prefers inhibitors of the renin-angiotensin system (ie, ACE inhibitors, ARBs) because of their proven renal protection effects in patients with diabetes. Many patients require multiple agents. Diuretics or calcium channel blockers frequently are useful as second and third agents.

The ALTITUIDE Trial investigating the impact of direct renin inhibitor with aliskiren on cardio-renal outcomes in patients with diabetes mellitus when used as an adjunct to angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy failed to show any benefit. On the contrary, it might be harmful due to an increased risk for hyperkalemia and hypotension despite marked reduction in proteinuria.[355]

A study by Hermado et al showed that treatment with antihypertensive medications taken at bedtime provides better ambulatory blood pressure control, as well as significant reduction in cardiovascular morbidity and mortality when compared with taking medications upon waking.[356] The study was conducted in patients taking 1 or more antihypertensive drugs and had a median follow-up of 5.4 years.

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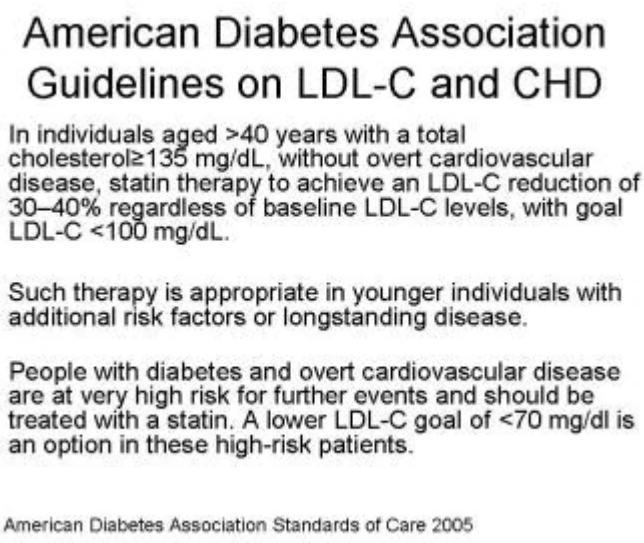
Management of Dyslipidemia

Statins

Dyslipidemia is common in patients with type 2 diabetes mellitus and often takes the form of high triglyceride and low HDL cholesterol levels. Trials have shown that the use of statins is effective for primary and secondary prevention of coronary heart disease (CHD) events in patients with diabetes. ADA guidelines relating with LDL cholesterol management and CHD in patients with type 2 diabetes mellitus are detailed in the image below.



American Diabetes Association guidelines for low-density lipoprotein cholesterol in diabetes mellitus type 2.

See Management of Coronary Heart Disease for guidelines on statin use in persons with diabetes.

Fibrates

Fibrates may reduce CHD events in patients with isolated low HDL cholesterol. Whether therapy aimed more at triglyceride reduction and HDL cholesterol elevation (ie, fibrates, niacin) is effective in CHD-event reduction in primary prevention remains to be determined.[357]

Beta blockers

Small studies have led to a suggestion that a lower LDL cholesterol goal, of less than 70 mg/dL, be considered in patients at very high risk, including patients with diabetes. However, the National Cholesterol Education Program (NCEP) lists this as a therapeutic option rather than a formal recommendation as of this writing.

Vasoconstricting beta blockers are known to reduce HDL cholesterol levels and increase triglyceride, LDL cholesterol, and total cholesterol levels. The vasodilating beta blocker carvedilol (mixed alpha1, beta1, and beta2 blocker) has not been associated with the aforementioned effects.

In a randomized, double-blind trial in patients with type 2 diabetes mellitus receiving renin-angiotensin blockers, the addition of carvedilol for blood pressure control resulted in a significant decrease in triglyceride, total cholesterol, and non–HDL cholesterol

levels. Patients given metoprolol (a vasoconstricting beta blocker) were significantly more likely to be started on statin therapy or, if already on statin therapy, to require an increase in the dose, than were patients taking carvedilol.[358]

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Management of Coronary Heart Disease

There is contradictory epidemiologic evidence as to whether diabetes is in fact a CHD risk equivalent. For the present, however, that is the position adopted by most groups, such as the National Cholesterol Education Program (NCEP) and the ADA.[357]

Although the risk for CHD is 2-4 times greater in patients with diabetes than it is in individuals without diabetes, control of conventional risk factors is probably more important in event reduction than is glycemic control. Control of hypertension, aspirin therapy, and lowering of LDL cholesterol levels are vitally important in reducing CHD risk.

Aspirin

The ADA recommends that patients with diabetes who are at high risk for cardiovascular events receive primary preventive therapy with low-dose, enteric-coated aspirin. For patients with aspirin hypersensitivity or intolerance, clopidogrel is recommended.[359]

However, a randomized, controlled trial from Japan found that using low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events in patients with type 2 diabetes.[360] These investigators subsequently reported that low-dose aspirin therapy reduces cardiovascular risk only in patients with a glomerular filtration rate (GFR) of 60-89 mL/min; low-dose aspirin had no beneficial impact if the GFR was above 90 mL/min or below 60 mL/min.[361]

A study by Okada et al reported that low-dose aspirin therapy (81-100 mg) in patients with diabetes who are taking insulin or oral hypoglycemic agents does not reduce atherosclerotic events.[362] This is yet another argument against using low-dose aspirin for primary prevention of cardiovascular disease in patients with moderate or severe diabetes.

Statins

The Scandinavian Simvastatin Survival Study (4S) showed a 42% reduction in CHD events in diabetic patients with simvastatin therapy (mean dose 27 mg daily, with LDL reduction approximately 35%). Participants in 4S had known CHD and very high LDL cholesterol levels.[363]

A smaller reduction was seen in the Heart Protection Study (HPS) in patients with CHD or other vascular disease and diabetes.[364] Patients in the HPS treatment arm received simvastatin 40 mg daily. Lesser degrees of risk reduction have been shown in other secondary prevention studies in patients treated with pravastatin with mild to moderate LDL cholesterol elevation at baseline.

Atorvastatin, 10 mg daily, did not reduce CHD risk among diabetic patients with hypertension and no previous CHD who were enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[365] In contrast, the Collaborative Atorvastatin Diabetes Study (CARDS) showed a significant reduction in CHD risk in patients with type 2 diabetes mellitus and 1 other risk factor when treated with atorvastatin 10 mg daily.[366]

Some studies have suggested that statin therapy may be associated with an increased risk of developing diabetes. In a pooled analysis of data from five statin trials, intensive-dose statin therapy was associated with increased risk of new-onset diabetes compared with moderate dose statins.[367]

A study by Ahmadizar et al of subjects over age 45 years who had no diabetes at baseline reported that compared with individuals who have never used statins, the risk of incident type 2 diabetes development in persons who have ever taken statins is 38% greater, with the likelihood being particularly high in persons with impaired glucose homeostasis and in individuals who are overweight/obese. However, analyses stratified at baseline for gender and body mass index (BMI) indicated that statin use was not significantly associated with type 2 diabetes in women or in persons with a normal body mass index (BMI).[368, 369]

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.[370]

- 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/m2 (instead of 25 kg/m2) 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 HbA1c 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 HbA1c target of less than 7.5% for children is now recommended.

HDL cholesterol therapy

The benefits of raising HDL cholesterol levels in patients with type 2 diabetes remains uncertain. Some of the statin trials suggest that statin therapy eliminates some of the excess risk from low HDL cholesterol levels in patients with LDL cholesterol elevation at baseline.

The Veterans Administration HDL Intervention Trial (VA-HIT) showed an approximately 22% reduction in CHD events in patients with diabetes and known CHD when HDL cholesterol levels were increased by approximately 6% by gemfibrozil.[371] This was a population with low LDL cholesterol levels, however, so whether these same benefits would accrue in patients with elevated LDL cholesterol who are treated with a statin before their low HDL cholesterol is addressed is unclear.

Triglyceride therapy

An elevated triglyceride level is a common abnormality in type 2 diabetes mellitus. However, whether therapy to reduce triglycerides helps to reduce CHD events has not been determined from clinical end-point trials.

Revascularization

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study, which was conducted in 2368 patients with type 2 diabetes mellitus and heart disease, showed no significant difference in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy with insulin or insulin-sensitizing drugs.[372] These data emphasize the need to customize therapy to the patient’s circumstances and therapeutic goals.

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Management of Ophthalmologic Complications

Patients with established retinopathy should see an ophthalmologist at least once every 6-12 months, as necessary. Three-year retinal screening may be feasible for patients with mild diabetes and no retinopathy.[373]

Early background retinopathy may reverse with improved glycemic control. More advanced retinopathy does not regress with improved glycemia and may worsen, although rarely, with short-term marked improvements in glycemia. Hypertension control is of paramount importance in these latter patients. Results of the randomized, placebo-controlled DIRECT-Protect 2 trial suggested that treatment with the ARB candesartan may improve mild to moderate retinopathy in patients with type 2 diabetes.[374]

Macular edema has been reported in a proportion of patients who experience fluid retention as a side effect of TZDs.[375] Resolution typically follows cessation of the TZD, although diuretics have been prescribed in such cases.

Laser photocoagulation has markedly improved the ability of ophthalmologists to preserve sight in patients with diabetes and proliferative retinopathy or macular edema. Laser therapy is effective in decreasing macular edema and preserving vision but is less effective in restoring lost vision.

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 also tend to develop senile cataracts sooner than persons without diabetes. Development of senile cataracts is not related to the degree of glycemic control, however.

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Management of Diabetic Neuropathy

Peripheral neuropathy is the most common complication observed in patients with type 2 diabetes in outpatient clinics. Patients may have paresthesias, numbness, or pain. The feet are involved more often than the hands.

Improved glycemic control early may alleviate some of the symptoms, although sometimes symptoms actually worsen with lowering of blood glucose levels. Later symptomatic therapy largely is empirical and may include the following:

- Low-dose tricyclic antidepressants
- Duloxetine
- Anticonvulsants (eg, phenytoin, gabapentin, carbamazepine)
- Topical capsaicin
- Various pain medications, including nonsteroidal anti-inflammatory drugs (NSAIDs)

Protection of the feet by applying lubricating agents (but not between the toes) and wearing appropriate footwear (shoes and socks or stockings) is important. Daily inspection of the feet after bathing is mandatory. In patients with advanced neuropathy, water temperature must be checked by a companion or with a thermometer. Soaking the feet generally is not recommended and may be harmful.

Gastroparesis is usually less of a problem in patients with type 2 diabetes mellitus than in those with type 1. Improved glycemic control, discontinuation of medications that slow gastric motility, and the use of metoclopramide may be helpful. Metoclopramide use preferably should be limited to a few days at a time, as long-term use has been linked to tardive dyskinesia.[376]

Autonomic neuropathy may manifest as orthostatic hypotension. Such patients may require volume expanders or adrenergic agents. Patients with cystopathy may benefit from cholinergic agents.

Acute-onset mononeuropathies in diabetes include acute cranial mononeuropathies, mononeuropathy multiplex, focal lesions of the brachial or lumbosacral plexus, and radiculopathies. It is important to consider nondiabetic causes for cranial nerve palsies, including intracranial tumors, aneurysms, and brainstem stroke.[377]

For more information see Diabetic Neuropathy and Diabetic Lumbosacral Plexopathy.

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Management of Infections

Diabetes predisposes patients to a number of infectious diseases, including the following:

- Malignant otitis externa
- Rhinocerebral mucormycosis
- Bacteriuria

- Pyuria
- Cystitis
- Upper urinary tract infection
- Intrarenal bacterial infection
- Skin and soft tissue infections
- Osteomyelitis

For more information, see Infections in Patients with Diabetes Mellitus.

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Management of Intercurrent Medical Illness

Patients with intercurrent illness become more insulin resistant because of the effects of increased counterregulatory (ie, anti-insulin) hormones. Therefore, despite decreased nutritional intake, glycemia may worsen.

Patients on oral agents may need transient therapy with insulin to achieve adequate glycemic control. In patients who require insulin, scheduled doses of insulin, as opposed to sliding scale insulin, are far more effective in achieving glycemic control.[378, 379]

Metformin is a special case. If patients taking metformin have any illness that leads to dehydration or hypoperfusion, the drug should be temporarily discontinued because of a possible increased risk of lactic acidosis.

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Management of Critical Illness

Standard practice in intensively ill patients has been to provide tight glycemic control through intensive insulin therapy. Research evidence, however, has called this practice into question.

A meta-analysis found that in critically ill adult patients, tight glucose control is associated with an increased risk of hypoglycemia but not with significantly reduced hospital mortality.[380] A large, international, randomized trial among adults treated in an intensive care unit (ICU) found that intensive glucose control (target, 81-108 mg/dL) resulted in higher mortality than did a blood glucose target of 180 mg/dL or less.[381]

However, large, single-center studies using more accurate glucose measurements have shown a benefit to intensive glycemic control in critical illness.[382] This remains an area of important ongoing research.

Results of the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial suggested improved outcomes in patients with type 2 diabetes with acute myocardial infarction or stroke who receive constant IV insulin during the acute phase of the event to maintain blood glucose values of approximately 100-150 mg/dL.[383] However, these results were not confirmed in the follow-up trial, DIGAMI-2.[384]

A post-hoc analysis of the DIGAMI-2 study revealed that glucose-lowering drugs impact prognosis differently. Insulin may be associated with increased risk of nonfatal cardiac events, whereas metformin seems to be protective against risk of death.[385]

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Pharmacologic Considerations in Surgery

Surgical patients may experience worsening of glycemia for reasons similar to those listed above for intercurrent medical illness. Patients on oral agents may need transient therapy with insulin to maintain blood glucose at approximately 100-180 mg/dL.

In patients who require insulin, scheduled doses of insulin (eg, glargine once daily plus glulisine before meals, as opposed to sliding-scale insulin, are far more effective in controlling glucose. Intensive glucose control in surgical ICU patients appears to reduce the risk of septicemia, but as with other critically ill patients, this may come at the cost of increased risk of hypoglycemia. [380]

A standardized protocol can be effective in transitioning patients who have diabetes and acute coronary syndrome to subcutaneous insulin once oral feeding has resumed. This is based on insulin requirement during the previous 12 hours. Half of the amount is given as basal insulin, and the remainder is given as prandial insulin.[386]

For patients who can eat soon after surgery, the time-honored approach of administering half of the usual morning dose of neutral protamine Hagedorn (NPH) insulin with 5% dextrose in the IV infusion is acceptable, with resumption of scheduled insulin (perhaps at reduced doses) within the first 1-2 days. With the availability of newer basal insulins (ie, glargine, detemir), options have expanded. A full dose of basal insulin can be given, and rapid-acting insulin can be administered when meals are consumed.

Patients receiving basal insulin can often receive their usual dose if they are given IV glucose during surgery, with appropriate intraoperative and postoperative monitoring of glucose. Oral antidiabetic agents can be restarted when the patient is stable and eating.

Insulin secretagogues should be used with caution in the hospital, since food intake may be interrupted by diagnostic tests and procedures. Metformin may have to be started at a lower dose and gradually titrated to full dose due to GI side effects. Since TZDs have such a long biologic effect, their omission in the hospital is usually inconsequential. The role of incretins in the hospital has not yet been defined.

For patients who require more prolonged periods without oral nutrition and for major surgery, such as coronary artery bypass grafting and major abdominal surgery, constant infusion IV insulin is preferred. Discontinue metformin temporarily after any major surgery until the patient is clearly hemodynamically stable and normal renal function is documented. Discontinuing metformin for at least 48 hours in this situation until proof of normal renal function is established is the current standard.

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Prevention of Type 2 Diabetes Mellitus

Guidelines from the American College of Clinical Endocrinologists for the prevention of type 2 diabetes mellitus in patients at risk recommend the following measures:

- Weight reduction
- Proper nutrition
- Regular physical activity
- Cardiovascular risk factor reduction
- Aggressive treatment of hypertension and dyslipidemia

Lifestyle improvement

The Diabetes Prevention Program (DPP) trial has shown that modest lifestyle changes (eg, 4-5% sustained weight reduction for approximately 3 y) reduce the risk for diabetes in patients at high risk by 58%.[387] Eight health-care facilities participated in an instructive study of group-based lifestyle intervention that should help other agencies/states emulate strategies used to affect positive lifestyle changes for the prevention of diabetes.[388]

In an 11-year, population-based cohort study of over 200,000 men and women without evidence of diabetes, heart disease, or cancer at baseline, good lifestyle decisions in combination significantly reduced the risk of developing diabetes. For each additional positive lifestyle factor (eg, with regard to diet, physical activity, or smoking) in the low-risk group, the odds for diabetes were 31% lower[389]

Yeh et al found that although cigarette smokers are at increased risk for type 2 diabetes, smoking cessation leads to higher short-term risk.[390] In this prospective cohort study in 10,892 middle-aged, nondiabetic adults, 1254 persons developed type 2 diabetes during 9 years of follow up.

The adjusted hazard ratio of incident diabetes among persons in the highest tertile of pack-years was 1.42, compared with persons who had never smoked. However, in the first 3 years after quitting smoking, the hazard ratio was 1.73; the risk then gradually decreased, disappearing completely at 12 years. Yeh et al recommended that smoking cessation in smokers at risk for diabetes be coupled with strategies for prevention and early detection of diabetes.

A significant inverse correlation has been found between the risk of diabetes and the intake of magnesium, which plays an important role in insulin action and glucose homeostasis. In a meta-analysis, the summary relative risk of type 2 diabetes for every 100 mg/day increment in magnesium intake was 0.86.[391]

Interest in the impact of phylloquinone intake on glucose tolerance and insulin sensitivity has a long history. A 2012 report suggests a beneficial role for phylloquinone in diabetes prevention in elderly subjects with high cardiovascular risk. However, caution is advised in patients who are concurrently being treated with anticoagulant drugs such as warfarin.[392]

Pharmacologic prevention

Drugs from several classes have been studied in the prevention of diabetes. However, the FDA has not approved any drug for the treatment of prediabetes or the prevention of type 2 diabetes.[393]

Metformin

The ADA recommends that, in addition to lifestyle counseling, metformin be considered in selected patients with prediabetes.[2] ADA criteria for preventive metformin therapy are as follows:

- Obesity
- Age younger than 60 years
- Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)
- Other risk factors (eg, HbA1C >6%, hypertension, low HDL cholesterol, elevated triglycerides, or a family history of diabetes in a first-degree relative)

In the DPP, metformin 1700 mg daily was about half as effective as lifestyle intervention in reducing risk among subjects with elevated fasting and postload plasma glucose concentrations.[387] Over an average follow-up period of 2.8 years, the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively.

Thiazolidinediones

Analysis of available data from the DPP suggests that troglitazone was effective in preventing diabetes. This effect was also seen in the Troglitazone in Prevention of Diabetes (TRIPOD) study of Hispanic women with a history of gestational diabetes. After troglitazone was withdrawn from the market because of hepatotoxicity, the continuation of TRIPOD in the Pioglitazone in the Prevention of Diabetes Study demonstrated slowed progression of subclinical atherosclerosis with glitazone treatment.[394]

In the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial, investigators concluded that rosiglitazone at 8 mg daily reduces the incidence of type 2 diabetes mellitus in patients with IFG and/or IGT. At the end of this prospective, multicenter study, composite outcome of diabetes or death from any cause was 11.6% in the rosiglitazone group versus 26% in the placebo group.[205] Ramipril did not produce significant reduction in the same composite outcome.[395]

Acarbose

Acarbose (100 mg three times a day) was shown in the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) to reduce diabetes rates by approximately 25% in patients at high risk for the development of type 2 diabetes.[396] This 6-year, international, multicenter, double-blind, placebo-controlled, randomized investigation included 1,368 subjects with IGT.

Stroke Prevention in Diabetes

The 2010 American Heart Association/American Stroke Association (AHA/ASA) guidelines for the primary prevention of stroke include the following recommendations for patients with diabetes:

- Regular blood pressure screening
- Physical activity; 30 minutes or more of moderate-intensity activity on a daily basis
- A low-sodium, high-potassium diet to reduce blood pressure; a diet emphasizing consumption of fruits, vegetables, and low-fat dairy products (eg, the Dietary Approaches to Stop Hypertension [DASH] diet) may lower stroke risk
- A blood pressure goal of less than 130/80 mm Hg
- Drug therapy with ACE inhibitors or ARBs
- Statin therapy, especially in patients with other risk factors; monotherapy with fibrates may also be considered to lower stroke risk

The AHA/ASA guidelines note that the benefit of taking aspirin for the reduction of stroke risk has not been fully demonstrated in diabetic patients.

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Consultations

Primary care providers can care for patients with type 2 diabetes mellitus adequately. The multiple facets of disease treatment (eg, nutrition, exercise, smoking cessation, medications, complications monitoring) and data management (eg, glucose levels, blood pressure, lipids, complications monitoring) must be continually addressed.

Inability to achieve adequate glycemic (or blood pressure or lipid) control usually should be a clear indication to consult a diabetes specialist. When a patient has developed advanced complications, a diabetes specialist cannot be expected to be able to lessen the burden of these complications.

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Guidelines

Guidelines Summary

ADA guidelines on managing hypertension

Guidelines published in 2017 by the American Diabetes Association (ADA) on managing hypertension in patients with diabetes state the following[397, 398] :

- 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

ADA Standards of Medical Care in Diabetes

The 2022 edition of the ADA's Standards of Medical Care in Diabetes features several important changes with regard to diabetes screening and management, including the following[4, 5] :

- The recommended age at which people should be screened for prediabetes and type 2 diabetes, regardless of the presence or absence of risk factors, has been lowered from age 45 years to age 35 years
- It is recommended that all women, regardless of risk factors, be tested for undiagnosed diabetes at the time they are planning to become pregnant or else at their first prenatal visit; gestational diabetes screening should be carried out at 24-28 weeks "in pregnant women not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy"
- In persons being screened for diabetes via oral glucose tolerance testing, at least 150 g/day of carbohydrate intake should be assured for 3 days prior to the screen
- It is recommended that, in a research study setting or perhaps in first-degree family members of a proband with type 1 diabetes, screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 be used to screen for presymptomatic type 1 diabetes
- A risk factor for clinical diabetes, the development and persistence of multiple islet autoantibodies may indicate the need "for intervention in the setting of a clinical trial or screening for stage 2 type 1 diabetes"
- Persons with prediabetes should be monitored at least annually for the development of type 2 diabetes, with modifications made according to individual risk/benefit assessment
- Care goals for adults with overweight/obesity for whom the risk of type 2 diabetes is high "should include weight loss or prevention of weight gain, minimizing progression of hyperglycemia, and attention to cardiovascular risk and associated" comorbidities
- If insulin is used in adults with type 2 diabetes, it is recommended that, for better efficacy and durability of treatment effect, combination therapy be employed using a glucagon-like peptide 1 receptor agonist
- Consideration may be given to combined therapy employing a sodium–glucose cotransporter 2 inhibitor and a glucagon-like peptide 1 receptor agonist, both with demonstrated cardiovascular benefit, "for additive reduction in the risk of adverse cardiovascular and kidney events" in patients "with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease"
- If they are capable of using a continuous glucose monitoring (CGM) device safely (either alone or with the aid of a caregiver), youth with type 2 diabetes who are on multiple daily injections or continuous subcutaneous insulin infusion should be offered the option of real-time or intermittently scanned CGM for diabetes management; the patient's circumstances, desires, and needs should govern the choice of device

ADA guidelines for youth-onset type 2 diabetes

In November 2018, the ADA released a position statement the evaluation and management of youth-onset type 2 diabetes. It includes the following points[399] :

- Severe peripheral and hepatic insulin resistance occurs when type 2 diabetes develops in adolescents with obesity, with peripheral insulin sensitivity being about 50% below that of adolescents who have obesity without diabetes; the disposition index (the mathematically described product of insulin sensitivity and β-cell function) in youth with both obesity and type 2 diabetes is about 85% lower
- Risk-based screening should be considered in overweight and obese children over age 10 years or who have commenced puberty
- Risk factors for type 2 diabetes in youth should be taken into account, including whether the child's mother has a history of diabetes or experienced gestational diabetes while pregnant with the child, as well as whether close family members have a history of type 2 diabetes; other risk factors to consider include signs of insulin resistance, as well as the youth's ethnicity (ie, whether he or she is from a non-Caucasian background, such as African American or Latino)
- As part of diagnosis, a panel of pancreatic autoantibodies should be employed to exclude the presence of autoimmune type 1 diabetes
- Adherence to medication therapy and the impact of treatment on weight should be taken into account when glucose-lowering agents and other medications are being chosen for patients who are overweight or obese
- A chronic approach to lifestyle management should be employed, with education, weight management, exercise, nutrition, and psychological factors emphasized
- Education and lifestyle management programs need to be culturally and contextually sensitive
- If their BMI is greater than 35 kg/m ^{2}, uncontrolled glycemia and/or serious comorbidities are present, and lifestyle and pharmacologic approaches have failed, adolescents with type 2 diabetes may be considered for metabolic surgery (but only by an experienced surgeon and only in tandem with input from a multidisciplinary team that also includes an endocrinologist, a nutritionist, a behavioral health specialist, and a nurse)
- A transfer to adult care should be arranged only when the patient and provider deem it appropriate

ADA/EASD recommendations on hyperglycemia management

In October 2018, in an update to previous position statements, the ADA and the European Association for the Study of Diabetes (EASD) released new recommendations regarding adults with type 2 diabetes. The guidelines, on the management of hyperglycemia, include the following[400] :

- Providers and health-care systems should prioritize the delivery of patient-centered care
- All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support (DSMES) programs
- Facilitating medication adherence should be specifically considered when selecting glucose-lowering medications
- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease (ASCVD), sodium-glucose cotransporter–2 (SGLT2) inhibitors or glucacon-like peptide 1 (GLP-1) receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management
- Among patients with ASCVD in whom heart failure coexists or is of special concern, SGLT2 inhibitors are recommended
- For patients with type 2 diabetes and chronic kidney disease (CKD), with or without CVD, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression
- An individualized program of medical nutrition therapy (MNT) should be offered to all patients
- All overweight and obese patients with diabetes should be advised of the health benefits of weight loss and encouraged to engage in a program of intensive lifestyle management, which may include food substitution
- Increased physical activity improves glycemic control and should be encouraged in all people with type 2 diabetes
- Metabolic surgery is a recommended treatment option for adults with type 2 diabetes and 1) a body mass index (BMI) of 40.0 kg/m ^{2} or higher (BMI of 37.5 kg/m ^{2} or higher in people of Asian ancestry) or 2) a BMI of 35.0-39.9 kg/m ^{2} (32.5-37.4 kg/m ^{2} in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods
- Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes
- The stepwise addition of glucose-lowering medication is generally preferred to initial combination therapy
- The selection of medication added to metformin is based on patient preference and clinical characteristics; important clinical characteristics include the presence of established ASCVD and other comorbidities such as heart failure or CKD; the risk for specific adverse medication effects, particularly hypoglycemia and weight gain; and safety, tolerability, and cost
- Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost
- In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin; for patients with extreme and symptomatic hyperglycemia, insulin is recommended
- Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin
- Access, treatment cost, and insurance coverage should all be considered when selecting glucose-lowering medications

Diabetes Canada guidelines for family physicians

The following clinical practice guidelines for family physicians caring for patients with type 2 diabetes mellitus were released in 2018 by Diabetes Canada[401] :

- Patients without clinical cardiovascular disease (CVD) who fail to achieve glycemic targets with existing antihyperglycemic drug therapy and in whom reduced risk of hypoglycemia and weight gain are priorities should be considered for add-on treatment with incretin agents (dipeptidyl peptidase IV [DPP-4] inhibitors or glucagonlike peptide–1 [GLP-1] agonists) or selective sodium-glucose transporter–2 (SGLT-2) inhibitors, as alternatives to insulin secretagogues, insulin, and thiazolidinediones (TZDs)
- Patients without clinical cardiovascular disease (CVD) who fail to achieve glycemic targets with existing antihyperglycemic drug therapy should additionally receive an antihyperglycemic agent with demonstrated cardiovascular (CV) outcome benefit (such as empagliflozin or liraglutide) to decrease the likelihood of major CV events
- In patients who fail to achieve glycemic targets with existing noninsulin antihyperglycemic drug therapy, consider adding a once-daily basal insulin regimen as an alternative to premixed insulin or bolus-only regimens, as a means of reducing weight gain and hypoglycemia
- To decrease the likelihood of nocturnal and symptomatic hypoglycemia, long-acting insulin analogues should be considered as an alternative to neutral protamine Hagedorn (NPH) insulin
- Patients receiving insulin who fail to achieve glycemic targets should undergo dose adjustment or the administration of additional antihyperglycemic medication (noninsulin or bolus insulin), with the following kept in mind: (1) to achieve better glycemic control with weight loss and a lower hypoglycemia risk than with single- or multiple-bolus insulin injections, consider administering a GLP-1 agonist as add-on treatment prior to initiating bolus insulin or intensifying insulin therapy; (2) consider add-on therapy with an SGLT-2 inhibitor as a means of improving glycemic control with weight loss and reducing the likelihood of hypoglycemia, compared with the administration of additional insulin; (3) consider add-on therapy with a DPP-4 inhibitor as a means of improving glycemic control without weight gain or greater likelihood of hypoglycemia, compared with the administration of additional insulin
- All persons with diabetes should engage in a comprehensive, multifaceted approach to CV risk reduction, including the following: (1) hemoglobin A1c (HbA1c) target of ≤7.0% instigated early in the course of diabetes; (2) systolic and diastolic

blood pressure (BP) of < 130 mm Hg and < 80 mm Hg, respectively; (3) additional vascular protective medications in most adults with diabetes; (4) reaching and maintaining a healthy weight; (5) engaging in healthy nutrition; (6) regular physical activity; (7) smoking cessation

- To lower the CV risk in adults with type 1 or type 2 diabetes, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be employed at vascular-protective doses when any of the following exist (note: among women with childbearing potential, ACE inhibitors, ARBs, or statins should be used only in the presence of reliable contraception): (1) clinical CVD, (2) age >55 y with an additional CV risk factor or end organ damage (albuminuria, retinopathy, left ventricular hypertrophy), (3) microvascular complications
- To prevent CV events in patients with established CVD, employ low-dose acetylsalicylic acid (ASA) therapy (81-162 mg)
- The failure of existing antihyperglycemic drug therapy to achieve glycemic targets In adults with type 2 diabetes with clinical CVD should prompt the addition of an antihyperglycemic agent with demonstrated CV outcome benefit (such as empagliflozin or liraglutide) to lower the risk of major CV events
- The failure of existing antihyperglycemic drug therapy to achieve glycemic targets in older people with type 2 diabetes who have no other complex comorbidities (but who do have clinical CVD) can prompt the addition of an antihyperglycemic agent with demonstrated CV outcome benefit (such as empagliflozin or liraglutide) to lower the risk of major CV events
- Interprofessional teams should provide collaborative care for individuals with diabetes and depression to improve the following: (1) depressive symptoms, (2) adherence to the use of antidepressant and noninsulin antihyperglycemic medications, (3) glycemic control
- Psychosocial interventions, including the following, should be woven into diabetes care plans: (1) motivational interventions, (2) stress management strategies, (3) coping skills training, (4) family therapy, (5) case management
- To achieve better glycemic control and lower the risk of CVD and overall mortality, patients with diabetes should, over the course of at least 3 days per week, engage in a minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise, with no more than 2 consecutive nonexercise days; glycemic control can also be aided, though to a lesser extent, by 90-140 minutes per week of exercise or planned physical activity
- In patients with type 2 diabetes who are able to perform interval training, this form of physical activity (in which short periods of vigorous exercise are alternated with short recovery periods employing low to moderate intensity or rest) can be recommended to aid cardiorespiratory fitness
- Resistance exercise should be performed by patients with diabetes, including elderly ones, two or (preferably) three times per week
- As a means of increasing physical activity and improving HbA1c levels, a patient with diabetes and his/her health-care provider should collaborate on setting exercise goals, resolving potential barriers to exercise, and determining where and when the patient should exercise, with self-monitoring performed
- Timely education aimed at improving self-care practices and behavior should be offered to patients with diabetes
- Self-management aimed at improving glycemic control can be technologically supported, including with Internet-based computer programs and glucose-monitoring systems, brief text messages, and mobile applications

Endocrine Society guidelines on diabetes management in older adults

In 2019, the Endocrine Society released the following clinical practice guidelines on the diagnosis and management of diabetes and its comorbidities in older adults[402, 403] :

- Screening for diabetes or prediabetes with the fasting plasma glucose test or HbA1c analysis is recommended for patients aged 65 years or older without known diabetes
- A 2-hour glucose post–oral glucose tolerance test is suggested for patients aged 65 years or older without known diabetes in whom results from fasting plasma glucose or HbA1c analysis have indicated that prediabetes is present
- To delay the onset of diabetes, it is recommended that patients aged 65 years or older with prediabetes adopt a lifestyle in line with that presented in the Diabetes Prevention Program
- It is recommended that patients aged 65 years or older with diabetes participate in outpatient regimens specifically conceived to minimize hypoglycemia
- Lifestyle modification is recommended as the first-line treatment for hyperglycemia in ambulatory individuals aged 65 years or older with diabetes
- Nutritional status assessment for the detection and management of malnutrition is recommended in patients aged 65 years or older with diabetes
- It is recommended that along with lifestyle changes, patients aged 65 years or older with diabetes undergo initial oral drug treatment with metformin, for glycemic management; significant kidney function impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or gastrointestinal intolerance should preclude implementation of this recommendation
- If metformin therapy and lifestyle changes have not led a patient aged 65 years or older with diabetes to achieve his/her glycemic target, it is recommended that metformin treatment be combined with therapy employing other oral or injectable agents and/or insulin
- To reduce the risk of cardiovascular disease outcomes, stroke, and progressive chronic kidney disease, it is recommended that the target blood pressure in patients aged 65-85 years with diabetes be 140/90 mm Hg
- It is recommended that an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker be administered as first-line therapy in patients aged 65 years or older with diabetes and hypertension

- Statin therapy and an annual lipid profile are recommended in patients aged 65 years or older with diabetes to reduce absolute cardiovascular disease events and all-cause mortality
- For detection of retinal disease, annual comprehensive eye examinations are recommended for patients aged 65 years or older with diabetes
- It is recommended that patients aged 65 years or older with diabetes who are not on dialysis be screened annually for chronic kidney disease, with determination of the estimated glomerular filtration rate and urine albumin-to-creatinine ratio

ESC guidelines on CVD management and prevention

In September 2019, the European Society of Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes (EASD), released updated guidelines aimed at managing and preventing cardiovascular disease (CVD) in patients with diabetes or prediabetes. Patient CV risk is classified in the guidelines as follows[404] :

- Medium CV risk - Young patients without other CV risk factors who have had diabetes for less than 10 years
- High CV risk - Patients who lack target-organ damage but have had diabetes for over 10 years and in whom at least one other risk factor exists
- Very high CV risk - Patients with CVD or target-organ damage or in whom type 1 diabetes has been present for more than 20 years

The recommendations include the following[404] :

- In drug-naïve patients with type 2 diabetes and established CVD, administration of a sodium-glucose cotransporter–2 (SGLT-2) inhibitor or glucagonlike peptide-1 (GLP-1) receptor agonist should be immediately initiated or added to existing metformin treatment
- Based on a cardiovascular outcome trial (CVOT), it is recommended that aspirin be used in high- and very high–risk patients (on an individual basis) but not in moderate-risk patients
- Very high–risk patients in whom low-density lipoprotein (LDL) cholesterol levels are persistently high even with maximal statin and ezetimibe therapy or who have statin intolerance should undergo proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor treatment
- An HbA1c level of under 7% is advised, particularly in young adults who have had diabetes for only a short time
- In patients with medium, high, and very high CV risk, lipid targets of 2.5 mmol/L, 1.8 mmol/L, and below 1.4 mmol/L, respectively, are recommended

Expert panel: management of diabetes in patients with coronavirus disease 2019 (COVID-19)

Recommendations for the management of diabetes in patients with COVID-19 were published on April 23, 2020, by an international panel of diabetes experts.[405, 406]

Regarding infection prevention and outpatient care:

- Patients with diabetes, particularly those with type I diabetes mellitus, should be sensitized to the importance of optimal metabolic control
- Current therapy should, if appropriate, be optimized
- Telemedicine and connected health models should be used, if possible, to maintain maximal self-containment

All patients hospitalized with COVID-19 should be monitored for new-onset diabetes.

Regarding management in the intensive care unit (ICU) of infected patients with diabetes:

- Plasma glucose monitoring, electrolytes, pH, blood ketones, or β-hydroxybutyrate
- There is liberal indication for early intravenous insulin therapy in severe disease courses (acute respiratory distress syndrome, hyperinflammation) for exact titration, with variable subcutaneous resorption avoided, and management of commonly encountered very high insulin consumption

Therapeutic goals include the following:

- Plasma glucose concentration: 4-8 mmol/L (72-144 mg/dL) for outpatients or 4-10 mmol/L (72-180 mg/dL) for inpatients/intensive care, with, for frail individuals, the lower value possibly adjusted upward to 5 mmol/L (90 mg/dL)
- A1c < 53 mmol/mol (7%)
- Continuous glucose monitoring/flash glucose monitoring targets: Time-in-range (3.9-10 mmol/L) >70% of time (or >50% in frail and older patients)
- Hypoglycemia < 3.9 mmol/L (< 70 mg/dL): < 4% (< 1% in frail and older patients)

The panel advises stopping administration of metformin and sodium-glucose cotransporter–2 (SGLT2) inhibitors in patients with COVID-19 and type 2 diabetes in order to lower the risk of acute metabolic decompensation.

Fluid balance requires considerable care, “as there is a risk that excess fluid can exacerbate pulmonary edema in the severely inflamed lung.”

Potassium balance requires careful consideration in the context of insulin treatment, “as hypokalemia is a common feature in COVID-19,” with initiation of insulin possibly exacerbating it.

The panel recommends screening for hyperinflammation, owing to the possibility of increased risk for cytokine storm and severe COVID-19 in patients with type 2 diabetes and fatty liver disease.

ADA guidelines on pharmacologic means of glycemic therapy in type 2 diabetes

In September 2020, the ADA published clinical guidelines on pharmacologic means of glycemic therapy in type 2 diabetes. They include the following:

- Metformin therapy is the preferred initial pharmacologic treatment for type 2 diabetes
- To extend the time to treatment failure, early combination therapy can, in some patients, be considered at treatment initiation
- If evidence of ongoing catabolism exists (weight loss), if symptoms of hyperglycemia are present, or when HbA1c or blood glucose levels are very high (HbA1c >10% [86 mmol/mol], blood glucose ≥16.7 mmol/L [300 mg/dL]), consider early introduction of insulin
- Employ a patient-centered approach to guide the choice of pharmacologic agents, with factors such as cardiovascular comorbid conditions, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences taken into account
- It is recommended that a sodium-glucose cotransporter–2 (SGLT2) inhibitor or glucagonlike peptide-1 receptor agonist (GLP-1 RA) with demonstrated cardiovascular disease benefit be administered to patients with type 2 diabetes who have established atherosclerotic cardiovascular disease (ASCVD), indicators of high ASCVD risk, established kidney disease, or heart failure
- The use of GLP-1 RAs, when possible, is preferred over insulin therapy in the treatment of patients with type 2 diabetes who need greater glucose reduction than oral agents can provide
- Reevaluate the patient’s medication regimen and medication-taking behavior every 3 to 6 months, adjusting them as needed to incorporate specific factors that affect treatment choice

AACE guidelines for use of advanced technology

In May 2021, the American Association of Clinical Endocrinology (AACE) released guidelines on the use of advanced technologies in diabetes management. The following recommendations are among those published.[407, 408]

The percentage of time in range (%TIR) and below range (%TBR) should serve as a starting point for the evaluation of the quality of glycemic control and form the basis for therapy adjustment.

For all persons with diabetes who are undergoing intensive insulin therapy (ie, three or more injections of insulin per day or treatment with an insulin pump), continuous glucose monitoring (CGM) is strongly recommended. For individuals on insulin therapy for whom success with CGM has been limited (or for those who are unable or unwilling to use CGM), structured self-monitoring of blood glucose (SMBG) is recommended. CGM is recommended for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness), for children/adolescents with type 1 diabetes; for pregnant women with type 1 or type 2 diabetes treated with intensive insulin therapy, and for women with gestational diabetes mellitus (GDM) on insulin therapy. CGM may be recommended for women with GDM who are not undergoing insulin treatment and for individuals with type 2 diabetes who are undergoing less intensive insulin therapy.

For persons with diabetes who have problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness) and need predictive alarms/alerts, real-time CGM (rtCGM) should be recommended over intermittently scanned CGM (isCGM). Consideration should also be given, however, to a patient’s lifestyle and to other factors.

The management of persons with diabetes who meet one or more of the following criteria should entail the use of diagnostic/professional CGM:

- Newly diagnosed with diabetes mellitus
- Not using CGM
- No access to personal CGM, despite having problematic hypoglycemia
- Persons with type 2 diabetes who, although undergoing non-insulin therapy, would derive educational benefit from episodic use of CGM
- Persons who, before committing to daily use of CGM, wish to know more about it

Importantly, continued adjunctive use of SMBG must be employed by patients who are using “masked” or “blinded” diagnostic/professional CGM, to assist in daily diabetes self-care.

Persons with diabetes in whom glycemic targets are being reached with minimal TBR, infrequent episodes of symptomatic hypoglycemia are being reported, and SMBG is being used on a regular basis (at least 4 times daily for persons with type 1 diabetes) could employ an insulin pump without CGM.

In all persons with diabetes who are undergoing intensive insulin management but who prefer to forgo the use of automated insulin suspension/dosing systems or have no access to them, use of an insulin pump with CGM or a sensor-augmented pump (SAP) is recommended.

To reduce hypoglycemia's severity and duration in persons with type 1 diabetes, low-glucose suspend (LGS) is strongly recommended; for mitigation of hypoglycemia in these patients, predictive low-glucose suspend (PLGS) is strongly recommended.

It is strongly recommended that all persons with type 1 diabetes use automated insulin dosing (AID) systems; these have been shown to raise the TIR, especially in the overnight period, without increasing the hypoglycemia risk.

In persons with diabetes who are hospitalized but are suffering no cognitive impairment, consideration should be given to the continuation of CGM and/or continuous subcutaneous insulin injection (CSII) (insulin pump, SAP, LGS/PLGS). The presence of a family member who is knowledgeable and educated in the use of these devices or the availability of a specialized inpatient diabetes team for advice and support is ideal in such situations.

To enable persons aged 65 years or older with insulin-requiring diabetes to improve glycemic control, reduce episodes of severe hypoglycemia, and improve quality of life, use of rtCGM is recommended. Owing, however, to this population's increased comorbidities and lowered capacity to detect and counter-regulate against severe hypoglycemia, glycemic goals should be individualized.

As a means of tracking glucose before, during, and after exercise in persons with diabetes; monitoring the glycemic response to exercise; and helping to direct insulin and carbohydrate consumption to prevent the development of hypoglycemia and hyperglycemia, clinicians should prescribe CGM.

It is strongly recommended that telemedicine be used in the treatment of diabetes, provision of diabetes education, remote monitoring of glucose and/or insulin data, and improvement of diabetes-related outcomes/control.

As a means of teaching/reinforcing diabetes self-management skills, encouraging engagement, and supporting/encouraging desired health behaviors, clinically validated smartphone applications should be recommended to persons with diabetes.

Comprehensive training in the proper use and care of insulin delivery technology should be provided to all persons with diabetes using that equipment.

It is strongly recommended that, in the absence of pump therapy, FDA-cleared and clinically validated smartphone bolus calculators be used to reduce the frequency of hypoglycemia or severe postprandial hyperglycemia.

SID/AMD treatment guidelines

Clinical guidelines on the treatment of type 2 diabetes mellitus were published in March 2022 by the Società Italiana di Diabetologia (SID) and the Associazione Medici Diabetologi (AMD). They include the following[409] :

- In patients with type 2 diabetes who are undergoing treatment with drugs that can induce hypoglycemia, it is recommended that the target hemoglobin A1c (HbA1c) level be between 49 mmol/mol (6.6%) and 58 mmol/mol (7.5%)
- In patients with type 2 diabetes who are undergoing treatment with drugs that cannot induce hypoglycemia, it is recommended that the target HbA1c level be below 53 mmol/mol (7%)
- It is suggested that structured medical nutrition therapy (made up of nutritional assessment, diagnosis, intervention, and monitoring) be employed in type 2 diabetes treatment
- Regular physical exercise is suggested for type 2 diabetes treatment
- Combined (aerobic and resistance) training, rather than aerobic training alone, is suggested for type 2 diabetes treatment
- In patients with type 2 diabetes who have not had previous cardiovascular events, metformin is recommended as a first-line, long-term treatment; as second-line agents, sodium-glucose cotransporter-2 (SGLT-2) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists are recommended, while as third-line treatments, consideration should be given to pioglitazone, dipeptidyl peptidase 4 (DPP-4) inhibitors, acarbose, and insulin
- In patients with type 2 diabetes with previous cardiovascular events but without heart failure, the use of metformin, SGLT-2 inhibitors, or GLP-1 receptor agonists is recommended as first-line, long-term treatment; as second-line treatments, consideration should be given to DPP-4 inhibitors, pioglitazone, acarbose, and insulin
- In patients with type 2 diabetes who have suffered previous heart failure, SGLT-2 inhibitors are recommended for first-line, long-term treatment; consideration should be given to GLP-1 receptor agonists and metformin as second-line treatments, and to DPP-4 inhibitors, acarbose, and insulin as third-line treatments
- It is recommended that all patients with type 2 diabetes who require treatment with basal insulin receive basal insulin analogues rather than neutral protamine Hagedorn (NPH) insulin

- It is not suggested that in patients with type 2 diabetes who are on basal-bolus insulin therapy, continuous glucose monitoring (continuous or on demand) instead of self-monitoring of blood glucose be practiced

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Medication

Medication Summary

Pharmacologic therapy of type 2 diabetes has changed dramatically in the last 10 years, with new drugs and drug classes becoming available. These drugs allow for the use of combination oral therapy, often with improvement in glycemic control that was previously beyond the reach of medical therapy.

Agents used in diabetic therapy include the following:

- Biguanides
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Glucagonlike peptide–1 (GLP-1) agonists
- GLP-1 and glucose-dependent insulinotropic polypeptide agonists
- Dipeptidyl peptidase IV (DPP-4) Inhibitors
- Selective sodium-glucose transporter-2 (SGLT-2) inhibitors
- Insulins
- Amylinomimetics
- Bile acid sequestrants
- Dopamine agonists

Traditionally, diet modification has been the cornerstone of diabetes management. Weight loss is more likely to control glycemia in patients with recent onset of the disease than in patients who are significantly insulinopenic. Medications that induce weight loss, such as orlistat, may be effective in highly selected patients but are not generally indicated in the treatment of the average patient with type 2 diabetes mellitus.

Patients who are symptomatic at initial presentation with diabetes may require transient treatment with insulin to reduce glucose toxicity (which may reduce beta-cell insulin secretion and worsen insulin resistance) or an insulin secretagogue to rapidly relieve symptoms such as polyuria and polydipsia.

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Antidiabetics, Biguanides

Class Summary

These agents are considered the first choice for oral type 2 diabetes treatment. They reduce hyperglycemia by decreasing hepatic gluconeogenesis (primary effect) and increasing peripheral insulin sensitivity (secondary effect). They do not increase insulin levels or cause weight gain. Alone, they rarely cause hypoglycemia.

Biguanides are absorbed from the intestines and are not bound to plasma proteins. They are not metabolized and are rapidly eliminated by the kidneys. Drug levels increase markedly in renal insufficiency. Lactic acidosis is a rare, but serious,

complication that may occur with drug accumulation.

Metformin (Glucophage, Fortamet, Glumetza, Riomet)

Metformin is used as monotherapy or in combination with sulfonylureas, thiazolidinediones, or insulin. It is taken with food to minimize adverse GI effects. Metformin is available in immediate-release and extended-release formulations, as well as in combination with other antidiabetic drugs.

Metformin is contraindicated in patients with impaired renal function, as indicated by a serum creatinine level of greater than 1.5 mg/dL in men or of more than 1.4 mg/dL in women, or an estimated GFR of less than 60 mL/min. It also should not be used within 48 hours of IV iodinated contrast medium.

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Antidiabetics, Sulfonylureas

Class Summary

Sulfonylureas are time-honored insulin secretagogues (ie, oral hypoglycemic agents). They have been used as monotherapy and in combination with other oral hypoglycemic agents or with insulin, although glimepiride is the only sulfonylurea approved by the FDA for combination therapy. Sulfonylureas function by stimulating the release of insulin from pancreatic beta cells and can usually reduce HbA1c by 1-2% and blood glucose concentrations by about 20%.

Glyburide (DiaBeta, Glynase)

Glyburide is a second-generation sulfonylurea. It is more potent and exhibits fewer drug interactions than first-generation agents. It also has a longer half-life than most sulfonylureas., Glyburide has been used as an alternative to insulin for the treatment of gestational diabetes, although it is not FDA approved for this indication. Glyburide (known as glibenclamide in the United Kingdom) was one of the sulfonylureas used in the United Kingdom Prospective Diabetes Study (UKPDS).[63]

Glipizide (Glucotrol, Glucotrol XL)

Glipizide is also a second-generation sulfonylurea. It is more potent and exhibits fewer drug interactions than first-generation agents. It may cause more physiologic insulin release with less risk for hypoglycemia and weight gain than other sulfonylureas.

Glimepiride (Amaryl)

Stimulates insulin secretion from beta cells; may also decrease rate of hepatic glucose production and increase insulin receptor sensitivity.

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Antidiabetics, Meglitinide Derivatives

Class Summary

Meglitinides are much more short-acting insulin secretagogues than sulfonylureas. Preprandial dosing potentially achieves more physiologic insulin release and less risk for hypoglycemia. Meglitinide monotherapy has efficacy similar to that of sulfonylureas.

Repaglinide (Prandin)

Repaglinide is probably most useful in patients at increased risk for hypoglycemia who still need an insulin secretagogue. It works by stimulating insulin release from pancreatic beta cells. Better control of postprandial glycemic excursions also may be

achieved with repaglinide. It is FDA approved for monotherapy and for combination therapy with metformin or thiazolidinediones.

Nateglinide (Starlix)

Nateglinide mimics endogenous insulin patterns, restores early insulin secretion, and controls mealtime glucose surges. It works by stimulating insulin release from pancreatic beta cells. It is indicated as monotherapy for type 2 diabetes or as combination therapy with metformin or a thiazolidinedione. Nateglinide is available in 60-mg and 120-mg tablets.

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Antidiabetics, Alpha-Glucosidase Inhibitors

Class Summary

Alpha-glucosidase inhibitors prolong the absorption of carbohydrates and thus help to prevent postprandial glucose surges. Their induction of flatulence greatly limits their use. Doses of these agents should be titrated slowly to reduce GI intolerance. Their effect on glycemic control is modest, affecting primarily postprandial glycemic excursions.

Acarbose (Precose)

Acarbose was the first alpha-glucosidase inhibitor approved by the FDA. It is absorbed to a small degree, so liver function abnormalities can occur rarely. It can be used as monotherapy or in combination with other treatment modalities. The modest effect of acarbose on glycemia and its high degree of GI adverse effects (flatulence) limit its use.

Miglitol (Glyset)

Miglitol is not absorbed, so liver function abnormalities do not occur. It is FDA approved for use as monotherapy or in combination with sulfonylureas. Its modest effect on glycemia and high degree of GI adverse effects (flatulence) limit its use.

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Antidiabetics, Thiazolidinediones

Class Summary

Thiazolidinediones reduce insulin resistance in the periphery (ie, they sensitize muscle and fat to the actions of insulin) and perhaps to a small degree in the liver (ie, insulin sensitizers, antihyperglycemics). They activate peroxisome proliferator–activated receptor (PPAR) gamma, a nuclear transcription factor that is important in fat cell differentiation and fatty acid metabolism. The major action of thiazolidinediones is probably actually fat redistribution. These drugs may have beta-cell preservation properties.

Thiazolidinediones have moderate glycemic efficacy, between that of alpha-glucosidase inhibitors and sulfonylureas.

Pioglitazone (Actos)

Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control. It improves target-cell response to insulin without increasing insulin secretion from the pancreas. It also increases insulin-dependent glucose use in skeletal muscle and adipose tissue. Pioglitazone lowers triglycerides more than rosiglitazone, probably because of its PPAR-alpha effect.

Long duration of pioglitazone use and high cumulative doses have been linked with slightly increased risk for bladder cancer. The FDA currently recommends not prescribing pioglitazone for patients with active bladder cancer and using it with caution in patients with a history of bladder cancer.

Rosiglitazone (Avandia)

Rosiglitazone is an insulin sensitizer with a major effect on the stimulation of glucose uptake in skeletal muscle and adipose tissue. It lowers plasma insulin levels. It is indicated for type 2 diabetes associated with insulin resistance, as monotherapy and in conjunction with sulfonylureas and/or metformin and insulin. It may preserve beta-cell function and yields positive effects on vasculature and inflammation. It changes LDL and HDL particle size.

Because of data suggesting an elevated risk of myocardial infarction in patients treated with rosiglitazone, this agent is currently available only via a restricted access program. Patients currently taking rosiglitazone and benefiting from the drug are permitted to continue using it if they choose to do so. Rosiglitazone is available to new patients only if they are unable to achieve glucose control on other medications and are not willing to take pioglitazone, the only other thiazolidinedione.

As of November 18, 2011, rosiglitazone was no longer available in retail pharmacies. It can be purchased only through specially certified pharmacies participating in the Avandia-Rosiglitazone Medicines Access Program.

Antidiabetics, Glucagonlike Peptide-1 Agonists

Class Summary

Glucagonlike peptide–1 (GLP-1) agonists mimic the endogenous incretin GLP-1, stimulating glucose-dependent insulin release (as opposed to oral insulin secretagogues, which may cause non–glucose-dependent insulin release and hypoglycemia), reducing glucagon, and slowing gastric emptying.

Semaglutide (Ozempic, Rybelsus)

When blood glucose is high, semaglutide, a GLP-1 receptor agonist, lowers it by stimulating insulin secretion and reducing glucagon secretion. It may be administered as a once daily oral tablet or a weekly SC injection. The SC product is also indicated for cardiovascular risk reduction in adults with type 2 diabetes mellitus and heart disease.

Exenatide injectable solution (Byetta)

Exenatide is a GLP-1 agonist that improves glycemic control in patients with type 2 diabetes mellitus. Like endogenous incretins, it enhances glucose-dependent insulin secretion by pancreatic beta cells, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. The drug's 39–amino acid sequence partially overlaps that of the human incretin GLP-1.

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who have not achieved glycemic control with metformin or a sulfonylurea. The solution is an immediate-release product administered by SC injection twice daily.

Exenatide injectable suspension (Bydureon, Bydureon BCise)

The injectable suspension is administered SC once weekly. The patient does not need to have undergone treatment with Byetta (short-acting exenatide injectable solution) prior to initiating therapy with the injectable suspension. Treatment with Byetta should be discontinued if it is already being used when Bydureon or Bydureon BCise (autoinjector) therapy is started.

Liraglutide (Victoza, Saxenda)

Liraglutide is a once-daily SC injectable GLP-1 receptor agonist that stimulates G-protein in pancreatic beta cells. It increases intracellular cyclic adenosine monophosphate (cAMP), leading to insulin release in the presence of elevated glucose concentrations. Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. In addition, evidence from the LEADER clinical trial resulted in liraglutide’s approval for risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

It is also indicated for children aged 10 years or older with type 2 diabetes mellitus.

The drug has not been studied in combination with prandial insulin.

Liraglutide is not recommended as first-line pharmacologic therapy, because of potential serious adverse effects. Liraglutide is contraindicated in patients with a history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, as dose- and duration-dependent thyroid C-cell tumors have occurred in animal studies of liraglutide.

In addition, clinical studies suggest that liraglutide may cause pancreatitis, although conclusive evidence has not been established. Nevertheless, patients should be monitored for unexplained, persistent, severe abdominal pain, with or without vomiting, and liraglutide should be discontinued if pancreatitis is suspected.

Note that the brand Saxenda is not indicated for the treatment of type 2 diabetes mellitus. Used as an adjunct to a reduced-calorie diet and increased physical activity, Saxenda is indicated for chronic weight management in adults with a BMI of 30 kg/m2 or greater (obesity) or adults with a BMI of 27-29.9 kg/m2 (overweight) and one or more weight-associated conditions (eg, hypertension, type 2 diabetes, dyslipidemia). Saxenda may also be prescribed for persons with overweight and a risk factor for type 2 diabetes. Do not use Saxenda in combination with another GLP-1 agonist or with insulin.

Albiglutide (Tanzeum)

Albiglutide is a once-weekly SC injectable GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It may be used with other antidiabetic agents, although a dose reduction may be needed for insulin secretagogues (eg, sulfonylureas) or insulin if coadministered. GLP-1 receptor agonists augment glucose-dependent insulin secretion.

Dulaglutide (Trulicity)

Dulaglutide is a glucagonlike peptide-1 (GLP-1) agonist that acts as an incretin mimetic. It increases insulin secretion in the presence of elevated blood glucose, delays gastric emptying to decrease postprandial glucose, and decreases glucagon secretion. It is administered as a once-weekly SC injection. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is also indicated for major adverse cardiovascular (CV) event reduction (with regard to CV death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus in whom established CV disease or multiple CV risk factors exist.

Lixisenatide (Adlyxin)

GLP-1 agonist indicated as adjunctive therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is administered as a once daily SC injection.

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Dual GIP/GLP-1 Agonists

Class Summary

Glucagon-like peptide-1 (GLP-1) receptors are expressed in pancreatic beta cells and the gastrointestinal tract. Signaling elicited by GLP-1 enhances glucose-stimulated insulin secretion, delays gastric transit, decreases plasma glucagon levels, and reduces body weight through activation of the brain’s anorexigenic pathways. Involved in glucose homeostasis, the peptide hormones glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 impact the pancreatic beta cells, promoting glucose-stimulated insulin secretion from these. Additionally, GIP responds to food intake by exerting insulinotropic effects.

Tirzepatide (Mounjaro)

Indicated, in adults with type 2 diabetes mellitus, for the improvement of glycemic control, serving as an adjunct to diet and exercise.

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Antidiabetics, Dipeptidyl Peptidase IV Inhibitors

Class Summary

Incretin hormones are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. They increase insulin release and decrease glucagon levels in the circulation in a glucose-dependent manner. DPP-4 degrades numerous biologically active peptides, including the endogenous incretins GLP-1 and glucose-dependent insulinotropic peptide (GIP). DPP-4 inhibitors prolong the action of incretin hormones.

Sitagliptin (Januvia)

Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses. Sitagliptin can be used as a monotherapy or in combination with metformin or a thiazolidinedione. It is given once daily and is weight neutral.

Saxagliptin (Onglyza)

Saxagliptin inhibits DPP-4 and thereby increases concentrations of GLP-1 and GIP, which stimulate insulin release in response to increased blood glucose levels following meals. This action enhances glycemic control. Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Linagliptin (Tradjenta)

Linagliptin is a DPP-4 inhibitor that increases and prolongs incretin hormone activity. It is indicated for adults with type 2 diabetes mellitus, along with diet and exercise, to lower blood glucose levels. It may be used as monotherapy or in combination with other common antidiabetic medications, including metformin, sulfonylurea, or pioglitazone; it has not been studied in combination with insulin.

Alogliptin (Nesina)

Selective dipeptidyl peptidase-4 (DPP-4) inhibitor; slows inactivation of incretin hormones (eg, GLP-1, GIP), thereby reducing fasting and postprandial glucose concentrations in a glucose-dependent manner

Antidiabetics, Amylinomimetics

Class Summary

These agents mimic endogenous amylin effects by delaying gastric emptying, decreasing postprandial glucagon release, and modulating appetite.

Pramlintide (Symlin, SymlinPen 120, SymlinPen 60)

This agent is a synthetic analogue of human amylin, a naturally occurring hormone made in pancreatic beta cells. It slows gastric emptying, suppresses postprandial glucagon secretion, and regulates food intake because of centrally mediated appetite modulation.

Pramlintide is indicated for the treatment of type 1 or type 2 diabetes in combination with insulin. It is administered before mealtime in patients who have not achieved desired glucose control despite optimal insulin therapy. It helps to achieve lower blood glucose levels after meals, less fluctuation of blood glucose levels during the day, and improvement of long-term control of glucose levels (ie, HbA1C levels), compared with insulin alone. Additionally, less insulin use and a reduction in body weight are observed.

Selective Sodium-Glucose Transporter-2 Inhibitors

Class Summary

These agents lower the renal glucose threshold.

Canagliflozin (Invokana)

Canagliflozin is an SGLT-2 inhibitor and lowers the renal glucose threshold (ie, the plasma glucose concentration that exceeds the maximum glucose reabsorption capacity of the kidney). Lowering the renal glucose threshold results in increased urinary glucose excretion. Indicated as an adjunct to diet and exercise, canagliflozin therapy is aimed at improving glycemic control in adults with type 2 diabetes. In addition, in adults with type 2 diabetes and diabetic nephropathy with albuminuria of more than 300 mg/day, canagliflozin is indicated to lower the chances of end-stage renal disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure.

Dapagliflozin (Farxiga)

Dapagliflozin reduces glucose reabsorption in the proximal renal tubules and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. It is indicated as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus. It is indicated as monotherapy, as initial therapy with metformin, or as an add-on to other oral glucose-lowering agents, including metformin, pioglitazone, glimepiride, sitagliptin, and insulin. It is also indicated to lower the risk of adults with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors being hospitalized for heart failure.

Empagliflozin (Jardiance)

Empagliflozin, an SGLT2 inhibitor, decreases blood glucose by increasing urinary glucose excretion. SGLT-2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. SGLT2 inhibitors reduce glucose reabsorption and lower the renal threshold for glucose.

It is indicated as an adjunct to diet and exercise, empagliflozin therapy is aimed at improving glycemic control in adults with type 2 diabetes. It is also indicated for lowering the cardiovascular death risk in adults with type 2 diabetes and cardiovascular disease.

Ertugliflozin (Steglatro)

An SGLT2 inhibitor, ertugliflozin is indicated for improvement of glycemic control in adults with type 2 diabetes, serving as an adjunct to diet and exercise. It can also be found in the combination products ertugliflozin plus metformin and ertugliflozin plus sitagliptin.

Bile Acid Sequestrants

Class Summary

Colesevelam is FDA approved as an adjunctive therapy to improve glycemic control in adults with type 2 diabetes mellitus.

Colesevelam (WelChol)

Colesevelam is a high-capacity bile acid sequestrant. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The precise mechanism by which colesevelam improves glycemic control is largely unknown.

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Antidiabetics, Rapid-Acting Insulins

Class Summary

Rapid-acting insulins have a short duration of action and are appropriate for use before meals or when blood glucose levels exceed target levels and correction doses are needed. These agents are associated with less hypoglycemia than regular insulin.

Insulin aspart (NovoLog, Fiasp)

Insulin aspart has a short onset of action of 5-15 minutes and a short duration of action of 3-5 hours. The peak effect occurs within 30-90 minutes. Insulin aspart is FDA approved for use in insulin pumps.

Fiasp also has a rapid onset of action, with its first measurable effect occurring within 16-20 minutes. The peak effect occurs within 91-133 minutes, and the usual duration of action is 5-7 hours.

Insulin glulisine (Apidra)

Insulin glulisine has a rapid onset of action of 5-15 minutes and a short duration of action of 3-5 hours. The peak effect occurs within 30-90 minutes. Insulin glulisine is FDA approved for use in insulin pumps.

Insulin lispro (Humalog, Admelog, insulin lispro-aabc, Lyumjev)

Insulin lispro has a rapid onset of action of 5-15 minutes and a short duration of action of 4 hours.

Insulin inhaled (Afrezza)

Orally inhaled rapid-acting insulin in powder form. When 8 units were administered, maximum serum insulin concentration was reached by 12-15 minutes and declined to baseline by about 180 minutes.

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Antidiabetics, Short-Acting Insulins

Class Summary

Short-acting insulins are commonly used when a slower onset of action or a longer duration of action is desired.

Regular insulin (Humulin R, Novolin R, Myxredlin)

Regular insulin has a rapid onset of action of 0.5-1 hours and duration of action of 4-6 hours. The peak effects are seen within 2-4 hours. Preparations that contain a mixture of 70% neutral protamine Hagedorn (NPH) and 30% regular human insulin (ie, Novolin 70/30, Humulin 70/30) are also available.

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Antidiabetics, Intermediate-Acting Insulins

Class Summary

Intermediate-acting insulins have a slow onset of action and a longer duration of action. These agents are commonly combined with faster-acting insulins to maximize the benefits of a single injection.

Insulin NPH (Humulin N, Novolin N)

Insulin neutral protamine Hagedorn (NPH) has an onset of action of 3-4 hours. The peak effect occurs within 8-14 hours, and its usual duration of action is 16-24 hours. The drug appears cloudy and must be gently mixed and checked for clumping; if clumping occurs, the insulin should be discarded.

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Antidiabetics, Long-Acting Insulins

Class Summary

These insulins provide a longer duration of action, and, when combined with rapid- or short-acting insulins, they provide better glucose control.

Insulin detemir (Levemir)

Insulin detemir is indicated for once- or twice-daily dosing in patients with type 1 or 2 diabetes mellitus. The duration of action is up to 24 hours, the result of slow systemic absorption of detemir from the injection site.

Insulin glargine (Lantus, Lantus SoloStar, Toujeo, Toujeo Max, Basaglar)

Insulin glargine stimulates proper utilization of glucose by the cells and reduces blood sugar levels. It has no pronounced peaks of action, because a small amount of insulin is gradually released at a constant rate over 24 hours. The amount of insulin in Toujeo and Toujeo Max is three times greater (300 Units/mL) than in Lantus or Basaglar (100 Units/mL).

Insulin degludec (Tresiba)

Ultralong-acting basal insulin indicated to improve glycemic control in adults with diabetes mellitus who require basal insulin. It is highly protein bound, and following SC, the protein-binding provides a depot effect. The elimination half-life is 25 h and its duration of action is beyond 42 h.

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Dopamine Agonists

Class Summary

Quick-release bromocriptine acts on circadian neuronal activities within the hypothalamus to reset the abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in patients with insulin resistance.

Bromocriptine (Cycloset)

This quick-release formulation is the only bromocriptine product indicated for type 2 diabetes mellitus. It is indicated as an adjunct to diet and exercise to improve glycemic control.

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Questions & Answers

Overview

What questions should be included in a focused diabetes history of established type 2 diabetes mellitus (DM)?

What is the dawn phenomenon (effect) in type 2 diabetes mellitus (DM)?

What is included in a diabetes-focused physical exam?

Why is continued measurement of vital signs indicated for type 2 diabetes mellitus (DM)?

What should funduscopic exam for type 2 diabetes mellitus (DM) include?

What is the prevalence at diagnosis of diabetic retinopathy in type 2 diabetes mellitus (DM)?

What are the stages of diabetic retinopathy?

What is the effect of larger retinal arteriolar and venular calibres on cognitive functioning in type 2 diabetes mellitus (DM)?

What is the effect of ruptured intraretinal capillaries in type 2 diabetes mellitus (DM)?

What is the effect of macular edema in type 2 diabetes mellitus (DM)?

What are preproliferative and proliferative diabetic retinopathy?

What are the signs of retinal hemorrhage in type 2 diabetes mellitus (DM) and how can damage be reduced?

What findings should be noted during foot exams for type 2 diabetes mellitus (DM)?

How should type 2 diabetes mellitus (DM) patients be educated regarding foot care if peripheral neuropathy is present?

How are type 1 and type 2 diabetes mellitus (DM) differentiated on the basis of history and physical exam?

DDX

How is diabetes mellitus (DM) type determined?

What is the treatment for diabetes mellitus in the ED when the type is unknown?

How is prediabetes defined?

What causes metabolic syndrome (also called syndrome X or the insulin-resistance syndrome)?

How is metabolic syndrome (also called syndrome X or the insulin-resistance syndrome) diagnosed?

How does metabolic syndrome (also called syndrome X or the insulin-resistance syndrome) progress into insulin resistance?

Workup

What are the ADA diagnostic criteria for diabetes mellitus (DM)?

What tests are needed to confirm a diabetes mellitus (DM) diagnosis if unequivocal hyperglycemia is absent?

What additional testing is required if 2 different test results are discordant for diabetes mellitus (DM) diagnosis?

What testing should be performed in an asymptomatic patient with random serum glucose level that suggests diabetes mellitus (DM)(>140 mg/dL)?

What HbA1c levels are considered diagnostic for prediabetes and diabetes mellitus (DM)?

What testing is done in the ED for all patients with diabetes mellitus (DM)?

How is a plasma glucose level determined?

How does a serum glucose measurement compare to a plasma glucose measurement in diabetes mellitus (DM)?

How are capillary whole blood measurements used in the diagnosis of diabetes mellitus (DM)?

How are fasting glucose measurements used in the diagnosis of diabetes mellitus (DM)?

What are the WHO diagnostic criteria for impaired glucose tolerance?

What timespan does glycated hemoglobin measurements reflect?

Treatment

Guidelines

What are the ESC guidelines on cardiovascular disease (CVD) management and prevention in patients with diabetes or prediabetes?

What expert panel recommendations have been put forward on the management of diabetes mellitus (DM) in patients with coronavirus disease 2019 (COVID-19)?

What are the ADA guidelines on the pharmacologic means of glycemic therapy in type 2 diabetes mellitus (DM)?

What are the AACE guidelines for the use of advanced technology in the management of diabetes mellitus (DM)?

Medications

What drugs are used in the treatment of type 2 diabetes mellitus (DM)?

When are weight loss medications indicated in the treatment of type 2 diabetes mellitus (DM)?

What is the initial treatment for symptomatic patients with type 2 diabetes mellitus (DM)?

Which medications in the drug class Antidiabetics, Biguanides are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Sulfonylureas are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Meglitinide Derivatives are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Alpha-Glucosidase Inhibitors are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Thiazolidinediones are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Glucagonlike Peptide-1 Agonists are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Dual GIP/GLP-1 Agonists are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Dipeptidyl Peptidase IV Inhibitors are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Amylinomimetics are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Selective Sodium-Glucose Transporter-2 Inhibitors are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Bile Acid Sequestrants are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Rapid-Acting Insulins are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Short-Acting Insulins are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Intermediate-Acting Insulins are used in the treatment of Type 2 Diabetes Mellitus?

Which medications in the drug class Antidiabetics, Long-Acting Insulins are used in the treatment of Type 2 Diabetes Mellitus?

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