

# Redefining Diabetes: Is It Really Necessary?

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It has been known that the diagnosis of diabetes should be made early to prevent cardiovascular and other metabolic complications (such as malignancy, etc). So far, determination of blood glucose levels has been used to diagnose diabetes. As a matter of fact, some diabetic patients had already had chronic complication at the first time of diagnosis. It shows why the glucose-centric definition for diagnosing diabetes that has been used so far could not be applied to the sole diagnosis criteria for a group of patients with such “syndrome”.

Blood glucose examination and the cut-off point for diagnosing diabetes have become controversial debates for a long time.

In 1979, the National Diabetes Data Group (NDDG) made diagnostic criteria for diabetes, which subsequently have been used for over 2 decades. At that time, the Committee used the cut-off point of blood glucose level based on distribution and it was not associated with the correlation between blood glucose level and chronic complication. Diagnosis of diabetes was established when fasting plasma glucose level (FPG) >140 mg/dL; 2-hour post-prandial blood glucose or 2-hours PPG >200 mg/dL.<sup>1-5</sup>

In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus reviewed the principles of diagnosis for diabetes. The Committee used the new approach for diagnosing diabetes by correlating the blood glucose level with the distribution of long-term complications. The Committee considered three epidemiological studies, i.e. the population study in Egypt (n=1018)<sup>6</sup>, US National Health and Nutrition Examination Survey (NHANES) survey (n=2821), PIMA Indians study with Hb A1c as diagnostic criteria (n=960).<sup>7</sup> Those three studies used retinopathy complication as the dependent variable for determining the cut-off point of blood glucose level. By applying such approach, the criteria of diabetes has been changed,

particularly from FPG >140 mg/dL into >126 mg/dL. The cut-off point may reveal more linearity association between FPG and PPG. In addition to establishing diagnosis criteria for diabetes, the Committee also introduced the terms “impaired fasting glucose” (IFG) and “impaired glucose tolerance” (IGT) to differentiate metabolic conditions between the normal groups and diabetics; with the criteria of 110-125 mg/dL and 140-199 mg/dL, respectively. Consequently, WHO adapted such approach and suggested individual with IFG should have oral glucose tolerance test (OGTT) to avoid the false-negative result and recommended OGTT as the gold standard for diagnosing diabetes.

In 2003, the Committee revised the criteria from IFG >110 mg/dL into >100 mg/dL. However, WHO still used the criteria of 110 mg/dL for IFG.

Since a long time ago, the experts have realized that determination of cut-off point for diagnosing diabetes will be revised over time with the lower blood glucose level as the more sensitive diagnosis for detecting the occurring complication.

## **A1c FOR DIAGNOSING DIABETES**

If the diagnosis of diabetes is determined by how sensitive are the variables for predicting chronic complications, then there will be some parameters that can be used such as fasting plasma glucose, post-prandial blood glucose and A1c.

A study conducted by Tapp et al demonstrated that A1c had stronger correlation in predicting retinopathy compared to the fasting plasma glucose (FPG).<sup>8</sup> The correlation between A1c and complications has also been demonstrated in Diabetes Controlled Clinical Trial / DCCT study for type-1 DM<sup>9</sup> and Post review 35 UKPDS study for type-2 DM.<sup>10</sup> Those studies showed that high glucose exposure in a long period of time, as shown by A1c, is better for biomarker in diagnosing

diabetes compared to the random blood glucose level. The advantage of A1c for diagnosis is due to smaller intra-individual variation (<2%) compared to FPG (12-15%).<sup>11-13</sup> A1c examination is also more convenient for the patients since they do not have in fasting state for the examination. The main problem is standardization of instruments. Until now, HPLC method has been recommended for standard A1c examination.

The diagnosis of diabetes has been shifted since it has not been glucose-centric as the old time and various parameters of glucose exposure such as A1c has been considered more. In the future, there might be more sensitive criteria to diagnose such "syndrome".

### STRATIFICATION OF DIABETIC STAGE

If we take a look at the consensus on diabetic management, all patients will have the same treatment without considering the stratification of duration of illness, age and the existing complications. New findings in some studies such as the ACCORD study and VADT study, showed that in certain groups (long term DM and the elderly) that have been treated aggressively as the new DM and young patients, will demonstrate a very low A1c results in some people (<6%). As a matter of fact, the very low level of A1c has higher risk of cardiovascular death compared to the group with A1c between 6-7%. Therefore, stratification of diabetic patients is necessary to provide optimal treatment approach.

Hereby are some postulates on stratification of diabetic patients to provide more optimal treatment results.

- A. The first group: new diabetic patients, young age (<65 years), without complication, A1c <8%. The group may have aggressive treatment, not only for controlling the blood glucose, but also to suppress the rate of reduced pancreatic beta-cells. Optimal treatment is also provided to anticipate the complications that may occur in the future. All kinds of oral anti-diabetic agents can be administered; however, be careful with hypoglycemia effect. The non-sulfonylurea agents are the first-line choice.
- B. The second group: old or new diabetic patients, young age (<65 years), A1c >8%. This group may already have complications. Their potency on insulin secretion is lower than the first group. If the dose of sulfonylurea has already been more than ¾ maximal dose, incretin-based therapies should not be given since there are great levels of advance glycosylated end product.
- C. The third group: old or new diabetic patients, elderly

age (>65 years), A1c <8%. The group should be managed progressively, not too aggressive, little by little, preventing hypoglycemia. The wise target for A1c for such group is about 7%. In this group, there may be comorbidities associated with degenerative process and increased blood glucose level will exaggerate the illness. If the intake is not optimal, consider short-acting drugs. Small divided dose and combination drugs may become alternatives to minimize the side effect since the excretion function has relatively been declining.

- D. The fourth group: old or new diabetic patients, elderly age (>65 years), A1c >8%. The group should be managed cautiously. Some of them need insulin. The dose of insulin is not necessarily increased in aggressive manner based on the random blood glucose level during their visit to the physician office. The principles of fix fasting first should be kept in mind to monitor the basal requirements first. After having the insulin injection, the patients should directly have some meal in order to prevent hypoglycemia. Optimal treatment is not only considering the firm clinical aspects but also the better quality of life.

In this editorial note, we can see that the definition for diabetes is not unbending anymore and is not always about blood glucose levels. Redefinition of diagnostic approach and treatment will be discussed in this edition.

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