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EDITORIAL

Diagnostic criteria of diabetes

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Introduction

The Japan Diabetes Society (JDS) revised diagnostic criteria of diabetes mellitus in 2010 [1]. The major revision was that HbA1c became the first line, that a diagnosis of diabetes was enabled using HbA1c and the plasma glucose level at one time. Early diagnosis and treatment of diabetes are expected by this revision. Prior to it, the American Diabetes Association (ADA) proposed a revision of the diagnostic criteria for diabetes [2]. They also adopted HbA1c in diagnostic criteria to reflect chronic hyperglycemic states better.

Revision of the diagnosis is the difficult problem because it is not the simple thing to replace it by something else. It needs the continuity with the previous diagnostic criteria, the scientific validity based on evidence, the consistency with overseas diagnostic criteria, and the clinical feasibility.

In this paper, we will define problems of HbA1c and the international challenge in the future, referring to the history of the diagnosis of diabetes.

The history of the revision of diagnostic criteria of diabetes

The JDS has announced the report of diagnostic criteria of diabetes mellitus four times including the recent revision of 2010 so far [1, 3–5]. In addition, a small revision about the normal range of fasting plasma glucose level was introduced in 2008 [6].

Firstly, in 1970, JDS suggested the classification of types of plasma glucose level in oral glucose tolerance test (OGTT). In other words, glucose tolerance was classified into normal type, borderline type, and diabetic type by division of OGTT. A basic position that the diagnosis of diabetes should be generally determined with one's glucose tolerance was shown [5].

In 1979, the National Diabetes Data Group (NDDG) in the United States gave a presentation on diagnostic criteria based on 75gOGTT and a classification of diabetes [7]. At the same time, the concept to assume mild glucose tolerance disorder to be impaired glucose tolerance (IGT) was presented. The expert committee of WHO did make an announcement to follow NDDG in 1980 [8]. The JDS set up the second Committee and announced the classification of types and diagnostic criteria of diabetes with 75gOGTT in 1982 [4].

The ADA performed a review of the plasma glucose level used to diagnose diabetes in 1997 [9]. As for the plasma glucose level, $\geq$126 mg/dl in fasting or $\geq$200 mg/dl for 2-h value after 75 g glucose load were diagnosed as diabetes. Furthermore, it recommended diagnosis of diabetes only in fasting plasma glucose by the general medical treatment. Here, to take the place of IGT, impaired fasting glucose (IFG) was proposed. The expert committee of WHO also performed a suggestion like IFG (impaired fasting glycemia) in 1999 [10], but recognized continuing the need of OGTT in the clinical situations.

Having received these reports, the JDS arranged the third Committee in 1999 and announced the committee report about the classification and diagnostic criteria of diabetes [3]. The committee considered etiology and

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pathophysiology states to be important about the classification, and related to the diagnosis, and showed that confirmation of chronic hyperglycemia was indispensable. In other words, as for the plasma glucose level, if there is either ≥126 mg/dl at fasting, and/or ≥200 mg/dl for 2-h after a 75 g glucose load, and/or ≥200 mg/dl at any time, those are diagnosed as diabetic type and, for those <110 mg/dl at fasting, and <140 mg/dl for 2-h after 75 g glucose load are diagnosed as the normal type. In addition, the borderline type is indicated by a plasma glucose level outside both ranges of the diabetic type and the normal type. A diagnosis of diabetes was made if the diabetic type was confirmed twice on another day, but if the diabetic type was checked only once, it was decided to call that the diabetic type. However, in the case of (1) showing typical symptoms of diabetes mellitus, or (2) indicating HbA1c(JDS) 6.5 % or higher, or (3) defining unequivocal diabetic retinopathy, it was decided to be diabetes, even though the result of hyperglycemia of diabetic type was indicated only once.

The ADA reduced the normal upper limit of the fasting plasma glucose level to <100 mg/dl from <110 mg/dl in 2003 [11]. It was a judgment not to miss IGT, but the WHO did not change the level in 2006 because too many people became diagnosed as abnormal for the fasting plasma glucose level of ≥100 mg/dl and that level did not reflect the risk of macroangiopathy better only at the time of fasting [12]. In 2008, the JDS admitted that in the range of 100–109 mg/dl of fasting plasma glucose, there are so many people who have glucose intolerance and then admitted that the level of fasting plasma glucose treated as a high normal fasting plasma glucose level. Then in 2008, the JDS introduced this small revision of the criteria [8].

The adoption and problems of HbA1c

The transition of diagnostic criteria was roughly described above, and the JDS inherited a basic standard that the confirmation of the hyperglycemic state was indispensable. The most distinctive feature with the revision of 2010 [1] was that HbA1c was adopted as the diagnostic criteria of the diabetic type. This revision was thought by the result that HbA1c has been admitted to be an index to reflect a chronic hyperglycemia. As for the new diagnostic criteria of diabetes in 2010 in the United States [2], it is based on admitting (1) HbA1c ≥6.5 %, or (2) fasting plasma glucose level ≥126 mg/dl, or (3) plasma glucose level for 2-h after 75gOGTT ≥200 mg/dl, or (4) plasma glucose level at any time ≥200 mg/dl with typical hyperglycemic symptoms. And in the absence of unequivocal hyperglycemia, criteria (1–3) should be confirmed by repeat testing. The characteristic of these new diagnostic criteria is in the points of having adopted HbA1c in diagnostic criteria and reevaluation of 75gOGTT. Both the JDS and the ADA are featuring such criteria as "the case when 75gOGTT is recommended" and "categories of increased risk for diabetes", respectively, to ascertain the state suspected diabetes .

It is HbA1c which built in the certain position as an index to reflect a chronic hyperglycemic state, but there still are problems for introducing HbA1c into the diagnostic criteria. The cut-off point, the standardization of the measurement, expense and processing for the measurement, and the diseases which have an influence on HbA1c are problems of HbA1c.

It is difficult to define a diagnostic cut-off point for diabetes. Chronic complications of diabetes are microvascular diseases and macrovascular diseases, and a cut-off level of HbA1c about both vascular diseases should be able to be decided, but there is a limit because there is a close relationship between hypertension or dyslipidemia and macrovascular diseases. Therefore, to define a cut-off level, consideration of the presence of microvascular complications, especially diabetic retinopathy is needed. The current diagnostic criteria are according to this concept. Ito et al. [13] reported that frequency of diabetic retinopathy at HbA1c (JDS) ≥4.5 % was 0.06 %, but frequency clearly rises to 0.59 % at HbA1c (JDS) 6.1–6.5 %. Therefore, it is thought that the cut-off level was determined at HbA1c (JDS) 6.1 %. In the United States, Pima Indian [14] and an Egyptian study [15] referred to a cut-off level in the past, but in a recent revision, the cut-off level was determined by the numerical value acquired from the report of DETECT-2 [16] based on the database of 48,418 people. Furthermore, the consistency with the cut-off level of plasma glucose levels in 75gOGTT was necessary, too. The definition of diagnostic cut-off point of HbA1c by JDS was considered to be consistent with the most important onset of complications, plasma glucose levels [17], and an international value. However, in Europe and the United States, the clear cut-off level of HbA1c is not proved by recent statistics and mathematics; it is thought that a epidemiologic study is necessary to define a clear cut-off level [18, 19].

There are some problems remaining to solve about the standardization of HbA1c. In Japan, HbA1c (JDS) ≥6.5 % criteria was introduced as assistance for the diabetes diagnosis by the committee report about classification and diagnostic criteria of diabetes in 1999 [3]. The validity of introducing HbA1c into the diagnosis of diabetes has been also considered in an ADA expert committee, but they postponed the decision of introduction because of a major concern for the method used to determine HbA1c in 1997 [9]. In Japan, "the committee on an interlaboratory standardization of HbA1c determination" was established by JDS in 1993. Then, HbA1c standard material (JDS lot1)

was introduced which was set to measure stable HbA1c in 1994 [20]. Afterwards, the Japan Society of Clinical Chemistry (JSCC) also established a "committee on diabetes mellitus index" in 1995, and the working group of the glycohemoglobin developed a method to isolate stable HbA1c almost perfectly by the KO500 method and the method was set in a standard measurement manual of JSCC/JDS [21]. The setting of the standardization material using JDS lot2 was done by the KO500 methods and the standardization of HbA1c was accomplished with enabled traceability of this standard material in a clinical setting. The capability for the method has been maintained constantly so far.

On the other hand, in 1996, the National Glycohemoglobin Standardization Program (NGSP) was started to succeed the HbA1c standard measurement institution (reference laboratory) of the Diabetes Control and Complications Trial (DCCT) [22] targeted for type 1 diabetes mellitus. It was a problem that values differed in a clinically unacceptable magnitude between methods and laboratories. Because, no internationally accepted reference system, to which the routine assays could be adjusted, existed nor do any internationally approved primary or secondary reference materials or a reference method [23]. In the first place, due to standardization, the definition of the measurement object, a standard material as a standardization system, a standard measuring method, a laboratory network and maintenance are necessary. Therefore, a consensus statement about the international standardization of the HbA1c measurement was announced in 2007 by 4 international research groups which consist of the ADA, the European Association for the Study of Diabetes (EASD), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Diabetes Federation (IDF) [24]. The HbA1c which is indicated by IFCC is combined glucose with the β chain-N-terminus valine of hemoglobin, and the result was determined to be expressed in mmol/mol by the measurement system of the IFCC method as anchor [25]. However, this IFCC value has not yet prevailed, the JDS decided to adopt the NGSP value which is used by many countries globally and to start in April 2012. The IFCC value is based on standardization as well, but is not based on actual results such as epidemiology data. On the other hand, the NGSP value has a standardization method which is not established well, but has actual results being used by many clinical studies such as DCCT and the United Kingdom Prospective Diabetes Study (UKPDS) [26]. Recently countries mainly in Europe have been increasedly adopting the IFCC value, and it is expected to achieve actual international standardization of the HbA1c value.

The advantages of adopting HbA1c as diagnostic criteria are the lower cost and no necessary time restriction in comparison with 75gOGTT. The reason why there still are one-third possibilities of diabetes patients who are not yet diagnosed as diabetes in Europe, is that they need a glucose tolerance test because they do not refer to a diabetes range of fasting plasma glucose level [27]. The HbA1c can be measured at any time of a day which is not relevant to meal time, and it is easier to handle the sample after the drawing blood than to measure plasma glucose level precisely. The advantage of adopting HbA1c is that we can diagnose diabetes more speedily because the diagnosis can be done at one time with the value of the plasma glucose level and HbA1c according to the new diagnostic criteria in Japan. On the other hand, from the economic aspect, the measurement of HbA1c costs less than 75gOGTT, but more than the blood glucose level measurement. In addition to that, the measurement of HbA1c can not be done anywhere in the world. This is one of the serious disadvantages for some countries which do not have facilities for the measurement of HbA1c to diagnose diabetes, even if HbA1c will be the international diagnostic criteria of diabetes. One of other disadvantages is that it is impossible for everyone to be diagnosed with diabetes by HbA1c, because there are those who have anemia needless to say or those who have complications of the abnormal hemoglobin. When HbA1c was adopted as a diagnostic criteria of diabetes, the decision not to diagnose diabetes only by HbA1c was made by considerations of such disadvantages above.

Closing

Renewed diagnostic criteria of diabetes mellitus were announced in Japan and the United States in 2010. In Japan, the diagnostic criteria of diabetes mellitus have been revised by considering a global standard and the next goal without changing the basic policy in which confirmation of chronic hyperglycemia is essential. In the United States, aiming at simplifying the blood test, prioritizing the plasma glucose level in fasting, reviewing plasma glucose level after a glucose tolerance test, and adopting HbA1c have been performed. Those measures seem to be flexible, but to contain some problems, because diagnosis of diabetes tends to be uncertain depending on the situation of the blood test.

Also, diagnosis of diabetes based on the same diagnostic criteria in the whole world will be expected in the future. The criteria have been discussed only in developed countries, but from now on, increases of diabetes onset in developing countries will be anticipated and diagnosis at a global point of view with epidemiology will be necessary. It is said that without treatment of diabetes, many children die before being given a diagnosis of diabetes in some developing countries. International standardization of HbA1c has not reached the consensus at the present time

even among developed countries. The diagnostic criteria of diabetes needs to be considered more for the sake of early discovery of diabetes with prevalence of the blood sample measurement which can be done in all countries in the world.

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