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## Serum Total Homocysteine and Premature Coronary Heart Disease: Prospective Study in Middle Aged Patients

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**Abstract:** Homocysteine was found to be an independent risk factor for coronary artery disease in many epidemiological studies. The aim of the present study was to examine the relationship between total homocysteine levels and premature coronary artery disease events. A case - control study was carried out in patients aged 35 to 50 years with angiographically shown coronary heart disease and in age and sex matched control subjects with normal coronary angiography. Samples from 38 patients with coronary heart disease, and their paired controls were analyzed for homocysteine. Plasma homocysteine was measured by high performance liquid chromatography. Mean

serum total homocysteine was slightly higher in cases (16.7 mmol/L) than in controls (15.9 mmol/L), but the difference did not reach statistical significance (P=0.6). Twenty (52.6%) coronary heart disease patients and 14 (44%) control subjects had homocysteine levels above 15 mmol/L. In conclusion, homocysteine is not a major risk factor for premature coronary heart disease in the Çukurova region of Turkey. Larger studies are warranted to establish the role of homocysteine for premature coronary heart disease.

**Key Words:** Homocysteine, Premature Coronary Artery Disease

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### Introduction

Homocysteine, a sulphur-containing amino acid, is an intermediate formed during the catabolism of the essential dietary amino acid methionin (1,2). The factors known to influence homocysteine metabolism are vitamin B12, vitamin B6, folate and genetic aberration in the methylenetetrahydrofolate reduction gene (3,4). Genetic aberrations in the methylenetetrahydrofolate reductase gene may account for reduced enzyme activity and elevated plasma homocysteine concentrations (5,6).

Since McCully (7) first proposed the homocysteine theory of atherosclerosis, a lot of observational studies have reported a relation between blood levels of homocysteine and coronary artery disease (CAD) (8,9). The possible mechanisms of homocysteine-induced atherogenesis are endothelial injury, platelet activation, smooth muscle proliferation, oxidative modification of low-density lipoproteins, and endothelial leukocyte interactions (10).

As a predictor of coronary risk, serum total homocysteine may also be related to geographical variation, age and race. The aim of this prospective study was to determine the relation between total homocysteine and premature CAD.

### Materials and Methods

Thirty-eight patients aged  $\leq 50$  years (mean age 45.3 years, range 35-50, 35 men and 3 women) with angiographically proven to have symptomatic coronary artery disease and 25 age and sex-matched control subjects with chest pain (mean age 44.6 years, range 33-50, 23 men and 2 women) without CAD were studied.

Blood was collected in EDTA tubes, placed on ice, and plasma was separated within 30 minutes. Plasma homocysteine was analysed with a high-performance liquid chromatographic assay (11). Informed consent was obtained from all subjects and the study design was approved by the ethics committee of the University of Cukurova, Turkey.

Data were analysed with the use of SPSS for Windows 8.0. Means and 95% confidence intervals were used to describe continuous variables. The distributions of discrete and continuous variables between groups were compared by means of Student's t tests and Pearson's coefficient test. Statistical significance was inferred at  $p < 0.05$ .

## Results

The characteristics of cases and controls are shown in Table 1.

Higher but statistically insignificant homocysteine levels were seen in patients with coronary heart disease,  $16.7 \pm 7.1$  mmol/L, as against  $15.9 \pm 4.7$  mmol/L in control subjects. Twenty (52.6%) coronary heart disease patients and 14 (44%) control subjects had homocysteine levels above 15 mmol/L. Total homocysteine was not related to several other factors, including body mass index (BMI), total cholesterol, LDL cholesterol, HDL cholesterol, and glucose in patients with CAD and in control subjects.

The extent of coronary atherosclerosis evaluated by an angiographic coronary score correlated insignificantly to plasma homocysteine levels. Homocysteine in patients with atherosclerosis in two or three coronary arterial sites differed insignificantly from patients with CAD in only one site. (Mean homocysteine levels were  $15.6 \pm 5.3$  mmol/L in 19 patients with CAD in one site, and  $16.2 \pm 4.2$  mmol/L in 19 patients with CAD in two or three coronary arterial sites respectively,  $p=0.7$ ).

Table 1. Characteristics of cases and controls.

	Cases (n: 38)	Controls (n: 25)	P
Age (years)	$45.3 \pm 4.2$ (35-50)	$44.6 \pm 4.8$ (33-50)	0.5
Homocysteine (mmol/L)	$16.7 \pm 7.1$ (9.8-49.7)	$15.9 \pm 4.7$ (9.1-26.4)	0.6
Number of patients had homocysteine level >15 mmol/L	20/38 (52.6%)	14/25 (44%)	0.7
Serum cholesterol (mg/dl)	$191.3 \pm 39.1$ (105-264)	$190.2 \pm 32.9$ (135-284)	0.9
LDL cholesterol (mg/dl)	$107.4 \pm 31.5$ (42.0-175)	$115.6 \pm 31.1$ (77-195)	0.3
HDL cholesterol (mg/dl)	$45.6 \pm 7.5$ (29-62)	$46.0 \pm 8.3$ (34-67)	0.8
Glucose (mg/dl)	$109.4 \pm 39.5$ (76-311)	$101.2 \pm 11.4$ (87-130)	0.3

## Discussion

Homocysteine concentrations rise with age in both sexes (12). At a population level, the most important causes are probably lower concentrations of folic acid, vitamins B12 and B6 (13). Geographical variation is also important in total homocysteine levels. The finding would be consistent with the well documented geographical variations in dietary fruit and vegetable intake, and particularly in dietary folate intakes (14). There are also some studies reporting that modification of dietary patterns have substantial effects on levels of total serum homocysteine (15,16). Geographical variations in the frequency of genetic polymorphisms could also play a role in these regional variations (17).

Many case-control studies have shown that homocysteine is an independent risk factor for atherosclerotic coronary disease (18-20). The results of earlier population based prospective studies examining the relation between total homocysteine and premature CAD have been conflicting. In some studies, plasma homocysteine was more important in the development of premature CAD than it is that of late-onset CAD (20,21), but in others, elderly patients had homocysteine levels greater than that of younger patients (22). There were also studies reporting that homocysteine levels were not higher among patients with premature CAD than in control subjects (23-26).

Our results are likely to be non-linear on-association between total homocysteine and coronary risk. The results suggest that serum total homocysteine is not related to an increased risk of premature CAD events.

Further studies are needed to define the relative importance of geographical and genetic determinants of total homocysteine in patients with CAD.

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