САХАРНЫЙ ДИАБЕТ: ОПРЕДЕЛЕНИЕ, ПРОФИЛАКТИКА, ТЕРАПЕВТИЧЕСКИЕ ПОДХОДЫ

DIABETES MELLITUS: DEFINITION, PREVENTION, TREATMENT APPROACHES

Учебно-методическое пособие

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LIST OF ABBREVIATIONS

ADA — American Diabetes Association
BMI — body mass index
CFRD — Cystic fibrosis–related diabetes
CGM — continuous glucose monitoring
CVD — cardiovascular disease
DASH — Dietary Approaches to Stop Hypertension
DCCT — Diabetes Control and Complications Trial
DKA — diabetic ketoacidosis
DPP — Diabetes Prevention Program
DPPOS — Diabetes Prevention Program Outcomes Study
FPG — fasting plasma glucose
GAD — glutamic acid decarboxylase
GDM — gestational diabetes mellitus
HIV — The human immunodeficiency viruses
IA — islet antigen
IFG — impaired fasting glucose
IGT — impaired glucose tolerance
LADA — latent autoimmune diabetes in adults
MODY — maturity-onset diabetes of the young
OGTT — oral glucose tolerance test
NGSP — National Glycohemoglobin Standardization Program
NHANES — National Health and Nutrition Examination Survey
NODAT — New-onset diabetes after transplantation
PPDM — postpancreatitis diabetes mellitus
PTDM — posttransplantation diabetes mellitus
TIR — time in range
WHO — World Health Organization
2-h PG — the 2-h plasma glucose

MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Lesson topic: Diabetes mellitus.

Total class time: 7h.

Diabetes is a complex, chronic condition requiring continuous medical care with multifactorial risk-reduction strategies beyond glucose management. Ongoing diabetes self-management education and support are critical to empowering people, preventing acute complications, and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The purpose is intended to provide clinicians, researchers and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.

Objectives:

1. To acquire a general idea of the pathogenetic features of diabetes mellitus, be able to differentiate various types of the disease.

2. To study the classification of diabetes mellitus.

3. To study diagnostic tests for diabetes mellitus.

4. To study the main directions of diabetes prevention, taking into account lifestyle modification and pharmacological options.

5. Consider the main therapeutic approaches to normalize glycemic levels.

Requirements to the initial level of knowledge. To learn the topic completely student should know:

– main mechanisms regulating blood glucose levels;

– pancreas physiology.

Test questions from related disciplines:

1. Anatomy and topography of the pancreas.

2. Physiological role of insulin, regulation of synthesis and secretion.

Test questions:

1. Definition of the concept of diabetes, main clinical manifestations, mechanisms of development.

2. Classification of diabetes mellitus and differential diagnosis of types.

3. Diagnostic approaches for assessing glycemia: serum glucose, glycated hemoglobin, oral glucose tolerance test.

4. Type 1 diabetes mellitus, diagnostic features, screening and prevention options.

5. Prediabetes — definition of the concept, diagnostic criteria, therapeutic options for correction.

6. Type 2 diabetes mellitus, diagnosis, risk factors for development.

7. The main approaches to the prevention of type 2 diabetes — modification of the image of fat, behavioral programs, nutrition, physical activity.

8. Glycemic targets for diabetes management, including measures of long-term glycemic monitoring.

9. Possibilities of pharmacological treatment of type 2 diabetes.

DEFINITION OF CONCEPT DIABETES

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the pancreatic β-cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (discussed in greater detail below). In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory

insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load or by A1C. Diabetes can be classified into the following general categories.

CLASSIFICATION

The last classification, which is still valid in most countries of the world, was proposed in 1999 and is considered as the etiological classification of DM (table 1).

Table 1

Classification of diabetes mellitus (WHO, 1999)

Type 1 diabetes	Due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood
Type 2 diabetes	Due to a non-autoimmune progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome
Specific types of diabetes	Due to other causes, e. g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
Gestational diabetes mellitus	Diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation

For the first time, the principle of separating the types of DM was proposed depending on the main etiopathogenetic mechanisms that led to the development of hyperglycemia. The need to prescribe insulin no longer determined the type of diabetes. The degree of hyperglycemia (if any) may change over time, depending on the extent of the underlying disease process (fig. 1).

A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose-lowering agents. These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without it. Individuals with extensive

β-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

Stages / Types	Normoglycemia	Hyperglycemia		
	Normal Glucose Regulation	Impaired Glucose Tolerance or Impaired Fasting Glucose (Prediabetes)	Diabetes Mellitus	
			Not insulin requiring / Insulin requiring for control	Insulin requiring for survival
Type 1*	←——————————————————————————————→			
Type 2	←———————————————————————→			
Other Specific Types**	←———————————————————————→			
Gestational Diabetes**	←———————————————————————→			

Fig. 1. Disorders of glycemia: etiologic types and stages:
*even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i. e., «honeymoon» remission); **in rare instances, patients in these categories (e. g., Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival

In 2019 World Health Organization (WHO) updated the 1999 classification of diabetes. It prioritized clinical care and guides health professionals in choosing appropriate treatments at the time of diabetes diagnosis, and provides practical guidance to clinicians in assigning a type of diabetes to individuals at the time of diagnosis. It is a compromise between clinical and etiological classification because there remain gaps in knowledge of the etiology and pathophysiology of diabetes.

While acknowledging the progress that is being made towards a more precise categorization of diabetes subtypes, the aim of this document was to recommend a classification that is feasible to implement in different settings throughout the world. The revised classification is presented in table 2.

Table 2

Types of diabetes

Type of diabetes	Brief description	Change from previous classification
Type 1 diabetes	β-cell destruction (mostly immune mediated) and absolute insulin deficiency; onset most common in childhood and early adulthood	Type 1 sub-classes removed
Type 2 diabetes	Most common type, various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity	Type 2 sub-classes rem

Type of diabetes	Brief description	Change from previous classification
Hybrid forms of diabetes		New type of diabetes
Slowly evolving, immune mediated diabetes of adults	Similar to slowly evolving type 1 in adults but more often has features of the metabolic syndrome, a single GAD autoantibody and retains greater β-cell function	Nomenclature changed — previously referred to as latent autoimmune diabetes of adults (LADA)
Ketosis-prone type 2 diabetes	Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune-mediated	No change
Other specific types		
Monogenic diabetes – Monogenic defects of β-cell function – Monogenic defects in insulin action	Caused by specific gene mutations, has several clinical manifestations requiring different treatment, some occurring in the neonatal period, others by early adulthood Caused by specific gene mutations has features of severe insulin resistance without obesity; diabetes develops when β-cells do not compensate for insulin resistance	Updated nomenclature for specific genetic defects
Diseases of the exocrine pancreas	Various conditions that affect the pancreas can result in hyperglycaemia (trauma, tumor, inflammation, etc.)	No change
Endocrine disorders	Occurs in diseases with excess secretion of hormones that are insulin antagonists	No change
Drug- or chemical-induced	Some medicines and chemicals impair insulin secretion or action, some can destroy β-cells	No change
Infection-related diabetes	Some viruses have been associated with direct β-cell destruction	No change
Uncommon specific forms of immune-mediated diabetes	Associated with rare immune mediated diseases	No change
Other genetic syndromes sometimes associated with diabetes	Many genetic disorders and chromosomal abnormalities increase the risk of diabetes	No change
Unclassified diabetes	Used to describe diabetes that does not clearly fit into other categories. This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis	New types of diabetes
Hyperglycaemia first detected during pregnancy		
Diabetes mellitus in pregnancy	Type 1 or type 2 diabetes first diagnosed during pregnancy	No change
Gestational diabetes mellitus	Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy	Defined by 2013 diagnostic criteria

Unlike the previous classification, this classification does not recognize subtypes of type 1 diabetes and type 2 diabetes and includes new types of diabetes («hybrid types of diabetes» and «unclassified diabetes»).

DIFFERENTIAL DIAGNOSIS OF DIABETES

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both age groups. Children with type 1 diabetes often present with the hallmark symptoms of polyuria/polydipsia, and approximately half present with diabetic ketoacidosis (DKA).

The onset of type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for insulin.

The features most useful in discrimination of type 1 diabetes include:
– younger age at diagnosis (< 35 years);
– lower BMI (< 25 kg/m^2), unintentional weight loss;
– ketoacidosis;
– glucose >360 mg/dL (20 mmol/L) at presentation.

Occasionally, people with type 2 diabetes may present with DKA, particularly members of ethnic and racial minorities. It is important for the health care professional to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis is common (e. g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes, individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes). Although difficulties in distinguishing diabetes type may occur in all age groups at onset, the diagnosis becomes more obvious over time in people with β-cell deficiency as the degree of β-cell deficiency becomes clear.

In both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β-cell demise or dysfunction. Across the globe, many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing

personalized treatment approaches. Many of these studies show great promise and may soon be incorporated into the diabetes classification system.

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is now clear from prospective studies that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes. The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA.

Three distinct stages of type 1 diabetes can be identified (table 3) and serve as a framework for research and regulatory decision-making.

Table 3

Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Chara-cteristics	Autoimmunity	Autoimmunity	Autoimmunity
	Normoglycemia	Dysglycemia	Overt hyperglycemia
	Presymptomatic	Presymptomatic	Symptomatic
Diag-nostic criteria	Multiple islet autoantibodies No IGT or IFG	Islet autoantibodies (usually multiple); Dysglycemia: IFG and/or IGT; FPG 100–125 mg/dL (5.6–6.9 mmol/L); 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L); A1C 5.7–6.4 % (39–47 mmol/mol) or ≥ 10 % increase in A1C	Autoantibodies may become absent; Diabetes by standard criteria

FPG — fasting plasma glucose; IFG — impaired fasting glucose; IGT — impaired glucose tolerance; 2-h PG — 2-h plasma glucose

There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. The clinical priority with detection of LADA is awareness that slow autoimmune β-cell destruction can occur in adults leading to a long duration of marginal insulin secretory capacity. For the purpose of this classification, all forms of diabetes mediated by autoimmune β-cell destruction are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to have progressive autoimmune β-cell destruction, thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA.

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is

associated with insulin secretory defects related to genetics, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction.

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) or A1C criteria (table 4).

Table 4

Criteria for the diagnosis of diabetes

FPG ≥ 126 mg/dL (7.0 mmol/L) Fasting is defined as no caloric intake for at least 8 h*
OR
2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water*
OR
A1C ≥ 6.5% (48 mmol/mol) The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

DCCT — Diabetes Control and Complications Trial; FPG — fasting plasma glucose; OGTT — oral glucose tolerance test; NGSP — National Glycohemoglobin Standardization Program; WHO — World Health Organization; 2-h PG — 2-h plasma glucose.

*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. It should be noted that detection rates of different screening tests vary in both populations and individuals. Moreover, the efficacy of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria.

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (table 5).

Table 5

Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4 % (39–47 mmol/mol)

FPG — fasting plasma glucose; IFG — impaired fasting glucose; IGT — impaired glucose tolerance; OGTT — oral glucose tolerance test; 2-h PG — 2-h plasma glucose.

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Diabetes may be identified anywhere along the spectrum of clinical scenarios — in seemingly low-risk individuals who happen to have glucose testing, in individuals screened based on diabetes risk assessment, and in symptomatic patients.

Fasting and 2-Hour Plasma Glucose. The FPG and 2-h PG may be used to diagnose diabetes. The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes. In people in whom there is discordance between A1C values and glucose values, FPG and 2-h PG are more accurate

Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes.

A1C. To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes.

In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes.

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and fewer day-to-day perturbations during stress, changes in nutrition, or illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated

cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. The A1C test, with a diagnostic threshold of ≥ 6.5 % (48 mmol/mol), diagnoses only 30 % of the diabetes cases identified collectively using A1C, FPG, or 2-h PG, according to National Health and Nutrition Examination Survey (NHANES) data/ Despite these limitations with A1C, in 2009, the International Expert Committee added A1C to the diagnostic criteria with the goal of increased screening.

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, such as hemodialysis, pregnancy, HIV treatment, age, race/ethnicity, genetic background, and anemia/hemoglobinopathies.

Age. The epidemiologic studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations. However, recent ADA clinical guidance concluded that A1C, FPG, or 2-h PG could be used to test for prediabetes or type 2 diabetes in children and adolescents.

Race/Ethnicity/Hemoglobinopathies. Hemoglobin variants can interfere with the measurement of A1C, although most assays in use in the U.S. are unaffected by the most common variants. Marked discrepancies between measured A1C and plasma glucose levels should prompt consideration that the A1C assay may not be reliable for that individual. For individuals with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used.

African American individuals heterozygous for the common hemoglobin variant HbS may have, for any given level of mean glycemia, lower A1C by about 0.3 % compared with those without the trait. Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11 % of African American individuals, was associated with a decrease in A1C of about 0.8 % in homozygous men and 0.7 % in homozygous women compared with those without the variant. For example, in Tanzania, where there is a high likelihood of hemoglobinopathies in people with HIV, A1C may be lower than expected based on glucose, limiting its usefulness for screening.

Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia. For example, African American individuals may have higher A1C levels than non-Hispanic White individuals with similar fasting and post–glucose load glucose levels. Though conflicting data exist, African American individuals may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher. Similarly, A1C levels may be higher for a given mean glucose concentration when measured with continuous

glucose monitoring. A recent report in Afro-Caribbean people demonstrated a lower A1C than predicted by glucose levels. Despite these and other reported differences, the association of A1C with risk for complications appears to be similar in African American and non-Hispanic White populations. In the Taiwanese population, age and sex have been reported to be associated with increased A1C in men; the clinical implications of this finding are unclear at this time.

Other Conditions Altering the Relationship of A1C and Glycemia. In conditions associated with increased red blood cell turnover, such as sickle cell disease, pregnancy (second and third trimesters), glucose-6-phosphate dehydrogenase deficiency, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes. A1C is less reliable than blood glucose measurement in other conditions such as the postpartum state, HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), and iron-deficient anemia.

Confirming the diagnosis. Unless there is a clear clinical diagnosis (e. g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose $\geq$ 200 mg/dL [11.1 mmol/L]), diagnosis requires two abnormal screening test results, either from the same sample or in two separate test samples. If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay.

For example, if the A1C is 7.0 % (53 mmol/mol) and a repeat result is 6.8 % (51 mmol/mol), the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold when analyzed from the same sample or in two different test samples, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of the possibility of A1C assay interference. The diagnosis is made on the basis of the confirmatory screening test. For example, if a patient meets the diabetes criterion of the A1C (two results $\geq$6.5 % [48 mmol/mol]) but not FPG (< 126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Each of the screening tests has preanalytic and analytic variability, so it is possible that a test yielding an abnormal result (i. e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with the patient and repeat the test in 3–6 months.

People should consume a mixed diet with at least 150 g of carbohydrates on the 3 days prior to oral glucose tolerance testing. Fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

Diagnosis. In a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose $\geq$ 200 mg/dL [11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some health care professionals may also want to know the A1C to determine the chronicity of the hyperglycemia.

TYPE 1 DIABETES

Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or can be considered an option for first-degree family members of a proband with type 1 diabetes. Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for stage 2 type 1 diabetes.

Immune-Mediated Diabetes. This form, previously called «insulin-dependent diabetes» or «juvenile-onset diabetes», accounts for 5–10 % of diabetes and is due to cell-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (glutamic acid decarboxylase, GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2β, and zinc transporter 8. Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the DQB1 and DRB1 haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing or protective.

The rate of β-cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults). Children and adolescents often present with DKA as the first manifestation of the disease, and the rates in the U.S. have increased dramatically over the past 20 years. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress.

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Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission or decreased insulin needs for months or years and eventually become dependent on insulin for survival and are at risk for DKA. At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals do not typically have obesity when they present with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves' disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (FOXP3) gene, and another caused by the autoimmune regulator (AIRE) gene mutation. As indicated by the names, these disorders are associated with other autoimmune and rheumatological diseases.

Introduction of immunotherapy, specifically checkpoint inhibitors, for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of type 1 diabetes can develops, with DKA and low or undetectable levels of C-peptide as a marker of endogenous β-cell function. Fewer than half of these patients have autoantibodies that are seen in type 1 diabetes, supporting alternate pathobiology. This immune-related adverse event occurs in just under 1 % of checkpoint inhibitor-treated patients but most commonly occurs with agents that block the programmed cell death protein 1/programmed cell death ligand 1 pathway alone or in combination with other checkpoint inhibitors. To date, the majority of immune checkpoint inhibitor–related cases of type 1 diabetes occur in people with high-risk HLA-DR4 (present in 76 % of patients), whereas other high-risk HLA alleles are not more common than those in the general population. To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications should be mindful of this adverse effect and educate patients appropriately.

Idiopathic Type 1 Diabetes. Some forms of type 1 diabetes have no known etiologies. These individuals have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of people with type 1 diabetes fall into this category. Individuals with autoantibody-

negative type 1 diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (possibly ketosis-prone diabetes). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent. Future research is needed to determine the cause of β-cell destruction in this rare clinical scenario.

Screening for Type 1 Diabetes Risk. The incidence and prevalence of type 1 diabetes are increasing. People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 40–60 % are diagnosed with life-threatening DKA. Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes or in children from the general population can effectively identify those who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70 % developed type 1 diabetes within 10 years and 84 % within 15 years. These findings are highly significant because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population.

Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both «sporadic» and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases. In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21 % of 363 subjects with at least one autoantibody at 3 years of age (80). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and prevent DKA.

While widespread clinical screening of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions, several innovative research screening programs are available in Europe (e. g., Fr1da, gppad.org) and the U. S. (trialnet.org, askhealth.org). Participation should be encouraged to accelerate development of evidence-based clinical guidelines for the general population and relatives of those with type 1 diabetes. Individuals who test positive should be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention.

Numerous clinical studies are being conducted to test various methods of preventing and treating stage 2 type 1 diabetes in those with evidence of autoimmunity with promising results (see clinicaltrials.gov and trialnet.org). Delay of overt diabetes development in stage 2 type 1 diabetes with the anti-CD3 antibody teplizumab in relatives at risk for type 1 diabetes was reported in 2019,

with an extension of the randomized controlled trial in 2021. Based on these data, this agent has been submitted to the FDA for the indication of delay or prevention of clinical type 1 diabetes in at-risk individuals. Neither this agent nor others in this category are currently available for clinical use.

SCREENING FOR PREDIABETES AND TYPE 2 DIABETES

Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian American individuals) who have one or more risk factors (table 6).

Table 6

Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors: – First-degree relative with diabetes   – High-risk race/ethnicity (e. g., African American, Latino, Native American, Asian American, Pacific Islander)   – History of CVD   – Hypertension ($\geq 140/90$ mmHg or on therapy for hypertension)   – HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)   – Individuals with polycystic ovary syndrome   – Physical inactivity   – Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥ 5.7 % [39 mmol/mol], IGT, or IFG) should be tested yearly
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years
4. For all other people, testing should begin at age 35 years
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status
6. People with HIV

CVD — cardiovascular disease; GDM — gestational diabetes mellitus; IFG — impaired fasting glucose; IGT — impaired glucose tolerance.

For all people, screening should begin at age 35 years. If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (i. e., weight gain). To screen for

prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are each appropriate (table 4 and table 5).

When using oral glucose tolerance testing as a screen for diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors.

Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥ 85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes (table 7).

Table 7

Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥ 85th percentile) or obesity (≥ 95th percentile) and who have one or more additional risk factors based on the strength of their association with diabetes: – Maternal history of diabetes or GDM during the child's gestation   – Family history of type 2 diabetes in first- or second-degree relative   – Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)

GDM — gestational diabetes mellitus.

*After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors

People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually.

PREDIABETES

«Prediabetes» is the term used for individuals whose glucose levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism. People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4 % (39–47 mmol/mol) (table 5). Prediabetes should not be viewed as a

clinical entity in its own right but rather as a risk factor for progression to diabetes and cardiovascular disease (CVD). Criteria for screening for diabetes or prediabetes in asymptomatic adults are outlined in table 6. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

Diagnosis. IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (82,83) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L). It should be noted that the World Health Organization and numerous other diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5 % and 6.0 % (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9 % to 25 %). Those with an A1C range of 6.0–6.5 % (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25 % and 50 % and a relative risk 20 times higher compared with A1C of 5.0 % (31 mmol/mol).

In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose. Other analyses suggest that A1C of 5.7 % (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up.

Hence, it is reasonable to consider an A1C range of 5.7–6.4 % (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4 % (39–47 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks.

Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately. Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e. g., those with A1C > 6.0 % [42 mmol/mol]). Table 5 summarizes the categories of prediabetes, and table 6 outlines the criteria for screening for prediabetes.

The ADA Diabetes Risk Test is an additional option for assessment to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (Add. 1, diabetes.org/socrisktest).

Also, Finnish Diabetes Risk Score (FINDRISC) which is one of the most frequently used instruments for assessing the risk of DM [4]. FINDRISC assesses whether an individual has Undiagnosed T2DM or dysglycaemia or the probability of developing T2DM during the following 10 years (Add. 2) It is a practical screening tool to estimate the diabetes risk and the probability of asymptomatic type 2 diabetes.

TYPE 2 DIABETES

Type 2 diabetes, previously referred to as «non-insulin-dependent diabetes» or «adult-onset diabetes», accounts for 90–95 % of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, people with type 2 diabetes have overweight or obesity. Excess weight itself causes some degree of insulin resistance. Individuals who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

DKA seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection or myocardial infarction or with the use of certain drugs (e. g., corticosteroids, atypical antipsychotics, and sodium–glucose cotransporter 2 inhibitors). Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms caused by hyperglycemia, such as dehydration or unintentional weight loss. Nevertheless, even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.

People with type 2 diabetes may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion. Thus, insulin secretion is defective in these individuals and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive diet and exercise or surgical weight loss have led to diabetes remission

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in individuals with prior gestational diabetes mellitus (GDM) or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial/ethnic subgroups (African American, Native American, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes are poorly understood and under intense investigation in this era of precision medicine. In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing (e. g., GAD65 autoantibodies) to exclude the diagnosis of type 1 diabetes

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care. General practice patients between the ages of 40 and 69 years were screened for diabetes and randomly assigned by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups. The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes; moreover, screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (< \$11,000 per quality-adjusted life year gained — 2010 modeling data). Cost-effectiveness of screening has been reinforced in cohort studies.

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic individuals include the following.

Age. Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people. Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

BMI and Ethnicity. In general, BMI ≥ 25 kg/m^2 is a risk factor for diabetes. However, data suggest that the BMI cut point should be lower for the Asian American population. The BMI cut points fall consistently between 23 and 24 kg/m^2 (sensitivity of 80 %) for nearly all Asian American subgroups (with levels slightly lower for Japanese American individuals). This makes a rounded cut point of 23 kg/m^2 practical. An argument can be made to push the BMI cut point to lower than 23 kg/m^2 in favor of increased sensitivity; however, this would lead to an

unacceptably low specificity (13.1 %). Data from the World Health Organization also suggest that a BMI of ≥ 23 kg/m² should be used to define increased risk in Asian American individuals. The finding that one-third to one-half of diabetes in Asian American people is undiagnosed suggests that testing is not occurring at lower BMI thresholds.

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m² in non-Hispanic White individuals was equivalent to a BMI of 26 kg/m² in African American individuals.

Medications. Certain medications, such as glucocorticoids, thiazide diuretics, some HIV medications, and atypical antipsychotics, are known to increase the risk of diabetes and should be considered when deciding whether to screen.

HIV. Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies; a screening protocol is therefore recommended. The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring. In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among people with HIV and diabetes, preventive health care using an approach used in people without HIV is critical to reduce the risks of microvascular and macrovascular complications. Diabetes risk is increased with certain PIs and NRTIs. New-onset diabetes is estimated to occur in more than 5 % of individuals infected with HIV on PIs, whereas more than 15 % may have prediabetes.

PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available. Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Testing Interval. The appropriate interval between screening tests is not known. The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced, and individuals with false-negative tests will be retested before substantial time elapses and complications develop. In especially high-risk individuals, particularly with weight gain, shorter intervals between screening may be useful.

Community Screening. Ideally, screening should be carried out within a health care setting because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-

up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed.

Screening in Dental Practices. Because periodontal disease is associated with diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored, with one study estimating that 30 % of patients ≥ 30 years of age seen in general dental practices had dysglycemia. A similar study in 1,150 dental patients > 40 years old in India reported 20.69 % and 14.60 % meeting criteria for prediabetes and diabetes, respectively, using random blood glucose. Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

CYSTIC FIBROSIS-RELATED DIABETES

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20 % of adolescents and 40–50 % of adults. Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test; however, recent publications suggest that an A1C cut point threshold of 5.5 % (5.8 % in a second study) would detect more than 90 % of cases and reduce patient screening burden. Ongoing studies are underway to validate this approach, and A1C is not recommended for screening. Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening. The Cystic Fibrosis Foundation Patient Registry evaluated 3,553 people with cystic fibrosis and diagnosed 445 (13 %) with CFRD. Early diagnosis and treatment of CFRD was associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (increased 10 % per decade), genotype, decreased lung function, and female sex. Coninuous

glucose monitoring or HOMA of β-cell function may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside of the research setting.

CFRD mortality has significantly decreased over time, and the gap in mortality between people with cystic fibrosis with and without diabetes has considerably narrowed. There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in people with cystic fibrosis and diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and participants gained 0.39 (± 0.21) BMI units (P = 0.02). The repaglinide-treated group had initial weight gain, but it was not sustained by 6 months. The placebo group continued to lose weight. Insulin remains the most widely used therapy for CFRD. The primary rationale for the use of insulin in people with CFRD is to induce an anabolic state while promoting macronutrient retention and weight gain.

POSTTRANSPLANTATION DIABETES MELLITUS

Several terms are used in the literature to describe the presence of diabetes following organ transplantation. «New-onset diabetes after transplantation» (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge. Another term, «posttransplantation diabetes mellitus» (PTDM), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90 % of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant. In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge. Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes care health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression. Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents.

Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance immunosuppression and in the absence of acute infection.

In a recent study of 152 heart transplant recipients, 38 % had PTDM at 1 year. Risk factors for PTDM included elevated BMI, discharge from the hospital on insulin, and glucose values in the 24 h prior to hospital discharge. In an Iranian cohort, 19 % had PTDM after heart and lung transplant. The OGTT is considered the gold-standard test for the diagnosis of PTDM (1-year posttransplant). Pretransplant elevation in hs-CRP was associated with PTDM in the setting of renal transplant. However, screening people with fasting glucose and/or A1C can identify high-risk individuals requiring further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM. Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization. Insulin therapy is the agent of choice for the management of hyperglycemia, PTDM, and preexisting diabetes and diabetes in the hospital setting. After discharge, people with preexisting diabetes could go back on their pretransplant regimen if they were in good control before transplantation. Those with previously poor glycemic stability or with persistent hyperglycemia should continue insulin with frequent home glucose monitoring to determine when insulin dose reductions may be needed and when it may be appropriate to switch to noninsulin agents.

No studies to date have established which noninsulin agents are safest or most efficacious in PTDM. The choice of agent is usually made based on the side effect profile of the medication and possible interactions with the patient's immunosuppression regimen. Drug dose adjustments may be required because of decreases in the glomerular filtration rate, a relatively common complication in transplant patients. A small short-term pilot study reported that metformin was safe to use in renal transplant recipients, but its safety has not been determined in other types of organ transplant. Thiazolidinediones have been used successfully in people with liver and kidney transplants, but side effects include fluid retention, heart failure, and osteopenia. Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials. Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in people with PTDM are needed.

MONOGENIC DIABETES SYNDROMES

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of people with diabetes (< 5 %). Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. Children and young adults who do not

have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. Table 8 describes the most common causes of monogenic diabetes.

Most common causes of monogenic diabetes

	Gene	Inheritance	Clinical features
MODY	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (> 90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically, does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
Neonatal diabetes	KCNJ11	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (PLAGL1, HYMA1)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD — autosomal dominant; AR — autosomal recessive; IUGR — intrauterine growth restriction; OGTT — oral glucose tolerance test; UPD6 — uniparental disomy of chromosome 6; 2-h PG — 2-h plasma glucose.

Neonatal Diabetes. Diabetes occurring under 6 months of age is termed «neonatal» or «congenital» diabetes, and about 80–85 % of cases can be found to have an underlying monogenic cause. Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient

diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin.

Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (KCNJ11) and SUR1 subunit (ABCC8) of the β-cell KATP channel. A recent report details a de novo mutation in EIF2B1 affecting eIF2 signaling associated with permanent neonatal diabetes and hepatic dysfunction, similar to Wolcott-Rallison syndrome but with few severe comorbidities.

The recent ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing. Correct diagnosis has critical implications because 30–50 % of people with KATP-related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (INS) mutations are the second most common cause of permanent neonatal diabetes, and while intensive insulin management is currently the preferred treatment strategy, there are important genetic counseling considerations, as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young. MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date. The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

For individuals with MODY, the treatment implications are considerable and warrant genetic testing. Clinically, people with GCK-MODY exhibit mild, stable fasting hyperglycemia and do not require antihyperglycemic therapy except commonly during pregnancy. Individuals with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy; in some instances, insulin will be required over time. Mutations or deletions in HNF1B are associated with renal cysts and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes, including PDX1 (IPF1) and NEUROD1.

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Pancreatic diabetes includes both structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. Hyperglycemia due to general pancreatic dysfunction has been called «type 3c diabetes», and, more recently, diabetes in the context of disease of the exocrine pancreas has been termed pancreoprivic diabetes. The diverse set of etiologies includes pancreatitis (acute and chronic), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed elsewhere in this chapter), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders, and idiopathic forms; as such, pancreatic diabetes is the preferred umbrella terminology.

Pancreatitis, even a single bout, can lead to postpancreatitis diabetes mellitus (PPDM). Both acute and chronic pancreatitis can lead to PPDM, and the risk is highest with recurrent bouts. A distinguishing feature is concurrent pancreatic exocrine insufficiency (according to the monoclonal fecal elastase 1 test or direct function tests), pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography), and absence of type 1 diabetes-associated autoimmunity. There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications appears to be similar to that of other forms of diabetes. In the context of pancreatectomy, islet autotransplantation can be done to retain insulin secretion. In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirement.

GESTATION DIABETES MELLITUS

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy, regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations. First, the best available evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. It is the severity of hyperglycemia that is clinically important with regard to both short- and long-term maternal and fetal risks.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy. Ideally, undiagnosed diabetes

should be identified preconception in individuals with risk factors or in high-risk populations, as the preconception care of people with preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission. If individuals are not screened prior to pregnancy, universal early screening at < 15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (table 6), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify these health disparities so that they can begin to be addressed.

Standard diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in the nonpregnant population (table 4). Individuals found to have diabetes by the standard diagnostic criteria used outside of pregnancy should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9 % (39 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, perinatal death), are more likely to need insulin treatment, and are at high risk of a later GDM diagnosis. An A1C threshold of 5.7 % has not been shown to be associated with adverse perinatal outcomes.

If early screening is negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT, as well as the GDM screening and diagnostic criteria used in the two-step approach, were not derived from data in the first half of pregnancy and should not be used for early screening. To date, most randomized controlled trials of treatment of early abnormal glucose metabolism have been underpowered for outcomes. Therefore, the benefits of treatment for early abnormal glucose metabolism remain uncertain. Nutrition counseling and periodic «block» testing of glucose levels weekly to identify individuals with high glucose levels are suggested. Testing frequency may proceed to daily, and treatment may be intensified, if the fasting glucose is predominantly > 110 mg/dL prior to 18 weeks of gestation.

Both the fasting glucose and A1C are low-cost tests. An advantage of the A1C is its convenience, as it can be added to the prenatal laboratories and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of increased red blood cell turnover and hemoglobinopathies (usually reads lower) and higher values with anemia and reduced red blood cell

turnover. A1C is not reliable to screen for GDM or for preexisting diabetes at 15 weeks of gestation or later.

GDM is often indicative of underlying β-cell dysfunction, which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery. As effective prevention interventions are available, individuals diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time.

Thus, screen for early abnormal glucose metabolism using fasting glucose of 110–125 mg/dL (6.1 mmol/L) or A1C 5.9–6.4 % (41–47 mmol/mol). Screen for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. Screen individuals with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. Individuals with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. Individuals with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes.

LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7 % of initial body weight through healthy reduced-calorie diet and ≥ 150 min/week of moderate-intensity physical activity. A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. A Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed. Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered.

The Diabetes Prevention Program. Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial, the Finnish Diabetes Prevention Study (DPS), and the Da Qing Diabetes Prevention Study (Da Qing study), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2

diabetes and improving other cardiometabolic markers (such as blood pressure, lipids, and inflammation). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial. The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58 % over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39 % reduction at 30 years in the Da Qing study, 43 % reduction at 7 years in the Finnish DPS, and 34 % reduction at 10 years and 27 % reduction at 15 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7 % weight loss and 150 min moderate-intensity physical activity per week, such as brisk walking. The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals. Although weight loss was the most important factor in reducing the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44 %.

The 7 % weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve the ≥ 7 % weight loss during the first 6 months of the intervention. Further analysis suggests maximal prevention of diabetes with at least 7–10 % weight loss. The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced.

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal.

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population.

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors, and guidance on managing psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions.

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories. However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Based on other intervention trials, a variety of eating patterns characterized by the totality of food and beverages habitually consumed may also be appropriate for individuals with prediabetes, including Mediterranean-style and low-carbohydrate eating plans. Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes. Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes.

Physical Activity. Just as 150 min/week of moderate-intensity physical activity, such as brisk walking, showed beneficial effects in those with prediabetes, moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults. Based on these findings, health care professionals are encouraged to promote a DPP-style program, including a focus on physical activity, to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training. Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels. The preventive effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM).

PHARMACOLOGICAL INTERVENTION
FOR THE PREVENTION TYPE 2 DIABETES

Because weight loss through behavior changes in diet and physical activity alone can be difficult to maintain long term, people at high risk of diabetes may benefit from support and additional pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists (liraglutide, semaglutide), thiazolidinediones, testosterone, and insulin have been shown to lower the incidence of diabetes in specific populations, whereas diabetes prevention was not seen with nateglinide.

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16 % reduction in risk of progression over 3.2 years. In postpartum individuals with GDM, the risk of type 2 diabetes increased by 18 % for every 1-unit BMI above the preconception baseline. Several medications evaluated for weight loss (e. g., orlistat, phentermine topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of diabetes to various degrees in those with prediabetes.

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs. Although the Vitamin D and Type 2 Diabetes (D2d) prospective randomized controlled trial showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk, post hoc analyses and meta-analyses suggest a potential benefit in specific populations. Further research is needed to define characteristics and clinical indicators where vitamin D supplementation may be of benefit.

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for a specific indication of type 2 diabetes prevention. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost, side effects, and efficacy considerations. Metformin has the longest history of safety data as a pharmacologic therapy for diabetes prevention.

Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPPOS, and metformin may be cost-saving over a 10-year period. In the DPP, metformin was as effective as lifestyle modification in participants with BMI $\geq$ 35 kg/m^2 and in younger participants aged 25–44 years. In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50 % reduction in diabetes risk. Both interventions remained highly effective during a 10-year follow-up period. By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose ($\geq$ 110 mg/dL vs.

95–109 mg/dL), those with a higher A1C (6.0–6.4 % vs. < 6.0%), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that benefitted the most from metformin. In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; of note, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP.

Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e. g., those with a history of GDM or those with BMI ≥ 35 kg/m^2). Consider periodic monitoring of vitamin B$_{12}$ levels in those taking metformin chronically to check for possible deficiency. While there is not a universally accepted recommended periodicity of monitoring, it is notable that the lowering effect of metformin on vitamin B$_{12}$ increases with time, with a significantly higher risk for vitamin B$_{12}$ deficiency (< 150 pmol/L) noted at 4.3 years in the HOME (Hyperinsulinaemia: the Outcome of its Metabolic Effects) study and significantly greater risk of low B$_{12}$ levels ($\leq$ 203 pg/mL) at 5 years in the DPP. It has been suggested that a person who has been on metformin for more than 4 years or is at risk for vitamin B$_{12}$ deficiency should be monitored for vitamin B$_{12}$ deficiency annually.

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued.

In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. Lower doses may mitigate the risk of adverse effects.

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia, and are at increased risk for cardiovascular disease. If indicated, evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes, a time when individuals should be monitored for diabetes development and receive

concurrent evidence-based lifestyle behavior change for diabetes prevention described in this section.

The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors. In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study. The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up. Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular diseases risk factors.

Statins have been associated with a modestly increased risk of diabetes. In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio (95 % CI) for incident diabetes 1.36 (1.17–1.58). In studies of primary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes, suggesting a favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins is not recommended in this population due to concerns of diabetes risk.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk. The IRIS (Insulin Resistance Intervention after Stroke) trial was a dedicated study of people with a recent (< 6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance, as defined by a HOMA of insulin resistance index of ≥ 3.0, evaluating pioglitazone (target dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower within the pioglitazone group than with placebo, though risks of weight gain, edema, and fracture were higher in the pioglitazone treatment group. Lower doses may mitigate the adverse effects, though further study is needed to confirm the benefit at lower doses.

PERSON-CENTERED CARE GOALS

In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include weight loss or prevention of weight gain, minimizing the progression of hyperglycemia, and attention to cardiovascular risk and associated comorbidities. Pharmacotherapy (e. g., for weight management, minimizing the

progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals. More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI $\geq$ 35 kg/m^2, those at higher glucose levels (e. g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, A1C $\geq$ 6.0 %), and individuals with a history of gestational diabetes mellitus.

Individualized risk/benefit should be considered in screening, intervention, and monitoring to prevent or delay type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications. In the DPP, which enrolled high-risk individuals with impaired glucose tolerance, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo arm was 11.0 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 28.9 %. Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases/100 person-years) included BMI $\geq$ 35 kg/m^2, those at higher glucose levels (e. g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, and A1C $\geq$ 6.0 %), and individuals with a history of gestational diabetes. In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of older adults (mean age 75 years) with laboratory evidence of prediabetes (based on A1C 5.7–6.4 % and/or fasting glucose 100–125 mg/dL), but not meeting specific BMI criteria, found much lower progression to diabetes over 6 years: 9 % of those with A1C-defined prediabetes, 8 % with impaired fasting glucose.

GLYCEMIC TARGETS

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed patients and/or those without comorbidities that limit life expectancy may benefit from intensive control proven to prevent microvascular complications. Assign glycemic targets based on the individualized criteria are shown in fig. 2.

Thus, a finite period of intensive control to near-normal A1C may yield enduring benefits even if control is subsequently deintensified as patient characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive control. Also, with longer disease duration, diabetes may become more difficult to

control, with increasing risks and burdens of therapy. Thus, A1C targets should be reevaluated over time to balance the risks and benefits as patient factors change. Recommended glycemic targets for many nonpregnant adults are shown in table 9.
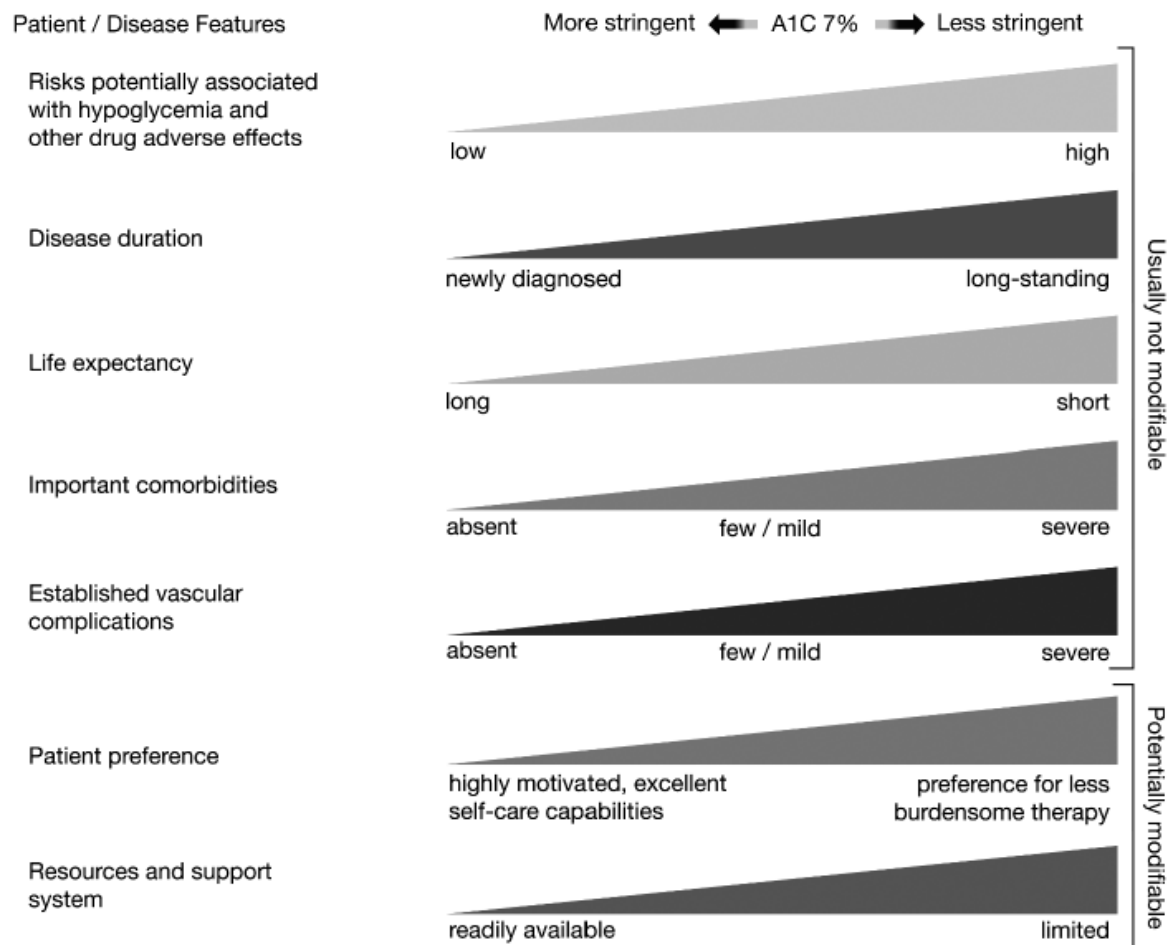

Fig. 2. Approach of individualization of glycemic targets

Summary of glycemic recommendations for many nonpregnant adults with diabetes

Parameters	Range
A1C	< 7.0 % (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	< 180 mg/dL* (10.0 mmol/L)

* More or less stringent glycemic goals may be appropriate for individual patients.

\# CGM may be used to assess glycemic target. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

† Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

Thus, it is important to individualize the risk/benefit of intervention and consider person-centered goals. Risk models have explored risk-based benefit, generally finding higher benefit of the intervention in those at highest risk.

Standardized, single-page glucose reports from *continuous glucose monitoring (CGM)* devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. Time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (table 10).

Table 10

Standardized CGM metrics for clinical care

Parameters	Range
1. Number of days CGM device is worn	recommend 14 days
2. Percentage of time CGM device is active	recommend 70% of data from 14 days
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV)	target ≤ 36 %*
6. TAR, time above range	% of readings and time > 250 mg/dL (>13.9 mmol/L) Level 2 hyperglycemia
7. TAR, time above range	% of readings and time 181–250 mg/dL (10.1–13.9 mmol/L) Level 1 hyperglycemia
8. TIR, time in range	% of readings and time 70–180 mg/dL (3.9–10.0 mmol/L) In range
9. TBR, time below range	% of readings and time 54–69 mg/dL (3.0–3.8 mmol/L) Level 1 hypoglycemia
10. TBR, time below range	% of readings and time < 54 mg/dL (< 3.0 mmol/L) Level 2 hypoglycemia

CGM — continuous glucose monitoring; CV — coefficient of variation.

*Some studies suggest that lower % CV targets (< 33 %) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas.

CGM is rapidly improving diabetes management. As stated in the recommendations, time in range (TIR) is a useful metric of glycemic control and glucose patterns, and it correlates well with A1C in most studies. New data support the premise that increased TIR correlates with the risk of complications.

PHARMACOLOGIC APPROACHERS TO GLYCEMIC TREATMENT

Pharmacologic Therapy for Adults with Type 1 Diabetes. Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity.

Insulin Therapy. Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily injections for the six or seven decades after the discovery of insulin. However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes. The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7 %) led to ~50 % reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated fewer macrovascular as well as fewer microvascular complications in the group that received intensive treatment.

Insulin replacement regimens typically consist of basal insulin, mealtime insulin, and correction insulin. Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins. More recently, two injectable insulin formulations with

enhanced rapid-action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain, and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA.

In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes. Despite the advantages of insulin analogs in individuals with type 1 diabetes, for some individuals the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.

Pharmacologic Therapy for Adults with Type 2 Diabetes. Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals.

In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (Add. 3). Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy (Add. 4.).

Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals (Add. 3, 4).

Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure.

The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (> 10 % [86 mmol/mol]) or blood glucose levels ($\geq$ 300 mg/dL [16.7 mmol/L]) are very high.

A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (Add. 3, 4).

Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established

kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors.

In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (fig. 3).
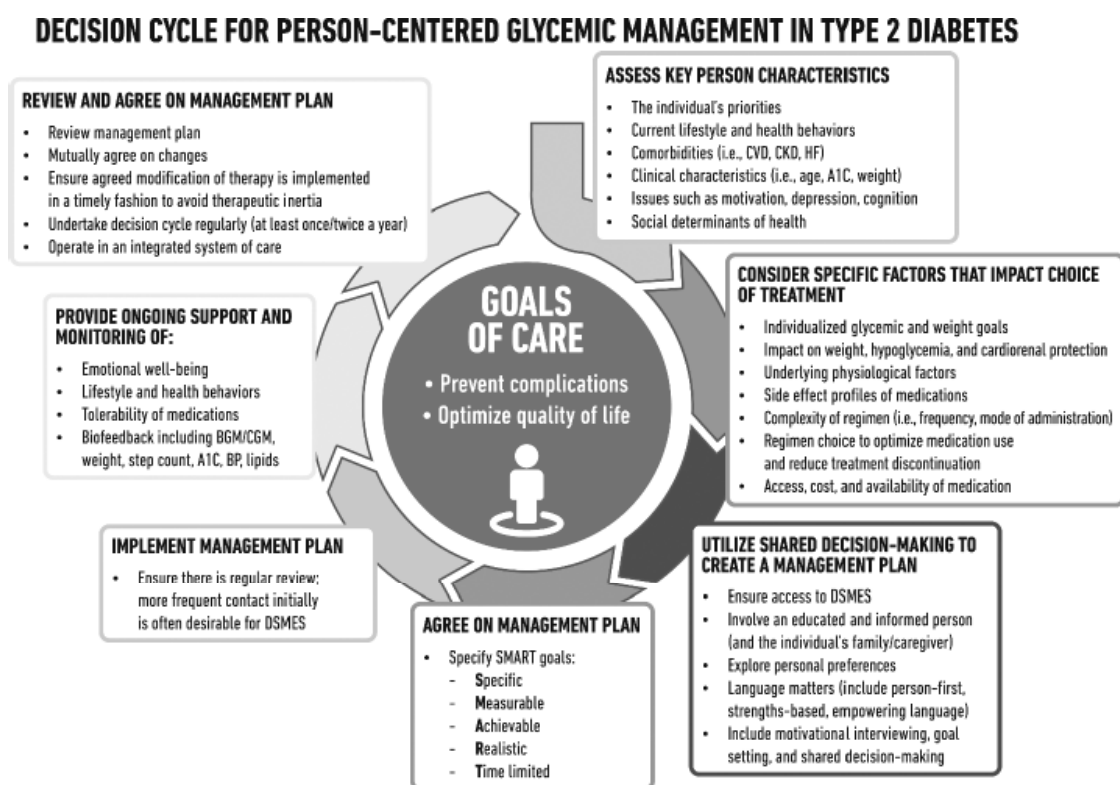

Fig. 3. Decision cycle for person-centered glycemic management in type 2 diabetes

Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or postpreprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy.

CLINICAL CASES

1. Patient S is 48 years old. The body height is 167 cm, body weight is 103 kg. She visited the surgeon to complain about recurrent furunculosis. The fasting glucose test showed fasting glucose 9.4 mmol/L. What is the preferred management strategy?

2. Patient N is 49 years old, a driver. A periodic health examination detected Fasting glucose 8.1 mmol/l. The body height is 170 cm, body weight is 90 kg, blood pressure is 140/85 mm hg. What management are you going to choose?

3. Patient R is 55 years old, a teacher. A periodic health examination detected Fasting glucose 13.1 mmol/L. The body height is 157 cm, body weight is 59 kg, blood pressure is 150/90 mm hg. What is your diagnosis and treatment?

4. Patient A is 35 years old, a programmer. A periodic health examination detected Fasting glucose 9.3 mmol/L. The body height is 163 cm, body weight is 88 kg, blood pressure is 130/80 mm hg. What is your further management?

LITERATURE

Basic

1. *Harrison`s* principles of internal medicine. Vol. 1 / ed. by D. L. Longo, D. L. Kasper, J. L. Jameson [et. al]. 20th ed. New York [etc.] : McGrawHill Medical, 2018. 1796 p.

Additional

2. *Endocrinology* : textbook for students of higher medical with the 4th level of accreditation with English as the language of instruction / P. M. Bodnar [et. al.] ; ed. by P. M. Bodnar. 4th ed., updated. Vinnytsia : Nova Knyha, 2017. 327 p.

3. *Williams* textbook of endocrinology / S. Melmed [et al.]. 14th ed. Philadelphia : Elsevier, 2020. 1777 p.

4. American Diabetes Association, Standards of Care in Diabetes — 2023. Diabetes Care 1 January 2023 ; Volume 46, Issue Supplement_1. 298 p.

5. *American* Diabetes Association Standarts of Medical care in Diabetes : vol. 44 : Diabetes Care : suppl. 1,1. 2021. 232 p.

6. *Harrison`s* principles of internal medicine. Vol. 2 / ed. by D. L. Longo, D. L. Kasper, J. L. Jameson [et. al]. 20th ed. New York [etc.] : McGrawHill Medical, 2018. 3610, [158] p. + 1 электрон. опт. диск (DVD-ROM).

7. *Internal* medicine : critical care : textbook / O. Ya. Babak [et. al.] ; ed. by. O. Ya. Babak, O. M. Bilovol. Kyiv : AUS Medicine Publishing, 2018. 368 p.

THE ADA DIABETES RISK TEST IS AN ADDITIONAL OPTION FOR ASSESSMENT TO DETERMINE THE APPROPRIATENESS OF SCREENING FOR DIABETES OR PREDIABETES IN ASYMPTOMATIC ADULTS (DIABETES.ORG/SOCRISKTEST)

American Diabetes Association®
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you? ....
- Less than 40 years (0 points)
- 40–49 years (1 point)
- 50–59 years (2 points)
- 60 years or older (3 points)

2. Are you a man or a woman? ....
- Man (1 point)
- Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?.................
- Yes (1 point)
- No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? ....
- Yes (1 point)
- No (0 points)

5. Have you ever been diagnosed with high blood pressure? ....
- Yes (1 point)
- No (0 points)

6. Are you physically active? ....
- Yes (0 points)
- No (1 point)

7. What is your weight category? ....
- *See chart at right.*

ADD UP YOUR SCORE.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Diabetes Risk Test | American Diabetes Association®

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

FINNISH DIABETES RISK SCORE (FINDRISC) IS A PRACTICAL SCREENING TOOL TO ESTIMATE THE DIABETES RISK AND THE PROBABILITY OF ASYMPTOMATIC TYPE 2 DIABETES

Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

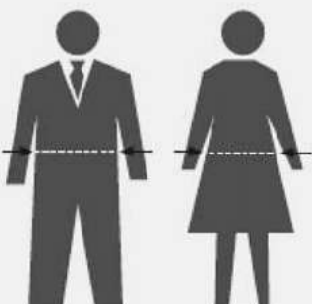Circle the right alternative and add up your points.

1. Age
0 p.   Under 45 years
2 p.   45–54 years
3 p.   55–64 years
4 p.   Over 64 years

2. Body-mass index
(See reverse of form)
0 p.   Lower than 25 kg/m²
1 p.   25–30 kg/m²
3 p.   Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm

4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?
0 p.   Yes
2 p.   No

5. How often do you eat vegetables, fruit or berries?
0 p.   Every day
1 p.   Not every day

6. Have you ever taken medication for high blood pressure on regular basis?

0 p.   No
2 p.   Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?

0 p.   No
5 p.   Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?

0 p.   No
3 p.   Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p.   Yes: parent, brother, sister or own child

Total Risk Score

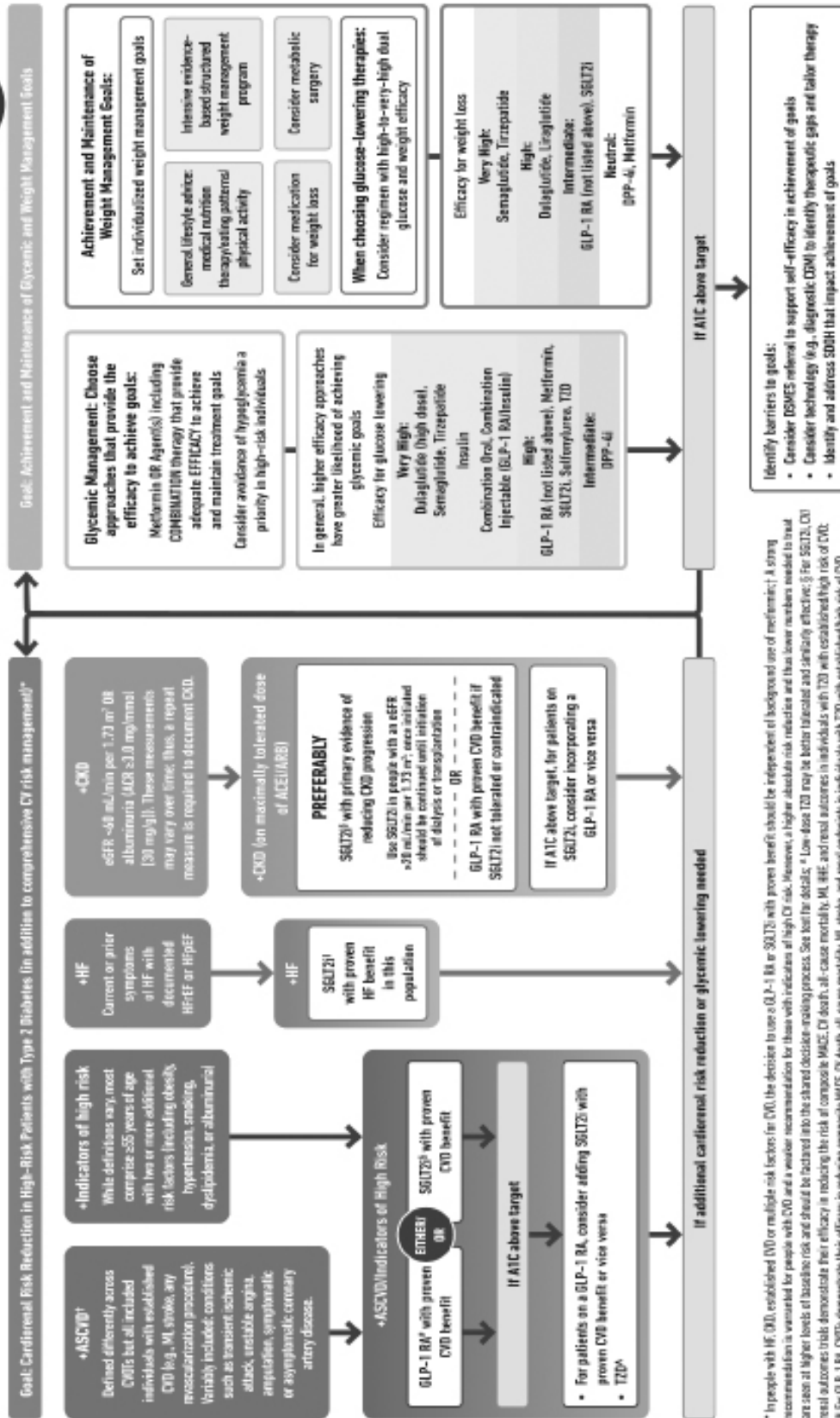The risk of developing type 2 diabetes within 10 years is

Lower than 7	Low: estimated 1 in 100 will develop disease
7–11	Slightly elevated: estimated 1 in 25 will develop disease
12–14	Moderate: estimated 1 in 6 will develop disease
15–20	High: estimated 1 in 3 will develop disease
Higher than 20	Very high: estimated 1 in 2 will develop disease

Please turn over

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki and Jaana Lindström, MFS, National Public Health Institute.

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

- General lifestyle advice: medical nutrition therapy/eating patterns/physical activity
- Intensive evidence-based structured weight management program
- Consider medication for weight loss
- Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss
- Very High: Semaglutide, Tirzepatide
- High: Dulaglutide, Liraglutide
- Intermediate: GLP-1 RA (not listed above), SGLT2i
- Neutral: DPP-4i, Metformin

If A1C above target

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering
- Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide, Insulin, Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
- High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
- Intermediate: DPP-4i

If A1C above target

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY
SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR >20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

— — — OR — — —

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF
SGLT2i with proven HF benefit in this population

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

EITHER / OR

GLP-1 RA with proven CVD benefit

SGLT2i with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD

+ASCVD

Defined differently across CVDTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably includes: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

If additional cardiorenal risk reduction or glycemic lowering needed

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

MEDICATIONS FOR LOWERING GLUCOSE, SUMMARY OF CHARACTERISTICS

	Efficacy¹	Hypoglycemia	Weight change²	CV effects — Effect on MACE	CV effects — HF	CV effects — Progression of DKD	Renal effects — Dosing/use considerations*	Oral/SQ	Cost	Clinical considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m²	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3-4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports; institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ); Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing); discontinue if suspected
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin — Human / Analogs	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled / SQ	Low (SQ) / High	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs

CONTENTS

Учебное издание

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САХАРНЫЙ ДИАБЕТ: ОПРЕДЕЛЕНИЕ, ПРОФИЛАКТИКА, ТЕРАПЕВТИЧЕСКИЕ ПОДХОДЫ

DIABETES MELLITUS: DEFINITION, PREVENTION, TREATMENT APPROACHES

Учебно-методическое пособие

На английском языке

Ответственная за выпуск Т. В. Мохорт
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