Short Communication

The K469E Polymorphism of the Intracellular Adhesion Molecule 1 *(ICAM-1)* Gene Is Not Associated with Myocardial Infarction in Caucasians with Type 2 Diabetes

(K469E polymorphism of the *ICAM* gene / myocardial infarction / type 2 diabetes / association study)

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Abstract. Type 2 diabetes is one of the major risk factors for the development of CAD and subsequent MI. Inflammation, whereby ICAM-1 plays an important role, has been implicated in the pathogenesis of MI. The K469E polymorphism of the *ICAM-1* gene has recently been associated with ischemic stroke, atherosclerosis of femoral arteries and microvascular complications of type 2 diabetes. We examined the association between the K469E polymorphism of the *ICAM-1* gene and MI among the patients with type 2 diabetes in Slovenian population. Genotyping of the K469E polymorphism of the *ICAM-1* gene was performed for 367 subjects with type 2 diabetes: 152 patients with MI and 215 with no history of CAD. The K469E *ICAM-1* genotype distribution in patients with MI (EE = 21.7 %, EK = 47.4 %, KK = 30.9 %) did not differ from genotype distribution in patients without CAD (EE = 19.1 %, EK = 50.7 %, KK = 30.2 %), and the EE genotype was not associated with MI in subjects with type 2 diabetes (P = 0.5). In conclusion, the K469E polymorphism of the *ICAM-1* gene was not associated with MI in patients with type 2 diabetes, and therefore may not be used as a genetic marker for MI in patients with type 2 diabetes.

Introduction

The inflammatory process is associated with the expression of adhesion molecules such as intracellular adhesion molecule (ICAM), which interacts with leukocyte integrins and promotes the atherothrombotic process (Ross, 1999; Blankenberg et al., 2003) at the surface of endothelial cells (van de Stolpe et al., 1996; Jiang et al., 2002; Luc et al., 2003). Expression of ICAM-1 can be rapidly upregulated several fold in atherosclerotic lesions by inflammatory mediators (Dustin et al., 1986; Davies et al., 1993). Due to the important role of inflammation in atherothrombosis, these adhesion molecules have gained much attention in pathogenesis of myocardial infarction (MI) (Ross, 1999).

Recently, several polymorphisms of the *ICAM-1* gene have been reported (Jiang et al., 2002; Pola et al., 2003). The C/T polymorphism of the *ICAM-1* gene (exon 6, codon 469) was reported to be associated with coronary artery disease (CAD) and MI in general population, and the K469E polymorphism of the *ICAM-1* gene has been found to be related to ischemic stroke (Jiang et al., 2002; Pola et al., 2003).

The object of this study was to investigate the association between the K469E polymorphism of the *ICAM-1* gene and MI among the patients with type 2 diabetes in Slovene population (Caucasians).

Material and Methods

The study population of this cross-sectional analysis consisted of 367 subjects with type 2 diabetes lasting more than 10 years: 152 patients with MI (MI group) and 215 patients (control group) with no history of CAD, no signs of ischemic changes on electrocardiogram and no ischemic changes during submaximal stress testing. The *ICAM* gene polymorphism was evaluated as described previously (Vora et al., 1994). Chi-square (χ^2) test was used to compare discrete variables and to compare genotype distributions. Statistical analysis was performed using the SPSS program for Windows 2000 version 13 (SPSS Inc., Chicago, IL).

Results and Discussion

The *ICAM-1* genotype distribution in patients (MI group) and controls was compatible with Hardy-Weinberg expectations (Table 1; patients $\chi^2 = 0.30$, P = 0.58; ICAM: controls $\chi^2 = 0.15$, P = 0.69). Patients were younger (59.2 ± 11.2 years vs. 66.5 ± 10.2 years, P < 0.001), predominantly of male sex (65.1 % vs. 45.6, P < 0.001) and had a higher incidence of cigarette smoking (34.2 % vs. 14.4, P < 0.001) compared to the control group. Additionally, they had higher total cholesterol (5.9 ± 1.4 vs. 5.5 ± 1.3 mmol/l, P = 0.007)

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Abbreviations: CAD – coronary artery disease, ICAM-1 – intercellular adhesion molecule-1, MI – myocardial infarction.

Table 1. Genotype distribution of the K469E polymorphism of the ICAM-1 gene in patients with MI and in the control group

Genotype	MI group	Control group	P	OR (95% CI)[1]
EE	33 (21.7)	41 (19.1)	0.52	1.2 (0.7-2.0)[2]
EK	72 (47.4)	109 (50.7)		
KK	47 (30.9)	65 (30.2)		

[1]Odds ratio (95% confidence interval)

[2]P-value and OR for the recessive model (EE genotype versus EK genotype plus KK genotype).

and LDL cholesterol (3.7 ± 1.3 vs. 3.2 ± 1.0 mmol/l, P < 0.001) levels, and lower HDL cholesterol (1.1 ± 0.3 vs. 1.2 ± 0.4, P = 0.027) levels than the controls (Table 1). There were no significant differences in the incidence of hypertension, and triglyceride levels between the cases and control subjects.

In cross-sectional study we failed to demonstrate an association between the EE genotype of the K469E polymorphism of the *ICAM-1* gene and MI in patients with type 2 diabetes (OR = 1.2; 95 % CI = 0.7–2.0; P = 0.5). In contrast to our study, a report in Caucasians in Italy (Pola et al., 2003) demonstrated a positive association between the EE genotype of the K469E polymorphism of the *ICAM-1* gene and ischemic stroke, whereas a report in Chinese population demonstrated a positive association between the KK genotype and restenosis after coronary stenting (Liu et al., 2004). Different populations represent different gene pools, suggesting that gene-disease associations can be expected to vary between populations due to the differences in a complex genetic background.

Moreover, in type 2 diabetic patients, ICAM-1 may have partly different meaning in its function in progression of vascular damage from non-diabetic subjects. Kamiuchi et al. (2002) reported that the KK genotype of the *ICAM-1* gene polymorphism was associated with increased risk for retinopathy in type 2 diabetic patients. Recently, the EE genotype of the K469E polymorphism of the *ICAM-1* gene has been reported to be associated with the lower plasma fibrinogen levels in patients with type 2 diabetes (Yokoyama et al., 2005). In our study neither the EE genotype nor the KK genotype was associated with MI in subjects with type 2 diabetes, and therefore the K469E polymorphism of the *ICAM-1* gene may not be used as a genetic marker for MI in patients with type 2 diabetes.

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