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Increased Serum Pigment Epithelium Derived Factor Levels in Type 2 Diabetes Patients

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Abstract

Serum PEDF levels (mean(SD)) were increased in 96 Type 2 diabetic versus 54 non-diabetic subjects; 5.3(2.8) vs. 3.2(2.0)μg/ml, $p < 0.001$. In diabetes, PEDF correlated with BMI, serum creatinine and LDL-cholesterol, but not with other lipids, HbA1c or CRP. PEDF did not differ by drugs, complications, or gender.

Pigment epithelium-derived factor (PEDF) is an anti-angiogenic, anti-inflammatory, and antioxidant factor implicated in diabetic complications [1–6]. Previously we reported elevated serum PEDF levels in Type 1 diabetic patients with microvascular complications vs. complication-free patients, and associations with BMI, HbA1c, inflammation, triglycerides, renal and vascular dysfunction [2]. We now compare serum PEDF levels in Type 2 diabetic patients with those in non-diabetic subjects, and relate them to age, gender, vascular risk factors, complications, and medications.

Research Design and Methods

The study, which meets Declaration of Helsinki principles, was approved by Ethics Committees, and each participant gave written informed consent. Microvascular complications were defined as laser-treated retinopathy and/or increased albuminuria. Macrovascular disease was defined as clinically evident cardiovascular, cerebrovascular, or peripheral vascular disease. Blood was collected from 96 Type 2 diabetic and 54 non-diabetic subjects. Sixty-three diabetic and 32 non-diabetic subjects were fasting. HbA1c, lipids, and renal function tests were performed by the Clinical Chemistry Department, and serum CRP was quantified by nephelometry (Dade-Behring, Marburg, Germany) with intra- and inter-assay CVs < 8%.

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PEDF was quantified by ELISA (Chemicon Int., Inc Temecula, CA) as previously reported [2], with intra- and inter-assay CVs of 5.6% and 9%, respectively.

Statistics

Descriptive statistics were calculated for each group, and by gender, smoking, complications, and drug use. Differences between groups were analyzed by Student's t-test and chi-squared test. Non-normally distributed measures (CRP, triglycerides and serum creatinine) were transformed logarithmically. Generalized Linear Models were used to perform regressions of co-variables (in Table 1) on PEDF; first using each singly, then in a stepwise multiple regression setting $p=0.1$ to enter and $p=0.05$ to remove. Excel 2003 (Microsoft Corp., 2003) and SPSS for Windows 15.0 (SPSS Inc., 2006) were used. As non-fasting status can increase triglyceride levels, the relationship between PEDF and triglyceride levels was also examined in the subset of fasting subjects.

Results

Group characteristics and PEDF levels are shown in Table 1. PEDF levels were significantly increased in Type 2 diabetic patients compared with non-diabetic subjects. PEDF levels did not differ significantly by diabetes complication status, nor by gender or smoking in either group. In Type 2 diabetes, PEDF levels correlated with BMI ($r=0.23$, $p=0.024$), serum creatinine ($r=0.30$, $p=0.006$) and LDL-cholesterol ($r=-0.25$, $p=0.025$) concentrations, but not with age, HbA1c, CRP, triglycerides, total or HDL-cholesterol. Nor did PEDF levels differ by use of lipid drugs, aspirin, or by type of hypoglycaemic agent. In controls, PEDF concentrations correlated only with BMI ($r=0.28$, $p=0.046$) and did not correlate significantly with triglyceride levels in the fasted diabetic or non-diabetic subjects. However, none of the determinants predicted serum PEDF levels on multiple regression analyses in both groups.

Discussion

We previously reported increased serum PEDF levels in Type 1 diabetic patients with microvascular complications vs. healthy subjects, but no increase in complication-free Type 1 diabetic subjects [2]. In contrast, in the present study, PEDF levels were increased in Type 2 diabetes *per se*, but did not differ by complications. Our findings differ from a cross-sectional Japanese Type 2 diabetes study in which PEDF levels were higher in men than in women, and in patients with proliferative retinopathy vs. healthy control subjects, but did not differ significantly between control subjects and diabetic patients with less severe retinopathy [7]. In a Chinese study, PEDF levels were increased in Type 2 diabetes, including nephropathy-free subjects [8] as in our study, but were significantly higher in patients with vs. without nephropathy. Also, PEDF levels are increased in renal failure [10]. Thus in each of these Type 2 diabetes studies in three ethnic groups, PEDF levels were related to renal dysfunction and lipids [7,8].

Serum PEDF levels have been correlated with body habitus in this and other studies [2,9]. A potential explanation could be PEDF production by adipocytes, and/or PEDF functioning as a regulator of adipogenesis and lipid metabolism. As yet there are no publications related to PEDF production in human adipose tissue.

In the Japanese and Chinese diabetes studies, PEDF correlated positively with triglycerides, but in our study it did not, but was correlated inversely with LDL-cholesterol levels, and did not differ with use of lipid-lowering agents [7,8]. PEDF has anti-inflammatory effects and correlated with CRP in the Chinese study [8] but not in our study. PEDF may also relate to insulin resistance as levels are increased in the metabolic syndrome [9] and Type 2 diabetes in

this and other [7,8] cross-sectional studies. However, in the present study PEDF levels did not differ between patients on vs. not on insulin sensitizers (metformin or thiazolidinediones).

Increased PEDF levels in Type 2 diabetes and in Type 1 diabetic patients with microvascular complications [2] are now established, but the clinical effects of PEDF in diabetes are not fully known. Cell culture and animal studies support beneficial effects of PEDF, but in our Type 1 diabetes study, elevated PEDF levels were associated with vascular dysfunction [2]. Prospective studies are needed to elucidate relationships between PEDF and adiposity, vascular events, lipid lowering, and insulin sensitizing drugs. If PEDF concentration predicts adverse outcomes, its measurement may facilitate risk estimation, and PEDF-based interventions might be considered.

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Table 1

Clinical characteristics and serum PEDF levels in healthy control subjects and patients with Type 2 diabetes. PEDF values are mean $\pm$ SD for continuous variables and percentage (%) for categorical variables.

	Controls	Type 2 Diabetes
N : M / F	54 : 27 / 27	96 : 61 / 35
Age (yrs)	41 $\pm$ 11	56 $\pm$ 10 *
Diabetes duration (yrs)	0	10 $\pm$ 9
HbA1c (%)	5.2 $\pm$ 0.4	7.8 $\pm$ 1.5 *
BMI (kg/m ²)	26.4 $\pm$ 5.0	34.7 $\pm$ 9.0
Renal function		
Serum creatinine (mmol/l)	0.81 $\pm$ 0.20	0.93 $\pm$ 0.31 *
Microalbuminuria (% with)	1.9%	22.2% *
Hypertension (%)	7.4%	67.7% *
CRP (mg/l)	2.7 $\pm$ 3.2	5.5 $\pm$ 7.5 *
Lipid levels		
Total Cholesterol (mg/dl)	194 $\pm$ 41	184 $\pm$ 56
Triglycerides (mg/dl)	117 $\pm$ 67	244 $\pm$ 360 *
LDL-Cholesterol (mg/dl)	121 $\pm$ 35	104 $\pm$ 38 *
HDL-Cholesterol (mg/dl)	50 $\pm$ 13	40 $\pm$ 9 *
Lipid drugs (% taking)	3.8%	64.6% *
Any complication (% with)	0	70.6%
Microvascular disease (% with)	0	32.4%
Macrovascular disease (% with)	0	54.4%
Smoking (% current)	11.3%	21.1%
Anti-platelet drugs (% taking)	3.8%	58.5% *
PEDF levels (ug/ml)	3.2 $\pm$ 2.0	5.3 $\pm$ 2.8 *
PEDF range (ug/ml)	0.8 – 10.0	1.0 – 14.5
PEDF levels by group		
Smokers	3.2 $\pm$ 1.9 (6)	4.7 $\pm$ 3.0 (20)
Non-smokers	3.2 $\pm$ 2.1 (47)	5.4 $\pm$ 2.8 (75)
Males	3.2 $\pm$ 1.8 (27)	5.1 $\pm$ 2.4 (61)
Females	3.2 $\pm$ 2.2 (27)	5.6 $\pm$ 3.3 (34)
No complications	-	4.8 $\pm$ 2.3 (20)
Any complication	-	5.6 $\pm$ 2.8 (48)
No microvascular disease	-	5.2 $\pm$ 2.6 (46)
Any microvascular disease	-	5.7 $\pm$ 2.9 (22)
No macrovascular disease	-	4.9 $\pm$ 2.4 (31)
Any macrovascular disease	-	5.6 $\pm$ 2.9 (37)

* Controls vs Type 2 Diabetic Patients, $p < 0.05$.