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Relation of Serum and Vitreous Concentrations of Fetuin-A with Diabetic Retinopathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Fetuin-A, a liver-derived glycoprotein, is correlated with diabetes. The aim of the present investigation was to evaluate serum and vitreous concentrations of fetuin-A in patients with diabetic retinopathy (DR).

Material/Methods: We randomly selected 224 diabetic patients and 68 control subjects for this study.

Results: There were markedly higher serum and vitreous fetuin-A concentrations in proliferative diabetic retinopathy (PDR) patients than in the other three groups. NPDR patients exhibited elevated vitreous fetuin-A concentrations compared with patients without DR. However, no significant differences in serum fetuin-A concentrations were observed between NPDR patients and patients without DR. In addition, there were significantly lower concentrations of serum and vitreous fetuin-A in control subjects compared with the other three groups.

Conclusions: The occurrence and severity of DR is correlated with serum and vitreous fetuin-A concentrations.

MeSH Keywords: alpha-2-HS-Glycoprotein • Angiogenesis Inducing Agents • Diabetic Retinopathy

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Background

Diabetic retinopathy (DR), a serious complication of diabetes mellitus, is characterized by epiretinal outgrowth of fibrovascular membranes at the vitreoretinal interface [1]. The prevalence of blindness resulting from DR is estimated as more than 10 000 individuals each year [2]. The pathogenesis of DR is complicated, and many inflammatory cytokines are involved in the process. Much evidence indicates that chronic low-grade inflammation is involved in the pathogenesis of diabetic retinopathy [3].

Fetuin-A is a glycoprotein exclusively produced in the liver and then secreted into circulation in high concentrations [4]. It has been shown to inhibit insulin action at the step of the insulin receptor tyrosine kinase in rodents [5]. In addition, fetuin-A knockout mice showed improved insulin sensitivity and were resistant to weight gain after being fed a high-fat diet compared with wild-type controls [6]. Patients with type 2 diabetes mellitus (T2DM) had higher fetuin-A levels than healthy controls [7]. These data indicate the role of fetuin-A in the development of insulin resistance and diabetes.

The relationship between fetuin-A and DR has not been investigated to date. Therefore, the aims of the present investigation were to assess circulating and vitreous concentrations of fetuin-A in patients with DR and to compare results with the controls.

Material and Methods

Study population

This study consisted of 224 patients with T2DM who underwent vitreoretinal surgery for prolonged vitreous hemorrhage and tractional retinal detachment involving macular lesions. T2DM was diagnosed according to the American Diabetic Association criteria with a fasting glucose level ≥7.0 mmol/L or 2-hour postprandial plasma glucose level ≥11.1 mmol/L. All patients were evaluated by biomicroscopy using a fundus contact lens and gonioscopy with a slit-lamp. The severity of diabetic retinopathy was graded according to the international clinical classification of diabetic retinopathy [8]: diabetic patients without DR: No abnormalities; non-proliferative diabetic retinopathy (NPDR): microaneurysms, intraretinal hemorrhages, definite venous beading, or prominent intraretinal microvascular abnormalities, and no signs of proliferative retinopathy; proliferative diabetic retinopathy (PDR): neovascularization, vitreous/preretinal hemorrhage. Based on that classification, these patients were then divided into three groups: 68 diabetic patients without DR, 54 patients with PDR, and 102 patients with NPDR. Exclusion criteria included the following: previous vitrectomy, other ocular disorders such as uveitis, glaucoma and corneal neovascularization, other systemic diseases including heart failure, renal failure, hematologic, cardiologic, and metabolic disorders other than diabetes, photocoagulation, and intra-vitreal hemorrhages during the past three months. The control group comprised 68 patients matched for age, sex, and body mass index (BMI) who underwent vitrectomy for retinal detachment. These patients were determined to be without systemic disease, including diabetes.

The study was approved by the university ethics board and all patients provided written informed consent.

Laboratory methods

Vitreous samples were obtained by manual suction into a syringe through the aspiration line of vitrectomy, before the infusion line was opened. Blood samples were collected and the vitreous samples were immediately centrifuged for 10 minutes at 4°C at 3000 rpm. The serum and vitreous samples were analyzed for fetuin-A using commercially available enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, MN, USA).

Statistical analysis

The results are displayed as means ± standard errors (interquartile range). Comparisons of the characteristics between control subjects, diabetic patients without DR, NPDR patients, and PDR were performed by chi-square tests, one-way ANOVA, or Kruskal-Wallis test. All analyses reported significance at the $P<0.05$ level.

Results

Baseline parameters

There were increased systolic blood pressure (SBP), fasting plasma glucose (FPG), HbA1c, and triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), as well as reduced high-density lipoprotein cholesterol (HDL-C) in T2DM patients compared with the controls (Table 1).

Serum and vitreous fetuin-A

As displayed in Table 2, there were markedly higher serum and vitreous fetuin-A concentrations in proliferative diabetic retinopathy (PDR) patients than in the other three groups. NPDR patients exhibited higher vitreous fetuin-A concentrations compared with patients without DR. However, no significant differences in serum fetuin-A levels were observed between NPDR patients and patients without DR. In addition, there were significantly lower concentrations of serum and vitreous fetuin-A

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Table 1. Various characteristics of diabetic patients and controls.

	Controls	Diabetic patients			*P*
		Without DR	NPDR	PDR	
N	68	68	54	102	
Age (years)	56.60±9.34	57.49±11.18	57.76±8.96	57.12±11.42	0.934
Gender (M/F)	32/36	39/29	27/27	56/46	0.612
BMI (Kg/m^2)	25.68±1.91	25.96±4.44	26.63±3.41	26.35±4.03	0.471
SBP (mmHg)	122.28±12.60	137.21±24.12*	141.39± 24.98*	142.22±24.84*	<0.001
DBP (mmHg)	76.53±8.41	83.53±19.38*	81.30±15.15	84.32±13.98*	0.006
FPG (mmol/L)	5.09±0.43	8.26±1.70*	8.34±1.52*	8.33±1.76*	<0.001
HbA1c (%)	5.08±0.73	7.79±1.32*	7.86±1.36*	8.08±1.28*	<0.001
TC (mmol/L)	4.93±0.80	5.22±1.20	5.14±1.04	5.18±1.03	0.348
TG (mmol/L)	1.09± 0.35	1.87±0.62*	1.71± 0.51*	2.00±0.68*	<0.001
LDL-C (mmol/L)	3.13±0.68	3.49±0.98*	3.50±0.95*	3.47±0.86*	0.038
HDL-C (mmol/L)	1.45±0.28	1.15±0.25*	1.10±0.20*	1.09±0.21*	<0.001

* *P*<0.05 *vs.* control.

Table 2. Serum and vitreous fetuin-A levels in controls, diabetic patients without DR, NPDR patients, and PDR patients.

Fetuin-A (ng/mL)	Controls (n=68)	Without DR (n=68)	NPDR (n=54)	PDR (n=102)	*P* value
Serum	262.17 (196.22–316.02)**,***	289.43 (236.79–341.18)*	310.52 (243.78–361.98)*	345.79 (297.35–379.76)*,**,***	<0.001
Vitreous	87.29 (70.89–107.22)**,***	99.46 (85.86–115.24)*	108.24 (93.99–133.33)*,**	134.26 (110.12–152.40)*,**,***	<0.001

* *P*<0.05 *vs.* control; ** *P*<0.05 *vs.* diabetic patients without DR; *** *P*<0.05 *vs.* NPDR patients.

in control subjects compared with diabetic patients without DR, NPDR patients, and PDR patients.

Discussion

Fetuin-A, a 60 kDa glycoprotein, is produced exclusively by the liver. Fetuin-A is an endogenous natural inhibitor of insulin receptor tyrosine kinase [9]. In comparison to wild-type mice, fetuin-null mice demonstrated a lower fasting insulin resistance index, significantly lower blood glucose and insulin levels, and improved insulin sensitivity [10]. Furthermore, compared to wild-type mice, fetuin-null mice demonstrated increased skeletal muscle and liver insulin receptor autophosphorylation [10]. Fetuin-A decreased skeletal muscle glucose uptake by downregulating Akt and subsequent glucose transporter type 4 (GLUT-4) translocation to the plasma membrane [11]. These findings point to the promoting role of fetuin-A in diabetes. Serum fetuin-A concentrations were higher in an impaired glucose tolerance group than in a normal glucose tolerance group [7]. Plasma fetuin-A levels were positively associated with diabetes risk after adjustment [12]. Newly diagnosed type 2 diabetes patients showed higher serum fetuin-A levels than healthy controls [7]. These findings indicate that fetuin-A may be involved in the pathogenesis of diabetes.

Fetuin-A is known to inhibit ectopic calcium deposition and protect from vascular calcification. Fetuin-A is correlated with macrovascular disease of diabetes [13]. Fetuin-A levels were significantly lower in T2DM patients with calcified plaques than in those without calcified plaques [14]. Eraso et al. reported that lower level of circulating fetuin-A was associated with peripheral arterial disease in T2DM beyond traditional and novel cardiovascular risk factors [15]. Another study demonstrated that serum fetuin-A levels are independently correlated with the presence and severity of coronary artery disease (CAD) in T2DM patients [16].

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Fetuin-A was also demonstrated to be associated with microvascular complications of diabetes. Serum levels of fetuin-A were significantly higher among T2DM patients with diabetic nephropathy (DN) when compared to those with normoalbuminuria [17]. Fetuin-A levels in T2DM patients with microalbuminuria were determined to be lower than in those with macroalbuminuria [18]. Urinary excretion of fetuin-A significantly increased during the progression of albuminuria and glomerular filtration rate (GFR) stages [19]. Fetuin-A has been demonstrated to be a risk factor for both microalbuminuria and reduction of GFR in DN [19]. DR is another microvascular complication of diabetes. The results of the present study show elevated serum and vitreous fetuin-A levels in DR patients compared with the controls. Jung et al. reported that mean serum fetuin-A levels were not significantly different between T2DM patients with and without DR [20]. These conflicting data may be due to disease progression differences, different populations or assays applied, or incomplete control for confounding variables.

Angiogenesis plays a key role in the mechanism of DR. A variety of angiogenic factors, among which vascular endothelial growth factor (VEGF) is the most important, are involved in the pathogenesis of DR. Fetuin-A was demonstrated to cause a significant stimulation of interleukin-6 (IL-6) and IL-8, as well as VEGF mRNA expression in both perivascular fat cells and endothelial cells [21]. This suggests that fetuin-A is an angiogenic mediator and plays an important promoting role in the development of DR through the angiogenic effects.

Vitreous fetuin-A concentrations are lower compared with serum fetuin-A concentrations, which suggests that vitreous fetuin-A may partly come from the bleeding of the vascular system of the eyes. In addition, fetuin has been found in retinal tissues [22]. Thus, vitreous fetuin-A may partly come from the retinal tissues. Fetuin-A in eyes may promote DR development. Therefore, increased vitreous fetuin-A concentrations in DR patients may explain the presence and progression of DR.

Conclusions

Serum and vitreous fetuin-A concentrations are correlated with the occurrence and disease progression of DR.

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