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The association of serum glycated albumin with the prevalence of diabetic retinopathy in Korean patients with type 2 diabetes mellitus

Won Seon Jeon, Se Eun Park, Eun-Jung Rhee, Won-Young Lee, Ki-Won Oh, Sung-Woo Park, Cheol-Young Park *

Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

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ABSTRACT

Aims: To determine the clinical relationship between serum glycated albumin (GA) and diabetic retinopathy in Korean patients with type 2 diabetes mellitus (T2DM).
Methods: A cross-sectional study including 424 patients with T2DM was conducted. Patients were divided into groups based on the presence of diabetic retinopathy and tertiles of serum GA and 1,5-anhydroglucitol levels.
Results: Patients in the highest tertile of GA had a higher risk of diabetic retinopathy than those in the lowest tertile. Further analysis divided the groups based on glycated hemoglobin (HbA1c) levels, either above or below 8% (64 mmol/mol), and revealed that in those with a HbA1c below 8% (64 mmol/mol), the higher GA subgroup had an increased presence of diabetic retinopathy.
Conclusions: An increased GA level was significantly correlated with the presence of diabetic retinopathy, and measuring GA levels in addition to HbA1c was beneficial as a marker for retinopathy, especially in patients with moderate glycemic control.

1. Introduction

Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of visual disability in people of working age [1,2]. Many studies have investigated various risk factors for the onset and progression of diabetic retinopathy. The duration of diabetes, systolic blood pressure (SBP), and urinary albumin excretion have all been identified as major factors, but glycemic control is one of the most important risk factors [3,4].

Glycated hemoglobin (HbA1c) has traditionally been the standard marker of glycemic control and is also a measure for the risk of diabetic complications. Several studies have reported that a patient's mean HbA1c level is associated with the prediction of vascular complications, and achieving lower HbA1c levels by strict glycemic control impedes progression of complications, including retinopathy [5,6]. Therefore, glycemic control in patients with type 2 diabetes mellitus (T2DM) was confirmed as a very important factor for lowering a patient's risk for developing diabetic retinopathy.

* Corresponding author at: Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108, Pyeong-dong, Jongno-gu, Seoul 110-746, Republic of Korea. Tel.: +82 2 2001 1552; fax: +82 2 2001 1588.
E-mail address: cydoctor@chol.com (C.-Y. Park).
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However, it is also known that diabetic complications result from both sustained hyperglycemia and acute glucose fluctuations [7,8], and recent studies have suggested a role of glycemic variability or postprandial glucose excursion in diabetic micro- and macroangiopathy [9,10]. These reports indicate that even for the same HbA1c level, diabetic complications can occur at different rates depending upon the patient's glucose fluctuation status. Therefore, a special indicator for monitoring glucose fluctuations and excursions could have a potential role for helping to predict the development of diabetic complications.

Glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG) are markers that reflect glycemic variability [11,12]. GA has been reported to be a rapid indicator of glucose exposure over the previous two to four weeks, as the turnover of serum albumin is shorter than that for HbA1c [13]. Clinically, GA is recognized as an index that more strongly reflects postprandial glucose levels, which may possibly be a better predictor of retinopathy than the mean glucose level [11,14]. GA is also an early Amadori-type glycation product, which has been reported to play a role in atherogenesis by inducing inflammatory mediators in the vascular wall [13]. These results could suggest that GA is closely related to vascular complications that occur in patients with diabetes. The GA/HbA1c ratio is also a well-known marker for glycemic variability, and some studies have found that the GA/HbA1c ratio also correlates significantly with atherosclerosis [13,15,16].

Unlike GA, serum 1,5-AG has an inverse relationship with glycemic index as its renal reabsorption is competitively inhibited by glucose at elevated concentrations. As glucose concentrations surpass the renal threshold, 1-5-AG is excreted in the urine, leading to a reduction in serum levels [17]. Additional caution is also needed when interpreting 1,5-AG under special clinical conditions, such as renal failure, elevated serum creatinine levels, or pregnancy. Furthermore, a meaningful difference of 1,5-AG levels was reported between genders [18]. Conversely, GA could be used in patients with renal failure, on dialysis treatment, or pregnancy [13].

Recent studies have found that predicting glycemic variability could differ depending on glucose status. For example, in well- or moderately-controlled patients with diabetes (i.e., HbA1c under 7.5 [58 mmol/mol] or 8% [64 mmol/mol]), 1,5-AG or GA more strongly reflects glycemic excursion, as found in a study using a continuous glucose monitoring system (CGMS) [12,19,20].

The purpose of this study was to determine the clinical relationship between GA, GA/HbA1c, and 1,5-AG, which are markers of glycemic variability, and the presence of diabetic retinopathy. Furthermore, we tried to compare the performance of these markers of glycemic variability in predicting the presence of diabetic retinopathy in a moderately-controlled glycemic status.

2. Methods

2.1. Participants

A cross-sectional analysis was conducted in patients with T2DM that had been involved in the Seoul Metro City Diabetes Prevention Program (SMC-DPP) between August 2011 and February 2012.

The SMC-DPP was a community-based follow-up program that consisted of a pre-diabetes arm and a diabetes arm that recruited patients from public health centers in Seoul, Korea. In 2009, which was the baseline year, 700 patients with diabetes were enrolled in the SMC-DPP. This study analyzed the third-year study of SMC-DPP participants who had enrolled in 2009; 563 patients with diabetes were examined by the SMC-DPP between August 2011 and February 2012. We excluded 139 participants who had no record of fundoscopic imaging, non-diabetic ophthalmic lesions, unclear fundus readings, or insufficient laboratory data. Our final analysis included 424 patients with T2DM. We used a structured questionnaire to collect information on the participants' current smoking status, diabetes duration, and use of hypertensive medications. This study protocol was approved by the Institutional Review Board and the Ethics Committee of Kangbuk Samsung Hospital, and was carried out according to the principles of the Declaration of Helsinki. All participants provided written informed consent before the study began.

2.2. Laboratory measurements

Serum GA levels were measured by an enzymatic method using an albumin-specific proteinase, ketoamine oxidase, and an albumin assay reagent (LUCICA GA-L, Asahi Kasei Pharma Co., Tokyo, Japan) on an automated clinical immunology analyzer (Modular P800, Roche/Hitachi, Japan). The coefficients of variation for GA were 2.80–6.79% for the lower level and 1.59–2.95% for the higher level. GA (%) was calculated using the following formula: GA (%) = [(Glycoalbumin/total albumin) × 100/1.14] + 2.9 [21]. Serum 1,5-AG (Kyowa Medex, Tokyo, Japan) level was measured by an enzymatic colorimetric assay using an ADVIA 1800 Autoanalyzer (Bayer Diagnostics, Leverkusen, Germany). The coefficients of variation for 1,5-AG were 4.77–10.49% for the lower level and 4.01–8.94% for the higher level. HbA1c levels were measured by quantitative ion-exchange high-performance liquid chromatography using a Variant II Turbo (Bio-Rad Laboratories, Hercules, CA, USA). Glucose concentrations were obtained from a Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA, USA). Total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum creatinine levels were determined using enzymatic colorimetric assays (Siemens, Tarrytown, NY, USA). Serum insulin level was measured by an immunoradiometric assay (DIASource, Nivelles, Belgium). High-sensitivity C-reactive protein (hsCRP) levels were measured by a nephelometric assay using a BNII nephelometer (Dade Behring, Deerfield, IL, USA).

Blood samples were drawn for measurements of fasting plasma glucose, HbA1c, GA, 1,5-AG, fasting insulin, fasting c-peptide, hsCRP, total cholesterol, TG, HDL-C, and LDL-C after 12 h of overnight fasting. The two-hour postprandial glucose levels were sampled after all patients had eaten the same meal (a sandwich and low fat milk: 490 kcal, 50% carbohydrate, 24% protein, 26% fat). Urine albumin excretion was assessed based on the ratio of urinary albumin to creatinine (A/C ratio). The glomerular filtration rate (GFR) was estimated