Increased Plasma S100A12 Levels Are Associated With Diabetic Retinopathy and Prognostic Biomarkers of Macrovascular Events in Type 2 Diabetic Patients

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Diabetes mellitus (DM) has been a leading public health problem in China for the last 10 years and has imposed a heavy economic burden on Chinese patients. In addition, DM has become a global health problem, and the number of people with diabetes is expected to reach 366 million worldwide by 2030. With the increasing prevalence of type 2 diabetes mellitus in the community, the development of macrovascular (coronary artery disease, peripheral artery disease, and stroke) and microvascular (retinopathy, nephropathy, and neuropathy) diabetic complications has become a serious public health issue. Diabetic retinopathy (DR) is one of the most significant complications of DM, and it occurs in 90% of patients after 20–30 years from the disease diagnosis; however, the pathogenesis of diabetic retinopathy (DR) is not well understood. The major risk factors for the development of DR are longer duration of diabetes, poor metabolic control, hypertension, high blood cholesterol, nephropathy, age, sex, smoking, and genetic disposition; the risk factors are not completely understood, and a sensitive biomarker to predict the development of this diabetic complication has not been demonstrated.

Increasing evidence indicates that inflammation plays a pivotal role in the pathogenesis of DR. Worldwide research efforts have established several nonspecific biomarkers of inflammation associated with the development of DR, such as C-reactive protein (CRP), which is related to the innate immune response and inflammation. Some studies have shown that CRP is not significantly associated with DR. A useful biomarker for DR should be a characteristic that is objectively measured and evaluated as an indicator of pathogenic processes. In view of these considerations, we aimed to explore a better diagnostic and prognostic biomarker of DR.

Nonenzymatic modification of proteins, advanced glycation end products (AGEs), are formed by reducing sugars, because of prolonged high glucose in diabetes. The receptor for advanced glycation end products (RAGE) has emerged as a central regulator of vascular inflammation and subsequent atherosclerosis. Previous studies have confirmed that AGEs and RAGE interaction activates multiple signaling pathways, which induce oxidative stress and inflammation, cytokine release, stimulation of the coagulation cascade, and an increase in lipid metabolism, leading to a series of pathophysiological changes. Among the multiple types of advanced glycation products characterized in humans to date, pentosidine is chemically well defined, and a useful biomarker for DR should be a characteristic that is objectively measured and evaluated as an indicator of pathogenic processes. In view of these considerations, we aimed to explore a better diagnostic and prognostic biomarker of DR.

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bovine lung extract and has been reported to be a ligand for RAGE. S100A12 is a member of the S100 multigene family. Serum S100A12 levels are elevated in chronic inflammatory diseases. A previous study reported that the plasma S100A12 levels were more than twice as high in patients with diabetes than in those without diabetes. The associations of plasma S100A12 levels and the development and the severity of DR have not been elucidated, to the best of our knowledge.

In addition to these associations, a soluble form of RAGE (sRAGE), a RAGE isoform lacking the transmembrane domain, has recently been identified in human serum. It has been reported that sRAGE confers protection of blood vessels against AGE-RAGE–mediated microvascular damage in DM. It has been determined using a commercially available enzyme-linked immunosorbent assay kit (Cusabio, Wuhan, China).

**METHODS**

**Subjects**

From March 2010 to April 2012, we recruited 372 subjects for participation in the study (264 relatively healthy subjects with type 2 diabetes and 108 nondiabetic subjects) at Beijing Shijitan Hospital of Capital Medical University. Diabetes mellitus was diagnosed according to the 1999 World Health Organization (WHO) criteria. For each participant, a full medical interview with a physical examination was completed. The patients and controls with ischemic cerebrovascular and cardiovascular disorders, chronic renal disease, liver disease, immunological disorders, the presence of hematological diseases, and history of malignancy were excluded. In addition, the exclusion criteria included the following: (1) any other ocular condition (e.g., glaucoma, uveitis), (2) a history of ocular surgery, (3) a history of intravitreal injection of triamcinolone or anti-VEGF therapy, and (4) patients who had undergone laser therapy.

The study was approved by the Ethics Committee of Beijing Shijitan Hospital of the Capital Medical University in Beijing, People's Republic of China, and was performed in accordance with the Declaration of Helsinki. Each subject received a detailed information leaflet and provided informed written consent before participation.

**Procedure**

The patients were subjected to a complete ophthalmologic examination and general physical examination including best-corrected visual acuity (BCVA), relative afferent pupillary defect (RAPD), electroretinogram (ERG), slit lamp-assisted biomicroscopy of the anterior segment, and fundus examination. Standard fundus photographs were performed by an experienced operator through a dilated pupil before fluorescence fundus angiography (FFA). The diagnosis and assessment of DR was made by standard fundus photographs and FFA, which were performed by two DR specialist at least. A total of 151 T2DM patients with DR, 113 age- and body mass index (BMI)-matched T2DM patients without DR, and 108 age- and BMI-matched subjects without DM were enrolled and underwent all the examinations. For the subgroup analysis, 151 T2DM patients with DR were further divided into the following four subgroups: mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR) based on the fundus examination and FFA. Mild NPDR, moderate NPDR, severe NPDR, and proliferative DR were defined based on the international clinical DR severity scale.

In total, 264 patients with type 2 diabetes were followed through office visits and medical records for an average of 17.6 ± 1.5 months to determine the occurrence of major adverse disease end points. The occurrence of major adverse disease end points was defined as death from any cause, cerebrovascular events (a transient ischemic attack, ischemic cerebrovascular disorders), and cardiovascular disorders (a nonfatal myocardial infarction, nonfatal stroke, cardiac surgery).

**Sample Collection and Measurement**

The blood was collected from patients and controls in the morning after an overnight fast of at least 8 hours, and which was used to measure the concentrations of glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), triglycerides, creatinine, hs-CRP at the Clinical Diagnostic Laboratory, Beijing Shijitan Hospital, Capital Medical University.

In addition to these, another whole blood sample was centrifuged at 3000 g for 10 minutes at 4 °C. Then, the plasma was extracted and stored at −70 °C for subsequent analyses. Plasma pentosidine concentrations were measured with sandwich ELISA standard kit (USCNK Life Science, Inc., Wu Han, China), according to the manufacturer's protocol. Plasma sRAGE levels were measured with sandwich ELISA standard kit (Biovendor Laboratorni Medicina akciová společnost, Brno, Čechovice, Czech Republic). Plasma S100A12 levels were determined using a commercially available enzyme-linked immunosorbent assay kit (Cusabio, Wuhan, China).

**Data Analysis**

Data were recorded as the means ± SD or the median and range. The statistical analyses were performed using the program SPSS for Windows Version 17.0 (SPSS, Inc., Chicago, IL, USA). Logarithmic transformations (CRP, pentosidine, sRAGE, and S100A12) were performed on the continuous variables of nonnormal distribution. The Pearson χ² test was used to compare the proportions of qualitative variables. Student’s t-test was used to compare the means of the quantitative variables between two independent groups. One-way ANOVA test and post hoc test of Tukey’s multiple comparisons were used to compare multiple groups. Simple and multivariate logistic regression was performed to identify independent predictors for DR. The receiver operating characteristic (ROC) curves was used to compare the diagnostic sensitivity and specificity for DR among CRP, pentosidine, sRAGE, and S100A12. The Kaplan–Meier cumulative event curve was used to assess disease end points, as reflected by the unique S100A12 upregulation. A P value less than 0.05 was accepted as statistically significant.

**RESULTS**

Table 1 shows the demographic and clinical characteristics in the included 108 nondiabetic subjects, 113 T2DM subjects without DR, and 151 T2DM subjects with DR. The sex, age, BMI, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, smoking status, systolic blood pressure, diastolic blood pressure, creatinine, statin use, and angiotensin-converting enzyme inhibitor (ACEI) use were not significantly different among the three groups. However, the duration of DM, HbA1c, Log S100A12, Log pentosidine, Log sRAGE, and Log hs-CRP values were significantly different among the three groups (Fig. 1).

A simple logistic regression analysis indicated that the duration of DM, HbA1c, Log S100A12, and Log pentosidine values showed a trend (P < 0.05) toward an association with
on statins, Creatinine, mg/dL 0.96 6
Diastolic blood pressure, mm Hg 78.6 6
Systolic blood pressure, mm Hg 129.4
Smoking (n [%]) 43 (39.8) 56 (49.6) 71 (47.0) 0.318*
Log hs-CRP 2.58
hs-CRP (ng/mL) 373.25 (221.31–662.22) 408.32 (139.64–1633.05) 473.15 (153.46–1713.96)
HDL cholesterol, mM 1.3 6
LDL cholesterol, mM 2.4
Triglycerides, mM 1.3
Pentosidine (pg/mL) 354.81 (229.61–657.67) 616.59 (315.56–1023.29) 637.74 (257.03–1702.16)
Cholesterol, mM 4.3
S100A12 (ng/mL) 57.02 (16.22–163.68) 61.94 (17.26–233.35) 142.23 (30.83–407.38)
Duration of DM, y - 8.7
P
Log sRAGE and Log hs-CRP values did not show a trend (the presence of DR in the patients with T2DM (Table 2). The Log sRAGE and Log hs-CRP values did not show a trend (P > 0.05) toward an association with the presence of DR in the patients with T2DM.

The Kaplan-Meier cumulative event curve was used to assess the disease end points, as reflected by the unique S100A12 upregulation with Log S100A12 values greater than 125% or less than 125% at baseline (a cutoff value of 145.38 ng/mL). In 264 T2DM subjects with DR, the Log S100A12 values of the 186 patients (19.35%). In 264 T2DM subjects with DR, the Log S100A12 values of the 186 patients (19.35%).

The ROC curves for developing DR using the Log S100A12, Log pentosidine, Log sRAGE, and Log hs-CRP values revealed that the area under the receiver operating characteristic curves (AUC) were 0.822 (P < 0.001), 0.561 (P = 0.092), 0.572 (P = 0.051), and 0.566 (P = 0.068), respectively (Table 4, Fig. 3A).

To determine the cutoff value, we selected the maximum of the combined sensitivity value and one minus specificity value. With a cutoff value of 90.16 ng/mL for S100A12, the diagnostic sensitivity and specificity for DR development were 78.1% and 77.0%, respectively.

Figure 3B displays the Log S100A12 values as a biomarker for predicting the occurrence of major adverse disease end points. The Kaplan-Meier cumulative event curve was used to assess the disease end points, as reflected by the unique S100A12 upregulation with Log S100A12 values greater than 125% or less than 125% at baseline (a cutoff value of 145.38 ng/mL).

In 151 T2DM subjects with DR, the number of patients with mild, moderate, and severe NPDR and PDR was 42, 35, 38, and 36, respectively. Table 3 shows the demographic, clinical, and laboratory characteristics of the four subgroups. In the subgroup analysis, sex, age, BMI, HbA1c, cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, smoking status, systolic blood pressure, diastolic blood pressure, creatinine, statin use, and ACEI use were not significantly different among the four subgroups. The DM duration was significantly different among the subgroups. The Log pentosidine and Log sRAGE values were not significantly different (Fig. 2). The Log S100A12 and Log hs-CRP values were significantly different among the four subgroups (Fig. 2).

The ROC curves for developing DR using the Log S100A12, Log pentosidine, Log sRAGE, and Log hs-CRP values revealed that the area under the receiver operating characteristic curves (AUC) were 0.822 (P < 0.001), 0.561 (P = 0.092), 0.572 (P = 0.051), and 0.566 (P = 0.068), respectively (Table 4, Fig. 3A).

**DISCUSSION**

Predictors of diabetic microvascular and macrovascular complications might be important in the prevention and manage-
ment of these complications. This study aimed to evaluate the plasma CRP, pentosidine, sRAGE, and S100A12 levels in Chinese patients with DR and examined whether these biomarkers are associated with the presence and severity of DR. The results of the study indicated an increase in the plasma levels of S100A12, pentosidine, sRAGE, and hs-CRP from healthy to T2DM to T2DM with DR. A multivariate logistic regression revealed that the plasma S100A12 levels were independently associated with the presence of DR in the patients with T2DM (odds ratio, 1.421; 95% CI, 0.364–2.531; \( P = 0.033 \)). Hence, the increase in the levels of plasma S100A12 in DM and an independent association with the presence of DR lead to the suggestion that S100A12 could be a potential biomarker for chronic inflammation in diabetes and the severity of DR.

C-reactive protein (CRP), which is predominantly produced by hepatocytes, is an acute-phase reactant released in response to inflammatory cytokines, such as IL-6, IL-1, and TNF-\( \alpha \). An association between serum hs-CRP levels and the duration of diabetes in type 2 diabetic patients has been found; hence, circulating CRP levels are an inflammation marker of DM.\(^{21,22}\) In addition to these findings, one recent study showed that CRP is increased in DR\(^{11}\); however, other studies have shown that CRP was not significantly associated with DR.\(^{12,13}\) In light of these studies, CRP might not be sufficiently specific to the diabetic disease process. The discrepancy in these studies might reflect that CRP levels respond to chronic and acute inflammatory processes and that CRP levels fluctuate following changes in inflammatory cytokines or the effects of confounding factors, such as drugs or liver disease. The results of our study indicated an increase in the plasma levels of hs-CRP from healthy to T2DM to T2DM with DR. A simple logistic regression analysis revealed that the plasma hs-CRP levels were not independently associated with the presence of DR in the patients with T2DM (odds ratio, 1.089; 95% CI, 0.734–1.401; \( P = 0.187 \)), which is consistent with a previous study.\(^{12,13}\) Although the log hs-CRP shows a statistically significant difference in the subgroup analysis of 151 T2DM subjects with

![Figure 1](https://iosv.arvojournals.org/)

**Figure 1.** An increase in the plasma levels of S100A12, pentosidine, sRAGE, and hs-CRP from healthy to T2DM to T2DM with DR. (A) Log S100A12, (B) Log pentosidine, (C) Log sRAGE, and (D) Log hs-CRP (* \( P < 0.05 \)).
DR, the Log hs-CRP of moderate NPDR show less reduction than that of mild NPDR (Table 3; Fig. 2). These findings indicate that CRP might not be a biomarker for chronic inflammation in diabetes and the presence and the severity of DR.

Accumulating evidence suggests that diabetes is associated with chronic low-grade inflammation; however, the underlying mechanism is not well understood. AGEs are the result of oxidative stress caused by hyperglycemia in patients with diabetes, and they have been implicated in the inflammatory pathogenesis of many of the complications of diabetes via reactive oxygen species production and nuclear factor-kB transcriptional activation. Tan suggested that the serum concentration of AGEs is increased in patients with diabetes. Patient-based studies have revealed that serum AGEs levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Simple Regression</th>
<th>Multiple Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, yes/no</td>
<td>1.101 (0.626–2.121)</td>
<td>0.087</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.016 (0.921–1.131)</td>
<td>0.821</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.032 (0.912–1.164)</td>
<td>0.878</td>
</tr>
<tr>
<td>Duration of DM, y</td>
<td>1.415 (1.008–1.956)</td>
<td>0.015</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>1.207 (1.085–1.683)</td>
<td>0.273</td>
</tr>
<tr>
<td>Cholesterol, mM</td>
<td>1.089 (0.633–1.621)</td>
<td>0.623</td>
</tr>
<tr>
<td>Triglycerides, mM</td>
<td>1.109 (0.374–1.823)</td>
<td>0.347</td>
</tr>
<tr>
<td>LDL cholesterol, mM</td>
<td>1.106 (0.412–1.598)</td>
<td>0.354</td>
</tr>
<tr>
<td>HDL cholesterol, mM</td>
<td>0.903 (0.451–1.389)</td>
<td>0.502</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>0.956 (0.473–1.863)</td>
<td>0.675</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.025 (0.553–1.601)</td>
<td>0.812</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>1.035 (0.412–1.768)</td>
<td>0.852</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.988 (0.743–1.215)</td>
<td>0.915</td>
</tr>
<tr>
<td>On statins, yes/no</td>
<td>1.186 (0.721–1.453)</td>
<td>0.286</td>
</tr>
<tr>
<td>On ACEI, yes/no</td>
<td>1.082 (0.812–1.206)</td>
<td>0.766</td>
</tr>
<tr>
<td>Log S100A12</td>
<td>1.368 (1.021–2.469)</td>
<td>0.008</td>
</tr>
<tr>
<td>Log Pentosidine</td>
<td>1.013 (0.955–1.693)</td>
<td>0.026</td>
</tr>
<tr>
<td>Log sRAGE</td>
<td>1.103 (0.465–1.752)</td>
<td>0.213</td>
</tr>
<tr>
<td>Log hs-CRP</td>
<td>1.089 (0.734–1.401)</td>
<td>0.187</td>
</tr>
</tbody>
</table>

association between plasma S100A12 levels and DR.
correlate with the severity of diabetic complications, including nephropathy and retinopathy. However, multiple regression analyses have revealed that serum AGEs levels were not an independent determinant of the presence of diabetic retinopathy. The discrepancy in these studies might arise from differences in AGEs adducts. There are multiple types of immunologically distinct and structurally identified AGEs such as crossline, pentosidine, furoyl-furanyl imidazole (FFI), hydroimidazolone, argpyrimidine, glyoxal lysine dimer (GOLD), and methylglyoxal lysine dimer (MOLD). In addition, clinically, the serum concentration of AGEs has been based on an ELISA determination of a range of AGE-antibodies; however, this method has frequently produced confounding outcomes. Among the multiple types of AGEs characterized in humans to date, pentosidine is chemically well defined. Consistent with the previous study, our study showed an increase in the plasma levels of pentosidine from healthy to T2DM to T2DM with DR. However, a multivariate logistic regression analysis revealed that the plasma pentosidine levels were not independently associated with the presence of DR in the patients with T2DM (odds ratio, 1.119; 95% CI, 0.578–1.823; P = 0.151).

Table 4. ROC Curves for S100A12, pentosidine, sRAGE, and hs-CRP for Predicting the Presence of DR in Type 2 Diabetic Patients

<table>
<thead>
<tr>
<th>Cutoff Value</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100A12, ng/mL</td>
<td>1.955, S100A12 = 90.16</td>
<td>0.822</td>
<td>0.781</td>
<td>0.770</td>
<td>0.771–0.874</td>
</tr>
<tr>
<td>Pentosidine, pg/mL</td>
<td>2.865, AGEs = 732.82</td>
<td>0.561</td>
<td>0.351</td>
<td>0.805</td>
<td>0.492–0.629</td>
</tr>
<tr>
<td>sRAGE, pg/mL</td>
<td>2.418, sRAGE = 261.82</td>
<td>0.572</td>
<td>0.616</td>
<td>0.456</td>
<td>0.502–0.642</td>
</tr>
<tr>
<td>hs-CRP, ng/mL</td>
<td>2.712, hs-CRP = 514.04</td>
<td>0.566</td>
<td>0.457</td>
<td>0.690</td>
<td>0.495–0.637</td>
</tr>
</tbody>
</table>

Figure 2. Relationship between the severity of diabetic retinopathy and the plasma levels of S100A12, pentosidine, sRAGE, and hs-CRP. (A) Log S100A12, (B) Log pentosidine, (C) Log sRAGE, and (D) Log hs-CRP (*P < 0.05).
These findings indicate that pentosidine might not be stable biomarkers for the presence and the severity of DR.

There is a growing body of evidence that the AGE–RAGE axis plays an important role in the development and progression of diabetes. Although S100A12 has been hypothesized to be a decoy for RAGE ligands and to play a protective role against the actions of AGEs, it appears unlikely that the plasma S100A12 levels are sufficient to scavenge its ligands, because the S100A12 level is 1000 times lower than that needed for sufficiently binding to and capturing its ligands. In our study, statin use and ACEI use were not significantly different among the three groups; therefore, it is unlikely that such treatment could confound our results, although such treatments have been shown to increase sRAGE levels in human subjects. A consistent with the previous study, statin use and ACEI use were not significantly different among the three groups; therefore, it is unlikely that such treatment could confound our results, although such treatments have been shown to increase sRAGE levels in human subjects.

In addition to these findings, the breakdown of the vascular barrier might play a role, and the influx of macrophages and neutrophils is associated with the vascular complications of type 2 diabetes, and there are increased numbers of neutrophils throughout the retina of diabetic monkeys, leading to capillary obstruction, intraretinal hemorrhages, exudates, and microaneurysms. S100A12 is abundantly expressed in the esophageal epithelium, neutrophils, and monocytes/macrophages in humans as well as in human aortic endothelial cells (HAECs) incubated in high glucose, which might explain its elevated serum levels in DR patients. A study demonstrated that S100A12 showed a statistically significant difference in the subgroup analysis of 151 T2DM subjects with DR. Hence, the increase in the levels of plasma S100A12 is a potential biomarker to detect the presence of DR, as well as the severity of DR. Longer duration of diabetes, poor metabolic control, hypertension, high blood cholesterol, nephropathy, age, sex, smoking, and genetic disposition are risk factors for the development of DR, which ensures that the development of this diabetic complication could not be fully explained and that any factors could affect the aggravation of DR. Hence, although the ROC curves for developing DR using the Log S100A12, Log pentosidine, Log sRAGE and Log hs-CRP values only revealed that Log S100A12 is a potential biomarker to detect DR, the AUC was lower than expected (AUC = 0.822, P < 0.001).

In addition to these findings, increased plasma S100A12 levels might be predictive of future major adverse disease end points in DR patients without a previous diagnosis of macrovascular disease. Regarding a possible cause for this finding, cerebrovascular events and cardiovascular disorders are accompanied by an inflammatory response and are associated with neutrophil infiltration. Hence, high plasma S100A12 levels are observed in the patients with cerebrovascular events.
and cardiovascular disorders because S100A12 predominantly is secreted by neutrophils. Furthermore, the previous study indicated that high plasma S100A12 levels on admission are associated with a poor functional outcome in patients with acute ischemic strokes. These findings illustrate that plasma S100A12 levels are related to the development of macrovascular and microvascular diabetic complications, even mortality.

The limitations of our study should be noted. Although our results revealed that the increase in the levels of plasma S100A12 in DM and an independent association with the presence of DR, we unable to confirm S100A12 may predict risk of progression of DR because the DR levels were assessed at baseline only.

Our study suggests that the plasma levels of S100A12 are closely associated with DR presence and severity and might be a better predictor for presence of DR than the levels of CRP, pentosidine, and sRAGE. In addition, S100A12 might be predictive of future major adverse disease end points, such as death, cerebrovascular events, and cardiovascular disorders in DR patients.

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