NEW CLASSIFICATION AND DIAGNOSTIC CRITERIA OF DIABETES MELLITUS BY THE JAPAN DIABETES SOCIETY*

Takeshi KUZUYA**


Abstract: The major points of the report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus by the Japan Diabetes Society (1999) are described. For classification, both etiological classification and the staging of metabolic abnormality are adopted. For diagnosis, cutoff levels of fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) after 75g oral glucose load are proposed as follows; diabetic type, FPG ≥126mg/ dl or 2hPG ≥200mg/ dl; normal type, FPG <110mg/ dl and 2hPG <140mg/ dl; borderline type, neither diabetic nor normal type. Diabetes is diagnosed when persistent hyperglycemia of diabetic type is recognized on repeated tests, but if there is either of typical symptoms of diabetes, HbA1c≥6.5%, or diabetic retinopathy, diabetes can be diagnosed by a single plasma glucose of diabetic type. New criteria for gestational diabetes are also presented.

Key words: Diabetes mellitus; Diagnosis of diabetes; Classification of diabetes by etiologies; Staging of diabetes

Introduction

The main purpose of treating diabetes is to prevent the acute complications of diabetes, and to prevent and delay the chronic complications of diabetes. In selecting the diagnostic criteria for diabetes, the most important point is how to identify persons at risk of diabetes-specific complications, early and accurately.

Recently, new classification and diagnostic criteria have been proposed by the American Diabetes Association (ADA),1 World Health Organization (WHO),2) and Japan Diabetes Society (JDS).3) This article describes the major points of the report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus of the Japan Diabetes Society.

The Concept of Diabetes Mellitus

Diabetes mellitus is a group of diseases sharing the following features in com-
mon despite heterogenous etiologies.

(1) Chronic hyperglycemia and other characteristic metabolic abnormalities occur due to the decreased action of insulin, which results from decreased secretion of insulin, and/or decreased insulin sensitivity (insulin resistance). Various mechanisms can cause the deficiency of insulin action.

(2) Symptoms may be absent when metabolic abnormalities are mild, but typical symptoms (i.e., thirst, polydipsia, polyuria, and weight loss) occur with the development of overt hyperglycemia. In severe cases, ketoacidosis or hyperglycemic-hyperosmolar state may occur, sometimes leading to coma.

(3) Patients with diabetes are at risk to develop specific complications (retinopathy, nephropathy, and neuropathy). Arteriosclerosis is also accelerated in patients with diabetes.

### Classification of Diabetes Mellitus and Related Glucose Intolerance

The new classification is primarily based on etiologies (Table 1). The staging of patho-physiology by degree of deficiency of insulin is also adopted. The previous terms, insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), are abandoned. Instead, the terms type 1 and type 2 diabetes mellitus are used for etiological classification.

#### 1. Etiological classification

Type 1 diabetes occurs by deficiency of insulin due to the destructive lesions of pancreatic beta cells, which usually leads to absolute insulin deficiency. Auto-
The immune process is thought to be the main mechanism to destroy beta cells, but in a few cases the evidence for autoimmune mechanism cannot be obtained. Such cases are classified as a group of idiopathic etiology.

Type 2 diabetes comprises the majority of diabetic patients. This type of diabetes develops by a decrease in insulin secretion and/or a decrease in insulin sensitivity (insulin resistance). The relative contribution of these two factors varies among patients. Obesity is common, and even if the patients are not obese at present, many of them have been obese before the onset of diabetes. Probably, the genetic and precipitating environmental factors of type 2 diabetes are quite heterogenous.

Other types of diabetes and glucose intolerance due to specific causes are divided into two groups. Group A includes diabetes in which specific DNA abnormalities have been identified as a cause of diabetes, and Group B includes diabetes associated with other pathologic conditions or diseases. Group A is further divided into genetic abnormalities of beta cell function, and genetic abnormalities of insu-
lin action mechanisms. Group A (1) includes so-called MODYs (maturity-onset type diabetes of the young), non-insulin-dependent diabetes of autosomal dominant inheritance with onset at young ages. Several different DNA abnormalities have been recently discovered in MODY families. Group A (1) also includes abnormalities of insulin gene and mitochondrial DNA. Group A (2) includes various abnormalities of insulin receptor gene. Diabetes and glucose intolerance associated with other diseases or conditions (Group B) are similar to the previous classification. This group includes so-called 'secondary diabetes' such as pancreatic diseases, endocrine diseases and so on.

Gestational diabetes mellitus is given a special place, because mild degree of glucose intolerance may produce special problems during pregnancy. It will be discussed later.

2. Staging of patho-physiological states by the degree of metabolic abnormality

(Fig. 1)

Staging of patho-physiological states includes normal, borderline and diabetic ranges according to the degree of hyperglycemia and deficiency of insulin action. Diabetic range is further divided into 3 stages; (1) insulin is not necessary for treatment, (2) it is necessary for glycemic control, and (3) insulin is indispensable to prevent ketosis and for survival. Stages (1) and (2) correspond to previous NIDDM, the stage (3) to previous IDDM.

In each individual, these stages may vary according to the deterioration and improvement of metabolic state, as expressed by arrows in Fig. 1. The arrow toward the right represents deterioration of metabolism, and the arrow toward the left represents its improvement. The filled portion of arrows is the state which can be called 'diabetes'. The arrows toward the left are expressed by as filled lines for their full length. It is based on the idea that, if diagnosis of diabetes is once established, the patient should be regarded as diabetes and should be followed, even when glucose tolerance is improved to borderline or normal ranges. The combined use of both etiological classification and staging of metabolic abnormality can better describe the state of each patient.

The Diagnosis of Diabetes Mellitus

Diagnosis of diabetes is an act to judge whether clinical and laboratory features of a patient fits to the concept of diabetes mellitus mentioned above. Confirmation of persistent hyperglycemia is essential for the diagnosis of diabetes. What degree of hyperglycemia is associated with the risk of specific complications will provide the basis to select the cutoff plasma glucose values for diagnosis. Glycemic criteria not only for 'diabetes', but for milder glucose intolerance are needed. Mild glucose intolerance is seldom associated with specific complications of diabetes, but increases the risk for arteriosclerosis and for the development of diabetes mellitus than those with normal glucose tolerance.

1. Cutoff values of plasma glucose

Table 2 shows the cutoff plasma glucose levels for fasting plasma glucose
These cutoff values are the same as in current ADA and WHO criteria, but the term for each category of glucose tolerance is called by adding the word 'type', such as 'diabetic type', 'normal type', and 'borderline type'. Table 2 shows venous plasma glucose values. The values will change when whole blood or capillary blood is used.

The diagnosis of ‘diabetes mellitus’ is made when persistent hyperglycemia of ‘diabetic type’ is recognized. To confirm persistent hyperglycemia, repeated tests for plasma glucose are necessary in general.
2. Clinical diagnosis

The procedures of clinical diagnosis are shown in Table 3. The methods to confirm hyperglycemia at the first and second tests need not be the same. Fasting plasma glucose is the value measured before breakfast without meal for more than 10 hours since the last evening. If FPG by the first test is less than 140 mg/dl, glucose tolerance test is recommended as the second test. If the first test was done by casual plasma glucose, other methods of plasma glucose test (FPG or GTT) are preferred.

Diabetes mellitus can be diagnosed on a single plasma glucose value of ‘diabetic type’, if there is one of the following three conditions; (1) typical symptoms of diabetes (thirst, polydipsia, polyuria, and weight loss), (2) HbA1c ≥ 6.5%, or (3) diabetic retinopathy.

HbA1c higher than 6.5% indicates that the patient has had chronic hyperglycemia. The inclusion of HbA1c as an aid for diagnosis of diabetes is unique to the report of JDS. For this purpose, only stable fraction of HbA1c should be measured and the assay value should be corrected by the standard samples of JDS.4) Very few portions of subjects with normal or borderline type glucose tolerance have HbA1c higher than 6.5%, but a considerable portion of subjects with HbA1c < 6.5% have diabetic type glucose tolerance. Therefore, the possibility of diabetes cannot be ruled out even if HbA1c is lower than 6.5%.

3. Normal and borderline types

The ‘normal type’ in the previous JDS report was defined as a group of subjects who were unlikely to progress to diabetes after a follow-up of several years.5) In the 1982 JDS report, FPG < 110 mg/dl, and 1hPG < 160 mg/dl and 2hPG < 120 mg/dl were the upper limits of the ‘normal type’. In the 1999 JDS report, the cutoff plasma glucose level for 2hPG was raised to 140 mg/dl and 1hPG value was omitted from the criteria. Thus, the upper limits of glycemia in ‘normal type’ are now the same as the lower limits for FPG and 2hPG of impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT), respectively. By this change of criteria, the incidence of ‘diabetic type’ from ‘normal type’ increases a little, but the annual incidence rate is still less than 1% according to the follow-up data of 4-5 years in Japan.3)

The ‘borderline type’ is a group neither of ‘normal type’ nor ‘diabetic type’. The new ‘borderline type’ corresponds to the sum of IFG and IGT by ADA and WHO. Compared with ‘normal type’, subjects belonging to borderline type are at higher risk to develop diabetes and arteriosclerosis but at little risk to get microangiopathy.

Table 2 shows cutoff levels only for FPG and 2hPG, but it is advised to measure 30-min and 60-min plasma glucose in clinical situation, and if possible, to measure insulin levels for these samples. Subjects with 1hPG higher than 180 mg/dl are at higher risk to develop diabetes than those with lower 1hPG even among people with ‘normal type’ glucose tolerance.3) The low insulin response at 30 minutes after 75 g glucose load is a characteristic feature of diabetes. A low insulinogenic index (the ratio of increment of plasma insulin (µU/ml) to that of plasma
glucose at 30 min (mg/dl) less than 0.4) indicates that the person is very likely to have diabetes. Furthermore, the incidence of diabetes is higher in subjects of borderline type with low insulinogenic index than those with insulinogenic index higher than 0.4.⁶

4. Epidemiology and screening

When the prevalence of diabetes is studied in an epidemiological survey, the ‘diabetic type’ by a single plasma glucose test may be regarded as ‘diabetes’. The use of $2hPG \geq 200\, mg/dl$ by 75 g glucose tolerance test is preferred. If it is difficult, however, $FPG \geq 126\, mg/dl$ can be used with description of the criteria in that particular survey.

For screening of diabetes, it is important not to overlook subjects with diabetes. In addition to glycemic parameters, clinical informations such as family history, obesity and the history of body weight changes, diabetic complications should be included to screen subjects for further testing.

5. Gestational diabetes mellitus (GDM)

The traditional concept of GDM has been “mild temporary glucose intolerance which occurs for the first time during pregnancy”, which implied that glucose intolerance would become normal after delivery. The reason to give a special consideration to GDM is that even mild glucose intolerance may give adverse effects on the mother and fetus during pregnancy, and it is one of the predictors of future diabetes.

The concept of GDM underwent subsequent modifications, and at the Fourth International Workshop on GDM, it was defined as “any glucose intolerance developed or detected for the first time during pregnancy, without regard to the degree of glucose intolerance and whether it antedated before pregnancy or it persists after delivery”⁷ By this definition, diabetes which has its onset before pregnancy but unnoticed and incidentally detected during pregnancy is also included in GDM.

Subjects who have hyperglycemia of diabetic type or diabetic retinopathy already at the first trimester of pregnancy are likely to have had diabetes since before pregnancy. These cases have a greater risk for fetal anomalies, and for perinatal troubles, so that they should be kept under closer supervision than those with GDM of milder glucose intolerance by traditional definition.⁸

There have been no universal criteria for GDM. The JDS Committee adopted the criteria, previously proposed by a Committee of the Japan Society of Gynecology and Obstetrics.⁹ Namely, the subject is regarded to have GDM, if either two of venous plasma glucose values exceeded following cutoff levels; $FPG \geq 100\, mg/dl$, $1hPG \geq 180\, mg/dl$, $2hPG \geq 150\, mg/dl$ by 75 g GTT.

As a screening test during pregnancy, subjects with casual plasma glucose exceeding $100\, mg/dl$ should be examined by a 75 g glucose tolerance test and evaluated by the above criteria.⁸ For subjects who are diagnosed to have GDM, glucose tolerance state should be re-evaluated at 1–3 months after delivery.
Conclusion

The main points of the new classification and diagnostic criteria of diabetes mellitus by JDS were described. For classification, both etiological classification and the staging of patho-physiology are to be considered. The cutoff levels of plasma glucose to classify diabetic, borderline and normal types are presented. Diabetes is generally diagnosed when persistent hyperglycemia of 'diabetic type' is confirmed, but if there is either (1) typical symptoms of diabetes, (2) HbA1c ≥ 6.5% or (3) diabetic retinopathy, diabetes can be diagnosed by a single plasma glucose test of 'diabetic type'. Cutoff values for plasma glucose do not give a definition of diabetes, but simply a guideline. The diagnosis of diabetes mellitus should be made not only on plasma glucose levels but clinical symptoms and other findings should also be taken into account.

REFERENCES


