EDITORIAL

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Association between estimated blood glucose levels and glycated hemoglobin levels

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For patients with diabetes, adequate glycemic control within a target range is key to preventing diabetes-related microvascular or macrovascular complications [1]. Many large epidemiological studies have highlighted the importance of intensive glucose control for patients with diabetes, especially for young subjects without diabetic complications who have been recently diagnosed [2]. For strict glycemic control, active lifestyle modification should be initiated as soon as possible after a diabetes diagnosis, and aggressive medical treatment using oral hypoglycemic agents and insulin injection should follow. To achieve glycemic target goals and enhance adherence to insulin therapy, a "patient-centered approach" is key [3]. This includes patient involvement in medical decision-making, a mutual exchange of information, and collaborative deliberation on options in order to reach a consensus on a patient's lifestyle choices and an appropriate therapeutic course of action [4]. To help patients make decisions about their own diabetic care, knowledge of their glycemic control status is essential. Therefore, given the options in diabetes education, glycemic measure methods (such as skills in self-monitoring of blood glucose [SMBG] and hemoglobin A1c [A1C]) should be emphasized so that patients understand their glycemic control status and can help to prevent hypoglycemia [5].

Simple markers of glycemia, such as glycated proteins (A1C, glycated albumin, fructosamine) and 1,5-anhydroglucitol have broad clinical utility in the evaluation of a patient's glycemic control status (Table 1) [6-8]. There are two main techniques to assess the effectiveness of a management plan on glycemic control: SMBG and A1C measurement [9]. Solid knowledge of the glycemic control status of a patient with diabetes is very important for the initiation of hypoglycemic agents, dose adjustment of their medication, prevention of hypoglycemia, and guidance in treatment decisions [9]. In addition, the Korean Diabetes Association recommends regular A1C testing every 3 to 6 months according to a patient's clinical situation [10]. The A1C is a simple, reproducible test that has an established association with risks for long-term diabetic complications in epidemiologic studies and clinical trials, and it has been used as a diagnostic criterion for diabetes after qualified standardization [11,12]. The A1C results are expressed as a percentage of glycated hemoglobin, which does not hold much appeal for patients because it is not easily understood. Translating the

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Table 1. Measures of glycemia

Method	Sampling site	Unit	Monitoring interval	Remark
Continuous glucose monitoring	Interstitial fluid	mg/dL	Every 5 min	Need calibration Use portable device
Self-monitoring of blood glucose	Capillary blood	mg/dL	Real time	Finger stick using glucometer
Hemoglobin A1c	Venous blood (plasma, serum)	%	3 mon	Need standardized assay
Glycated proteins (fructosamine, glycated albumin)	Serum	mmol/L, %	2–4 wk	Correlation with eAG is not clear; not affected by anemia
1,5-Anhydroglucitol	Serum	mg/mL	Several days–2 wk	Cannot be used with SGLT2 inhibitor use

eAG, estimated average glucose; SGLT2, sodium-glucose co-transporter 2.

A1C value into an estimated average glucose (eAG) level is more practical and much easier for patients to understand. Therefore, it would be very practical if healthcare providers could predict mean glucose levels (i.e., eAG level) from a single blood sample test (A1C) rather than through troublesome, multiple finger-stick glucose monitoring. Regarding its clinical usefulness, running comparisons between SMBG (or frequently measured BG levels) and A1C values would be beneficial to determining the efficiency of this measure.

Some studies have tried to define the relationship between A1C levels and average glucose levels. In the A1C-Derived Average Glucose (ADAG) study, a total of 507 subjects, including type 1 diabetics, type 2 diabetics, and non-diabetics from 10 international centers were evaluated. The average glucose level was calculated from 2,700 glucose values based on continuous glucose monitoring with a 7-point daily SMBG [13]. The relationship between A1C and eAG is described by the formula eAG = 28.7 × A1C – 46.7. This means that every 1% increase in A1C corresponds to an increase of approximately 29 mg/dL in eAG. This formula was adopted by the American Diabetes Association and is available at http://professional.diabetes.org/eAG [9]. The formula was calculated based on quarterly A1C data and corresponding 7-point capillary BG profiles from the Diabetes Control and Complications Trial (DCCT). This trial included 1,441 subjects with type 1 diabetes, and the relationship between mean plasma glucose (MPG) and A1C was determined to be: MPG (mg/dL) = 35.6 × A1C – 77.3 [14].

Regarding the present study [15], I would like to express my appreciation for the authors' efforts. They provided valuable evidence concerning the association between mean BG levels derived from oral glucose tolerance tests and A1C; this is the first for studies on the Korean population. The study included 1,000 subjects (391 males, 30 to 64 years old) with average serum glucose levels measured at 0, 30, 60, and 120 minutes after loading with 75 g of glucose. They estimated that a 1% increase in the A1C level was associated with a 50-mg/dL increase in the mean glucose level (mean glucose [mg/dL] = 49.4 × hemoglobin A1c [%] – 149.6). In this study, the correlation coefficient was somewhat lower than in previous studies.

There are some notable points of discussion regarding the results and clinical implications of this impressive study. As the authors described in their Discussion section, there were only 64 patients with diabetes (identified as those with A1C levels higher than 6.5%), which was too small a number to estimate the eAG for patients with diabetes. In this study, a single instance of 75-g glucose loading after 8 hours of fasting was used instead of a mixed meal stimulation before and after each meal; this is the process usually used to measure SMBG. Therefore, the glucose sampling time and site, as well as the serum glucose and capillary glucose concentrations, also differed from other studies. I suggest that this is one of the main reasons for the discrepancy between the DCCT cohort or ADAG studies and this Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study cohort.

Frequent discordances between eAG and self-mon-

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itored mean BG levels have recently been reported. Chalew et al. [16] showed that eAG is often over- or underestimated by 28.7 mg/dL in approximately 33% of patients with type 1 diabetes. In addition, eAG often underestimates the mean BG in patients with type 1 diabetes with a low hemoglobin glycation index and overestimates mean BG in those with a high hemoglobin glycation index [17]. A study by the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group included 252 subjects with type 1 diabetes and showed substantial individual variability between the measured and calculated mean BG concentrations [18]. In the Durability of Basal Versus Lispro Mix 75/25 Insulin Efficacy (DURABLE) trial, a study that included 1,879 participants with type 2 diabetes aged 30 to 80 years from 11 countries, eAG overestimated the actual mean BG at a mean SMBG level of ≤210 mg/dL; at >210 mg/dL, eAG underestimated the actual BG levels [19]. In a study comparing the slopes of the linear correlations between A1C and CGM-measured mean glucose generated from the ADAG study data in an older population with diabetes, the two correlation coefficients were significantly different from each other [20]. The eAG is clinically practical and easily understood by patients with diabetes; however, it still shows some discrepancies across study populations, type of diabetes, glucose monitoring method, age range, and ethnicity. More clinical evidence must be accumulated and a consensus must be reached on these varying methods.

In conclusion, A1C is highly accurate and precise and has become standardized. Although eAG is easily understood, applicable, and practical in clinical settings, eAG does not yet seem able to replace A1C. Caution is also needed in the interpretation of A1C levels in patients with an unstable glycemic control status, pregnancy, steroid treatment, anemia, treatment with medications and vitamins, and renal impairment. To avoid clinically significant discordance between the calculated average glucose and a patient's own self-monitored mean BG level, additional studies are warranted.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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