Plasma homocysteine level in cardiac syndrome X and its relation with duke treadmill score

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ABSTRACT

The objective of this study was to investigate the plasma homocysteine level and the relationship between plasma homocysteine level and Duke treadmill score (DTS) in cardiac syndrome X (CSX) patients.

Methods: Seventy-nine patients (36 male, 43 female, mean age: 50 ± 8.8 years) admitted to Gazi University Hospital, Ankara, Turkey with typical effort angina, positive stress test, and angiographically normal coronary arteries between January and September 2006 were included in this prospective and controlled study. Thirty asymptomatic patients (11 male, 19 female, mean age: 47.6 ± 8.3 years) with 2 cardiovascular risk factors were chosen as a control group. Plasma homocysteine level was measured in both groups and DTS was calculated in the CSX group. Plasma homocysteine was measured with the AxSYM homocysteine immunoassay method in both groups.

Results: Plasma homocysteine level was higher in the CSX group compared to the control group (16.5 ± 4.9 μmol/L, n=79, versus 12.4 ± 4.1 μmol/L, n=30, p<0.001). The DTS was -2.7 ± 5.3 in the CSX group. There was a negative correlation between the DTS and homocysteine levels in the CSX group. (r=-0.506, p<0.001).

Conclusion: Plasma homocysteine level, which is known to cause endothelial dysfunction and microvascular ischemia were higher in CSX patients. Also, this increase in homocysteine level inversely correlated with the DTS, which represents the magnitude of ischemia.


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Cardiac syndrome X (CSX) is an entity defined as typical angina with positive stress test and normal coronary angiogram.1 Although various pathophysiological mechanisms are proposed including endothelial dysfunction,2 altered autonomic status,3,4 increased platelet aggregability,5 vascular inflammation,6 and exaggerated pain perception,7 the exact mechanism is still unknown. Hyperhomocysteinemia is known

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to be an independent risk factor for atherosclerosis. Increased levels of homocysteine leads to prolonged exposure of endothelial cells to homocysteine resulting in endothelial dysfunction, oxidation of low-density lipoproteins (LDL), and activation of platelets. The Duke treadmill score (DTS) is a well established method for cardiac risk stratification. Patients with low risk scores have shown to have excellent prognosis and do not need further evaluation. The first aim of this study was to compare the plasma homocysteine level in patients with CSX and a normal control group. Secondly, we looked for the relationship between homocysteine level and inducible ischemia via DTS.

Methods. Seventy-nine patients (36 male, 43 female, mean age: 50.0 ± 8.8 years) admitted to Gazi University Hospital, Ankara, Turkey with typical effort angina, positive stress test, and angiographically normal coronary arteries between January and September 2006 were included in this study. Thirty asymptomatic patients (11 male, 19 female, mean age: 47.6 ± 8.3 years) with less than 2 major cardiovascular risk factors were chosen as a control group. Exclusion criteria were: chest pain not related to cardiovascular system, impaired renal function, high serum uric acid, macrocytic anemia, alcohol consumption, nitrate and vitamin use, left ventricular dysfunction (ejection fraction [EF]<40%), bundle branch block in resting ECG, and heavy smoking (20 cigarettes or more/day). Plasma homocysteine level was measured in both groups, and DTS was calculated in the CSX group. The ECG recordings were analyzed by 2 independent cardiologists. All treadmill exercise tests were performed according to a symptom limited modified Bruce protocol. Three ECG leads (V1, aVF, and V5) were continuously monitored during the test. A standard 12 lead ECG was printed, and blood pressure was measured at the onset of the test, at the end of each stage, and at peak exercise as well as at one mm ST segment depression, when chest pain occurred and when it was clinically indicated. Myocardial ischemia was diagnosed when a horizontal or down sloping ST segment depression of one mm at 0.08 seconds from the J-point was observed in at least one lead. No patient had left ventricular hypertrophy, valvular or myocardial disease, mitral valve prolapse, previous myocardial infarction and heart failure in past medical history and also defined by echocardiography. The plasma homocysteine levels were measured with a microparticle enzyme immunoassay (MEIA) (Abbott Laboratories, Abbott Park, IL, USA) method in both groups. Immunoassays were performed according to the manufacturer’s recommendations. This method is based on the determination of S-adenosyl-L-homocysteine (SAH) obtained from the enzymatic conversion of homocysteine, previously reduced with dithiothreitol, to SAH by bovine SAH hydrolase.

The DTS was calculated as: exercise time (in minutes) - (5 x maximum exercise induced ST segment deviation in millimeters) - (4 x age index; with 0=none, 1=nonlimiting, 2=exercise limiting angina). The DTS is then classified as: low risk > 5, moderate risk -10 to +4, and high risk ≤ 11. Informed consent was obtained from all subjects, and the local ethical committee approved the study protocol.

Analysis of the results was performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, Illinois). Nominal variables were presented as number of cases with percentage and continuous variables as mean ± SD. Chi-square test, or Fisher’s exact test was used for categorical comparisons. Whether the mean differences between patients with CSX and those without were significant or not, was evaluated using Student’s t test or nonparametric Mann-Whitney U test. In patients with CSX, the correlation between the DTS and plasma homocysteine levels was analyzed by Pearson’s test. A p-value <0.05 was considered statistically significant.

Results. Table 1 gives the general characteristics of the study population. Hypertension was more prevalent in the CSX cohort (p<0.001). Although total cholesterol and LDL-cholesterol levels were not different between the groups, triglyceride levels were higher in the CSX group (p<0.005) and high-density lipoprotein (HDL)-cholesterol levels were higher in the control group (p<0.008). Plasma homocysteine level was higher in the CSX group compared to control group (16.5 ± 4.9 μmol/L versus 12.4 ± 4.1 μmol/L, p<0.001). Duke treadmill score was -2.7 ± 5.3 in the CSX patient cohort. The distribution of the homocysteine level in relation to the DTS is shown in Figure 1. Although the receiver-operating characteristics curve analysis could not give a cut off point for detection of CSX, there was a negative correlation regarding the homocysteine level and DTS (r=-0.506, p<0.001). The area under the curve was 0.75 (95% confidence interval 0.64-0.85) (Figure 2).

Discussion. Homocysteine has been shown to be an important independent risk factor for atherosclerotic morbidity and mortality in many studies. Hyperhomocysteinemia is an important component of the syndrome X and as CSX and Syndrome X are recently stated to be related entities, homocysteine increases may also be related with the pathogenesis and prognosis of the patients with CSX. It was also recently reported that homocysteine tended to predict future cardiovascular events in CSX patients. Homocysteine levels were found to be higher among patients with CSX who had cardiovascular events. We also observed in our CSX patient population that homocysteine levels were increased compared to the control group, and
this increase in homocysteine is negatively correlated with DTS. As the homocysteine level increases, DTS decreases, meaning worse outcome for future cardiovascular events.

Although once defined as a benign condition, new data demonstrates that the prognosis of patients with CSX could be as poor as established coronary artery disease (CAD), especially in those with endothelial dysfunction. Endothelial dysfunction and subsequent microvascular ischemia are the main mechanism for angina in CSX patients, and these patients had a poorer cardiovascular and cerebrovascular prognosis even without CAD.\textsuperscript{21-24} As hyperhomocysteinemia leads to endothelial dysfunction, as one of the mechanisms of anginal pain observed in CSX patients, this endothelial dysfunction could have led to decreased DTS, which would mean long term adverse prognosis in the CSX population. An increased homocysteine level decreased the DTS in our CSX patient cohort. All the patients in the study group had positive stress test results, however, DTS was observed to be correlated negatively with the homocysteine level.
Recently, Lakkireddy et al.\textsuperscript{25} reported the prognostic value of DTS in diabetic patients, stating that DTS is a valuable tool for the long term major adverse cardiac events (MACE) free survival in both the diabetic and nondiabetic population. Utilization of DTS was shown to decrease the number of unnecessarily requested scintigraphies for CAD.\textsuperscript{26} The DTS is a noninvasive, cheap and easy to use scoring system for the future cardiovascular MACE prognosis. In patients with CSX, one of the important issues is to risk stratify the patient for future events. The new data\textsuperscript{21-24} supports that CSX patients are not a benign group as believed previously according to the cardiovascular end points. However, our data does not show the long term follow up to define the relationship between the DTS and homocysteine for long term prognosis and future adverse cardiac events. Those patients with higher duke risk scores might be appropriate candidates for intensive medical treatment,\textsuperscript{27} and more aggressive risk factor modification.

Our data investigated the relationship between homocystinemia and DTS. Measuring homocysteine level routinely in patients with CSX and long term follow up of these patients with increased levels of homocysteine in large cohorts might be helpful to define the long term effect of hyperhomocysteinemia on the prognosis of these patients. We believe that DTS, a noninvasive test would provide an effective tool for risk stratifying of this patient cohort.

References