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Serum glycated albumin predicts the progression of diabetic retinopathy—a five year retrospective longitudinal study

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ABSTRACT

Aims: To assess the predictive value of glycated albumin (GA) and other risk factors on a progression of diabetic retinopathy (DR).
Methods: In this retrospective longitudinal study, we enrolled the subjects with type 2 diabetes who had undergone fundus photography twice with a 5-years gap between January 2006 and December 2012, and had been measured consecutively for hemoglobin A1c (HbA1c) and GA levels every 3 or 6 months. The subjects were divided into two groups with or without a progression of DR. The mean HbA1c and mean GA were calculated separately by the sum of all measured values divided by the numbers of values throughout the study period.
Results: Of the 359 subjects, progression group showed significantly higher diabetes duration (8.41 ± 5.72 vs. 6.46 ± 5.77, $P < 0.01$), baseline HbA1c (9.13 ± 2.71 vs. 8.41 ± 2.32, $P < 0.05$), fasting plasma glucose (8.71 ± 2.78 vs. 7.94 ± 2.63, $P < 0.05$), 2 h-postprandial glucose (15.12 ± 11.20 vs.13.14 ± 4.72, $P < 0.05$), eGFR (114.81 ± 39.15 vs. 103.23 ± 32.18, $P < 0.01$), mean HbA1c (8.32 ± 1.69 vs. 7.39 ± 1.35, $P < 0.01$) and mean GA (22.66 ± 5.92 vs. 19.83 ± 5.18, $P < 0.01$) than non-progression group. The frequencies of subjects with DR progression increased obviously with the increment of baseline HbA1c, mean HbA1c and mean GA according to quartile stratification of the above three glucose parameters. Multivariable binary logistic regression analysis investigated that the factors affected the DR progression were the presence of DR at baseline (OR = 0.391, $P = 0.005$), mean HbA1c (OR = 1.389, $P = 0.021$), mean GA (OR = 1.087, $P = 0.039$) and eGFR (OR = 1.008, $P = 0.045$). The optimal cut-off values of mean HbA1c and GA to predict DR progression were 7.27% and 21.85%, respectively.
Conclusions: The presence of DR at baseline, poor glycemic control, glycated albumin, and impaired renal function predicted DR progression in patients with type 2 diabetes.

1. Introduction

Diabetic retinopathy (DR) is a major microvascular complication in type 2 diabetes and can lead to the consequence of blindness. Among the known mechanism of DR, advanced glycated end products (AGEs) mediated vascular inflammation has been confirmed to cause endothelial injuries. Glycated albumin (GA) has been used as a glucose monitoring index, reflecting the average glucose levels in the preceding 2–3 weeks among patients with diabetes, especially having priority in the subjects with end stage renal disease, gestational diabetes mellitus, and poorly controlled glycemia (Inaba et al., 2007; Koga et al., 2011). Besides, there are growing evidences that GA is a glycated protein and precursor of AGEs, also correlating with enhanced oxidative stress and endothelial injuries leading to DR (Liu, Xu, Jiang, & Tian, 2011; Rodiño-Janeiro, González-Peteiro, Ucieda-Somoza, González-Juanatey, & Alvarez, 2010). In a recent cross-sectional study of community-based population (Selvin, Francis, & Ballantyne, 2011), GA was found to be significantly associated with the microvascular complications including albuminuria and retinopathy. It is suggested that the serum glycemic marker, GA might provide important clinical values for the prediction of people at risk for microvascular conditions. Although a relationship between retinopathy and several common risk factors such as hyperglycemia,

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hypertension, diabetes duration has been widely demonstrated, few clinical studies have been conducted to investigate the predictive value of GA on a progression of DR.

In this study, we hypothesized that, in addition to poor glycemic control, a higher glycation index of GA might also predict or influence an onset or a progression of DR. According to this hypothesis, we aimed to characterize and compare the associations of GA and other risk factors with a progression of diabetic retinopathy in a hospital-based population of type 2 diabetes.

2. Subjects

This study was a retrospective longitudinal study on patients with type 2 diabetes who were registered on the Shanghai Clinical Center for Diabetes between January 2006 and December 2012. All the subjects met the type 2 diabetes diagnosis criteria of World Health Organization (1999) and were treated with either diet control or hypoglycemia agents at the time of recruitment. The subjects satisfying the following criteria were recruited in the present study: (1) had undergone fundus photography twice in this period with a 5-year gap; (2) had been examined consecutively for hemoglobin A1c (HbA1c) and GA every 3 or 6 months. We excluded the subjects who were unavailable for repeating HbA1c or GA detection within a 6 month period. The participants with previous history of liver disease, nephritic syndrome, thyroid dysfunction, malignancy, or pregnancy at the study baseline were also excluded. The study protocol was approved by the ethics committee of Shanghai Sixth People's Hospital. All participants gave signed written informed consent before study initiation.

3. Materials and methods

3.1. Laboratory measurements

Physical examinations (including blood pressure, height, and weight) and detailed medical history of each participant were recorded at outpatient department. Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the height in meters squared. Blood samples were drawn from all subjects after an overnight fasting for measurement of fasting plasma glucose (FPG), 2 h-postprandial plasma glucose (2 h-PG), HbA1c, GA, lipid profile and serum creatinine. Plasma glucose levels were measured using the glucose oxidase method (Shanghai Kehua Bioengineering, Shanghai, China) and a Glamour 2000 autoanalyzer (Molecular Devices, Sunnyvale, CA). Serum creatinine (Scr), and lipid profiles, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), were assayed by standard enzymatic procedures on an automated bioanalyzer (7600–020; Hitachi, Tokyo, Japan). The estimated glomerular filtration rate (eGFR; expressed as mL/min/1.73 m^2) was calculated according to the equation from the Modification of Diet in Renal Disease (MDRD) study: [186 × (Scr/88.4)-1.154 × (age)-0.203 × 0.742 (if female)] (Levey et al., 1999). HbA1c was detected using high-performance liquid chromatography and the Variant II HbA1c program (Bio-Rad Laboratories, Hercules, CA), which was standardized according to the Chinese Ministry of Health. Inter-assay and intra-assay coefficients of variation for HbA1c were 0.4% and 0.6%, respectively. GA was measured by an enzymatic method using an enzyme-based assay kit (Lucica GA-L, Asahi Kasei Pharma, Tokyo, Japan) and the Glamour 2000 autoanalyzer. GA was hydrolyzed to amino acids by an albumin-specific proteinase and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which was measured quantitatively. The GA value was calculated as the percentage of GA relative to total albumin; this was measured using the bromocresol purple method on the same serum sample (Paroni et al., 2007). Inter-assay and intra-assay coefficients of variation were 3.0% and 5.1%, respectively. The mean HbA1c and mean GA were calculated separately by the sum of all measured values divided by the numbers of values throughout the study period. GA/HbA1c ratio was determined by dividing GA by HbA1c.

3.2. Detection of diabetic retinopathy

Fundus photography was carried out following a standardized protocol. The participant was seated in a darkened room, and the posterior pole of each eye was photographed with a 45-degree 6.3-megapixel digital non-mydriatic camera (Canon CR6-45NM, Lake Success, New York, USA). Two independently trained ophthalmologists without the information of the clinical details read the photographs, separately. According to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales (Wilkinson et al., 2003), the severity of DR was divided into 3 groups: (1) no findings of diabetic retinopathy (NDR); (2) non-proliferative diabetic retinopathy (NPDR, including mild, moderate, and severe NPDR); (3) proliferative diabetic retinopathy (PDR). The subjects whose retinal diseases were of unequal severity in two eyes were staged according to the more severe one. Based on the progression of DR, we classified the subjects into non-progression group and progression group during the time interval of fundus photography. The cases with no findings of diabetic retinopathy (NDR) at baseline progressed to non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), and the cases with NPDR at baseline progressed to PDR were categorized as a progression of diabetic retinopathy. The patients with the same severity scales of DR in the 5 year study period were categorized as non-progression group.

3.3. Statistical analysis

All data were analyzed using SPSS version 11.0 (SPSS for Windows, Chicago, IL). Data are presented as means ± standard deviation, and variables are presented as percentages. Each variable was examined for normal distribution; variables with normal distributions were compared between groups using the unpaired Student's t test. Skew-distributed variables were analyzed by nonparametric statistics. Frequencies were compared using the χ^2 test. A multivariate binary logistic regression analysis was performed using the presence or absence of DR progression as the dependent variable, and correlated glycemic indices and microvascular risk factors as independent variables. A receiver operating characteristic (ROC) curve was plotted to assess the power of a screening tool to identify the progression of DR. The area under the curve (AUC) was calculated, and an AUC > 0.5 suggested that the test was a valuable screening tool. The cutoff point with a maximum Youden index was taken to provide the best predictive value for GA and HbA1c in the detection of DR progression (Perkins & Schisterman, 2006). A two-tailed p value < 0.05 was considered statistically significant.

4. Results

4.1. Characteristics of the study participants

A total of 359 subjects (181 men and 178 women) with mean age of 56.64 ± 12.58 years were finally enrolled in this study. At the study baseline, the frequency of the subjects with NDR, NPDR, PDR was 83.6%, 15.9%, 0.5%, respectively. The patients were treated with insulin monotherapy (n = 59), oral anti-diabetic agents (n = 152), a combination of insulin and oral anti-diabetic agents (n = 147) or only diet control (n = 1). After a 5-year follow-up, 22.7% of the subjects with NDR at baseline had an onset of DR, and 56.1% of the subjects with NPDR at baseline progressed to PDR. The enrolled subjects were classified into non-progression group (n = 251) and

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