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Increased Serum Glycated Albumin Level is Associated With the Presence and Severity of Coronary Artery Disease in Type 2 Diabetic Patients

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Background Glycated albumin is the predominant circulating Amadori-type glycated protein in vivo and plays a major role in the development of diabetic vascular complications. The aim of this study was to assess the relationship between increased serum glycated albumin level and the presence and severity of coronary artery disease (CAD) in patients with type 2 diabetes mellitus (T2DM).

Methods and Results In a total of 320 consecutive patients with T2DM, coronary angiography revealed normal coronary arteries in 83 patients (control group) and significant coronary stenosis (≥70% luminal diameter narrowing) in 237, of whom 51 patients had 1-vessel disease (Group I), 80 had 2-vessel disease (Group II), and 106 had 3-vessel disease (Group III). Serum glycated albumin, hemoglobin A_{1c} (HbA_{1c}) and tumor necrosis factor (TNF)-α levels, lipid profile, and renal function were measured. Logistic regression analysis was performed to determine the relative risk of serum glycated albumin level for the presence and severity of CAD. Multivariate stepwise linear regression analysis was done to identify independent determinants of the glycated albumin level. Serum glycated albumin (21.2±5.3% vs 19.4±4.3%, p=0.005) and TNF-α levels (123±115 pg/ml vs 65±59 pg/ml, p<0.001) were significantly higher in patients with CAD than in controls, but serum HbAlc level did not significantly differ between them (7.6±1.3% vs 7.4±1.2%, p=0.19). There was a significant difference in serum glycated albumin level between Groups I and III (19.5±3.3% vs 21.8±5.7%, p<0.001). The serum glycated albumin level correlated with the number of diseased arteries (Spearman r=0.205, p<0.001), and was closely related to serum levels on admission of glucose (r=0.495, p<0.001), TNF-α (r=0.123, p=0.028), blood urea nitrogen (r=0.167, p=0.004), triglycerides (r=0.129, p=0.021), and HbA_{1c} (r=0.795, p<0.001). Multivariate analysis indicated that serum levels of glucose (p<0.0001), TNF-α (p=0.001), blood urea nitrogen (p=0.004) and triglycerides (p=0.035) were independent determinants for glycated albumin. Logistic regression analysis revealed that glycated albumin ≥19% (odds ratio (OR) 2.9, p<0.001) was an independent predictor for CAD and glycated albumin ≥21% (OR 2.3, p=0.032) for 3-vessel disease prediction. The area under the receiver-operating characteristic curve for glycated albumin (0.620, 95% confidence interval (CI) 0.548 to 0.691, p=0.001) was superior to that for HbA_{1c} (0.543, 95% CI 0.473 to 0.613, p=0.243).

Conclusions An increased serum level of glycated albumin is associated with the presence and severity of CAD, and may be useful in screening patients with T2DM. (*Circ J* 2007; **71:** 1067 – 1073)

Key Words: Coronary artery disease; Diabetes mellitus; Glycated albumin; Tumor necrosis factor-α

The formation and subsequent impact of advanced glycation end-products (AGEs) exert pathophysiologic effects that accompany diabetes mellitus (DM) driven by hyperglycemia. Glucose reacts with amino groups of circulating or vessel wall proteins in the hyperglycemic milieu to form a Schiff base, which produces Amadori-type early glycation products in hours and weeks. Some of the Amadori products continue to undergo a complex series of chemical rearrangement for weeks and months, and finally resulting in the formation of AGEs. AGEs and Amadori-type glycated products potently modulate the initiating steps in atherogenesis involving blood–vessel wall interactions, triggering an inflammatory–proliferative process and, furthermore, critically contribute to the propagation of inflammation. Thus, AGEs, Amadori glycated products and vascular inflammation play an important role in accelerating atherosclerosis in DM[1–3] Although the production of AGEs is enhanced in DM, their accumulation also occurs in renal insufficiency[4,5] albeit to a lower degree, and is driven by oxidant stress[6] and inflammation[7,8] Atherosclerosis is considered to be a lingering chronic vascular wall inflammation[9] and oxidative stress[10] which warrants assuming that AGEs and Amadori glycated products may be further elevated in diabetic vascular complications.

Glycated albumin is a predominant early Amadori-type glycation product. AGE–albumin may form after long-term

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chemical rearrangement of further glycation for months. Glycated albumin has been shown to play a critical role in atherogenesis by inducing inflammatory mediators in the vessel wall, as well as the proliferation and migration of vascular smooth muscle cells![11] Recent studies indicate that glycated albumin causes parallel dose-dependent induction of nuclear factor-κB![12] increased inducible nitric oxide synthase mRNA expression and total nitric oxide synthase activity, and significantly enhances apoptosis of endothelial cells![13] suggesting that an increased serum level of glycated albumin may be associated with development of coronary artery disease (CAD). Determination of the serum level of glycated albumin, besides assessing the degree of glycemic control, to some extent may reflect the status of other AGEs, the in-vivo glycation load and even more, an accelerated process of inflammation and oxidative stress in diabetic patients, especially those complicated with CAD. This study was conducted to explore the relationship between the serum level of glycated albumin and the presence and severity of CAD in patients with type 2 DM (T2DM).

Methods

Study Population

A total of 320 consecutive patients with T2DM, who underwent coronary angiography for the diagnosis of CAD in the Department of Cardiology, Shanghai Rui Jin Hospital, were included. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and hyperlipidemia was diagnosed according to guideline of the National Cholesterol Education Program (ATP Ⅲ). T2DM was diagnosed using the American Diabetes Association criteria. Renal insufficiency was defined by serum creatinine concentration >133 μmol/L (1.5 mg/dl). Those with type 1 DM, acute coronary syndrome, previous myocardial infarction and other inflammation-related diseases were excluded. The protocol was approved by the hospital's Ethics Committee and written informed consent was given by all patients.

Coronary Angiography

Coronary arteriography was performed using standard Judkins techniques or a radial approach. Angiographic analysis was carried out by 2 experienced interventional cardiologists, who were unaware of the study protocol. Significant CAD was defined as the presence of luminal diameter stenosis ≥70% in the left anterior descending artery or its first diagonal branch, left circumflex artery or its first obtuse marginal branch, and right coronary artery. Left main stenosis (≥50% luminal narrowing) was considered as 2-vessel disease. In accordance with lesion severity previously correlated with reduced coronary flow reserve and with the clinical standards recognized in the American College of Cardiology/American Heart Association guidelines for coronary angiography, patients with severe disease had at least 1 coronary artery stenosis of ≥70%.

For the purpose of this study, patients were divided into 4 groups based on the visual angiographic results: control group consisted of 83 patients with normal coronary arteries, Group I comprised 51 patients with 1-vessel disease, Group Ⅱ included 80 patients with 2-vessel disease, and Group Ⅲ had 106 patients with 3-vessel disease. The severity of CAD was expressed as the number of diseased coronary arteries.

Biochemical Investigations

Blood samples were collected after overnight fasting and stored at –70°C prior to analysis. Admission glucose concentrations were assessed immediately after admission. Serum total cholesterol and triglyceride levels were measured by automated enzymatic procedures (Hoffman-La Roche, Basel, Switzerland). The low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and lipoprotein (Lp) (a) levels were determined after separating the lipoprotein fractions from fresh fasting sera by sequential ultracentrifugation. Concentrations of apolipoproteins A (apoA) and B (apoB) were measured by immunoturbidimetric methods using commercial kit (Boehringer-Mannheim, Mannheim, Germany). Serum concentrations of hemoglobin A_{1c} (HbA_{1c}), blood urea nitrogen, creatinine, and uric acid were assessed using standard methods. The serum glycated albumin level was measured with the improved bromocresol purple method using the Lucica TM glycated albumin-L assay kit (Asahi Kasei Pharma, Japan). Its linear range was 3.2–68.1% and the maximum intra- and interassay CV was 1.2% and 3.0%, respectively. Serum tumor necrosis factor (TNF)-α level was assessed using Human TNF-α/TNFSF1A Quantikine ELISA kit (R & D systems, USA) with an intra- and interassay CV of <5.4% and <7.4%, respectively.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows 13.0 (SPSS Inc, Chicago, IL, USA). Data are presented as frequencies and percentages for categorical variables and mean ± SD for continuous variables, unless otherwise indicated. Data of TNF-α measurement were logarithmically transformed and an analysis of variance (ANOVA) was performed. Differences between 2 groups were assessed using the Chi-square and unpaired t-tests. Because glycated albumin, triglycerides, Lp(a) and creatinine values were not normally distributed, between-group differences were assessed by the Mann-Whitney U-test. Correlation between continuous variables was determined by Pearson correlation coefficients. Spearman correlations were used to test the relationship between the serum levels of glycated albumin and HbA_{1c} and severity of CAD (control group was defined as 0-vessel disease). Binary and multinomial logistic regression analysis was performed to identify the relative risk of the serum glycated albumin level for the presence and severity of CAD, expressed as odds ratios (OR) with 95% confidence intervals (CI). The predictive values of glycated albumin and HbA_{1c} for the presence of CAD were calculated by constructing receiver-operating characteristic (ROC) curves. To establish independent determinants of glycated albumin, multivariate stepwise linear regression analysis was made with glycated albumin as a dependent variable control for glucose, age, blood pressure, cholesterol, triglycerides, Lp(a), blood urea nitrogen, creatinine, uric acid, and TNF-α. A value of $p<0.05$ was considered statistically significant.

Results

Clinical Characteristics

Diabetic patients with CAD were older, and more were male and cigarette smokers compared with the controls (Table 1). The 3 CAD subgroups did not differ significantly with respect to clinical demographics, lipid profile, and biochemical measurements, except the trend of an increasing

Table 1 Baseline Characteristics and Biochemical Assessments

	Control group (n=83)	*Patients with T2DM and CAD (n=237)*	*p value*
Men (%)	*38 (45.8)*	*161 (67.9)*	*<0.0001*
Age (years)	*62±10*	*66±10*	*0.001*
Cigarette smoking (%)	*11 (13.3)*	*67 (28.3)*	*0.007*
Hypertension (%)	*52 (62.7)*	*171 (72.2)*	*NS*
Blood pressure			
Systolic (mmHg)	*138±21*	*137±20*	*NS*
Diastolic (mmHg)	*81±10*	*79±11*	*NS*
Hyperlipidemia (%)	*47 (56.6)*	*134 (56.5)*	*NS*
Renal insufficiency (%)	*1 (1.2)*	*14 (5.9)*	*NS*
Statins (%)	*52 (62.7)*	*174 (73.4)*	*NS*
PPAR-gamma agonist (%)	*11 (13.3)*	*43 (18.1)*	*NS*
Insulin (%)	*25 (30.1)*	*98 (41.4)*	*NS*
Cholesterol			
Total cholesterol (mmol/L)	*4.8±1.3*	*4.7±1.1*	*NS*
HDL-C (mmol/L)	*1.2±0.30*	*1.1±0.4*	*NS*
LDL-C (mmol/L)	*2.8±0.9*	*2.7±0.9*	*NS*
Triglycerides (mmol/L)	*2.2±1.8*	*2.0±1.2*	*NS*
Lipoprotein-a (g/L)	*0.19±0.11*	*0.25±0.20*	*0.006*
ApoA (g/L)	*1.29±0.19*	*1.24±0.22*	*NS*
ApoB (g/L)	*0.94±0.26*	*0.96±0.25*	*NS*
Glucose (mmol/L)	*7.0±1.9*	*7.3±2.7*	*NS*
Blood urea nitrogen (mmol/L)	*5.5±1.6*	*6.0±2.3*	*NS*
Creatinine (μmol/L)	*75±16*	*91±28*	*<0.0001*
Uric acid (μmol/L)	*308±76*	*314±82*	*NS*
Glycated albumin (%)	*19.4±4.3*	*21.2±5.3*	*0.005*
Hemoglobin A_{1c} (%)	*7.4±1.2*	*7.6±1.3*	*NS*
TNF-α (pg/ml)	*65±59*	*123±115*	*<0.0001*

Data are mean ± SD and number (%).
T2DM, type 2 diabetes; CAD, coronary artery disease; PPAR, peroxisome proliferators-activated receptor; HDL-C, high-density lipoprotein-cholesterol; LDL-C, lower-density lipoprotein-cholesterol; ApoA, apoprotein-A; ApoB, apoprotein-B; TNF, tumor necrosis factor.

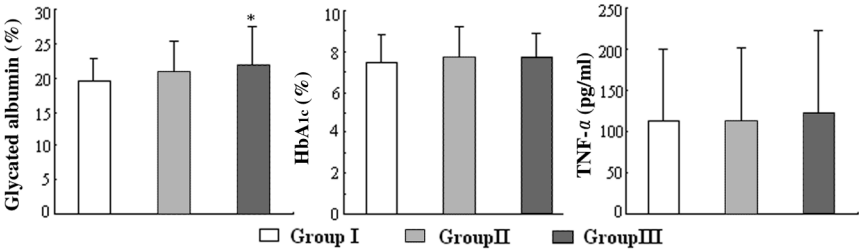

Fig 1. Comparison of the measurements among patients with various degrees of coronary artery disease. A significant difference in glycated albumin level was noted between Groups I and III. *p<0.001 vs Group I. HbA_{1c}, hemoglobin A_{1c}; TNF-α, tumor necrosis factor-α.

rate of elevated Lp(a) level with the increasing number of diseased coronary arteries (Group I: 0.19±0.18 g/L; Group II: 0.25±0.19 g/L; Group III: 0.28±0.20 g/L, p=0.02). In addition, most of the diabetic patients in the control group and the patients with T2DM and CAD were receiving statin medication (62.7% vs 73.4%, p>0.05), and did not differ significantly with respect to the use of peroxisome proliferators-activated receptor gamma agonists (13.3% vs 18.1%, p>0.05) and insulin (30.1% vs 41.4%, p>0.05), nor did it among patients of Groups I–III (data not show). There was no difference in treatment with other antidiabetic agents in diabetic patients with and without CAD.

Serum Glycated Albumin, HbA_{1c} and TNF-α Levels

Serum glycated albumin and TNF-α levels were significantly higher in patients with CAD than in the controls, but the serum HbA_{1c} levels did not significantly differ (Table 1). There was a significant difference between Group I and III in the serum glycated albumin levels (19.5±3.3% vs 21.8±5.7%, p<0.001), but there was no significant difference in the HbA_{1c} and TNF-α levels among the 3 CAD groups (Fig 1). Serum glycated albumin and TNF-α levels correlated significantly with the number of diseased coronary arteries (Spearman r=0.205, p<0.001 and r=0.148, p=0.01), but the serum HbA_{1c} level was not significantly related to the severity of CAD (Spearman r=0.105, p=0.059).

Relationship Between Glycated Albumin and Other Biochemical Parameters

Univariate analysis showed that the serum glycated albumin level was closely related to the serum admission glucose (r=0.495, p<0.001) and HbA_{1c} (r=0.795, p<0.001) levels, and correlated significantly with the serum levels of TNF-α (r=0.123, p=0.028), blood urea nitrogen (r=0.167, p=0.004), and triglycerides (r=0.129, p=0.021) (Fig 2), but not with the LDL and Lp(a) levels. In the final multivariate linear regression analysis model that explained 29.2% (adjusted multiple R^2=0.292) of the variation in glycated albumin, the independent determinants were admission glucose (p<0.0001), TNF-α (p=0.001), blood urea nitrogen (p=0.004) and triglycerides (p=0.035) (Table 2).

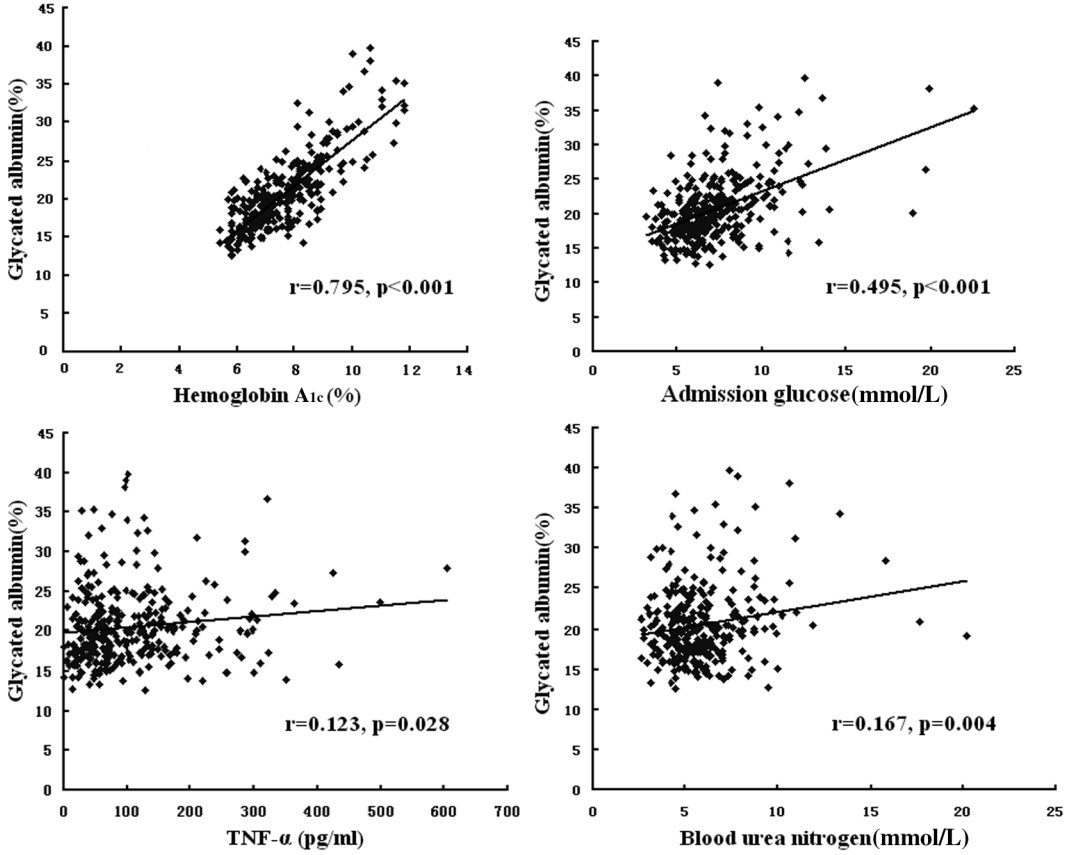

Fig 2. Simple linear regression among glycated albumin and hemoglobin A1c, glucose, tumor necrosis factor (TNF)-α and blood urea nitrogen in patients with type 2 diabetes.

Table 2 Multivariate Analysis of Determinants of Glycated Albumin

Independent variables	*Unstandardized coefficients*		*Standardized coefficients* β	*t*	*p value*
	B	*SE*			
Constant	*10.582*	*1.007*		*10.504*	*0*
Glucose	*0.913*	*0.092*	*0.485*	*9.916*	*0*
TNF-α	*0.008*	*0.003*	*0.135*	*2.774*	*0.006*
Blood urea nitrogen	*0.308*	*0.108*	*0.138*	*2.845*	*0.005*
Triglycerides	*0.37*	*0.176*	*0.104*	*2.124*	*0.035*
Adjusted multiple R^2	*0.292*				*0*

Abbreviation see in Table 1.

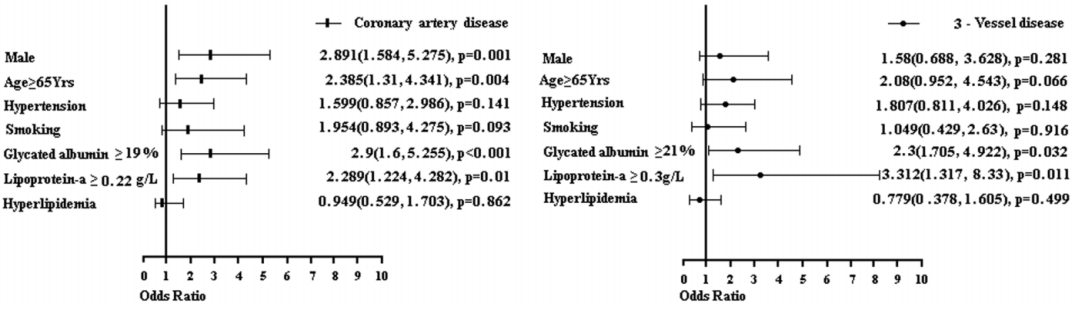

Fig 3. Multivariate analysis for independent determinants of coronary artery disease (CAD) and 3-vessel disease. Male gender, older age, glycated albumin and lipoprotein (Lp) (a) were independent risk factors for CAD, and glycated albumin and Lp(a) were for 3-vessel disease.

Binary and Multinomial Logistic Regression Analysis

Male gender, older age (≥65 years), glycated albumin and Lp(a) were found to be independent risk factors for the presence of CAD in diabetic patients, glycated albumin ≥19% and Lp(a) ≥0.22 g/L having OR 2.9 (p<0.001) and 2.29 (p=0.01), respectively. When using 1-vessel disease as the reference group, glycated albumin ≥21% (OR 2.3, p=0.032) and Lp(a) ≥0.30 g/L (OR 3.312, p=0.011) were independent predictors for 3-vessel disease (Fig 3).

ROC Curve for Glycated Albumin and HbA1c in Predicting CAD in T2DM

The area under the ROC curve for glycated albumin (0.620, 95%CI 0.548 to 0.691, p=0.001) was superior to that for HbA1c (0.543, 95%CI 0.473 to 0.613, p=0.243) (Fig 4).

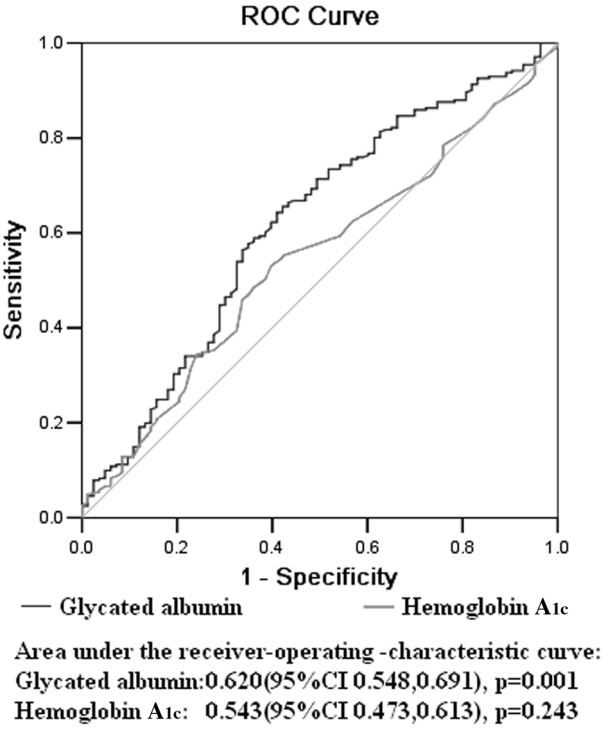

Fig 4. Receiver-operating characteristic (ROC) curve for glycated albumin and hemoglobin A1c (HbA1c) in predicting coronary artery disease (CAD) in patients with type 2 diabetes (T2DM). Glycated albumin, but not HbA1c, displayed significant value in predicting CAD in patients with T2DM.

Discussion

Serum Level of Glycated Albumin Predicts the Presence and Severity of CAD

Gycated albumin represents the largest fraction of circulating glycated proteins (≈80% of total) in vivo. Recent studies indicate that glycated albumin activates nuclear factor-κB and the extracellular signal-regulated kinases/c-Fos/activating protein-1 pathway, leading to induction of monocyte chemoattractant protein-1 and interleukin-6 gene expression and stimulation of cell proliferation and migration.[11] That suggests glycated albumin plays an important role in the occurrence and acceleration of atherosclerosis in DM.[14] In the present study, glycated albumin ≥19% was found to be an independent predictor for the presence of CAD (OR 2.9; p<0.001) in diabetic patients. Atherosclerosis is a chronic condition, commencing in youth, and as up to 30% of diabetic patients with CAD have silent ischemia,[15] surrogate measures of vascular disease are crucial for early identification of diabetic patients with vascular damage and for monitoring the efficacy of interventions. Determination of the serum glycated albumin level seems to be an alternative option, enabling a reduction in the economic burden of detecting vascular complications. Furthermore, in the present study the ROC plot also demonstrated that the serum glycated albumin level was a significant predictor for the presence of CAD (p=0.001), whereas HbA1c was not (p=0.243). Spearman correlation analysis showed that the serum level of glycated albumin (Spearman r=0.205, p<0.001) correlated positively with the number of significantly diseased coronary vessels, indicating a pronounced proatherogenic effect of an increased serum level of glycated albumin, which is consistent with previous findings.[12,13] Furthermore, logistic regression analysis revealed that glycated albumin was also an independent predictor for the severity of CAD, and a serum level of glycated albumin ≥21% has been consistently associated with a 2.3-fold (95%CI 1.075 to 4.922, p=0.032) increase in risk of progressing to 3-vessel disease when compared with a serum glycated albumin level <21%. These results indicate that inhibition of in-vivo glycated albumin is important for the prevention of CAD in patients with T2DM. In the current study, Lp(a) was found to be an independent risk factor for the presence and severity of CAD, whereas traditional risk factors such as HDL-C and LDL-C were not. This may be explained by the fact that majority of the study patients had been receiving lipid-lowering agents. However, there have been less effective medications for lowering the serum Lp(a) level, and Lp(a) is less sensitive to statin treatment.

Independent Determinants of Glycated Albumin

In this study, univariate analysis showed that glycated albumin correlated significantly with the serum level of admission glucose, TNF-α, blood urea nitrogen, and triglycerides. In order to establish a strategy of reducing the serum concentration of glycated albumin, we examined the independent determinants of glycated albumin using multivariate stepwise linear regression analyses. In the last model, the serum level of glucose was the most significant, but not the sole, independent determinant for glycated albumin, and serum levels of TNF-α, blood urea nitrogen and triglycerides were also independently related to glycated albumin in diabetic patients with CAD, which is consistent with previous findings.[16,17] The association between the serum level of blood urea nitrogen and glycated albumin is mostly explained by the accumulation of reactive carbonyl compounds,[18] oxidative stress and inflammation[19] in renal insufficiency. Anderson et al reported that inflammation activates myeloperoxidase pathways, resulting in AGEs formation.[20] Therefore, the inflammatory process may, at least partly, play a role in the formation of glycated albumin in diabetic patients with CAD. Our results indicate that intensive glycemic control may be not sufficient to inhibit glycated albumin in diabetic patients complicated with atherosclerosis, thus control of the inflammatory process is at least equally important as glycemic control for preventing the formation of glycated albumin in these patients. In the present study, the variables in the multivariate linear regression model only explained 29.2% of the variation in the serum level of glycated albumin. Thus, further research is required to find other determinants, the most likely of which will be those related to oxidative stress because of its

involvement in AGEs formation?[21]

Relationship Between Glycated Albumin and HbA1c

In this study, a significant correlation was found between the glycated albumin and HbA1c values (r=0.795, p<0.001), indicating that determination of the serum glycated albumin level may be a valuable adjunct to HbA1c measurement for evaluating short-term glycemic control in diabetic patients. In addition, our results demonstrated a close association between the serum glycated albumin level and the number of diseased coronary arteries, but the Spearman correlation between HbA1c and severity of CAD did not reach statistical significance level (r=0.105, p=0.059). Our results are different from previous findings that showed a significant increasing trend of HbA1c level over the increasing number of significantly stenotic coronary vessels;[22] which may be explained by the relative small sample size in our study and the different diagnostic criteria of significant CAD. Furthermore, the ROC curve indicated glycated albumin may be a valuable predictor for predicting CAD in T2DM, but that the serum HbA1c level was not.

Strategy for Controling Glycated Albumin and Inflammation

Inflammation of the vessel wall is closely associated with coronary atherosclerosis;[23,24] and glycated albumin and AGEs are involved in a vicious cycle of inflammation, generation of reactive oxygen species and amplification of AGEs production, thereby promoting atherogenesis![12,14,20,25] The current study showed that both the admission glucose level and the serum TNF-α level were major independent determinants for glycated albumin, so intensive control of both the inflammatory process and hyperglycemia may be crucial in the prevention of atherosclerosis in patients with DM. Previous studies have demonstrated that peroxisome proliferators-activated receptor gamma activators, such as pioglitazone and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), have lead to substantial glycemic improvement and reduction of inflammation;[26–28] indicating that both agents might be useful in preventing the initiation and progression of CAD, especially in diabetic patients.

Study Limitations

This was a retrospective study, and the sample size was relatively small, thus some subgroup comparisons may have lacked power to detect significant differences for select variables. The classification of significant CAD based on visual estimation of angiographic stenosis of coronary artery lesions at ≥70% is admittedly arbitrary. However, within the range of angiographically significant CAD, including lesions of ≥70%, this criteria of severity correlates well with physiologic significance, has relevance to commonly applied angiographic standards and is widely accepted clinical practice?[29,30] In addition, glycated albumin displayed only 10% increase (from 19.4% to 21.2%), although its mean value differed statistically significant between diabetic patients with and without CAD. This may make the measurement of glycated albumin itself very difficult to use as a daily laboratory test. However, detection of serial changes in the serum glycated albumin level may have value for predicting the progression of pathology in diabetic patients during close follow-up. Likewise, glycated albumin is only a type of early stage AGEs, and as previous studies have shown that some 'traditional' AGEs (eg, N^{ε}-[carboxymethl] lysine and S100) are associated with vascular complications in diabetic patients, the relationship between these AGEs and the presence and severity of CAD needs further investigation.

Conclusions

The present study demonstrated that the serum level of glycated albumin is associated with the presence and severity of CAD in patients with T2DM. Glycated albumin is mainly determined by the serum levels of glucose and TNF-α. Further studies are warranted to examine if intensive inhibition of in-vivo glycated albumin and inflammation has a substantial impact on CAD development in diabetic patients.

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