Early diagnosis, early treatment and the new diagnostic criteria of diabetes mellitus

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The main purpose of treating diabetes is to prevent chronic complications. Strict glycemic control is known to suppress the occurrence and progression of these complications. The test for plasma glucose is essential to identify diabetic patients, as mild hyperglycemia without symptoms can be a risk factor for complications. The new classification and diagnostic criteria for diabetes were proposed by the American Diabetes Association (ADA), WHO and Japan Diabetes Society (JDS) between 1997 and 1999. Diabetes is classified into four etiological categories; type 1, type 2, diabetes due to other specific mechanisms or conditions, and gestational diabetes. Another classification system according to the degree of metabolic abnormality has also been adopted. For diagnosis of diabetes, the JDS Committee classified the glycemic state into three categories based on fasting plasma glucose (FPG) and 2-h plasma glucose in the 75 g oral glucose tolerance test (2hPG); normal type (FPG <110 and 2hPG <140 mg/dl), diabetic type (FPG ≥126 and/or 2hPG ≥200 mg/dl), and borderline type (neither normal nor diabetic type). The borderline type corresponds to the sum of impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT) based on ADA and WHO. Using the JDS criteria, diabetes is diagnosed when hyperglycemia of ‘diabetic type’ is confirmed on two or more occasions. ADA recommends the use of FPG alone for the diagnosis of diabetes, but findings from both Japan and Europe indicate that many diabetic subjects would be classified as non-diabetic solely on the FPG test. JDS recommends the use of the glucose tolerance test when the elevation of FPG is mild. Keeping glycemia near-normal by periodic monitoring of glycemic parameters and by appropriate treatment would prevent or reduce the diabetic complications in patients to a minimum.

Concept of diabetes mellitus and the purpose of treatment of diabetes

Diabetes mellitus is a group of diseases characterized by chronic hyperglycemia and other metabolic abnormalities resulting from the deficient action of insulin. Various etiologies can cause diabetes. Whatever the etiology, diabetes-specific complications such as retinopathy, nephropathy and neuropathy may occur after a long duration of hyperglycemia. Arteriosclerosis is also precipitated by diabetes. Depending on the severity of metabolic disturbance, diabetes may show no symptoms, or characteristic symptoms such as thirst, polyuria, polydipsia or weight loss, and sometimes progress to ketoacidosis and coma.

The most important purpose of the treatment of diabetes is prevention and inhibition of chronic complications, because they are the major causes of morbidity and mortality of diabetic patients. Nephropathy may progress to renal failure necessitating in hemodialysis, and retinopathy may lead to blindness. Arteriosclerotic lesions cause myocardial infarction and cerebrovascular diseases.

Recent large-scale randomized clinical studies demonstrated that chronic complications of diabetes can be prevented or suppressed by treatment aiming to keep plasma glucose as normal as possible. DCCT (Diabetes Control and Complications Trial Research Group, 1993), Kumamoto Study (Ohkubo et al. 1995) and UKPDS (United Kingdom Prospective Diabetes Study Group, 1998) all reported that, strict glycemic control by intensive
treatment resulted in a significant reduction in the occurrence and progression of complications of both type 1 and type 2 diabetic patients. In addition, the UKPDS demonstrated that the strict control of blood pressure is also beneficial to prevent complications.

The need for early treatment

Patients with a mild degree of hyperglycemia may remain without symptoms. It is a problem that in such asymptomatic cases mild elevation of plasma glucose is sufficient to be a risk factor for specific diabetic complications. The diagnostic criteria of diabetes should, therefore, be able to identify such patients. Thus, it is important to assess what level of hyperglycemia is associated with increased risk of complications of diabetes.

It is often observed that patients with diabetes, particularly with type 2 diabetes, already have chronic complications at the time of diagnosis. In an epidemiological survey carried out in Funagata Machi, Yamagata Prefecture in Japan, retinopathy and microalbuminuria were detected in 7% and 31% of newly diagnosed diabetic patients, respectively (Igarashi et al. 1998). Harris et al. (1992) found that more than 7% of newly diagnosed type 2 diabetic patients already had retinopathy, and estimated that these patients had been diabetic for approximately 4–7 years before their diabetes was diagnosed. As the number of diabetic patients is increasing worldwide, patients with various complications will also gradually increase. To stop such a tendency, early recognition and treatment of these mild diabetic patients is important.

Recent reports on the classification and diagnostic criteria for diabetes

Diagnostic criteria for diabetes have been revised recently by the American Diabetes Association (ADA) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997), WHO (Alberti & Zimmet, 1998) and the JDS (Kuzuya et al. 1999). The report of the Committee of the Japan Diabetes Society was presented at the annual meeting of the JDS in May 1999. These studies used fasting plasma glucose (FPG) and 2-h plasma glucose in the 75 g glucose tolerance test (2hPG) to define ‘diabetes’ or ‘diabetic type’. The cutoff plasma glucose levels were the same among these three studies.

The demonstration of hyperglycemia is a prerequisite to diagnose diabetes. Particularly in patients without symptoms, hyperglycemia is the most easily recognizable expression of deficient action of insulin. It is also the most important risk factor to predict chronic diabetes-specific complications.

The following are the major points of revision in the recent reports of ADA and WHO. Regarding classification of diabetes: (1) classification is primarily based on etiologies, using the terms type 1 and type 2 instead of previous terms of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM); and (2) the introduction of staging of diabetes according to the degree of metabolic abnormalities.

As for the diagnostic criteria: (1) the cutoff level of FPG was lowered to ≥126 mg/dl from the previous level of ≥140 mg/dl. The cutoff level of 2hPG in the 75 g oral glucose tolerance test (OGTT) of ≥200 mg/dl was not changed. (2) The American Diabetes Association recommended the use of FPG alone in their clinical diagnosis and epidemiological study, but the WHO report put emphasis also on the use of OGTT. (3) An intermediate category, impaired fasting glucose (IFG) was newly introduced in consideration of situations in which only FPG is measured.

New classification of diabetes mellitus based on the JDS study

The report of the JDS Committee (Kuzuya et al. 1999) in general conforms with the reports of ADA (1997) and WHO (1998), although there are a few differing points. As in the ADA and WHO reports, diabetes is classified into four categories, type 1, type 2, diabetes due to other specific mechanisms or conditions, and gestational diabetes. There is a difference in the sub-classification of the third category that includes diabetes and related disorders of glycemia due to other specific mechanisms or conditions. In the JDS study, group A included diabetes in which specific mutations had been identified as a cause of susceptibility for diabetes. Group B included diabetes and related disorders associated with other diseases or conditions. The latter are so-called ‘secondary diabetes’ which have been known for a long time, whereas the mechanisms of diabetes in group A have been recently clarified by the progress of DNA analysis technology.

In Fig. 1, the etiologies are shown on the ordinal axis, and the degree of abnormality of glycemia or deficiency of insulin effect on the abscessa. Metabolic stage is classified into normo- and hyperglycemia, and the latter into borderline and diabetic areas. Diabetic area is further divided into three substages: (a) insulin is not necessary for treatment; (b) insulin is necessary for control of plasma glucose; and (c) insulin is indispensable for survival. This latter corresponds to the previous IDDM.

As shown in Fig. 1, the metabolic state can deteriorate and improve in any single individual, as indicated by right- and left-directed arrows, respectively. The portion of the arrows as broken lines represents infrequent phenomena. The filled line represents when the patient is regarded to have ‘diabetes’. Once the diagnosis of diabetes is made, the patient should be treated as diabetic even when he or she has improved to non-diabetic glycemic. This is the reason why the left-directed arrow is filled along its entire length.

Diagnosis of diabetes by the JDS criteria

The diagnosis of diabetes evaluates whether the patient shows the characteristic features mentioned in the previous section on the concept of diabetes. Confirmation of chronic hyperglycemia is necessary for the diagnosis of diabetes. Diabetes is diagnosed when two or more tests, examined on separate days, have revealed hyperglycemia of ‘diabetic type’ as shown in Table 1. Before confirmation by the second test, the patient is simply called ‘diabetic type’. If the patient has fulfilled the criteria of diabetes in the past,
he or she is diagnosed or should be suspected of diabetes, even if the present glycemia does not reach the level of ‘diabetic type’. In addition to the presence or absence of diabetes, the patient should be evaluated for etiology, the stage of glycemia and the status of complications.

The state of glycemia is classified into three categories (Table 1). ‘Diabetic type’ is defined when FPG is 126 mg/dl or higher, and/or 2hPG is 200 mg/dl or higher. ‘Normal type’ is defined when FPG is below 110 mg/dl and 2hPG is below 140 mg/dl. Casual plasma glucose of 200 mg/dl or higher is also regarded as indicating ‘diabetic type’. ‘Borderline type’ is defined in those with neither diabetic nor normal types. The JDS study is unique in that the term ‘type’ is added to each of the OGTT categories. This is because the classification of glycemic states is conceptually different from the diagnosis of disease, diabetes. The borderline type corresponds to the sum of IFG and IGT in the ADA and WHO criteria. In the JDS study, these two categories were not separated.

Table 1. Criteria of fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) following ingestion of 75 g glucose

<table>
<thead>
<tr>
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<th>Normal range</th>
<th>Diabetic range</th>
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<tbody>
<tr>
<td>FPG</td>
<td>&lt;110 (6-1)</td>
<td>≥126 (7-0)</td>
</tr>
<tr>
<td>2hPG after 75 g glucose</td>
<td>&lt;140 (7-8)</td>
<td>≥200 (11-1)</td>
</tr>
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Evaluation of OGTT: Normal type = if both values belong to normal range; Diabetic type = if either of two values fails in diabetic range; Borderline type = Neither normal type nor diabetic type.

Casual plasma glucose ≥200 mg/dl (11.1 mmol/l) is also regarded to indicate diabetic type. Subjects with 1hPG ≥180 mg/dl (10.0 mmol/l) should be followed similarly to subjects with borderline type, even if they belong to normal type, because such individuals are at higher risk to develop diabetes than those with 1hPG <180 mg/dl. Values are for venous plasma in mg/dl. Figures in brackets are values in mmol/l.

Fig. 1. Relationship between etiologies (mechanisms) and pathological states (stages) of diabetes mellitus. The arrows to the right and the left indicate deterioration and improvement of glucose metabolism, respectively. The broken lines indicate uncommon phenomena. The filled portion of the solid and broken lines represent ‘diabetes’. NID = non-insulin-dependent. ID = insulin-dependent. GDM = gestational diabetes mellitus. (Kuzuya et al. 1999).
recur with or without symptoms, by dietary failure, infections, and so on. Therefore, it is safer to keep periodic surveillance on such a case in order to prevent complications.

**Rationales for the selection of cutoff levels of glycemia**

The JDS Committee wished to adopt plasma glucose cutoff levels that conform to international criteria, if they are also supported by findings obtained in other studies in Japan. In addition, the previous JDS criteria proposed in 1982 (Kosaka *et al.* 1982) were taken into consideration. The analysis of a large collection of OGTT findings revealed that the FPG level corresponding to 2hPG of 200 mg/dl was approximately 125 mg/dl on average in subjects younger than 60 years (Ito, 1998). Therefore, we adopted 126 mg/dl as a cutoff level for FPG. Some epidemiological findings suggest that the level of glycemia, which is clearly associated with the increased risk of retinopathy, appears a little higher than the present cutoff levels (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; Kuzuya *et al.* 1999). However, it is suggested that it is better to begin the treatment for diabetes before hyperglycemia reaches the level definitely associated with the risk of diabetic complications. For these reasons, we selected the present criteria.

‘Normal type’ glucose tolerance was previously defined as a group not progressing to ‘diabetic type’ during a period of several years (Kosaka *et al.* 1982). The previous ‘normal type’ was defined as those who had FPG <110 mg/dl, 1hPG <160 mg/dl and 2hPG <120 mg/dl. In the present criteria, the cutoff value for 1hPG was deleted and that for 2hPG was raised from <120 mg/dl to <140 mg/dl. There was a small increase in the incidence of progression to ‘diabetic type’ in subjects with new ‘normal type’ than those with previous ‘normal type’, but the incidence rate is still less than 1 % each year (Kuzuya *et al.* 1999), which we considered small.

With regard to 1hPG, subjects with normal type (FPG <110 mg/dl and 2hPG <140 mg/dl) were stratified by the level of 1hPG, and the incidence of diabetic type was compared (Sasaki *et al.* 1998). The incidence increased with the elevation of 1hPG. Subgroups with 1hPG ≥180 mg/dl had a significantly higher incidence of diabetic type compared with subgroups with 1hPG <180 mg/dl. This is mentioned in the footnote to Table 1. Subjects whose 1hPG exceeds 220 mg/dl have a similar degree of incidence rate as those with ‘borderline type’. It is recommended to follow these high 1hPG cases.

**The need for OGTT to diagnose mild diabetes**

The American Diabetes Association advocated diagnosing diabetes using FPG criteria alone. Criticism has been raised for this proposal (Decode Study Group, 1998). The findings in Japan and in Europe indicate that many individuals with diabetic type would be classified as non-diabetic by the use of FPG criteria alone. Among people who were classified as ‘diabetic type’ by OGTT, 48 % in Japan and 31 % in Europe had an FPG below 126 mg/dl, respectively, despite their 2hPG exceeding 200 mg/dl (Kuzuya *et al.* 1999; Decode Study Group, 1998).

If subjects with an FPG <126 mg/dl were at a slight risk of developing diabetic complications regardless of the level of 2hPG, then the use of FPG alone for diagnosis might be justified. In contrast, findings from Japan show that 2hPG affects the incidence of retinopathy independent of FPG. Ito (1998) compared the incidence rate of retinopathy in groups with mild glucose intolerance classified by FPG and 2hPG levels. The groups with 2hPG ≥200 mg/dl had a higher incidence rate of retinopathy compared with groups with similar degree of FPG but with 2hPG <200 mg/dl. Therefore, 2hPG should not be neglected from a viewpoint of predicting the risk of diabetic complications.

**Intervention at various stages of diabetes**

The purpose of treatment of diabetes is to prevent or to suppress adverse phenomena due to diabetes. If diabetes is left untreated, patients may develop severe complications. Early complications are usually without symptoms, but they may progress to severe stages impairing the quality of life of patients. Interventions at various stages will prevent or delay this process of deterioration.
Figure 2 shows a scheme of progression of diabetic complications and the effects of interventions. The improvement of life-style (i.e. diet and exercise) may prevent the development of diabetes from the borderline stage. Even if diabetes has developed, early treatment may prevent or delay the occurrence of early complications. The progression to severe complications would be suppressed or delayed by proper treatment of patients with early complications. To avoid severe late complications is important to maintain a favorable quality of life.

The effort to keep glycemia near-normal should be continued by a combination of diet, exercise and drug therapy. The strict control of blood pressure is also important. It is expected that the incidence of diabetic complications will be reduced by periodic monitoring of glycemic parameters and by appropriate treatment.

References


