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The G972R Polymorphism in the Insulin Receptor Substrate (IRS)-1 Gene does not Correlate with Angiographic Presence of Significant Coronary Artery Disease

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A base change at codon 972 of the insulin receptor substrate-1 (IRS-1) gene resulting in an arginine for glycine substitution has been found to be associated with insulin resistance and predisposition to non-insulin dependent diabetes mellitus. Some data exist about the possible contribution of the G972R mutation to development of coronary artery disease (CAD). We conducted a case-control study in order to test the frequency and possible association of this common mutation with the presence of CAD in 436 consecutive Austrian subjects undergoing coronary angiography. Genotypes of IRS-1 polymorphism were determined in 215 patients with significant (stenosis > 50 %) CAD and in 221 controls free of coronary atherosclerosis. The frequency of G972R mutation carriers was identical in the patient and control group (12.1 % vs. 12.2 %, p = n.s.) except for a higher prevalence in a small subgroup of male subjects with diabetes. Consequently, regression analysis revealed no association between this common mutation and CAD independent of typical risk factors in both gender. The group of CAD contained 44 (20.6 %) patients with diabetes, whereas only 19 (8.6 %) diabetics were found in the control arm (p < 0.001). Among 63 diabetic individuals of the total study population the frequency of the IRS-1 mutation was almost 2-times higher than among non-diabetics (20.6 % vs. 10.7 %, p < 0.003). Male mutation carriers showed significantly higher values of fasting insulin, female mutation carriers of triglycerides and LDL cholesterol. Data of the present study do not suggest that the G972R mutation is a genetic marker for the presence of significant CAD in patients stratified by coronary angiography. J Clin Basic Cardiol 2005; 8: 61–4.

Key words: IRS-1 gene polymorphism, coronary artery disease, coronary angiography, insulin resistance, diabetes

Coronary artery disease (CAD) is a multifactorial disorder resulting from an interaction between genetic background, conventional risk factors and environmental factors [1]. The insulin resistance syndrome is considered a potent risk factor for the development of atherosclerotic vascular disease [2–4]. A base change at codon 972 of the insulin receptor substrate-1 (IRS-1) gene resulting in an arginine for glycine substitution has been found to be associated with the insulin resistance syndrome and predisposition to non-insulin dependent diabetes mellitus (NIDDM) [5, 6]. Some investigators reported that the G972R mutation in the IRS-1 gene was significantly associated with increased risk of CAD, particularly in subgroups of individuals with obesity and insulin resistance syndrome [7]. These results suggested that the IRS-1 gene variant might be a new genetic risk factor for CAD independent of diabetes or hypertension. However, there is evidence that the frequency of the G972R mutation in the IRS-1 gene is variable in different ethnic and regional populations [8, 9] complicating the interpretation of the influence of this polymorphism on CAD risk [10, 11].

We performed a case-control study in order to test the frequency and possible association of this common mutation with the presence of CAD in the Austrian population.

Methods

Study Population

The study population comprised a total of 436 consecutive unrelated subjects who underwent coronary angiography at our hospital. The patient group consisted of 215 subjects with CAD (163 male, 52 female patients, mean age 58 ± 8 years). Diagnostic criteria for recruitment to the patient cohort were one or more stenoses > 50 % in at least one major coronary artery. The control group consisted of 221 subjects (110 males, 111 females, mean age 60 ± 8 years), which showed a smooth outline of the epicardial arteries without visible signs of atherosclerotic lesions in the standard coronary angiogram. All individuals studied were of Austrian descent. Subjects were considered as hypertensive if their blood pressure readings exceeded 140/90 mm Hg at two separate check-ups. The diagnosis of diabetes was established according to WHO criteria.

DNA Analysis

After informed consent genotypes of IRS-1 polymorphism were determined in all subjects by nested polymerase chain reaction and BstN1 restriction enzyme digestion, as described previously [7].

Measurement of Lipoproteins and Biochemical Analysis

All blood samples were drawn after a fasting period of at least 12 hours and not less than 6 weeks after myocardial infarction. Fasting glucose, total cholesterol, serum triglycerides, and HDL cholesterol levels were determined enzymatically with commercial kits. Serum levels of apolipoprotein B, apolipoprotein A-1 and lipoprotein (a) were measured by commercially available immunoassays (Hoffmann-LaRoche GmbH, Vienna, Austria). Serum fibrinogen levels were determined by an automated coagulation test based on the method of Clauss. Plasma homocysteine levels were measured by HPLC (Chromosystems Inc. M. Chem. GmbH, Munich, Germany).

Statistical Analysis

The STATISTICA statistical software package (version 5.5, StatSoft, Tulsa, OK, U.S.A.) was used for all calculations.

Received: September 15th, 2004; accepted: November 19th, 2004.
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Mean levels of all tested clinical and biochemical parameters in the group of non-carriers were compared to mean levels in the group of carriers separated by gender using one-way ANOVA. Continuous variables were compared by t-test and categorical variables by χ²-test. Data for continuous variables were expressed as mean ± SD. The criterion for statistical significance was p < 0.05. The Bonferroni adjustment was applied for each post-hoc comparison of a single parameter to end up with a reasonable overall type I error rate of 5 %. Logistic regression analysis was used for calculation of significant predictors of CAD.

Table 3 compares various biochemical parameters between non-carriers and carriers of the IRS-1 mutation for male and female subgroups. Female mutation carriers presented significantly higher levels of triglycerides and LDL. Fasting-glucose concentrations did not differ between mutation carriers and non-carriers. However, male carriers showed significantly higher values of fasting-insulin, a parameter serving as surrogate for insulin sensitivity. Other biochemical data did not reach statistical significance when compared to the presence of the G972R mutation.

The whole study group comprised 63 (14.5 %) patients with type II diabetes mellitus. The patient group contained 44 (20.5 %) diabetics, whereas the control group contained only 19 (8.6 %) diabetics (p < 0.001). Diabetes was significantly more prevalent among male mutation carriers compared to non-carriers (p = 0.005). Among all diabetic individuals the frequency of IRS-1 mutation was significantly higher than in patients without diabetes (20.6 % [13/63] vs. 10.7 % [40/373], p = 0.03). As far as hypertension was concerned no difference existed between mutation carriers and non-carriers.

Logistic regression analysis revealed no association between the G972R mutation and CAD status independent of other risk factors, neither for male (p = 0.46) nor for female (p = 0.40) subjects. No significant interaction was observed between IRS-1 type and risk of CAD in obese patients (body mass index/BMI > median). The probability of a stenosis > 50 % given that the mutation is present and that the BMI is

### Results

Clinical characteristics and biochemical parameters of the study population are summarised in Table 1. The patient group (n = 215) comprised 163 male and 52 female subjects with angiographically verified CAD. The control group (n = 221) consisted of 110 male and 111 female subjects free of CAD documented by normal angiograms. Classical risk factors, such as cigarette smoking, hypertension, and diabetes mellitus, were more prevalent in the patient than in the control group, though with considerable gender differences. Patients of both gender had significantly higher levels of lipoprotein (a), female patients of triglycerides and male patients of fibrinogen compared to control subjects. Total cholesterol did not differ between the two groups, whereas HDL and LDL cholesterol levels followed the expected distributions among CAD patients. No differences existed between the two groups as far as plasma levels of fasting insulin, fasting glucose and homocysteine were concerned.

The genotype distribution of the G972R polymorphism in the IRS-1 gene was determined for all subjects. Genotype and allele frequencies of G972R mutation in CAD patients and controls are reported in Table 2. The genotype distribution was in Hardy-Weinberg equilibrium. In the total study cohort of 436 individuals 49 (11.2 %) subjects were found to be heterozygous for the G972R mutation in the IRS-1 gene. Overall, four homozygous carriers were found, two in the male patient group and two in the female control group. The frequency of the G972R mutation carriers in the patient group was 12.1 %, and in the control group 12.2 % (p = n.s.).

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### Methods

This study was designed as a case-control study. The patient group consisted of 110 male and 111 female patients with angiographically verified CAD. The control group comprised 163 male and 52 female subjects free of CAD documented by normal angiograms. Classical risk factors, such as cigarette smoking, hypertension, and diabetes mellitus, were more prevalent in the patient than in the control group, though with considerable gender differences. Patients of both gender had significantly higher levels of lipoprotein (a), female patients of triglycerides and male patients of fibrinogen compared to control subjects. Total cholesterol did not differ between the two groups, whereas HDL and LDL cholesterol levels followed the expected distributions among CAD patients. No differences existed between the two groups as far as plasma levels of fasting insulin, fasting glucose and homocysteine were concerned.

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### Discussion

The results of this study suggest that the G972R polymorphism in the IRS-1 gene might be a genetic marker for CAD. However, further studies are needed to confirm these findings and to elucidate the mechanism by which this polymorphism influences the risk of CAD.

### Conclusion

The G972R polymorphism in the IRS-1 gene was associated with an increased risk of CAD in a case-control study. The results support the hypothesis that this polymorphism may be a genetic marker for CAD, although further studies are needed to confirm these findings and to elucidate the mechanism by which this polymorphism influences the risk of CAD.
above the median was 63 % for male and 35.2 % for female subjects. The probability of a stenosis > 50 % given that the mutation is absent and the BMI is above the median was 56.3 % for male and 35.7 % for female subjects. Both probabilities, for male (63 % vs. 56.3 %) and for female (35.2 % vs. 35.7 %) subjects did not differ significantly (p = 0.61 and p = 0.97, respectively).

Discussion

The present study was conducted to determine the frequency of the G972R polymorphism and the relationship to the presence of significant CAD in a cross-sectional Austrian population. 215 patients with angiographically proven CAD were compared with 221 consecutive controls free of CAD as far as the G972R mutation, clinical and biochemical characteristics were concerned. Of note, we found no significant difference in genotype frequency between carriers and non-carriers with respect to clinical characteristics (such as BMI or hypertension) except for a higher prevalence in the small subgroup of male subjects with diabetes. Diabetes is a strong risk factor for CAD, and previous studies have reported that the G972R mutation is almost twice as frequent in NIDDM patients as in control subjects [8, 12]. We confirmed this finding by the observation that the IRS-1 gene variant was present in diabetics in about 21 % vs. 11 % in non-diabetics.

Insulin resistance syndrome and type II diabetes are nowadays thought to result from polygenic interactions of several inherited gene mutations. The IRS-1 gene may act as susceptibility gene predisposing to manifestation of NIDDM [12–15]. It has been suggested previously to include angiographically documented CAD in the disease cluster comprising the insulin resistance syndrome [16].

A group of investigators reported that the frequency of the G972R mutation in 318 CAD patients was 2.5-times higher than in 208 control individuals [7]. After adjustment for other risk factors, the relative risk for angiographic coronary disease attributable to the IRS-1 polymorphism was 3-fold, and even increased to 7-fold and 27-fold, respectively, in obese patients and in patients with the insulin resistance syndrome.

In contrast to the cited study, it is noteworthy that our control group consisted of patients who underwent coronary angiography with normal results. However, it is conceivable that some of those patients may present cardiac syndrome X, which is known to occur more frequently in patients with classical risk factors, such as high fasting insulin and lipoprotein levels [17–19]. Our results suggest that the prevalence of the IRS-1 variant in patients with normal epicardial coronaryities seems to be as high as in patients with angiographic evidence of CAD. Most likely, discrepancies in genetic epidemiological association studies may be explained by selection criteria of the control group, ethnic divergence as well as differences in sample size and power of the study.

In conclusion, present data do not suggest that the G972R mutation is associated with an increased risk of CAD independent of diabetes in an ethnically homogenous population. This finding is in line with previously published data indicating that the IRS-1 gene may not be implicated directly in the pathogenesis of atherosclerotic vascular disease [11, 20–23]. As far as the contribution of a single genetic polymorphism to CAD risk is concerned, we believe that the interplay between several environmental and genetic factors needs to be strongly considered.

References:


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