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Association between circulating monocyte chemoattractant protein-1 and urinary albumin excretion in nonobese Type 2 diabetic patients

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Abstract

In 70 nonobese inpatients with Type 2 diabetes [body mass index (BMI): 24.0±4.4 kg/m^2], we examined circulating monocyte chemoattractant protein (MCP) -1 as a candidate marker of atherosclerosis by comparison with established markers: serum high-sensitivity C-reactive protein (hsCRP), plasma fibrinogen, and combined carotid artery intimal–medial thickness (IMT). In addition, an association was sought between circulating MCP-1 and urinary albumin excretion (UAE), reflecting diabetic renal microangiopathy. Serum MCP-1 was determined by enzyme-linked immunosorbent assay (ELISA). Patients were grouped by UAE: normoalbuminuria, below 30 mg/g of creatinine (Cr); microalbuminuria, 30 to 300 mg/g Cr; or macroalbuminuria, over 300 mg/g Cr. Serum MCP-1 for all participants, men, and women was 280.0±78.9, 269.0±68.8, and 294.9±87.9 pg/ml, respectively, showing no difference between genders. No correlation was noted between MCP-1 and hsCRP, fibrinogen, or carotid artery IMT. No correlation of MCP-1 was observed with age, duration of diabetes, fasting plasma glucose (FPG), hemoglobin (Hb) A_{1C}, BMI, diastolic blood pressure (DBP), or serum lipid concentrations, but significant correlations were found with systolic blood pressure (SBP; R=.2723, P=.0225) and with $\log_{10}$-transformed (log) UAE (R=.3343, P=.0047). Patients with macroalbuminuria had significant higher circulating MCP-1 than did those with normo- or microalbuminuria (P=.0063 and P=.0188, respectively). By stepwise regression analysis, only log UAE independently predicted serum MCP-1 (β=.3700, P=.0020). Thus, in nonobese Type 2 diabetic patients, MCP-1 might not be a marker of atherosclerosis and might be influenced significantly by diabetic nephropathy.

Keywords: Circulating monocyte chemoattractant protein-1; Atherosclerosis; Urinary albumin excretion; Type 2 diabetes

1. Introduction

Monocyte chemoattractant protein (MCP)-1, which belongs to the CC chemokine family (Robinson et al., 1989), participates importantly in the early progression of atherosclerosis (Nelken, Coughlin, Gordon, & Wilcox, 1991; Reape & Groot, 1999; Takeya, Yoshimura, Leonard, & Takahashi, 1993; Yla-Herttuala et al., 1991). MCP-1 is produced primarily by vascular endothelial cells and macrophages in atherosclerotic lesions (Reape & Groot, 1999) in response to stimulation by such as oxidized LDL (Li & Mehta, 2000), angiotensin II (Chen, Tummala, Olbrych, Alexander, & Medford, 1998), shear stress (Shyy, Hsieh, Usami, & Chien, 1994; Yu, Zeng, Hu, & Li, 2002), and tumor necrosis factor (TNF)-α (Yamashiro, Kamohara, & Yoshimura, 2001). MCP-1 recruits monocytes to atherosclerotic lesions according to its concentration gradient and promotes the transformation of monocytes to macrophages (Gu et al., 1998; Krishnaswamy, Kelley, Yerra, Smith, & Chi, 1999; Kumar et al., 1997; Namiki et al., 2002). In turn, these macrophages produce proinflammatory cytokines including interleukin (IL)-6 and TNF-α that produce local chronic inflammatory response in arterial walls, contributing to the progression of atherosclerosis. Although MCP-1 is expressed abundantly with discrete atherosclerotic plaques (Nelken et al., 1991; Reape & Groot, 1999; Takeya et al., 1993; Yla-Herttuala et al., 1991), its action appears

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localized to these lesions. Whether quantities of circulating MCP-1 can reflect overall degree of atherosclerosis is not known fully, although some recent reports suggest an association with increased risk of mortality from coronary artery disease (de Lemos et al., 2003; Piemonti et al., 2003).

The present study in patients with Type 2 diabetes investigated whether circulating MCP-1 measurement was potentially useful as a marker of atherosclerosis by comparisons with established markers such as serum high-sensitivity C-reactive protein (hsCRP), plasma fibrinogen, and ultrasonically determined intimal–medial thickness (IMT) of the carotid artery (O'Leary et al., 1992; Pearson et al., 2003; Pignoli, Tremoli, Poli, Oreste, & Paoletti, 1986; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997; Ridker, Hennekens, Buring, & Rifai, 2000; Ridker, Stampfer, & Rifai, 2001). We hypothesized that not only local concentrations of MCP-1 in atheromas but also circulating MCP-1 might reflect the degree of atherosclerosis in patients with Type 2 diabetes, especially since such patients are likely to develop extensive systemic atherosclerosis. In addition, we assessed the correlations of circulating MCP-1 with fasting plasma glucose (FPG), hemoglobin (Hb) A_{1C}, serum lipid concentrations, and blood pressure, all associated with the progression of atherosclerosis. Finally, a possible association was investigated between circulating MCP-1 and urinary albumin excretion (UAE), a marker of diabetic nephropathy.

2. Patients and methods

2.1. Patients

We studied 70 Japanese patients with Type 2 diabetes who had been hospitalized for treatment of poor diabetic control. Patients included 33 men and 37 women. The mean age and duration of diabetes were 60.3±10.3 and 9.9±7.5 years, respectively. Mean FPG and HbA_{1C} were 193.8±73.2 mg/dl and 10.0±2.0%, respectively. Body mass index (BMI) was 24.0±4.4 kg/m^2.

Five patients were treated with dietary modification alone, while 48 patients were treated with diet and oral hypoglycemic agents (OHA), specifically sulfonylureas (glibenclamide, gliclazide, or glimepiride), and 17 patients were treated with diet and insulin injections. Twenty-four patients were taking antihypertensive drugs: angiotensin converting enzyme inhibitors (ACE-I) or an angiotensin II receptor blockers (ARB) alone (n=5), calcium channel blockers alone (n=12), and both (n=7). No patient had a past history of liver disease such as viral or autoimmune hepatitis, and none showed biochemical evidence of liver dysfunction on admission. Any patient suspected of having any infectious disease (including a common cold) shortly before or during the admission was excluded from study, as were patients with autoimmune disease. Twenty-eight patients were smokers.

Diabetic nephropathy was assessed in terms of UAE. Patients were classified into three groups: UAE below 30 mg/g of creatinine (Cr), normoalbuminuria (n=31); UAE 30 to 300 mg/g Cr, microalbuminuria (n=20); and UAE above 300 mg/g Cr, macroalbuminuria (n=19). Diabetic retinopathy was assessed according to the classification of Davis (1974) by each patient's ophthalmologist: no diabetic retinopathy or NDR (n=37); simple diabetic retinopathy or SDR (n=17); and proliferative diabetic retinopathy or PDR (n=16).

BMI and blood pressure were determined before breakfast in the morning on the day after admission.

Clinical data are summarized in Table 1.

2.2. Methods

All venous blood samples for biochemical examinations were collected from patients in the morning before breakfast on the day after admission after at least 10 h of overnight fasting.

2.3. Serum MCP-1 assay

Blood was centrifuged at 1500 rpm for 5 min to separate serum from the clot containing blood cells. Sera were stored at −70 °C until analysis.

Table 1
Clinical characteristics of the diabetic participants

	Diabetic participants
Number (male/female)	70 (33/37)
Age (year)	60.3±10.3
Duration of diabetes (year)	9.9±7.5
FPG (mg/dl)	193.8±73.2
HbA_{1C} (%)	10.0±2.2
BMI (kg/m^2)	24.0±4.4
Any antihypertensive drug (n: ±)	24/46
ACE or ARB (n)	12
Smoking (n)	28
Therapy (n)	
Diet	5
OHA	48
Insulin	17
Retinopathy (n)	
NDR	37
SDR	17
PDR	16
Nephropathy (n)	
Normo	31
Micro	20
Macro	19

FPG: fasting plasma glucose
ACE: angiotensin converting enzyme inhibitors
ARB: angiotensin II receptor blockers
OHA: oral hypoglycemic agents
NDR: no diabetic retinopathy
SDR: simple diabetic retinopathy
PDR: proliferative diabetic retinopathy
Normo: normoalbuminurea
Micro: microalbuminuria
Macro: macroalbuminuria