6 Definition, Diagnostic Criteria, Screening, Diagnosis, and Classification of Diabetes and Categories of Glucose Intolerance

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Abbreviations

AACC	American Association of Clinical Chemistry
ABCC8	ATP-binding cassette, subfamily C, member 8
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
FCPD	Fibrocalculous pancreatic diabetes
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
GLUT	Glucose transporter
HAPO	Hyperglycemia and pregnancy outcome
HbA1C	Hemoglobin A1c
IA-2	Islet antigen 2
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
KCNJ11	Potassium inwardly rectifying channel, subfamily J, member 11
MODY	Maturity-onset diabetes of the young
NDDG	National Diabetes Data Group
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Care Excellence
NODAT	New-onset diabetes after transplantation
OGTT	Oral glucose tolerance test
PDAC	Pancreatic ductal adenocarcinoma
PG	Plasma glucose
SSA	Somatostatin agonists
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
ZnT8	Zinc transporter 8

Objectives of the Chapter

- The aim of this chapter is to delineate the definition of diabetes mellitus and its diagnostic criteria. Following a brief discussion on evolution of the current diagnostic criteria, the recent ADA criteria and recommendations for screening will be discussed.
- The section on the diagnostic criteria for gestational diabetes compares and contrasts the various criteria recommended by different professional bodies and their merits. This section will also discuss the utility and fallacies of HbA1C as a measure of glycemic status.
- The section on classification of diabetes lists the various aetiologies of diabetes mellitus based on the pathophysiology or common mechanisms for better understanding. Few subsections like "endocrinopathies" and "drugs causing diabetes" are discussed in brief.

Definition

The word diabetes is derived from its Greek root which means "to pass through," referring to polyuria – the hallmark symptom of diabetes mellitus (DM). The word mellitus means "from honey," denoting glycosuria, differentiating it from its close mimic, diabetes insipidus [1].

DM is defined by the World Health Organization (WHO) as a metabolic syndrome characterized by chronic hyperglycemia resulting from any of the several conditions that cause defective insulin secretion and/or action. Prediabetes is a state characterized by metabolic abnormalities that increases the risk of developing DM and its complications.

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Diagnostic Criteria

The diagnostic criterion for DM has undergone a sea change over the last several decades with improved understanding of its pathophysiology and complications. Though the association between chronic hyperglycemia and its complications is well established, the specific cutoff points for diagnosing DM still remain a matter of intense debate.

The WHO, in the year 1965, published the first guidelines for diagnosing DM [2]. The National Diabetes Data Group (NDDG) proposed a criterion based on the observation of bimodal distribution of plasma glucose (PG) in Pima Indians and Nauruan populations and the risk of progression to DM and development of complications. The NDDG also recognized an intermediate group of individuals with raised PG above normal, but not satisfying the criterion for diagnosing DM. This group faced a risk of progression to DM at the rate of 1–5% annually and also had higher prevalence of atherosclerotic disease. The terminology "impaired glucose tolerance (IGT)" was introduced to identify this important group of persons in whom early intervention could avert DM and its complications [3].

The subsequent modifications of the diagnostic criteria by WHO saw revision of the fasting and 2-h post glucose load venous PG thresholds to 7.8 mmol/L and 11.1 mmol/L, respectively, based on the observations that complications of DM rarely occurred below these PG levels.

In 2003, the American Diabetes Association (ADA) made a controversial change to its existing guideline by reducing the cutoff point for defining the upper limit fasting plasma glucose (FPG). This modification was based on data from four population-based epidemiological studies which showed that the ideal FPG cutoff point fell between 5.22 and 5.72 mmol/L and the cutoff of 5.55 mmol/L was arbitrarily chosen [4].

Glycated hemoglobin (HbA1c) was included as a modality to diagnose DM by the ADA in 2010 and the WHO in 2011.

The latest ADA criteria for diagnosing DM are given below: in asymptomatic individuals, these tests need to be repeated on another day for confirmation of diagnosis [5].

- FPG ≥ 7.0 mmol/L. Fasting is defined as no caloric intake for at least 8 h.
  or
- 2-hour PG ≥ 11.1 mmol/L during an oral glucose tolerance test (OGTT). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
  or
- HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
  or
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥ 11.1 mmol/L.

ADA Criteria for Diagnosis of Prediabetes

In addition to fasting and post glucose load PG levels, HbA1c is also recommended as a screening test for prediabetes.

The cutoff points recommended for the diagnosis of prediabetes are given below:

(a) FPG – 5.6 to 6.9 mmol/L [impaired fasting glucose (IFG)]
(b) 2-hour PG in the 75-g OGTT – (7.8 to 11.0 mmol/L) (IGT)
(c) HbA1c 5.7% (39 mmol/mol)

Criteria for Screening for Diabetes or Prediabetes in Asymptomatic Adults

The ADA 2017 guidelines have laid down certain risk factors for screening for diabetes and prediabetes. These include:

1. Overweight or obese (BMI ≥ 25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - HbA1c > 5.7% (39 mmol/mol), IGT, or IFG on previous testing
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who were diagnosed with gestational diabetes mellitus (GDM)
   - History of cardiovascular disease
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - High-density lipoprotein cholesterol level ˂0.90 mmol/L and/or a triglyceride level ≥ 2.82 mmol/L
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance, e.g., severe obesity and acanthosis nigricans
2. For all patients, testing should begin at age 45 years.
3. 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 (e.g., those with prediabetes should be tested yearly) and risk status.

Screening for Prediabetes and Diabetes

Prediabetes is an intermediate state of hyperglycemia characterized by elevated PG levels above normal though not qualifying for the diagnosis of DM. Its significance lies in the fact that 5–10% of patients can progress to develop DM annually without intervention [6, 7]. The dreaded complications of DM are also observed in this group of patients, stressing the need for early recognition and reversal of this state.

According to the WHO, prediabetes constitutes two distinct entities, namely, IFG and IGT. Different pathogenic mechanisms are believed to underlie these two distinct entities, and persons with a combination of both the abnormalities have more advanced metabolic abnormalities than those with either of the two. Similar to the increasing prevalence of DM globally, the prevalence of prediabetes is also expected to rise with an estimated 472 million people to be affected by this condition by the year 2030 [8]. Although a significant proportion of people progress to develop DM, several remain static and many go on to revert to normal state, although the rate of conversion has been reported to be different in various studies [7, 9].

It is well recognized that beta cell dysfunction and insulin resistance are already present in patients at the time of detection of prediabetes [10, 11]. It thus represents a phase in the continuum of worsening beta cell dysfunction and insulin resistance. Insulin resistance is a feature of both IFG and IGT, though the site of resistance varies. IFG is characterized by hepatic insulin resistance, while in IGT, resistance is mainly at the level of skeletal muscles. The beta cell dysfunction is however seen in both [10, 12]. This difference in the pathophysiology is reflected in the PG changes following a glucose load with persons with IFG demonstrating impaired early response in contrast to those with IGT who show impairment of both early and late phases of insulin secretion [12–14].

The ADA recommends screening for DM and prediabetes in asymptomatic people in those who are obese or overweight and have one or more additional risk factors as listed above. For all others, testing should begin at 45 years of age, and repeat testing in those with normal results is to be done at a minimum interval of 3–5 years [5].

Diagnostic Methods

Glycated Hemoglobin

With sustained exposure to hyperglycemia, proteins undergo nonenzymatic glycation. Hemoglobin A (HbA), the predominant fraction of hemoglobin in normal adults, also undergoes a similar modification. Three minor fractions of glycosylated hemoglobin are known to occur, namely, HbA1a, HbA1b, and HbA1c, based on their elution properties during electrophoresis. The HbA1c fraction that has been widely employed as a diagnostic test has a hexose moiety attached covalently to the NH2-terminal valine residue of the β-chain of HbA [15]. Several methods have been used to separate this fraction from the nonglycated hemoglobin. These techniques exploit the differences in structure (affinity chromatography and immunoassay), charge (ion-exchange chromatography, high-performance liquid chromatography [HPLC] electrophoresis, and isoelectric focusing), or chemical nature (photometry and spectrophotometry) of the various fractions. HbA1c is a measure of average plasma glucose levels over preceding 3 months [16]. There are several advantages of HbA1c over the measurement of plasma glucose. HbA1c estimation can be done regardless of the time of day or fasting status. It also shows less day-to-day variability and analytical stability [17]. HbA1c also predicts the development of micro- and macrovascular complications of DM as observed in clinical trials like the DCCT and United Kingdom Prospective Diabetes Study (UKPDS). However, it is not free from limitations and can be influenced by other non-glycemic factors (Table 6.1). Diseases affecting red blood cell turnover rate can result in imprecise values.

Table 6.1 Factors affecting HbA1c estimation

Physiological characters	Change expected
Age	HbA_{1c} increases by approximately 0.1% with every 10 years of age – not relevant clinically
Race	Variably reported
Hematological conditions	
Iron deficiency anemia [18, 19]	Falsely elevated in most studies Mechanism – not clear
Hemolytic anemia	Falsely low due to shortened life span of RBCs
Hemoglobin variants (HbF, HbS, HbD, HbE) [20]	Variable based on assay methodology
Analytical interference	
Hyperbilirubinemia	Variably reported interference [20, 21]
Hypertriglyceridemia [20]	Falsely low
Others	
Malaria	Falsely low [22]
Transfusions [23]	Falsely low
Splenectomy	Increases life span of RBC in conditions like hereditary spherocytosis resulting in elevated HbA1c after splenectomy [24]
Renal failure	Falsely low due to shortened erythrocyte life span, frequent blood transfusions, erythropoietin-promoted erythrocytosis, and drug-induced anemia [25]
Alcohol abuse	Falsely low [26]
Aspirin [27]	Modest increase – not clinically relevant

Standardization of HbA1c

The clinical utility of HbA1c largely hinges on the quality of the analytical method used. A plethora of tests are available today for estimating HbA1c. In order to establish uniformity in testing, reporting, and interpreting the HbA1c results, the American Association of Clinical Chemistry (AACC) and the NGSP (National Glycohemoglobin Standardization Program) developed a protocol to standardize the HbA1c test results to those of the DCCT [28].

In 1995, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) sought to establish a true reference method for HbA1c estimation instead of standardizing to a comparison method like the NGSP. Here, hemoglobin is digested using enzymes that cleaves a hexapeptide off the amino terminal of the β-chain. The glycated and nonglycated hexapeptide components are then separated and quantified. HbA1c was calculated as the ratio of two fractions and was reported as a percentage [29]. This method is expensive and laborious making it unsuitable for routine analysis of samples.

Classification of Diabetes Mellitus

It is prudent to try and classify the type of DM in order to identify the best management plan, screen for associated complications and comorbidities, and also screen other members of the family. However, this may not be straightforward in all scenarios. DM can be classified based on the underlying pathogenic mechanisms into the following categories: type 1 DM, type 2 DM, GDM, and secondary DM (Table 6.2) [5, 30].

Table 6.2 Secondary causes of diabetes mellitus

A. Genetic defects of β-cell function
Maturity-onset diabetes of the young (MODY) 3 (HNF-1α)
MODY 1 (HNF-4α)
MODY 2 (glucokinase)
Other rarer forms of MODY
Transient neonatal diabetes
Permanent neonatal diabetes
Mitochondrial DNA
B. Genetic defects in insulin action
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes
C. Diseases of the exocrine pancreas
Pancreatitis
Pancreatectomy
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy
D. Endocrinopathies
Acromegaly
Cushing's syndrome
Glucagonoma
Pheochromocytoma
Hyperthyroidism
Somatostatinoma
Aldosteronoma
E. Drug or chemical induced
Glucocorticoids
Thiazides
Statins
Antipsychotic medication
Antiretroviral therapy
Phenytoin
Thyroid hormone
F. Infections
Congenital rubella
Cytomegalovirus
G. Other genetic syndromes
Down syndrome
Klinefelter syndrome
Turner syndrome
Wolfram syndrome
Friedreich ataxia
Huntington chorea

Type 1 Diabetes Mellitus

Type 1 DM is characterized by complete cellular-mediated destruction of the β-cells resulting in insulinopenia and insulin replacement therapy for survival. Majority of patients present with the constitutional symptoms of DM, namely, polyuria, polydipsia, and polyphagia. One third of the patients can present with diabetic ketoacidosis as the first manifestation [31]. The disease is believed to be precipitated by an environmental insult in a genetically predisposed individual. Type 1 DM is known to be strongly associated with human leukocyte antigen (HLA)-DR3-DQ2 and HLA-DR4-DQ8 haplotypes, alone or in combination [32, 33]. Some HLA haplotypes can offer protection from type 1 DM [34]. In addition, several other putative genes like cytotoxic T-lymphocyte-associated antigen 4, protein tyrosine phosphatase, non-receptor type 22, and insulin variable number tandem repeat affecting disease susceptibility have been identified [35]. Autoantibody against islet antigens like glutamic acid decarboxylase 65, insulin, insulinoma-associated antigen 2, and zinc transporter 8 are seen in majority of patients [36, 37]. The number of antibody positivity correlates with the rate of progression of β-cell failure with 70% of children with two or more antibodies progressing to develop DM [38]. In addition to islet cell autoimmunity, these patients are also predisposed to the development of other autoimmune disorders like Hashimoto thyroiditis, Graves' disease, Addison disease, celiac disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia [5].

A number of environmental triggers have been studied including cow's milk, certain viruses and gut microbiota, although none have been conclusively identified to influence the pathogenesis of type 1 diabetes mellitus [39–43]. A minority of patients with clinical picture consistent with type 1 DM do not have evidence of autoimmunity. This is particularly common in patients of Asian and African ancestry and is not HLA associated [44].

Type 2 Diabetes Mellitus

In contrast to type 1 diabetes, type 2 DM is characterized by relative insulin deficiency due to β-cell dysfunction and resistance to the action of insulin in target tissues. Unlike patients with type 1 DM, patients with type 2 DM at least initially are amenable with oral hypoglycemic agents. Beta-cell loss occurs progressively and can result treatment failure with oral hypoglycemic agents and requirement of insulin for control of hyperglycemia, especially in younger individuals [45]. The global epidemic of type 2 diabetes mellitus parallels that of its prime risk factors - obesity, physical inactivity, and lifestyle modifications. Excessive abdominal adiposity, prior history of GDM, and certain ethnicity (like Asian, African American, Hispanic) are other strong risk factors for developing type 2 DM [5].

Gestational Diabetes Mellitus

GDM has traditionally been defined as any degree of glucose intolerance that is first detected during pregnancy regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy [46]. This definition of GDM, which is based on PG level alone, does not distinguish the underlying pathological process. Hence, this heterogeneous group comprises women with pre-existing insulin resistance and insulin deficiency worsened by deteriorating glucose homeostasis in pregnancy and women with short-term alterations in glucose homeostasis resulting from pregnancy-related physiological changes. Irrespective of the aetiology, the management of these patients remains more or less the same, though women with pregestational diabetes need screening for long-term complications of dysglycemia, which can worsen further as pregnancy progresses [47].

The very first diagnostic criterion for GDM was proposed by O'Sullivan and Mahan in 1964. The authors had suggested a 50 g, 1-h glucose challenge test (GCT) for screening and follow-up of women with a 1-h post glucose load exceeding 140 mg/dl with a confirmatory test. A 100 gram, 3-h OGTT was suggested to confirm the diagnosis. The cutoff levels were validated for the risk of the mother developing diabetes in the future and not for the pregnancy outcomes [48].

This criterion was subsequently modified by the NDDG in the United States and later by Carpenter and Coustan to account for the changes in the methodology of glucose estimation and for using plasma samples instead of whole blood [3]. This modified criterion was widely accepted and endorsed by professional bodies like the ADA and WHO, until the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criterion was proposed, following the results of the pathbreaking hyperglycemia and pregnancy outcomes (HAPO) study. The American College of Obstetricians and Gynecologists (ACOG) still recommends the Carpenter and Coustan criterion [49].

HAPO was a large multinational, multicenter study which included over 23,000 pregnant women of diverse ethnicity. OGTT was administered between 24 and 32 weeks of gestation using 75 g of glucose. A linear relationship was noted between PG levels following OGTT and several primary (umbilical cord-blood C peptide level, birth weight, neonatal hypoglycemia, and rate of cesarean delivery) and secondary outcomes (delivery before 37 weeks of gestation, shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia). The outcomes were directly related to FPG level and independently to 1-h and 2-h PG values [50].

Based on the results of the HAPO trial, IADPSG suggested a single-step, 75 g OGTT to be performed in all pregnant women at 24–28 weeks of gestation. The defined diagnostic cut points for diagnosing GDM were those levels at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. A single value above the suggested cutoff was enough to make a diagnosis of GDM unlike the two-abnormality criteria earlier followed [51].

Universal implementation of the stringent IADPSG criteria is likely to increase the prevalence of GDM as many women with mild GDM are likely to be included. The cost-effectiveness of this approach and its impact on improving maternal and fetal outcome has been questioned. A few studies have however shown that the additional patients diagnosed using the IADPSG criterion when compared to other criteria are at risk for GDM-related complications [52–54]. The IADPSG also recommends diagnostic cutoff values to diagnose GDM in the first trimester. This recommendation was not based on any hard data and was an extrapolation of the results of HAPO study. In 2011, the ADA also adopted the IADPSG criteria.

The NICE in 2015 published its guidelines for diagnosing GDM and had suggested higher FPG cutoff values when compared to that of the IADPSG. The prime reason quoted for choosing higher FPG levels was to reduce the economic burden imposed by the application of lower FPG cutoff on the health-care system. Though this criterion strives to strike

a middle ground, it has not been tested clinically, and its impact on maternal and fetal health will be seen in coming years [55]. The cutoff values for diagnosing GDM using the one-step and two-step strategies according to the ADA are given below [5].

One-Step Strategy

75-g OGTT is recommended with PG measurement when patient is fasting and, at 1 h and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- FPG: 92 mg/dL (5.1 mmol/L)
- 1-hour PG: 180 mg/dL (10.0 mmol/L)
- 2-hour PG: 153 mg/dL (8.5 mmol/L)

Two-Step Strategy

Step 1: Perform a 50-g GCT (non-fasting), with PG measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. If the PG level measured 1 h after the load is ≥130 mg/dL, ≥135 mg/dL, or ≥140 mg/dL (7.2 mmol/L, 7.5 mmol/L, or 7.8 mmol/L), proceed to a 100-g OGTT. The ACOG recommends either 135 mg/dL (7.5 mmol/L) or 140 mg/dL (7.8 mmol/L).

Step 2: The 100-g OGTT should be performed when the patient is fasting. The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured at fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

- FPG: 95 mg/dL (5.3 mmol/L)
- 1-hour PG: 180 mg/dL (10.0 mmol/L)
- 2-hour PG: 155 mg/dL (8.6 mmol/L)
- 3-hour PG: 140 mg/dL (7.8 mmol/L)

Screening for GDM

Recommendations for choosing the target population for GDM screening are shrouded by controversies and lack of uniformity among the existing guidelines. The WHO and ADA recommend universal screening of all pregnant women, while the NICE guidelines recommend a selective screening strategy [55, 56]. The selective screening approach is likely to miss a significant proportion of women who develop GDM in the absence of traditional risk factors [57, 58]. The ADA recommends screening for diabetes in women with risk factors for diabetes at the first prenatal visit using its standard diagnostic criteria. Those who are not known to have diabetes are to be screened at 24–28 weeks of gestation using a one-step or a two-step approach [5].

Screening for Persistent Diabetes After Pregnancy

The majority of women diagnosed with GDM will revert to normalcy in the immediate postpartum period leaving a small proportion with continuing hyperglycemia. The lifetime risk of developing type 2 DM is as high as 50–70% [59]. The immediate postnatal period provides a window of opportunity to identify this precarious cohort of at-risk women. The ADA recommends screening at 4–12 weeks postpartum using the OGTT and advises lifelong follow-up and screening at least every 3 years [5]. The NICE guidelines recommend using FPG or HBA1c after 13 weeks, and an annual testing with HbA1c is recommended if the first test is normal [55].

Specific Types of Diabetes Due to Other Causes

This heterogeneous group includes monogenic forms of diabetes and others with an underlying genetic defect affecting insulin secretion and action, diseases affecting the pancreas, diabetes associated with endocrine disorders, drug-induced diabetes, and post-transplantation diabetes.

Monogenic Diabetes Syndromes

Single gene defects causing β-cell dysfunction constitute around 1–2% of all cases of DM [60]. MODY is characterized by defective insulin secretion with intact insulin action. Thirteen different genetic loci have been identified so far and are inherited in an autosomal dominant fashion [5]. The most commonly reported types include MODY 2, MODY 3, and MODY 1. There is wide variation in severity and clinical course of the disease among the various types. Some forms show excellent response to sulfonylurea, and certain subtypes require insulin therapy for management. Identification of additional malformations or multisystem involvement helps in arriving at a diagnosis and also necessitates a multipronged approach to the management of these patients.

Neonatal Diabetes

Infants developing DM within the first 6 months of life should undergo genetic testing for identifying potential genetic defects. Neonatal diabetes can be transient or permanent and in patients who have an initial transient presentation can develop DM later in life. Making the correct diagnosis in these patients cannot be overemphasized as switching to oral hypoglycemic agents is possible in a subset of them with potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11) and ATP-binding cassette, subfamily C, and member 8 (ABCC8) mutations, thus greatly reducing the burden of management on the afflicted family [61, 62].

Diabetes Mellitus Secondary to Pancreatic Disorders

Acute and Chronic Pancreatitis

Acute pancreatitis often results in defective glucose metabolism at presentation. In many patients this defect is transient. However, the risk of developing DM is increased during follow-up of these patients. Chronic inflammation and destruction of pancreatic tissue can occur due to several aetiologies. Although the islets are more resistant to the destructive process in the earlier stages, significant β-cell loss eventually ensues resulting in varying degree of dysglycemia.

Fibrocalculous Pancreatitis

Tropical chronic pancreatitis or fibrocalculous pancreatic diabetes (FCPD) is a specific form of chronic pancreatitis which is encountered in several tropical countries as the name suggests. The aetiology of this condition is elusive, and a number of hypotheses exist to explain its occurrence. The earlier popular theories linking consumption of cassava with FCPD have been challenged [63]. Familial clustering of cases makes genetic predisposition a plausible risk factor. Several candidate genes have been explored in this context with the most prominent ones being serum protease inhibitor Kazal type 1 (SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and chymotrypsinogen C [64, 65]. Increased oxidative stress has also been reported in patients with FCPD [66].

Almost 90% of patients develop diabetes eventually due to β-cell destruction [67]. Although defective insulin secretion is the cardinal defect, development of insulin resistance is also known [68]. Defects in shifting of glucose transporter 2 (GLUT2) into the hepatocyte membranes during the postabsorptive phase have been shown in animal models of chronic pancreatitis. This can result in postprandial glucose excursions [69]. Also, pancreatic polypeptide secreted by the islet cells plays a role in the expression of insulin receptor gene in the liver. Deficiency of pancreatic polypeptide along with insulin deficiency could contribute to the development of diabetes [70]. Glucagon levels on the other hand have been postulated to be relatively unaffected or even elevated in a few studies indicating a selective destruction of the islet cells [71, 72]. However, not all studies corroborate this theory and it needs further analysis.

In patients presenting with symptoms of chronic pancreatitis, typical large ductal calcifications and dilatation of the pancreatic ducts visualized on imaging point to a diagnosis of FCPD. Diabetes in this scenario is generally ketosis resistant with most patients requiring insulin therapy [68, 72]. Most patients also have evidence of exocrine pancreatic insufficiency at the time of diagnosis, and enzyme replacement therapy can worsen glycemic control by improving malabsorption.

Pancreatic Ductal Adenocarcinoma

The relationship between pancreatic ductal adenocarcinoma (PDAC) and DM is complex. DM is believed to be a risk factor for developing PDAC, while the malignancy per se has been postulated to affect glucose homeostasis. Around 85% of patients with PDAC have IGT or DM [73]. A meta-analysis of 36 studies indicated that risk of developing PDAC is two-fold higher in patients with DM [74]. Also, studies show that 25–50% of patients with PDAC develop diabetes in the preceding 1–3 years of their diagnosis [75]. Pancreatitis related to the tumor, destruction of islets, and development of insulin resistance are the postulated mechanisms to explain the development of diabetes. Animal studies suggest that secretory products of the tumor cells can impair glucose metabolism [76]. New-onset DM in these patients is known to improve with resection of the tumor, further strengthening the link between the two [73].

Endocrinopathies

Acromegaly

Majority of patients with acromegaly are diagnosed to have either prediabetes or diabetes at presentation. The reported prevalence of prediabetes varies between 16% and 46% [77–79] and that of DM is between 15% and 38% [80]. The risk of developing diabetes is strongly associated with higher growth hormone (GH) levels, family history of diabetes, hypertension, increasing age and disease duration [79, 80]. Identification and appropriate management of diabetes is essential to prevent the increased cardiovascular morbidity and mortality associated with it.

GH plays an important role in regulating intermediary metabolism. It stimulates lipolysis, suppresses lipogenesis and also antagonizes the insulin-induced suppression of gluconeogenesis, resulting in increased hepatic glucose output [81, 82]. Increased levels of free fatty acids induce a state of insulin resistance at the liver and peripheral tissues [83]. Inability of the β-cells to compensate this state of insulin resistance results in the development of diabetes. Direct inhibition of insulin signaling by interfering with the downstream signaling molecules like insulin receptor substrate-1 (IRS-1) and phosphatidylinositol 3 (Pi-3) kinase also contributes to the development of diabetes [84]. Most patients with acromegaly undergo surgical resection and radiotherapy. Some in addition require medical management for ameliorating disease activity. The treatment modality chosen can also influence glycemic status. Surgical removal of the tumor and subsequent reduction of GH and insulin-like growth factor-1 levels are associated with improvement of glycemic status [85, 86]. Dopamine agonists have a modest effect on reducing PG levels, and the effect of somatostatin agonists

(SSA) on glucose metabolism is conflicting [87]. SSA can inhibit insulin and incretin secretion and worsen glucose levels, especially in those with an underlying insulin secretion defect, though this is often offset by the reduction in GH level and improvement of disease status [87]. Among the SSA, pasireotide seems to have a greater propensity to alter glycemic control and its effect is dose dependent. This tendency can be explained by its greater affinity for somatostatin receptor subtype 5 expressed in the islet cells when compared to other SSA [88]. Pegvisomant is another agent which can improve glycemic control by containing disease activity. There is a reduction in FPG levels and improved insulin sensitivity has been noted in most studies [87].

Cushing's Syndrome

Glucocorticoids exert a multitude of effects on the various organs involved in carbohydrate metabolism. It stimulates lipoprotein lipase activity and lipolysis [89]. At the liver, increased glucose output results from increased rate of gluconeogenesis. These actions, in addition to reduced glucose uptake by muscles and increased proteolysis, result in a state of insulin resistance [90, 91]. Reduced expression of glucokinase and GLUT2 in the pancreatic β-cells results in reduced insulin secretion, which compounds the diabetogenic action of glucocorticoids [92]. Glucocorticoids can interfere with the action of insulin directly by inhibiting downstream signaling molecules like IRS-1 and Pi-3 kinase [93, 94]. Disordered glucose metabolism is seen in 50% of patients with endogenous Cushing's syndrome with two third of them developing diabetes [95, 96]. Increased prevalence of diabetes and prediabetes is also observed in cases of adrenal incidentaloma associated with subclinical Cushing's syndrome [97]. Glucose metabolism generally improves with cure, though these patients seem to have a continuing greater risk of cardiovascular morbidity. Most drugs used in the management of Cushing's syndrome like ketoconazole, dopamine agonists, and metyrapone have a favorable effect on glycemic control. Pasireotide on the other hand is known to worsen hyperglycemia [87]. The frequency of hyperglycemia-related adverse effects is lower in patients with acromegaly who are treated with pasireotide long-acting release (57.3–67%) than those with Cushing's syndrome who are treated with the subcutaneous formulation (68.4–73%) [98].

Treatment with metformin is recommended as first-line therapy for patients on pasireotide with persistent hyperglycemia. Dipeptidyl peptidase-4 inhibitor can be added on in patients failing monotherapy with metformin. Glucagon-like peptide-1 receptor agonist should be added in place of the dipeptidyl peptidase-4 inhibitor if HbA1C continues to remain above 7.0%. Insulin is started as a final resort if adequate glycemic control is not achieved with above measures [98].

Other Endocrine Disorders

Glucagonoma

Islet cell tumors secreting glucagon are rare with a reported incidence of 0.04–0.12 per million per year [99]. They are exclusively seen in the pancreas with the tail being the most common location [100]. In two third of the cases, the tumor is malignant and half of them have evidence of metastasis at the time of diagnosis [101]. DM is known to occur in 40–95% of patients, along with other symptoms like weight loss, gastrointestinal manifestations, and neurological symptoms like ataxia, dementia, optic atrophy, and proximal muscle weakness [102, 103]. The characteristic dermatological lesion called necrolytic migratory erythema is seen in 90% of patients. Glucagon increases hepatic gluconeogenesis and also increases lipolysis and fatty acid oxidation [104]. Diabetes mellitus is generally mild and nonketotic.

Somatostatinoma

Somatostatinomas are rarer than glucagonomas and occur in less than 1 in 40 million people [105]. They produce excess somatostatin which directly suppresses insulin and glucagon secretion causing diabetes. The most common clinical manifestation is related to mass effects, and metabolic manifestations occur in a minority [103, 106].

Drug-Induced Diabetes Mellitus

Thiazide Diuretics

Studies reporting the incidence of diabetes with thiazide diuretics have been conflicting. A recent meta-analysis of 22 studies showed an increased risk of diabetes with thiazides and beta blockers when compared to other antihypertensive agents like angiotensin converting enzyme inhibitors and angiotensin receptor blockers [107]. Hypokalemia caused by thiazides has been linked to impaired insulin secretion in addition to other mechanisms like decreased insulin sensitivity, increased hepatic glucose production, alteration in body fat composition, and stimulation of glucagon [108, 109].

Statins

Statins are widely used as the first choice for their potent low-density lipoprotein-lowering effect. Evidence for their diabetogenic potential was first demonstrated in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial in which 32% increased risk of new-onset diabetes was noted in the statin arm [110]. Subsequently, similar risk for diabetes has been reported for other statins, prompting the Food and Drug Administration (FDA) in 2012 to add a warning of the increased risk of diabetes with statin use. A meta-analysis of 113,394 subjects showed a 15%

added risk of new-onset diabetes with 80 mg of atorvastatin and 25% with rosuvastatin at a dose of 20 mg [111]. Statins are also known to worsen glycemic control in patients with DM. The risk for DM with statins is more pronounced in those who already have the traditional risk factors. Mechanisms by which statins induce and aggravate diabetes include impaired pancreatic secretion of insulin (by blocking calcium channels), reduced expression of glucose transporter 4 (GLUT4) interfering with glucose uptake and disposal by skeletal muscle, and exacerbation of insulin resistance in liver and peripheral tissues [112]. Lipophilic statins like simvastatin and atorvastatin are transported across cellular membranes with ease, explaining their greater propensity to cause diabetes [113].

Beta Blockers

β-Blockers impair insulin secretion, increase hepatic glucose production, and impair lipoprotein clearance. The risk of diabetes is higher with nonselective beta blockers [108, 114].

Antipsychotic Medications

Weight gain is a common adverse effect of almost all antipsychotic medications. The magnitude of weight gain varies with the different drugs, and the greatest risk is associated with clozapine and olanzapine [115]. Aripiprazole has minimal effect on weight gain [116]. Maximum weight gain occurs in the first year of therapy and is related to the duration of exposure. Increased appetite and consequent food intake, reduced satiety, and effects on adipose tissue like increased lipogenesis contribute to weight gain [117, 118].

The risk for diabetes is also greater, especially with second-generation antipsychotics. It is estimated to be 32% higher in this group. Drugs causing increased weight gain are associated with greater risk for diabetes. In some patients, this effect seems to be independent of the change in body weight. Blockage of muscarinic receptor 3 by the antipsychotic medication is known and this can hamper insulin secretion [119]. Impaired insulin sensitivity at the peripheral tissues is also known to occur, possibly by interfering with functioning of glucose transporters [118].

Antiretroviral Therapy

Risk of new-onset diabetes is a well-known complication of antiretroviral therapy, particularly with stavudine, indinavir, and didanosine. The drugs per se and lipodystrophy associated with their use contribute to metabolic derangements. PG abnormalities are seen in 25% of patients following initiation of protease inhibitors. Redistribution of adipose tissue is the key factor contributing to increased insulin resistance. Age, body mass index, and waist circumference are additional risk factors [120–122].

Post-transplantation Diabetes Mellitus

New-onset diabetes after transplantation (NODAT) refers to the occurrence of diabetes in previously nondiabetic persons after organ transplantation. Twenty to fifty percent of patients following kidney transplant, 9–21% after liver transplants, and approximately 20% after lung transplants are diagnosed to have NODAT at 12 months post-transplant [123]. NODAT increases the risk of allograft loss, infections, and mortality in post-renal transplant recipients [124–127]. Patients with NODAT also develop microvascular complications associated with diabetes at an accelerated rate and are at an increased risk for cardiovascular morbidity and mortality [128]. In addition to the traditional risk factors for DM, exposure to immunosuppressive agents, CMV and hepatitis C infection, and acute rejection post-transplantation augment the risk of developing NODAT [129–132].

The ADA recommends screening for hyperglycemia in all patients post-transplantation using OGTT. A diagnosis of NODAT can be made using the standard criteria if the patient is on a stable immunosuppressive regimen and is free from infections [5].

Concluding Remarks

- Diabetes mellitus is a global epidemic and is associated with multiple morbidities and mortality. The importance of adequate glycemic control in order to circumvent these complications is proven beyond doubt. However, there still exists a controversy over the appropriate diagnostic criteria for diabetes mellitus and prediabetes, which is constantly evolving.
- Diabetes mellitus is the final common outcome of disrupted insulin secretion and/or action. An array of aetiologies is known to cause this disruption, ranging from monogenic and polygenic predisposition to endocrinopathies and drug therapy.
- Prediabetes is an intermediate state of hyperglycemia and includes the states of impaired fasting glucose and impaired glucose tolerance. The rise in the incidence of prediabetes globally, mirrors that of diabetes mellitus. Screening for and detection of prediabetes is an opportunity to intervene and prevent the progression to diabetes mellitus and its complications.
- Gestational diabetes mellitus is defined as any degree of hyperglycemia that is first detected during pregnancy and encompasses true gestational mellitus and pre-existing diabetes mellitus. There is no one universal criteria for diagnosing GDM. Several countries have adopted differing criteria that best meet the needs of their population.

Glossary

Diabetes mellitus Diabetes is derived from its Greek root which means "to pass through," and the word mellitus means "from honey." Diabetes mellitus is defined by the World Health Organization as a metabolic syndrome characterized by chronic hyperglycemia resulting from any of the several conditions that cause defective insulin secretion and/or action.

Prediabetes It is a state characterized by metabolic abnormalities that increase the risk of developing diabetes mellitus and its complications.

Impaired glucose tolerance Defined as an intermediate state where blood glucose levels are above normal but do not satisfy the criteria for diagnosing diabetes mellitus.

Gestational diabetes mellitus Defined as any degree of glucose intolerance that was first detected during pregnancy regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy.

Neonatal diabetes Development of diabetes in the first 6 months of life.

NODAT (new-onset diabetes after transplantation) Defined as occurrence of diabetes in previously nondiabetic persons after organ transplantation.

Multiple-Choice Questions

1. Falsely low HBA1c levels can be seen in all of the following conditions except:
   (a) Hemolytic anemia
   (b) Hypertriglyceridemia
   (c) Postsplenectomy
   (d) Renal failure
   (e) Malaria
2. Maturity-onset diabetes of the young is inherited in _____ fashion.
   (a) Autosomal recessive
   (b) Autosomal dominant
   (c) X-linked dominant
   (d) X-linked recessive
   (e) Mitochondrial
3. Which of the following treatment modalities for acromegaly can worsen glycemic control:
   (a) Surgery
   (b) Radiotherapy
   (c) Dopamine agonists
   (d) Pasireotide
   (e) Pegvisomant
4. Glucocorticoid excess results in diabetes mellitus through which of the following mechanisms?
   (a) Stimulating lipolysis
   (b) Increasing rate of gluconeogenesis
   (c) Inducing a state of insulin resistance
   (d) Interfering with action of insulin by affecting downstream signaling molecules
   (e) All of the above
5. Which of the following drugs are known to cause or worsen diabetes mellitus?
   (a) Dopamine agonists
   (b) Thiazides
   (c) Loop diuretics
   (d) Alpha adrenergic blockers
   (e) All of the above
6. Genetic syndrome associated with diabetes mellitus is
   (a) Turner syndrome
   (b) Edward syndrome
   (c) Patau syndrome
   (d) Cri du chat syndrome
   (e) Down syndrome
7. Endocrinopathy associated with secondary diabetes is
   (a) Adrenal insufficiency
   (b) Somatostatinoma
   (c) Hyperthyroidism
   (d) Hypoparathyroidism
   (e) Insulinoma
8. ADA recommendations to begin screening for diabetes mellitus for all patients at _____ years of age.
   (a) 40 years
   (b) 45 years
   (c) 50 years
   (d) 35 years
   (e) 55 years
9. The rate of progression of prediabetes to diabetes mellitus in the absence of intervention is
   (a) 1–2% per year
   (b) 5–10% per year
   (c) 20% per year
   (d) 40% per year
   (e) 60% per year
10. The HbA1c cutoff recommended by the ADA for diagnosing diabetes mellitus is
    (a) ≥5.7%
    (b) ≥6.7%
    (c) ≥7%
    (d) ≥7.5%
    (e) ≥6.5%

Correct Answers

1. (c) Postsplenectomy
2. (b) Autosomal dominant
3. (d) Pasireotide
4. (e) All of the above

5. (b) Thiazides
6. (a) and (e)
7. (b) and (c)
8. (b) 45 years
9. (b) 5–10% per year
10. (e) ≥6.5%

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