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Plasma level of Connective Tissue Growth Factor is associated with vascular and renal damage in patients with type 2 diabetes of South Asian descent

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Submitted

Abstract

Objective

South Asians have a high burden of cardiovascular disease. Connective Tissue Growth Factor (CTGF), a profibrotic cytokine, has evolved as a risk marker for cardiovascular disease. The current study explores the relation between CTGF and vascular damage in type 2 diabetic South Asians.

Research design and methods

We performed a cross-sectional study in 54 type 2 diabetic South Asians. Vascular function testing (measurement of aortic Pulse Wave velocity and carotid artery Intima Media Thickness) was performed and plasma CTGF level and clinical parameters were assessed. The correlation between plasma CTGF level and measures of vascular damage was determined.

Results

Plasma CTGF correlated with pulse wave velocity ($r = 0.424$, $P = 0.002$), carotid artery intima-media thickness ($r = 0.324$, $P = 0.021$) and urinary albumin-to-creatinin ratio ($r = 0.376$, $P = 0.005$).

Conclusion

Plasma CTGF level is associated with vascular and renal damage in type 2 diabetic South Asians.

Introduction

Subjects of South Asian descent have a high burden of type 2 diabetes and cardiovascular disease. Type 2 diabetes presents at a younger age and once present, the risk of diabetic nephropathy is increased compared to Caucasians [1] Connective Tissue Growth Factor (CTGF) is a pro-fibrotic cytokine that is linked to development of vascular and renal disease [2,3].

Our aim was to determine the potential role of CTGF as a marker of vascular and renal dysfunction in subjects with type 2 diabetes of South Asian descent.

Methods and materials

Patient population and measurement of clinical parameters

All subjects belonged to a group of 465 South Asians that was previously studied [4] Patients with type 2 diabetes at baseline (n = 168) were contacted. Fifty-four patients agreed to participate in the current study. Data concerning medication, cardiovascular history and smoking habits were collected. Anthropometric measurements included weight, length, waist- and hip circumference. Laboratory parameters including lipids, creatinine, glucose, and urinary albumin/creatinine ratio (ACR) were measured according to standard methods. High sensitivity C-reactive protein (hsCRP) was measured with a fully automated Cobas Integra 800, according to the manufacturers protocol (Roche, Almere, the Netherlands). CTGF was measured in EDTA plasma drawn at study entry that had been stored at -80°C. CTGF was determined by a sandwich ELISA using monoclonal antibodies against two distinct epitopes on the N-terminal part of human CTGF (FibroGen, San Francisco, CA) detecting both full-length and N-terminal CTGF as described previously [2].

The study was approved by the Institutional Medical Ethics Committee. All subjects provided informed consent.

Assessment of pulse wave velocity and intima-media thickness

Arterial stiffness was assessed noninvasively by determination of the pulse wave velocity (PWV). Aortic PWV was calculated as the distance of the pulse wave traveling from the base of the neck to the right femoral artery per time frame (in m/s) as described previously [5]. For assessment of intima-media thickness (IMT) of the common carotid artery as a measure of atherosclerosis

the mean of eight ultrasound measurements (four measurements at different angles at each side of the neck) was taken as described previously [6]. All measurements were performed with subjects in the fasting state.

Statistical analysis

Normally distributed variables are expressed as mean $\pm$ 1 standard deviation and skewed distributed variables as median and interquartile range. Correlations were assessed using Pearson's correlation, with skewed distributed variables being log-transformed. Partial correlation was used to adjust for covariates. All test were two-sided and the level of significance was 0.05. All analyses were performed using SPSS for windows, version 17.

Results

Fifty-four type 2 diabetic South Asians were studied. Baseline characteristics are shown in table 1.

Median plasma CTGF level was 183 pmol/L (IQR 103-335). Plasma CTGF level positively correlated with PWV ($r = 0.424$, $P = 0.002$), carotid artery IMT ($r = 0.324$, $P = 0.021$), and log transformed urinary ACR ($r = 0.376$, $P = 0.005$). Plasma CTGF also positively correlated with age ($r = 0.310$, $P = 0.023$) but not with glycemic control (HbA1c $r = 0.028$, $P = 0.841$), systolic blood pressure ($r = 0.259$, $P = 0.059$), markers of inflammation (hsCRP $r = 0.102$, $P = 0.461$), or lipid parameters.

Adjustment for age and sex did not affect the relation between plasma CTGF and PWV and urinary albumin/creatinine ratio ($r = 0.376$, $P = 0.007$ and $r = 0.396$, $P = 0.004$, respectively) but the relation between plasma CTGF and IMT was no longer statistically significant ($r = 0.260$, $P = 0.071$). After addition of systolic blood pressure as a covariate to age and sex, only the relationship between CTGF and urinary albumin/creatinine ratio remained significant ($r = 0.367$, $P = 0.009$)

Pulse wave velocity additionally correlated with systolic blood pressure ($r = 0.504$, $P < 0.001$), BMI ($r = 0.307$, $P = 0.027$), waist circumference ($r = 0.331$, $P = 0.017$), hip circumference ($r = 0.292$, $P = 0.036$), HbA1c ($r = -0.344$, $P = 0.013$), Cockcroft-Gault creatinin clearance ($r = -0.282$, $P = 0.043$), fasting triglycerides ($r = 0.345$, $P = 0.013$) and LDL-cholesterol ($r = -0.354$, $P = 0.011$), but not with age, sex, smoking status, urinary albumin/creatinine ratio, and high-sensitivity C-reactive protein. After adjustment for age, sex, systolic blood pressure, fasting

triglycerides, LDL cholesterol, HbA1c and Cockcroft-Gault creatinin clearance, waist circumference remained independently associated with pulse wave velocity ($r = 0.308$, $P = 0.045$).

Table 1 Baseline characteristics of the study population

Age	56.8 ± 6.9
male sex (%)	48
Diabetes duration (yrs)	14 ± 6.3
HbA1c (%)	7.5 ± 1.4
Systolic bloodpressure (mm Hg)	147 ± 20
Diastolic bloodpressure (mm Hg)	88 ± 11
Body Mass Index	28.8 ± 4.4
Waist circumference (cm)	102 ± 12.8
Total cholesterol (mmol/L)	4.17 ± 0.88
LDL-cholesterol (mmol/L)	2.52 ± 0.82
HDL-cholesterol (mmol/L)	1.30 ± 0.35
Fasting triglycerides (mmol/L)	1.21 (0.98-1.80)
Previous cardiovascular event (%) [§]	26
Retinopathy (%)	74
Current or former smoking (%)	44
Oral anti-hyperglycemic agents without insulin (%)	52
Insulin (%)	11
Oral anti-hyperglycemic agents with insulin (%)	37
Urinary albumin/creatinine ratio (mg/mmol)	1.7 (0.7-5.3)
Cockcroft clearance (ml/min)	101 ± 35

[§] cardiovascular event is defined as a myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or stroke

Discussion

The current study demonstrates that in patients with type 2 diabetes of South Asian descent, plasma level of CTGF correlates with vascular and renal damage. These data suggest that the profibrotic cytokine CTGF may play a role in diabetic vascular and renal disease.

CTGF is produced by several cell types (including endothelial cells, vascular smooth muscle cells, renal mesangial and tubular epithelial cells) and its biological functions include proliferation, angiogenesis, migration, adhesion, and extracellular matrix production [7].

An increasing body of evidence points to the importance of vascular fibrosis in the pathogenesis of cardiovascular complications [8]. Decreased vascular elasticity results in systolic hypertension leading to an increased cardiac workload.

Our data indicate that CTGF, independent of age, may be a mediator of these changes given its profibrotic actions. Supporting this hypothesis, FG-3019, a CTGF inhibiting recombinant antibody, counteracted vascular fibrosis in diabetic rats [9].

Diabetic nephropathy occurs early in patients with type 2 diabetes of South Asian descent and blood pressure was shown to be a progression factor also in this subgroup [10]. Independent of blood pressure, plasma CTGF was strongly associated with urinary albumin/creatinin ratio as a measure of renal disease. Our data contribute to the observation that CTGF plays an important role in the pathophysiology of diabetic nephropathy [11]. A recent study showed reduction in albuminuria after administration of the CTGF-blocker FG-3019 to albuminuric patients with diabetes [12].

PWV was independently associated with waist circumference. The association between vascular stiffness and -mainly abdominal- obesity has been previously reported, and a beneficial effect of weight reduction on vascular stiffness has been shown [13]. Compared to Caucasians, South Asians have an increased prevalence of central obesity. We recently showed that in South Asians a high waist-to-hip ratio is a principal predictor of cardiovascular events [14]. Vascular stiffness therefore might be an important link between central obesity and increased cardiovascular events in South Asians.

In conclusion, plasma CTGF is associated with vascular stiffness, increased intima-media thickness and albuminuria in patients with type 2 diabetes of South Asian descent and may be a relevant mediator of vascular and renal damage.

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