INFLUENCE OF GENETIC POLYMORPHISMS ON CORONARY ARTERY DISEASE IN MEN AND WOMEN

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Introduction

Coronary artery disease (CAD) is the major cause of mortality in the developed Western world. CAD is a multifactorial disease, which appears to be due to interaction of multiple genetic and environmental factors. The pathogenesis of CAD is similar in man and woman, yet some risk factors have a greater impact on the development of CAD in men and others in women. The aim of this cross-sectional case-control association study was to identify a potential difference between men and women in genetic risk factors (gene polymorphisms) for CAD and their influence on lipid levels. The following gene polymorphisms in candidate genes for CAD were analysed: T/C polymorphism of the cytochrome P450c17 (CYP17) gene, tetranucleotide repeat $(TTTA)_n$ polymorphism of the cytochrome P450aro (CYP19) gene and dinucleotide (TA) polymorphism of estrogen receptor α gene. CYP17 and CYP19 are the key enzymes in biosynthesis of estrogens and androgens. Atheroprotective effect of estrogens is consequence of their action on serum lipid concentration and direct action on blood vessels and blood cells where biosynthesis occurs through action of CYP19. We also analysed relationship between insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene and CAD. The I/D polymorphism accounted for 47 % of the total variance of serum ACE concentration. The ACE deletion/deletion (DD) genotype is associated with increased serum and cellular concentrations of ACE, which result in enhanced conversion of angiotensin-I to angiotensin-II and degradation of bradykinin. We analysed association of apoprotein E (apoE) gene polymorphism with CAD. ApoE polymorphism influenced serum lipid concentration, but beside that, allele e4 predicted 40 % of the variation in mortality for CAD after adjustment for cholesterol levels. We also evaluated the effect of 4a/b polymorphism of the endothelial nitric oxide synthase (eNOS) gene on CAD. 4a/b polymorphism of the eNOS gene influence concentration of nitric oxide in vessel wall and through many biological actions modulate atherogenesis.

Material and methods

Slovene men and women with premature CAD were enrolled (men younger than 55 years and women younger than 65 years) and compared with the control group of men and women. We recruited 366 patients with CAD, which was confirmed by coronary angiography (215 men and 151 women) and 436 control subjects (207 men and 229 women) with no history of CAD and normal ECG. Genomic DNA was prepared from samples of whole blood by standard methods. The following polymorphism were identified by polymerase chain reaction (PCR) as described previously: I/D polymorphism of ACE gene, 4a/b polymorphism of the eNOS gene, $TTTA_n$ polymorphism of the CYP19 gene and TA polymorphism of estrogen receptor α gene. ApoE gene polymorphism and T/C polymorphism of the CYP17 gene were identified by PCR followed by restriction enzyme digestion of the amplified DNA, as described previously. Differences in mean values between CAD patients and control subjects were analysed by Student's t-test. The χ^2 test was used to compare discrete variables. Statistical analysis was performed using the SPSS program for Windows 98 version 12 (SPSS Inc.,Chicago, IL).

Results

The men patients with CAD were younger (45±7) than women patients with CAD (55±9). A higher incidence of cigarette smoking was found in woman patients (53 % vs. 38 %) and in men patients (68 % vs. 34 %) with CAD than in the control group. Women patients with CAD had a higher body mass index (28 vs. 25) higher incidence of hypertension (63 % vs. 26 %) and diabetes (20 % vs. 6 %) compared to control subjects. Man patients with CAD had a higher incidence of hypertension (40 % vs. 35 %) and diabetes (11 % vs. 6 %) compared to control subjects.

Multiple logistic-regression analysis showed that in men the deletion/deletion (DD) genotype of the I/D polymorphism of the ACE gene conferred a 1.8 fold independent risk for

CAD (odds ratio = 1.1–2.8; p = 0.013), whereas in women the ACE-DD genotype was not associated with CAD. Logistic regression analysis revealed no association between the E3E4 in E4E4 genotypes of the apoE polymorphism, aa genotype of the eNOS gene polymorphism, TT genotype of the CYP17 gene polymorphism, variable number of tetranucleotide repeat $(TTTA)_n$ polymorphism of the CYP19 gene, dinucleotide repeat polymorphism of the estrogen receptor α gene (higher number of repeats) and the risk for CAD either in men or in women.
Male subjects with risk genotypes of the apoE polymorphism, CYP17 gene polymorphism and the estrogen receptor α polymorphism had higher total cholesterol and LDL cholesterol compared to male subjects with no risk genotypes. In women the above mentioned polymorphisms did not influence total cholesterol and LDL cholesterol, the exception being the women with long repeat variants (both alleles of ≥ 19 repeats) of the estrogen receptor α polymorphism that had higher total cholesterol and LDL cholesterol in comparison with the women with short repeat variants. Subjects (men and women) with the E2E3 genotype of apoE polymorphism had statistically significantly higher triglycerides levels than the subjects with the E3E3 genotype. We did not observe any influence of tetranucleotide repeat $(TTTA)_n$ polymorphism of the CYP19 gene, and of 4a/b polymorphism of the eNOS gene on lipid levels either in men or women.

Discussion

The men and woman patients with CAD had a higher incidence of cigarette smoking, hypertension and diabetes than control subjects. We observed that women patient with CAD had higher triglycerides and lower HDL cholesterol beside other characteristic of metabolic syndrome what was in a strict distinction observed in men with CAD which had higher total cholesterol and LDL cholesterol.
The results of molecular genetic analysis revealed genetic diversity between men and women in respect of the DD genotype of the I/D polymorphism of the ACE gene, but not in other tested gene polymorphisms. What is the cause of gender different effect of ACE polymorphism on CAD is not known, but sex specific factors like hormonal status and interaction of renin-angiotensin system with estrogens and testosterone may explain gender related differences. Moreover, sex differences on lipid parameters were demonstrated in respect of the apoE gene polymorphism and the T/C polymorphism of the CYP17 gene, but not in other tested gene polymorphisms.