Association of Plasma Semaphorin 3A With Phenotypes of Diabetic Retinopathy and Nephropathy

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PURPOSE. To investigate whether diabetic retinopathy phenotypes and albuminuria are associated with the overexpression of plasma semaphorin 3A (Sema3A).

METHODS. The study group with severe nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), the diabetes without diabetic retinopathy group, and the control group without diabetes consisted of all consecutive patients who were scheduled to undergo intravitreal bevacizumab injection for treatment-naïve diabetic macular edema (DME) and senile cataract surgery, respectively. In all subjects, the plasma Sema3A levels before intravitreal bevacizumab injections or cataract surgery were measured by enzyme-linked immunosorbent assay. In the patients with DME, the capillary nonperfusion area (measured by fluorescein angiography), total macular volume (measured by spectral-domain optical coherence tomography), and the urine albumin-to-creatinine ratio were determined.

RESULTS. Severe NPDR (57 eyes) and PDR groups (51 eyes) both had significantly higher Sema3A levels than the control (58 eyes) and diabetes without diabetic retinopathy groups (54 eyes) ($P < 0.001$). Moreover, the PDR group had higher Sema3A levels than the severe NPDR group ($P < 0.001$). Plasma Sema3A levels correlated positively with the retinal nonperfusion area size ($r = 0.844$, $P = 0.004$), total macular volume ($r = 0.765$, $P = 0.005$), and the urine albumin-to-creatinine ratio ($r = 0.752$, $P < 0.001$). When DME patients were divided into normo-, micro-, and macroalbuminuria groups, the macroalbuminuria group had significantly higher plasma Sema3A levels than the microalbuminuria group or the normoalbuminuria group ($P = 0.002$ and $P < 0.001$, respectively).

CONCLUSIONS. The plasma Sema3A levels correlated significantly with the phenotypes of diabetic retinopathy and albuminuria. This suggests that Sema3A may be a potential biomarker for diabetic retinopathy and nephropathy.

Keywords: diabetic retinopathy, optical coherence tomography, fluorescein angiography

Macular edema in patients with ischemic retinopathies, particularly diabetic macular edema (DME), is the leading cause of vision loss in working-age populations. Ischemic retinopathies are characterized by hypoxia that is the result of retinal capillary obliteration; the hypoxia drives the deregulated growth of new blood vessels, which in turn can cause vision-impairing hemorrhage and retinal detachment. A key event in this retinal neovascularization cascade is the upregulation of vascular endothelial growth factor (VEGF) and other proangiogenic factors. As a result, various treatments that aim to control the production of proangiogenic factors have been developed.

Indeed, it was shown recently that intravitreal injections with anti-VEGF agents often improve the visual acuity of patients with DME. However, some patients show only a partial response to this therapy and thus continue to have persistent DME. This indicates the need to identify alternative therapeutic targets.

One of these novel targets may be semaphorin 3A (Sema3A), which is a classical neuronal guidance cue that is produced by surrounding cells to guide axon and cell migration during neuronal development. It is also produced by stressed retinal ganglion cells and appears to affect endothelial behavior. By binding the receptor neuropilin-1, Sema3A promotes the deviation of new vessels toward physiologically avascular regions of the retina. A recent experimental study on mice with streptozotocin (STZ)-induced diabetes showed that Sema3A is induced in the neuronal retina in the early hyperglycemic phases of diabetes and precipitates the initial breakdown of endothelial barrier function. The latter event then instigates pathologic vascular permeability.

Semaphorin 3A may also participate in diabetic nephropathy. Diabetes has become the primary cause of end-stage renal disease; approximately 44% of new patients entering dialysis in the United States are diabetics. The earliest indicator of kidney damage in diabetes is often the abnormal passage of the protein albumin into the urinary filtrate. This phenomenon is widely considered to reflect underlying endothelial dysfunction. Several lines of evidence indicate that Sema3A participates in this pathology: Adult podocytes and collecting tubules express Sema3A, and the glomerular endothelium expresses its receptor neuropilin-1. Moreover, Sema3A is required for the normal development of the glomerular filtration barrier and podocyte differentiation. In addition, when an acute tubular injury occurs (e.g., after cardiac surgery), Sema3A expression in the kidney is highly induced, leading to its increased urinary excretion; this has been observed in both mice and humans. Finally, both diabetic patients with albuminuria and...
Plasma Sema3A, Diabetic Retinopathy, and Albuminuria

METHODS

This prospective cross-sectional study was performed at the Department of Ophthalmology of Kyungpook National University, Daegu, South Korea. The study protocol was approved by the Institutional Review Board of Kyungpook National University Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects after the research purpose was explained.

Participants

The study group with diabetic retinopathy, the diabetes without diabetic retinopathy group, and the control group without diabetes consisted of all consecutive patients who were scheduled to undergo intravitreal bevacizumab injection for treatment-naïve DME and senile cataract surgery, respectively, between June 2013 and April 2015 in the Department of Ophthalmology of Kyungpook National University.

Participants were included in the study group if they met the following criteria at the first visit to the department: type 2 diabetes with severe nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), which were determined by the grading of color fundus photographs by a masked image grader, according to the modified Early Treatment Diabetic Retinopathy Study (ETDRS).23 A best-corrected visual acuity between 20/200 and 20/40; and a central subfield macular thickness of 300 µm or more on spectral-domain optical coherence tomography (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Patients with severe NPDR or PDR were excluded if they met any of the following criteria: presence of severe lens opacity or vitreous hemorrhage that obscured the fundus examination; previous treatments, including antiangiogenic medications such as bevacizumab, ranibizumab, and pegaptanib, laser photocoagulation, or previous vitrectomy; patients on peritoneal dialysis or hemodialysis; presence of infectious disease or prostate disease; patients with renal insufficiency, as indicated by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m²; patients with a history of liver diseases; patients with uncontrolled hypertension (HTN); and patients who were being treated with angiotensin-converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor blocker (ARB). In cases of bilateral lesions with the same grade of diabetic retinopathy, the first eye with more severe DME that received the intravitreal bevacizumab injection served as the study eye. Cases with asymmetric grades were excluded from the study. The study group was divided into the severe NPDR group and the PDR group. To compare plasma Sema3A levels between patients with severe NPDR or PDR and diabetic patients without diabetic retinopathy, type 2 diabetic patients were included in the diabetes without diabetic retinopathy group if they had neither diabetic retinopathy nor other retinal vascular diseases, based on the color fundus photographs. Subjects were excluded from the control group if they had a history of diabetes mellitus or HTN, fasting plasma glucose ≥100 mg/dL, uncontrolled HTN, or retinal vascular diseases, as determined by comprehensive ophthalmic examinations. Patients with autoimmune diseases, including rheumatoid arthritis or systemic lupus erythematosus,24 which can affect plasma Sema3A levels, were excluded from all groups.

Biochemical Analyses

Plasma was obtained immediately after blood was drawn from the antecubital vein to minimize hemoglobin interference. The sample was stored at −80°C until analysis, which took place within 6 months of venipuncture. Sema3A levels were evaluated using a commercially available enzyme-linked immunosorbent assay for Human Semaphorin 3A (cat no. CSB-E15913h; CUSABIO, Wuhan, China) in accordance with the manufacturer's instructions. The sensitivity of this assay was 0.039 ng/mL. Estimated GFR was calculated using the Modification of Diet in Renal Disease study formula and was expressed per 1.73 m² of body surface area. The urine albumin-to-creatinine ratio in morning spot urine samples was determined by using a radioimmunoassay (Immunotech, Prague, Czech Republic). Normoalbuminuria was defined as <30 µg albumin/mg creatinine, microalbuminuria was defined as 30 to 299 µg albumin/mg creatinine, and macroalbuminuria was defined as ≥300 µg albumin/mg creatinine.

Ophthalmic Examinations

All subjects underwent ophthalmic examinations at initial visit, including best-corrected visual acuity measurement using the Snellen chart and dilated fundus examination with slit-lamp biomicroscopy. In addition, the subjects with severe NPDR and PDR underwent fluorescein angiography and optical coherence tomography.

Measurement of the Capillary Nonperfusion Area by Fluorescein Angiography

At the venous phase (between 45 seconds and 2 minutes), fluorescein angiography images were obtained. After digital capture, the images were transferred to Adobe software (Adobe Systems, Inc., San Jose, CA, USA). The 30° circles in angiography were combined to create a seven standard field (7SF) image by using the ETDRS protocol.25 The 7SF protocol involves seven circular areas of the retina (three horizontally across the macula and four around the optic disc; Fig. 1A). The combined images cover nearly 75° of visualization. The capillary nonperfusion area was defined as dropout of the retinal capillary bed. The boundaries of the nonperfusion area were encircled by using the area measurement function. The total image area in 7SF was calculated in pixels and then converted into disc area (DA) for the purpose of clinical interpretation; for this, a scale factor based on the assumption that the DA was 2.7 mm² was used as described previously.25 The nonperfusion area of the encircled angiograph using the 7SF ETDRS protocol was evaluated and calculated by two independent masked retina specialists. The mean values of the nonperfusion areas in all photographs were measured by two retina specialists.

Measurement of Total Macular Volume by Coherence Tomography

Automated total macular volume measurements were obtained by using spectral-domain optical coherence tomography (Fig. 1B). The 6 × 6-mm area of the macular region centered on the
fovea was examined. Each scan consisted of 1024 A-scans per line. A macular profile of the central zone was obtained by using the fast macular volume preset, which consists of a 25-line horizontal raster scan that covers 20° × 20° and is centered on the fovea. Scans were obtained in the high-speed mode with the automated real-time feature enabled and set to nine frames. The measurements were recorded by a well-trained technician who was masked to patient information. Only images with a quality score of more than 16 dB (i.e., high-quality images) were selected.

Statistical Analyses

Statistical analyses were performed using SPSS software version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). The variables are expressed as the mean ± standard deviation or n (%). The groups were compared by 1-way analysis of variance with the post hoc Bonferroni method, analysis of covariance (ANCOVA), and χ² tests. To assess the relationship between plasma Sema3A levels and nonperfusion area, total macular volume, and the urine albumin-to-creatinine ratio, Pearson’s correlation coefficients were calculated. P values less than 0.05 were considered to indicate statistical significance. Multiple linear regression analysis was used to adjust for age, sex, severity of diabetic retinopathy, hemoglobin A1c (HbA1c), diabetes duration, presence of HTN, eGFR, and the urine albumin-to-creatinine ratio.

RESULTS

In total, 58 consecutive control subjects, 54 diabetic patients without diabetic retinopathy, and 129 consecutive diabetic retinopathy patients were scheduled to undergo senile cataract surgery and intravitreal bevacizumab injection for DME, respectively, during the study period. Three patients with DME were excluded because they had had previous treatments, including anti-VEGF. Another 11 patients with DME were excluded because they took ACE inhibitor or ARB; 3 of these also had eGFR < 60 mL/min/1.73 m². Seven patients were excluded because of asymmetric grades of severe NPDR and PDR in both eyes. Thus, the study consisted of 58 control subjects, 54 diabetic patients without diabetic retinopathy, and 108 patients with DME. Of the DME patients, 57 had severe NPDR and 51 had PDR.

The clinical characteristics of the four groups are summarized in the Table. The three groups did not differ in terms of eGFR (85.1 ± 13.1 vs. 78.8 ± 15.5 vs. 73.8 ± 12.7 mL/min; P = 0.10). However, the PDR group had a higher urine albumin-to-creatinine ratio than the severe NPDR group (739.4 ± 439.6 vs. 185.2 ± 184.3 μg/mg; P < 0.001). The diabetes without diabetic retinopathy, severe NPDR, and PDR groups differed significantly in terms of the rate of normoalbuminuria, microalbuminuria, and macroalbuminuria (P < 0.001).

Relationship Between Severity of Diabetic Retinopathy and Plasma Sema3A Levels

In the control, diabetes without diabetic retinopathy, severe NPDR, and PDR groups, the mean plasma Sema3A levels were 188.7 ± 126.1, 230.0 ± 88.3, 534.1 ± 205.9, and 1489.4 ± 207.6 ng/mL, respectively (Fig. 2A). These differences were statistically significant as determined by analysis of variance (P < 0.001). Closer analysis revealed that the severe NPDR and PDR groups both had significantly higher Sema3A levels than the control and diabetes without diabetic retinopathy groups (both P < 0.001). Moreover, the PDR group had higher Sema3A levels than the severe NPDR group (P < 0.001). Even after adjustment for age, sex, HbA1c, diabetes duration, HTN, eGFR, and the urine albumin-to-creatinine ratio, the PDR group had higher Sema3A levels than the severe NPDR group, as determined by analysis of covariance (P = 0.004). The control and diabetes without diabetic retinopathy groups did not differ significantly in plasma Sema3A levels (P = 1.0).
Correlation Between Plasma Semaphorin 3A Levels and Capillary Nonperfusion Area or Total Macular Volume

The PDR group had a significantly larger mean nonperfusion area than the severe NPDR group (23.5 ± 8.81 vs. 5.76 ± 3.29 DA; P < 0.001). When the severe NPDR and PDR groups were pooled, the nonperfusion area correlated positively with the plasma Sema3A levels (r = 0.844, P = 0.004; Fig. 2B). Even after adjustment for age, sex, severity of diabetic retinopathy, HbA1c, diabetes duration, HTN, eGFR, and the urine albumin-to-creatinine ratio, nonperfusion area was correlated positively with the plasma Sema3A levels (β = 0.709, R² = 0.681, P < 0.001).

The PDR group had a significantly larger mean total macular volume than the severe NPDR group (11.61 ± 1.42 vs. 9.35 ± 0.86 mm³; P < 0.001). When the severe NPDR and PDR groups were pooled, total macular volume was correlated positively with the plasma Sema3A levels (r = 0.765, P = 0.005; Fig. 2C). After adjusting for age, sex, severity of diabetic retinopathy, HbA1c, diabetes duration, HTN, eGFR, and the urine albumin-to-creatinine ratio, total macular volume was correlated positively with the plasma Sema3A levels (β = 0.513, R² = 0.764, P < 0.001).

Correlation Between Plasma Semaphorin 3A Levels and Severity of Albuminuria

When the severe NPDR and PDR groups were pooled, urine albumin-to-creatinine ratio was correlated positively with plasma Sema3A levels (r = 0.752, P < 0.001; Fig. 3). The combined severe NPDR and PDR group was then divided according to the severity of albuminuria. There were 15 patients with normalalbuminuria (12%), 42 patients with microalbuminuria (38.9%), and 53 patients with macroalbuminuria (49.1%). The three groups did not differ in terms of eGFR (84.9 ± 10.7, 77.9 ± 17.4, and 73.6 ± 11.9 mL/min, respectively; P = 0.08). However, the three groups did differ significantly in terms of plasma Sema3A levels as determined by analysis of variance (P < 0.001). A closer analysis showed that the macroalbuminuria group had significantly higher plasma Sema3A levels (1316.7 ± 420.7 ng/mL) than the microalbuminuria group (674.8 ± 258.4 ng/mL; P = 0.002) or the normalalbuminuria group (387.0 ± 48.8 ng/mL; P < 0.001).

DISCUSSION

Our study provides further clinical evidence for the notion that Sema3A may play a significant role in diabetic microvascular complications including diabetic retinopathy and diabetic nephropathy. In particular, we showed that patients with DME (both with severe NPDR or PDR) had significantly higher plasma Sema3A levels than the control subjects. This is consistent with the observation that in ischemic retinopathies such as that in diabetes, retinal ganglion neurons significantly increase their production of Sema3A. This is further supported by a study comparing 10 patients with DME to 11 patients with nonvascular ocular pathologies showing that DME associated with higher vitreous levels of Sema3A.

Sema3A in Diabetic Retinopathy

It was not clear why the ischemic retina does not revascularize when there is pathologic neovascularization into the vitreous until Joyal et al. described their oxygen-induced retinopathy model in 2011. This model showed that in the ischemic/avascular retina, Sema3A overexpression is limited to the avascular zone of the retina, primarily the ganglion cell layer. In addition, when Joyal et al. exposed retinal ganglion cells to 40 hours of hypoxia in vitro, it increased their expression of Sema3A. Moreover, when Sema3A expression in retinal ganglion cells was knocked down in vivo, normal vascular regeneration was observed in the ischemic retina. Thus, it appears that Sema3A is secreted by hypoxic neurons and inhibits the vascular regeneration of the retina while enhancing pathologic preretinal neovascularization. This possibility is supported by our observation that patients with PDR, who were characterized by the formation of new blood vessels on the retina, had higher plasma Sema3A levels than patients with severe NPDR.

Our observation also suggests that plasma Sema3A levels could serve as a biomarker for diabetic retinopathy severity. This possibility is further supported by our fluorescein angiography–based measurements of the nonperfusion areas of patients with severe NPDR and PDR. Since PDR associates with more severe retinal ischemia than NPDR, it was expected that the PDR patients would have a significantly larger mean nonperfusion area than the severe NPDR patients. More interestingly, when we combined the severe NPDR and PDR groups, we found that the nonperfusion area correlated positively with plasma Sema3A levels.

<table>
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<tr>
<th>Control, n = 58</th>
<th>Diabetes Without DR, n = 54</th>
<th>Severe NPDR, n = 57</th>
<th>PDR, n = 51</th>
<th>P Value</th>
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<tr>
<td>Age, y</td>
<td>60.3 ± 5.8</td>
<td>61.8 ± 6.9</td>
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<td>Male sex, n (%)</td>
<td>28 (48.3)</td>
<td>28 (51.9)</td>
<td>30 (52.6)</td>
<td>26 (51.0)</td>
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<tr>
<td>HbA1c, %</td>
<td>7.0 ± 1.0</td>
<td>8.5 ± 1.3</td>
<td>9.2 ± 2.1</td>
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<tr>
<td>Diabetes duration, y</td>
<td>11.8 ± 4.4</td>
<td>11.5 ± 4.4</td>
<td>15.4 ± 3.1</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>14 (25.9)</td>
<td>13 (22.8)</td>
<td>15 (29.4)</td>
<td>0.737†</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>85.1 ± 13.1</td>
<td>78.8 ± 15.5</td>
<td>73.8 ± 12.7</td>
<td>0.10*</td>
</tr>
<tr>
<td>Ualb/Cr, µg/mg</td>
<td>11.1 ± 4.6</td>
<td>185.2 ± 184.3</td>
<td>739.4 ± 439.6</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

The values shown are the mean ± standard deviation unless indicated otherwise. Normalalbuminuria is defined as <30 µg albumin/mg creatinine in morning spot collection, microalbuminuria as 30 to 299 µg albumin/mg creatinine, and macroalbuminuria as ≥300 µg albumin/mg creatinine. DR, diabetic retinopathy; macro, macroalbuminuria; micro, microalbuminuria; normo, normoalbuminuria; Ualb/Cr, urine albumin-to-creatinine ratio.

* One-way analysis of variance with post hoc Bonferroni multiple comparison tests.
† χ² test.
A previous study showed that Sema3A potently induces microvascular permeability by activating neuropilin-1 in the vascular endothelium. Intravitreal injection of Sema3A was also found to promote retinal vascular permeability. In addition, blocking Sema3A in diabetic mice decreased retinal vascular leakage by ~50% compared to that in unblocked control mice. The possibility that Sema3A may contribute to the development of DME is supported by the present study. When we determined the total macular volume of patients with severe NPDR and PDR by optical coherence tomography, we found that the patients with PDR had significantly higher total macular volumes than the patients with severe NPDR. More interestingly, when the two groups were combined, a positive correlation between total macular volume and plasma Sema3A levels was detected. Thus, our study provides additional clinical evidence for the relationship between Sema3A and DME, a representative diabetic microvascular complication.

Sema3A in Diabetic Nephropathy

Several studies have evaluated the role of Sema3A in the development of diabetic nephropathy by using diabetic animal models. One study found that Sema3A is upregulated in the kidneys of diabetic mice. Moreover, Aggarwal et al. showed that podocyte-specific Sema3A gain-of-function (Sema3A+) in diabetic mice resulted in diffuse foot process effacement, podocyte vacuoles, glomerular basement membrane thickening, and endothelial injury. The diabetic Sema3A+ mice also developed massive proteinuria and extensive nodular glomerulosclerosis that mimicked advanced diabetic nephropathy. Furthermore, podocyte Sema3A gain of function increased the plasma Sema3A concentrations in both nondiabetic and diabetic mice. These observations suggest that podocyte Sema3A secretion is a significant determinant of plasma Sema3A concentrations.

Despite these observations, the association of plasma Sema3A levels with albuminuria severity in patients with diabetic retinopathy has not yet been reported. The current study showed that patients with macroalbuminuria had significantly higher plasma Sema3A levels than patients with microalbuminuria or normoalbuminuria. This is consistent with the findings of a previous study showing that diabetics with microalbuminuria exhibited a significant increase in urinary Sema3A excretion, and that this was even more pronounced in diabetics with macroalbuminuria. We also found that when the PDR and severe NPDR groups were combined, plasma Sema3A levels correlated positively with the severity of albuminuria. Because the patients enrolled in our study had eGFR ≥ 60 mL/min, plasma Sema3A levels may also be useful as a biomarker of early-stage diabetic nephropathy, especially in patients with diabetic retinopathy.

Our observations also suggest that Sema3A may be a potential target in novel therapies for diabetic nephropathy. This is supported by Aggarwal et al., who showed that when Sema3A binding was inhibited in the podocyte-specific Sema3A gain-of-function diabetic mice by xanthofulvin, the mice showed less albuminuria and the pathologic glomerular changes were strongly suppressed. Similarly, when Mohamed et al. inhibited Sema3A with a novel inhibitory peptide, it suppressed the development of diabetic nephropathy.

Role of Sema3A-Mediated Endothelial Dysfunction in Diabetic Microvascular Complications

Although the mechanisms that drive diabetic albuminuria are still unclear, one of the major contributors is glomerular endothelial dysfunction. The close relationship between microalbuminuria and endothelial dysfunction is supported by the observation that patients with albuminuria have higher biochemical indices of endothelial dysfunction, including serum levels of von Willebrand factor, endothelin, tissue plasminogen activator, and fibrinogen.
Endothelial dysfunction also plays a central role in the development of diabetic retinopathy, especially DME. Neurrophilin-1, the receptor of Sema3A, is located in the endothelium of both the retina and the glomerulus. In addition, transmission electron microscopy of the Sema3Aþ mice indicated that Sema3A overexpression induces endothelial cell injury, as shown by glomerular endothelial cell swelling, detachment with expansion of the subendothelial space, and narrowing of the capillary lumen. Our findings that severe diabetic retinopathy and diabetic nephropathy associate significantly with increased Sema3A levels in human plasma also suggest that both diabetic microvascular complications could share abnormal variations in Sema3A levels, which could then be used as a common biomarker for these two diseases.

Study Limitations

This study has several limitations. First, the nonperfusion area was measured using the ETDRS 7SF protocol, which did not cover the far peripheral retina. Further studies using ultra-widefield fluorescein angiography will be necessary to confirm the positive correlation with the nonperfused areas. Second, this study showed only that the Sema3A level is associated with certain clinical features of diabetic retinopathy and nephropathy. It does not show that the Sema3A level is involved causally in the pathogenicity of these diseases. To establish a causal relationship, further studies using in vitro or in vivo models will be required. Third, this study measured plasma Sema3A levels, which do not necessarily reflect the ocular level of Sema3A. Further evaluation of vitreous and/or aqueous Sema3A levels in future studies could help to clarify its role. In addition, further analysis of the Sema3A levels in retina and kidney tissues from diabetic patients could help to elucidate the origins of high plasma Sema3A levels. Fourth, poor diabetic control and presence of HTN could affect the plasma Sema3A levels. However, even after adjustment for HbA1c, diabetes duration, and presence of HTN, the PDR group had higher Sema3A levels than healthy control subjects and diabetic patients without diabetic retinopathy, and the plasma Sema3A levels correlated positively with nonperfusion area and total macular volume in DME. Second, the plasma Sema3A levels of the combined severe NPDR and PDR patients also correlated positively with the severity of albuminuria. These results suggest that Sema3A may be a potential biomarker of diabetic microvascular complications.

Conclusions

The present study has shown an association between the Sema3A level and diabetic retinopathy and nephropathy. First, patients with severe NPDR and PDR had higher plasma Sema3A levels than healthy control subjects and diabetic patients without diabetic retinopathy, and the plasma Sema3A levels correlated positively with nonperfusion area and total macular volume in DME. Second, the plasma Sema3A levels of the combined severe NPDR and PDR patients also correlated positively with the severity of albuminuria. These results suggest that Sema3A may be a potential biomarker of diabetic microvascular complications.

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References


