Haemochromatosis-Causing Mutations C282Y and H63D Are Not Risk Factors for Coronary Artery Disease in Caucasians with Type 2 Diabetes

(hereditary haemochromatosis / C282Y mutation / H63D mutation / coronary artery disease / type 2 diabetes)

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Abstract. Iron metabolism might be involved in the pathogenesis of CAD, and C282Y and H63D mutations in the *HFE* gene are associated with increased serum iron levels and net iron accumulation. The aim of this study was to look for a relationship between the C282Y and H63D gene mutations of the *HFE* gene and coronary artery disease (CAD) in a group of patients with type 2 diabetes lasting more than 10 years. The C282Y and H63D gene mutations were tested in 338 Caucasians with type 2 diabetes: 156 cases with CAD and 182 subjects with no history of CAD. The C282Y and the H63D *HFE* gene distributions in patients with CAD (C282Y: YY 0.6%, CY 9.0%, CC 90.4%; H63D: DD 3.8%, HD 21.8%, HH 74.4%) were not significantly different from those of diabetic subjects without CAD (C282Y: YY 0%, CY 8.2%, CC 91.8%; H63D: DD 2.2%, HD 20.3%, HH 77.5%). In conclusion, we failed to demonstrate that the C282Y and H63D *HFE* gene mutations were risk factors for CAD in Caucasians with type 2 diabetes lasting longer than 10 years.

It has been proposed that iron accumulation may contribute to atherogenesis by increasing free radical formation and oxidative stress (Sempos et al., 1994). There are many reports about the role of haemochromatosis in the pathogenesis of coronary artery disease (CAD), but only a few in patients with type 2 diabetes (Tuomainen et al., 1999; Rasmussen et al., 2001; Kankova et al., 2002; Campbell et al. 2003; Malecki et al., 2003; Gunn et al., 2004). In this association study we tested the hypothesis whether the C282Y and the H63D *HFE* gene mutations are risk factors for CAD in type 2 diabetes lasting longer than 10 years.

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Abbreviation: CAD – coronary artery disease.

Material and Methods

The study population of this cross-sectional analysis consisted of 338 diabetic Slovene subjects with type 2 diabetes lasting longer than 10 years (Peterlin et al., 2003). The CAD group consisted of 156 cases, and the control group consisted of 182 diabetics with no history of CAD (Peterlin et al., 2003). The analysis of *HFE* gene mutations and statistical analysis were performed as described previously (Peterlin et al., 2003).

Results and Discussion

The C282Y and H63D genotype distributions in cases and controls were compatible with Hardy-Weinberg expectations (Table 1; C282: cases $P = 0.33$, $\chi^2 = 0.94$; C282: controls $P = 0.56$, $\chi^2 = 0.33$ 0.149; H63D: cases $P = 0.096$, $\chi^2 = 2.76$; H63D: controls $P = 0.4$, $\chi^2 = 0.69$). In cross-sectional study we failed to demonstrate that either the C282Y or H63D *HFE* gene mutation was associated with CAD in Caucasians with type 2 diabetes. Our findings are in accordance with most cross-sectional studies in general population and in diabetics (Tuomainen et al., 1999; Rasmussen et al., 2001; Kankova et al., 2002; Campbell et al. 2003; Malecki et al., 2003; Gunn et al., 2004). Contrary to most cross-sectional studies, two prospective studies reported an association between the C282Y heterozygosity and the risk of CAD (Tuomainen et al., 1999; Rasmussen et al., 2001). We may speculate that the disagreement between the findings of cross-sectional studies and prospective studies might be due to a survival bias in the cross-sectional studies. The C282Y heterozygous frequencies in diabetics in our study (9% in CAD group and 8.2% in the control group) were similar to other European reports (Njajou et al., 2002). Different populations represent different gene pools, suggesting that gene-disease associations can be expected to vary between populations. In conclusion, we provide evi-

Table 1. Genotype distributions of C282Y and H63D mutations in patients with CAD and in controls

Mutation/ genotype	CAD	Controls	OR (95% CI)[1]	P
C282Y				
YY homozygote	1 (0.6)	0 (0)		
CY heterozygote	14 (9.0)	15 (8.2)	1.2 (0.6-2.5)[2]	0.6[3]
CC homozygote	141 (90.4)	167 (91.8)		
H63D				
DD	6 (3.8)	4 (2.2)	1.2 (0.7-1.9)[4]	0.5[5]
HD	34 (21.8)	37 (20.3)		
HH	116 (74.4)	141 (77.5)		

[1]Odds ratio (95% confidence interval), [2]odds ratio (95% confidence interval) for dominant model (YY plus CY vs. CC), [3]P-value for dominant model (YY plus CY vs. CC), [4]odds ratio (95% confidence interval) for dominant model (DD plus HD vs. HH), [5]P-value for dominant model (DD plus HD vs. HH)

dence that the C282Y and H63D *HFE* gene mutations are not risk factors for CAD in Caucasians with type 2 diabetes lasting longer than 10 years.

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