

Insertion/Deletion Polymorphism of Angiotensin-Converting Enzyme Gene – Risk Factor for Coronary Artery Disease in the Tuzla Region Population (Bosnia and Herzegovina)

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ABSTRACT

Angiotensin II is the major effector molecule of renin-angiotensin system; its production can be conveniently interrupted by angiotensin-converting enzyme (ACE). Typical plasma levels of ACE accompany the I/D polymorphism; however, a controversy exists as to whether the DD genotype of the ACE polymorphism affects the risk for the development of coronary artery disease (CAD) and to what extent the ACE polymorphism is associated with CAD in different populations. We compared the I/D polymorphism in 212 CAD patients younger than 50 years with 165 healthy control individuals. They were all from the Tuzla region in Bosnia and Herzegovina. Patients with CAD had a higher prevalence of the DD genotype (36.3%) than controls (25.6%). The odds ratio for the ACE DD genotype in CAD patients was 1.7 (95% confidence interval 1.0–2.7; $p < 0.05$). We may conclude that the D/D genotype of the ACE gene polymorphism is associated with an increased risk for CAD in the Bosnian population.

Key words: insertion/deletion polymorphism, ACE gene, coronary artery disease, Bosnia and Herzegovina

Introduction

Angiotensin II is the major effector molecule in the renin-angiotensin system. It is involved in blood pressure hemostasis, cardiovascular pathophysiology, and it affects the pathogenesis of coronary artery disease (CAD)¹. Angiotensin II is produced by angiotensin-converting enzyme (ACE), not only in the systemic circulation, but also in a number of local tissues, including coronary arteries².

Insertion/deletion (I/D) polymorphism of the ACE gene influences serum and cellular concentrations of ACE. The deletion/deletion (DD) genotype is associated with increased concentrations of angiotensin II and degradation of bradykinin³. Many reports have been published during 11 years after the initial report of the association of the DD genotype with myocardial infarction^{4–6}.

Studies done in different populations yielded contrasting results of the I/D polymorphism of the ACE gene as a risk factor for CAD^{4–12}. We analyzed the frequency of different genotypes at the I/D polymorphism locus and the association of DD genotype to CAD in the population from the Tuzla region in Bosnia & Herzegovina.

Materials and Methods

We compared 212 patients with myocardial infarction or angina pectoris (CAD) and the control group of 165 healthy subjects. We used a structured questionnaire to characterize both the CAD patients and the controls. The diagnosis of CAD was confirmed with coronary angiography at the Cardiovascular Clinic Tuzla from 1998 to 2001. The controls had to be free of history of myocardial infarction and angina pectoris. All patients signed a written informed consent for participation in the study; they

were all from the Tuzla region in Bosnia and Herzegovina.

The I/D polymorphism of the ACE gene was evaluated at the Division of Medical Genetics, Department of Obstetrics and Gynecology in Ljubljana as described previously^{13,14}. Demographic characteristics of cases and controls were compared with the analysis of variance; chi-square analysis was used to compare discrete variables. All computations were carried out with the SPSS statistical package (SPSS Inc., Illinois).

Results

The mean age of CAD patients was 45.4 years (± 4.1 years), and the mean age of controls was 44.5 years (± 4.3 years). No statistically significant difference in age was found between two groups. Moreover, no significant difference was found in height (174.4 cm \pm 17.0 cm vs. 175.2 \pm 8.7) between the patients and control subjects, whereas patients were heavier than controls (85.1 kg \pm 10.3 cm vs. 79.5 \pm 14.2; $p=0.01$).

Among the patients (Table 1), the gene frequency of the I allele was 0.41 and that of the D allele 0.59; genotypes were in the Hardy-Weinberg equilibrium ($\chi^2=0.87$; $p=0.39$). Among the controls (Table 1), the gene frequency of the I allele was 0.49 and that of the D allele 0.51; genotypes were in the Hardy-Weinberg equilibrium ($\chi^2=0.71$; $p=0.79$). The distribution of genotype frequencies in patients with CAD versus the controls is shown in Table 1.

TABLE 1
DISTRIBUTION OF ACE I/D GENOTYPES
AMONG CAD PATIENTS AND CONTROLS

Variable	CAD patients N (%)	Controls N (%)
DD genotype	77 (36.3%)	34 (25.6%)
ID genotype	96 (45.3%)	68 (51.1%)
II genotype	39 (18.4%)	31 (23.3%)

Patients with CAD had a higher incidence of the DD genotype (36.3%) than controls (25.6%). The odds ratio for the ACE DD genotype in CAD patients was 1.7 (95% confidence interval 1.0–2.7; $p < 0.05$).

Discussion

The I/D polymorphism of the ACE gene was studied as a potential cause of CAD in the Tuzla region in Bosnia and Herzegovina. The DD genotype was associated with a 1.7-fold increased risk for CAD. These results are in agreement with some other studies performed in the Caucasian populations^{5,7,8} and with results of the meta-analysis reported by Samani⁶. However, in Austrian⁹, Danish¹⁰, Italian¹¹, Japanese¹², and in some other populations the DD genotype was not associated with an increased risk of

CAD. It is possible that certain alleles may be associated with risk for CAD in certain populations only^{15,16}. The discrepancies among studies may also be due to different selection criteria (sex, age)^{17–19}. Potential mechanisms by which the DD genotype can affect the risk for CAD include promotion of endothelial dysfunction, enhanced vasoconstriction, proliferation of smooth muscle cells, inhibition of fibrinolysis and progression of atherosclerotic plaque calcification^{20–23}.

We may conclude that the DD genotype of the ACE gene polymorphism is an independent risk factor for CAD in the Bosnian population. Because of involvement of the renin-angiotensin system in the pathogenesis of CAD primary prevention of CAD in high-risk group of diabetics, and secondary prevention of CAD with ACE inhibitors has already been suggested²⁴.

REFERENCES

1. — PARMLEY, W. W., *Am. J. Med.*, 105 Suppl. 1A (1998) 27S. — 2. CUSHMAN, D. W., H. S. CHEUNG, *Biochem. Biophys. Acta*, 20 (1971) 261. — 3. COUSTEROUSSE, O., J. ALLERGRINI, M. LOPEZ, F. ALHENE-GELAS, *Biochem. J.*, 290 (1993) 33. — 4. CAMBIEN, F., O. POIRIER, L. LACERF, *Nature*, 359 (1992) 641. — 5. TIRET, L., A. BONNARDEAUX, O. POIRIER, S. RICARD, P. MARQUES-VIDAL, A. EVANS, D. ARVEILER, G. LUC, F. KEE, P. DUCI-METIERE, *Lancet*, 344 (1994) 910. — 6. SAMANI, N. J., J. R. THOMPSON, L. O'TOOLE, K. CHANCER, K. L. WOODS, *Circulation*, 94 (1996) 708. — 7. POIRIER, O., J. L. GEORGES, S. RICARD, D. ARVEILER, J. B. RUIDAVETS, G. LUC, A. EVANS, F. CAMBIEN, L. TIRET, *J. Hypertens.*, 16 (1998) 1443. — 8. BERGE, K. E., A. BAKKEN, M. BOHN, J. ERIKSEN, K. BERG, *Clin. Genet.*, 52 (1997) 71. — 9. FRIEDL, W., F. KREMPLER, B. PAULWEBER, M. PICHLER, F. SANDORFER, *Atherosclerosis*, 112 (1995) 137. — 10. AGERHOLM-LARSEN, B., B. G. NORDESTGAARD, R. STEFFENSEN, T. I. A. SORENSEN, G. JENSEN, A. TYBJAERG-HANSEN, *Circulation*, 95 (1997) 127. — 11. ARCA, M., G. PANNITTERI, F. CAMPAGNA, *Eur. J. Clin. Invest.*, 28 (1998) 485. — 12. FUJIMURA, T., M. YOKOTA, S. KATO, *Am. J. Hypertens.*, 10 (1997) 1384. — 13. PETROVIĆ, D., I. KEBER, M. ZORC, B. PETERLIN, *Pflugers Arch.*, 431 Suppl. (1996) R197. — 14. PETROVIĆ, D., M. ZORC, V. KANIĆ, B. PETERLIN, *Angiology*, 52 (2001) 247. — 15. KLUIJTMANS, L. A. J., A. S. WHITEHEAD, *Eur. Heart J.*, 22 (2001) 294. — 16. PETROVIĆ, D., B. PETERLIN, *Cardiology*, 99 (2003) 163. — 17. DOGGEN, C. J. M., V. M. CATS, R. M. BERTINA, F. R. ROSENDAAL, *Circulation*, 97 (1998) 1037. — 18. RIDKER, P. M., C. H. HENNEKENS, K. LINDPAINTER, M. J. STAMPFER, P. R. EISENBERG, J. P. MILETICH, *N. Engl. J. Med.*, 322 (1995) 912. — 19. ROSENDAAL, F. R., D. S. SISCOVICK, S. M. SCHWARTZ, *Blood*, 89 (1997) 1747. — 20. PELC, L. R., G. J. GROSS, D. C. WARLTIER, *Circulation*, 83 (1991) 2048. — 21. CAMBIEN, F., *Clin. Genet.*, 46 (1994) 94. — 22. RIDKER, P. M., C. L. GABOURY, P. R. CONLIN, E. W. SEELY, G. H. WILLIAMS, D. E. VAUGHAN, *Circulation*, 87 (1993) 1969. — 23. PETROVIĆ, D., M. ZORC, B. PETERLIN, *Folia Biol (Praha)*, 46 (2000) 181. — 24. SMITH, S. C. JR., S. N. BLAIR, R. O. BONOW, *Circulation*, 104 (2001) 1577.

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**INSERCIJSKI/DELECIJSKI POLIMORFIZAM U GENU ANGIOTENZIN
KONVERTIRAJUĆEG ENZIMA (ACE) – ČIMBENIK RIZIKA BOLESTI
KORONARNIH ARTERIJA U STANOVNIŠTVU TUZLANSKE REGIJE
(BOSNA I HERCEGOVINA)**

S A Ž E T A K

Angiotenzin II je aktivna molekula renin-angiotenzin sustava, no njegova proizvodnja može se lako spriječiti angiotenzin-konvertirajućim enzimom (ACE). Uobičajene vrijednosti ACE u plazmi u skladu su s I/D polimorfizmom, no postoje nesuglasice o pitanju utječe li DD genotip ACE polimorfizma na rizik razvoja koronarne bolesti srca (CAD) i u kojoj je mjeri ACE polimorfizam povezan s koronarnom bolešću srca u različitim populacijama. Stoga je uspoređen I/D polimorfizam u 212 CAD bolesnika mlađih od 50 godina s onim u 165 zdravih kontrolnih osoba. Svi su ispitanici stanovnici regije Tuzle, Bosna i Hercegovina. Bolesnici s CAD imali su višu prevalenciju DD genotipa (36.3%) u odnosu na kontrolnu skupinu (25.6%). Proporcija za ACE DD genotip u CAD bolesnika iznosila je 1.7 (95% intervala pouzdanosti 1.0–2.7, $p < 0.05$). Može se zaključiti da je D/D genotip polimorfizma ACE gena povezan s povećanim rizikom obolijevanja od koronarne bolesti srca u stanovništvu Bosne i Hercegovine.