International Textbook of Diabetes Mellitus
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Fourth edition

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As the epidemic of diabetes continues to expand in parallel with the rapid spread of obesity, healthcare providers strive to find interventions to reduce the morbidity, mortality, and rising costs associated with this devastating disease, which ravages both the micro- and the macrovasculature. Although the increase in incidence of type 2 diabetes may be attributed to the expanding girth of the population coupled with a lack of physical activity, the marked increase in the incidence of type 1 diabetes remains unexplained. Our knowledge of the cellular, biochemical, and molecular etiology of impaired insulin action and beta-cell failure has expanded enormously, but the genetic basis of both type 1 and type 2 diabetes and their associated complications is still by and large undefined. Despite the introduction of multiple new classes of antidiabetic agents for the treatment of type 2 diabetes, and newer insulin preparations, insulin delivery systems, and glucose-sensing devices for the management of type 1 diabetes, glycemic control is suboptimal in approximately half of all diabetic patients and the excess risk for macrovascular complications is largely unexplained. In many parts of the world, these treatment advances are not available and instituting behavioral modification programs at the societal and individual level is proving to be inadequate in curbing the growing epidemic of obesity. Whether the introduction of novel weight loss medications will stem the tide of obesity remains to be determined.

The fourth edition of the *International Textbook of Diabetes Mellitus* will continue to be the most widely referenced textbook of diabetes worldwide and draws upon the expertise of leading basic scientists, clinicians, educators, and healthcare professionals globally to provide the most updated information on advances in diabetes research and clinical care. This information will be an invaluable resource and provide the practicing physician, as well as the basic scientist and clinical investigator, with the requisite resources to advance them to the frontiers of biomedical research in the fields of diabetes, metabolism, and obesity and to provide them with state-of-the-art knowledge to optimize clinical care for their diabetic patients.

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SECTION I

Epidemiology
CHAPTER 1
Classification of diabetes mellitus and other categories of glucose intolerance

Dianna J. Magliano, Paul Zimmet and Jonathan E. Shaw
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Key points

- The classification and diagnosis of diabetes is based on etiology and not on pharmacologic treatment.
- Diagnoses of diabetes are made using fasting plasma glucose, 2-hour postchallenge of glucose or HbA1c.
- Differentiation between type 1 and type 2 diabetes is usually straightforward but can be difficult among obese children and adults.
- Precise diagnoses of certain monogenic diabetes using genetic testing can be useful as the outcomes can influence treatment decisions.
- A range of commonly used drugs such as statins and glucocorticoid steroids can lead to the development of diabetes.

Historical perspective and current classifications

Previous classifications

In 1965, an Expert Committee on Diabetes Mellitus published the first World Health Organization (WHO) report on diabetes classification [1]. The report includes one of the first attempts at international consensus on a classification. They decided to classify diabetes: “… based on the age of recognized onset, which seemed to be the only reliable means of classification for universal use.”

The report also recognized certain specific types of diabetes including brittle, insulin-resistant, gestational, pancreatic, endocrine, and iatrogenic diabetes. Since then, several pathogenic mechanisms have been described and long-term studies have shown different courses and outcomes of different types of diabetes.

A revised classification of glucose intolerance, was formulated by the National Diabetes Data Group (NDDG) [2]. This was amended and adopted in the second report of the WHO Expert Committee in 1980 [3] and in a modified form in 1985. The 1980 Expert Committee proposed two major classes of diabetes mellitus and named them insulin-dependent diabetes mellitus (IDDM) or type 1, and non-insulin-dependent diabetes mellitus (NIDDM) or type 2 [3]. In the 1985 Study Group Report, the terms type 1 and type 2 were omitted, but the classes IDDM and NIDDM were retained and a new class of malnutrition-related diabetes mellitus (MRDM) was introduced [4]. The 1985 WHO classification was essentially based on clinical descriptions, with a specific focus on the pharmacologic management of patients (i.e., insulin-dependent, non-insulin-dependent, gestational). The question as to whether certain clinical forms

Introduction

A critical requirement for orderly epidemiologic, genetic and clinical research, and indeed for the management of diabetes mellitus and other forms of glucose intolerance is an appropriate classification system. Furthermore, a hallmark in the process of understanding the etiology of a disease and studying its natural history is the ability to identify and differentiate its various forms and place them into a rational etiopathologic framework. While there have been a number of sets of nomenclature and diagnostic criteria proposed for diabetes, no systematic categorization existed until the mid 1960s [1]. Now diabetes mellitus is recognized as being a syndrome, a collection of disorders that have hyperglycemia and glucose intolerance as their hallmark, due either to insulin deficiency or to impaired effectiveness of insulin’s action, or to a combination of these.
of diabetes (such as the so-called “tropical diabetes”) had been given adequate priority to correct hierarchic order that was raised many years before probably led to the introduction of MRDM, although more precise epidemiologic data and a better assessment were needed, and called for.

Both the 1980 and 1985 reports included other types of diabetes and impaired glucose tolerance (IGT) as well as gestational diabetes mellitus (GDM). The 1985 classification was widely accepted and used internationally, and represented a compromise between clinical and etiological classifications. Furthermore, it permitted classification of individual patients in a clinically useful manner even when the specific etiology was unknown. The 2011 American Diabetes Association (ADA) [5] classifications or staging of diabetes still include clinical descriptive criteria but a complementary classification according to etiology is recommended by both organizations.

In 1999, the WHO incorporated an approach developed by Kuzuya and Matsuda [6], which clearly separated the criteria related to etiology from those related to the degree of deficiency of insulin or insulin action, and defined each patient on the basis of these two sets of criteria (Figure 1.1). It is now well established that diabetes may progress through several clinical stages during its natural history, quite independent of its etiology. The clinical staging reflects this and, indeed, individuals may move from one stage to another stage in both directions (Figure 1.1). Even if there is no information concerning the underlying etiology, persons with diabetes or those who are developing the disease can be categorized by stage according to clinical characteristics.

**Current classification**

The current classification allows for various degrees of hyperglycemia in individuals irrespective of the disease process. These are glycemic stages ranging from normoglycemia (normal glucose tolerance) to hyperglycemia where insulin is required for survival. All individuals with the disease can be categorized according to clinical stage [7]. The stage of glycemia may change over time depending on the extent of the underlying disease processes. As shown in Figure 1.1, the disease process may be present but may not have progressed far enough to cause hyperglycemia. The etiological classification is possible as the defect or process which may lead to diabetes may be identified at any stage in the development of diabetes, even at the stage of normoglycemia. As an example, the presence of islet cell antibodies (ICA) and/or antibodies to glutamic acid decarboxylase (anti-GAD) [8] in a normoglycemic individual indicates the autoimmune process, which underlies type 1 diabetes, is present, although the individual may or may not ultimately develop diabetes [7.9]. For type 2 diabetes, there are few useful highly specific indicators, though the presence of risk factors such as obesity indicates the likelihood of developing type 2 diabetes. Hopefully, future research will reveal some specific markers of the type 2 diabetes disease process.

<table>
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<tr>
<th>Types</th>
<th>Normoglycemia Normal glucose tolerance</th>
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<tr>
<td>Type 1</td>
<td></td>
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<tr>
<td>• Autoimmune</td>
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<td>• Idiopathic</td>
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<td>Type 2</td>
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<td>• Predom.</td>
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<td>• insulin resistance</td>
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<td>• Predom. insulin secretory defects</td>
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<tr>
<td>Other specific types</td>
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<tr>
<td>• Genetic defects of β-cell function</td>
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<td>• Genetic defects of insulin action</td>
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<td>• Diseases of exocrine pancreas</td>
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<td>• Drug or chemical induced</td>
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<tr>
<td>• Others</td>
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<td>Gestational hyperglycemia</td>
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**Figure 1.1** Disorders of glycemia: etiologic types and clinical stages. Source: World Health Organization 1999 [7]. Reproduced with permission of the WHO.