The -455G/A Polymorphism of the β Fibrinogen Gene and the Bgl II Polymorphism of the α2β1 Integrin Gene and Myocardial Infarction in Patients with Type 2 Diabetes

(-455G/A polymorphism in the β fibrinogen gene / α2β1 integrin / myocardial infarction / type 2 diabetes)

G. POGLAJEN[1], J. KIRBIŠ[2], A. MILUTINOVIĆ[3]

[1]Medical Center Medicor Izola, Slovenia
[2]Department of Cardiovascular Surgery, Medical Centre Ljubljana, Slovenia
[3]Institute of Histology and Embryology, Medical Faculty, University of Ljubljana, Slovenia

Abstract. Platelets and fibrinogen might be involved in the pathogenesis of thrombus formation and MI. The Bgl II gene polymorphism of the α2β1 integrin, which is a platelet collagen receptor, and the -455G/A polymorphism in the β fibrinogen gene have been suggested as genetic risk factors for MI. The aim of this study was to look for a relationship between the -455G/A polymorphism in the β fibrinogen gene and the development of MI in Caucasians with type 2 diabetes. One hundred and forty-two subjects with type 2 diabetes and MI were compared to 234 diabetic subjects with no history of coronary artery disease. There were no significant differences in the frequency of the Bgl II gene polymorphism or of the -455G/A polymorphism in the β fibrinogen gene in the patients with MI compared to the patients without MI: Bgl II (+/+) genotype was found in 19.7% of patients with MI and 15.4% of controls and -455GG genotype was found in 58.4% of patients with MI and 57.7% of controls. The present study demonstrates that neither the Bgl II gene polymorphism nor -455G/A polymorphism in the β fibrinogen gene is a genetic marker for MI in Slovene population (Caucasians) with type 2 diabetes.

Several candidate genes have been implicated so far in the pathogenesis of atherothrombotic process on coronary arteries, i.e. myocardial infarction (MI), including the angiotensin-I converting enzyme gene, apoprotein E gene, oestrogen gene, and gene involved in the thrombotic process (Petrovic et al., 2000; Petrovic and Peterlin, 2003; Petrovic, 2004). MI results from the formation of a platelet-rich thrombus and fibrinogen accumulation at the site of a ruptured atherosclerotic plaque (Fuster et al., 1992). Platelets from diabetic patients, which are hyperreactive to aggregating agents such as collagen, thrombin, and adenosine diphosphate, are thought to be involved in the pathogenesis of microvascular and macrovascular complications of diabetes (Winocour, 1992; Petrovic et al., 2003b). Platelet membrane glycoprotein Ia/IIa, α2β1 integrin, mediates platelet adhesion to collagen, which is an essential first step in thrombus formation (Santoro and Zutter, 1995). Fibrinogen was reported to be an independent risk factor of MI, and the -455G/A polymorphism of the β fibrinogen gene was associated with the plasma fibrinogen level (Scarabin et al., 1993; Behague et al., 1996). The aim of the present study was to find whether the Bgl II polymorphism of the α2β1 integrin gene and the –455G/A polymorphism of the β fibrinogen gene are genetic markers for MI in Caucasians with type 2 diabetes.

Subjects and Methods

The study population of this cross-sectional analysis consisted of 376 diabetic Slovene subjects (Caucasians) with type 2 diabetes lasting more than 10 years (Petrovic et al., 2003a). The MI group consisted of 142 cases, and the control group consisted of 234 diabetics with no history of coronary artery disease (CAD), no signs of ischaemic changes on the electrocardiogram and no ischaemic changes during submaximal stress testing. Genotyping of the integrin Bgl II gene polymorphism and of the -455G/A polymorphism of the β fibrinogen gene was performed as described previously (Scarabin et al., 1993; Matsubara et al., 2000).

Results and Discussion

The Bgl II α2β1 integrin genotype (cases $\chi^2 = 0.815$, P = 0.367; controls $\chi^2 = 1.547$, P = 0.213) and the –455GA genotype distribution in cases and controls were compatible with Hardy-Weinberg expectations (cases $\chi^2 = 1.956$, P = 0.162; controls $\chi^2 = 0.435$, P = 0.51) (Table 1). In the cross-sectional study we failed to

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Corresponding author: Aleksandra Milutinović, Institute of Histology and Embryology, Medical Faculty, University of Ljubljana, Korytkova 2, 1105 Ljubljana, Slovenia.
Tel +386 1 543 7382; Fax +386 1 543 7361;
e-mail: sandramilutinovic@yahoo.com

Abbreviations: CAD – coronary artery disease, MI – myocardial infarction, OR – odds ratio.

Table 1. Distribution of the genotypes of the integrin Bgl II gene polymorphism (χ^2 = 1.8, P = 0.4) and the -455G/A polymorphism at the β fibrinogen gene (χ^2 = 0.4, P = 0.8) among MI patients and controls.

Variable	MI patients (%)	Controls (%)	OR (95% CI)[1]	P
Bgl II polymorphism[2]				
Bgl II (+/+) genotype	28 (19.7 %)	36 (15.4 %)	1.4 (0.8-2.3)[3]	0.3[3]
Bgl II (+/-) genotype	76 (53.5 %)	123 (52.6 %)		
Bgl II (-/-) genotype	38 (26.8 %)	75 (32.1 %)		
-455G/A polymorphism[4]				
-455GG genotype	83 (58.4 %)	135 (57.7 %)	1.0 (0.7-1.5)[5]	0.6[5]
-455GA genotype	47 (33.1 %)	83 (35.5 %)		
-455AA genotype	12 (8.5 %)	16 (6.8 %)		

[1]Odds ratio (95% confidence interval), [2]integrin Bgl II gene polymorphism, [3]OR (95% CI) and P value for the recessive model (Bgl II (+/+) genotype vs. Bgl II (+/-) genotype plus Bgl II (-/-) genotype), [4]-455G/A polymorphism at the β fibrinogen gene, [5]OR (95% CI) and P value for the recessive model (-455GG genotype vs. -455GA genotype plus -455AA genotype)

demonstrate that either the Bgl II gene polymorphism of the α2β1 integrin gene or the -455G/A polymorphism of the β fibrinogen was associated with MI in Caucasians with type 2 diabetes (Table 1). The Bgl II polymorphism of the α2β1 integrin has been reportedly associated with platelet α2β1 density, the extent of platelet adhesion to collagen, and the prevalence of non-fatal MI in the general population (OR = 1.57; P = 0.004), but not with CAD (Santoso et al., 1999). We did not demonstrate an association between the Bgl (+/+) genotype and MI in a group of Caucasians with type 2 diabetes. Contrary to the results of our current study on diabetics with MI, the Bgl II polymorphism of the α2β1 integrin has recently been reported associated with a microvascular complication of type 2 diabetes, diabetic retinopathy (Matsubara et al., 2000; Petrovic et al., 2003b). The discrepancy between both settings is most probably due to different pathogenetic mechanisms involved in both types of complications, i.e. due to differences between atherothrombotic and microvascular complications in diabetics: MI vs. diabetic retinopathy (Winocour, 1992). The -455G/A polymorphism in the β fibrinogen, a genetic marker for increased fibrinogen levels, was not associated with MI in Slovene population type 2 diabetes (Scarabin et al., 1993). Our findings are in agreement with the ECTIM study performed in the general population (Scarabin et al., 1993; Behague et al., 1996). In conclusion, the Bgl (+/+) genotype of the integrin α2β1 gene polymorphism and the -455G/G genotype of the –455G/A polymorphism in the β fibrinogen gene are not genetic markers for MI in Caucasians with type 2 diabetes.

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