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Evaluation for the HbA1c Value from Diabetic Clinical Point of View

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Abstract

In clinical practice for diabetes, HbA1c has been crucial biomarker for better control. When evaluating the HbA1c value, information would be integrated and then judged adequately, corresponding to the various situation of the patient.

Keywords: ***Glycoalbumin; Hemoglobin glycation index (HGI); Freestyle libre; Glucose management indicator (GMI); Estimated A1C (eA1C); Glycation gap***

HbA1c reflects the state of blood glucose over the past one to two months. It is easier to use as a control index than the fluctuating blood sugar level, and has been used as a treatment target [1]. There are some cases in which the HbA1c level deviates from the average blood glucose level. Such situation would be found in patients with iron deficiency, hemolysis, cirrhosis, blood transfusion, and so on. Furthermore, differences in red blood cell lifespan depend on genetic background, in each individual [2]. Actually, HbA1c has been highly evaluated, then it is frequently used in diabetes care across the world.

Recently, there has been controversy between American College of Physicians (ACP) and American Diabetes Association (ADA) [3,4]. The content is that the target value of HbA1c in the treatment of adult type 2 diabetes mellitus (T2DM) is 7%-8% or less than 7%. In actual practice, however, there are individual differences in the lifespan of red blood cells. HbA1c level shows a difference of 1% or more, even if two diabetic patients reveal the same blood glucose level. Consequently, it may be necessary to discuss the difference between the HbA1c value and the average blood glucose level, before discussing the target value of HbA1c.

The correlation has been known between HbA1c and average blood glucose levels by Nathan et al. [5,6]. There was not an obvious linear relationship between the two biomarkers. Actually, a certain degree of divergence and wide distribution were recognized in the correlation.

This divergence is thought to be part of the recent clinical trial failures. A typical example is Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. ACCORD was designed to evaluate the comparison between intensive glucose management and standard therapy [7]. The risk reduction of cardiovascular disease was studied by the incidence of a major adverse cardiac event (MACE) such as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke [8]. There was no significant difference of MACE between the two groups.

Subsequently, the ACCORD trial was subjected to various post-analyses. Above all, the post-analysis results reported in 2015 are noteworthy in the 3 following points [9]. First, the difference was calculated between the measured HbA1c value and the predicted HbA1c value calculated from the fasting blood glucose level. It was called as hemoglobin glycation index (HGI) (HGI = observed HbA1c - predicted HbA1c) [9]. Second, all patients were equally divided into three groups based on HGI. Third, the incidence of cardiovascular disease, overall death, and hypoglycemia were compared [9].

High HGI group is a group that blood glucose level was relatively lower compared with HbA1c value. Moderate HGI group showed standard level, and low HGI group showed relatively higher blood sugar than HbA1c [9]. As a result, only high HGI group showed significant increase in the overall mortality risk (HR 1.41; 95% CI 1.10-1.81; P = 0.02) due to intensive therapy. On the other hand, there was no significant difference in moderate HGI group (HR 1.06) and the low HGI group (HR 1.08). The risk of hypoglycemia was also greatest in the high HGI group [9].

From these results, even in subjects with the same HbA1c value, there are actually patients with lower blood glucose levels. In these cases, blood glucose may have dropped too much in the treatment using the HbA1c value as an index. In other words, the difference between the HbA1c level and blood glucose level may be responsible for the increased risk of death from intensive group in the ACCORD study.

Concerning blood glucose profile in diabetic patients, it was usually checked 2-4 times a day formerly. Authors have examined 7 circadian glucose variability and M values and have reported a dramatic improvement with the conversion of Calorie Restriction (CR) to Low Carbohydrate Diet (LCD) [10]. Recently, CGM by FreeStyle Libre became widespread, and then glucose fluctuations have been observed precisely [11,12].

One of them is the persistence of hypoglycemia during the night. In some cases, HbA1c levels are less than 7% and early morning fasting blood glucose levels are normal. However, the hypoglycemia persisted during night below 40 mg/dL with normal blood glucose in the early morning [13]. This is typical Somogyi effect. In such cases, the risk of sudden death from hypoglycemia or cardiovascular event at night may increase [13]. Even if HbA1c is an ideal value, there may be a risk with careful attention.

What should we choose the biomarker in order to evaluate blood glucose control? First, i) The usefulness of HbA1c has been basically highly evaluated for long. Next, if the large discrepancy is found between HbA1c and the actual blood glucose level, further evaluation is necessary. In other words, ii) blood glucose variability by Continuous Glucose Monitoring (CGM) [14], iii) glycoalbumin value reflecting short-term blood glucose, iv) the estimated HbA1c value from ii) and iii). If these i)-iv) would be judged comprehensively, safe and effective optimal treatment can be provided for each patient.

For estimating HbA1c value, there are some useful equations which are recommended in the clinical practice.

- HbA1c=0.009 x fasting plasma glucose (mg/dL) +6.8. This method is utilizing the fasting plasma glucose (FPG) [9]. It has some weak points such as the Somogyi effect. However, since it has been used in post-analysis of the ACCORD study, it can be applied to post-analysis in other clinical studies.
- HbA1c=3.31 + [0.02392 x average glucose (mg/dL)]. This utilizes the average blood glucose data obtaining from CGM [15]. It is the proposal of CGM-derived measure called glucose management indicator (GMI), which is included in CGM software to generate a metric conveying extended glucose exposure [16]. GMI was formerly called Estimated A1C (eA1C) and then the Food and Drug Administration (FDA) in US determined that the nomenclature of eA1C needed to change [17].
- HbA1c=3.31 + [0.02392 x HbA1c=glycated albumin (GA) x 0.245 + 1.73. This equation shows that 1% increase in HbA1c level corresponds to 4% increase in GA level. This report was in 2009, in which HbA1c was measured by Japan Diabetes Society (JDS) [18]. After that, HbA1c measurement was changed to National Glycohemoglobin Standardization Program (NGSP). It is expressed by adding 0.4% to the HbA1c (JDS). Then HbA1c (JDS) > or = 6.1% is comparable to NGSP 6.5%, which was introduced on July 1, 2010. Albumin metabolism is enhanced only in specific pathological conditions. Glycoalbumin has less individual differences than hemoglobin metabolism and less deviation from patient pathological conditions.

There is a reported correlation between eA1C and measured HbA1c, which is HbA1c=0.59 × eA1c + 3.06, R2=0.59, P<0.001 [19]. The difference between the estimated HbA1c value and the normally measured HbA1c value is called Glycation Gap [19]. This varies from patient to patient, but is stable unless there is pathological changes in the life of the red blood cell. Therefore, once the patient's Glycation Gap is obtained, the HbA1c value that reflects the actual condition of the patient can be always found.

In summary, this paper is expected to bring better HbA1c assessment in clinical practice of diabetes, which leads to better control and life of each patient.

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