

# Update on Diabetes Classification



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## KEYWORDS

- Classification of diabetes mellitus • Gestational diabetes mellitus
- Latent autoimmune diabetes of adults • Monogenic diabetes
- Maturity-onset diabetes of the young • Neonatal diabetes • Secondary diabetes
- Type 1 and Type 2 diabetes mellitus

## KEY POINTS

- The classification of diabetes mellitus is evolving as we work to fully understand the pathogenesis of the major forms.
- The goal of classification is to say something meaningful about the cause, natural history, genetics, heritability, clinical phenotype and optimum treatments of a disease. In the case of diabetes, this is getting harder to do rather than easier.
- Monogenic diabetes mellitus remains undiagnosed in more than 90% of the individuals who have this form of diabetes caused by one of the known gene mutations.

*“The first step in wisdom is to know the things themselves; this notion consists in having a true idea of the objects; objects are distinguished and known by classifying them methodically and giving them appropriate names. Therefore, classification and name-giving will be the foundation of our science.”*

—Carolus Linnaeus, 1735

## INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both. The chronic hyperglycemia of diabetes results in disturbances of carbohydrate, fat, and protein metabolism and is associated with long-term damage, dysfunction, and failure of various

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organs, especially the eyes, kidneys, nerves, heart, and blood vessels.<sup>1,2</sup> The goal in diagnosing diabetes mellitus is to identify those with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications. Although there are several existing useful classifications (see American Diabetes Association 2014 guidelines for example), one can envision three schema to classify the disease: (1) based on the pathophysiology, (2) based on a specific gene defect itself, or (3) based on another common phenotype. Some classifications are more appropriate for research, others for patient care. The goal of classification is to say something meaningful about the cause, natural history, genetics, heritability, clinical phenotype, and optimum therapies. In the case of diabetes, this is getting harder to do rather than easier. No classification scheme is ideal, and all have some inconsistencies and overlap. Diabetes mellitus classification will continue to evolve as we work to fully understand the pathogenesis of the major forms.

### DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

The World Health Organization (WHO) diagnostic criteria for diabetes mellitus include fasting plasma glucose level  $\geq 126$  mg/dL (7.0 mmol/L) or 2-hour plasma glucose level  $\geq 200$  mg/dL (11.1 mmol/L) after a 75-g oral glucose load.<sup>1</sup> More recently, a glycosylated hemoglobin level of  $\geq 6.5\%$  is recommended by WHO as the cut point for diagnosing diabetes.<sup>3</sup> Impaired glucose tolerance, a condition of intermediate hyperglycemia with increased risk of progression to frank diabetes, is defined as a 2-hour plasma glucose level  $\geq 140$  mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L) after a 75-g oral glucose load. Impaired fasting glucose is defined as fasting glucose level between 110 mg/dL and 125 mg/dL (6.1–6.9 mmol/L).

These categories, impaired glucose tolerance and impaired fasting glucose, as well as a glycosylated hemoglobin value between 5.7% and 6.4% are collectively associated with increased risk of diabetes development and are often known as prediabetes.<sup>4</sup>

### EXISTING CLASSIFICATIONS

Until recently, the prevailing conceptual classification was that there were two primary types of diabetes mellitus: autoimmune (type 1) and nonautoimmune (type 2). Every other metabolic disorder of glucose regulation was classified into a special category of (mostly type 2 related, nonautoimmune) diabetes, such as, monogenic, gestational, steroid induced, cystic fibrosis related, postpancreatectomy, acromegaly associated, human immunodeficiency virus (HIV) associated, hepatitis C virus associated, polycystic ovary syndrome related, and ketosis prone diabetes.

Classification of diabetes mellitus has suffered from a lack of clear etiology of either type 1 or type 2. Advances in classification terminology have included the evolution of autoimmune diabetes from juvenile to insulin dependent to type 1 diabetes mellitus (T1DM). However T1DM has been further divided into antibody positive (type 1a) and antibody negative (type 1b).<sup>5</sup> Others have shown that the slower adult-onset forms (latent autoimmune diabetes of adults [LADA]) can also be further subdivided and may include more subtle forms of immune involvement, which furthermore may include a subset of individuals otherwise thought to have type 2 (Fig. 1).<sup>6</sup>

#### *Type 1 Diabetes Mellitus*

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T1DM is generally autoimmune in etiology with, 1 of 4 autoantibodies to  $\beta$ -cell antigens are being positive, including islet cell antibodies, glutamic acid decarboxylase-65 antibody, insulinoma antigen-2 antibody, or insulin autoantibodies.<sup>6,7</sup> Autoantibodies that

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