Association between serum homocysteine concentration with coronary artery disease in Iranian patients

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Abstract

BACKGROUND: The role of novel biomarkers like homocystein as a risk factor of coronary artery disease (CAD) is being increasingly recognized. Since there is a marked geographical variation in plasma homocystein concentration and because of importance of hyperhomocysteinemia as a CAD risk factor and due to the paucity of studies in Iran evaluating this risk factor in our population, we evaluated the association between plasma total homocysteine (tHcy) concentration and CAD risk in Iranian population.

METHODS: In a case-control study, we compared the level of tHcy of forty five patients of angiographically proven CAD with forty five subjects without CAD as control group matched for age and gender. The patients with diabetes, hypertension, thyroid dysfunction, chronic renal failure, hyperlipidemia and obesity and other conventional CAD risk factors were excluded from the study. Plasma tHcy was measured using immunoturbidimetry. The results were compared between groups using student t test.

RESULTS: CAD patients had significantly higher mean plasma tHcy than control group (17.1±5.3 versus 14.2±3.8, P= 0.004).

CONCLUSION: This study denoted that high plasma homocysteine concentration was associated to CAD risk in Iranian people.

Keywords: Coronary Artery Disease, Homocysteine.

ARYA Atherosclerosis 2011; 7(2): 63-67.

Date of submission: 6 May 2011, ***Date of acceptance:*** 12 Jul 2011

Introduction

Coronary artery disease is the leading cause of death and disability worldwide. Although Most of coronary artery disease patients have at least one of cardiovascular risk factors, 20% of patients with coronary artery disease have no conventional risk factors.[1] The role of novel biomarkers including homocysteine in atherothrombotic vascular disease and prediction of risk of CAD is being increasingly recognized.[2-6] Many studies found homocysteine level to be associated to atherosclerotic disease including CAD.[7-10] Another investigation showed this risk rises with increasing level of plasma homocysteine and has no threshold.[11] Hyperhomocysteinemia increases the risk of coronary artery disease by increased thrombosis, adverse effects on endothelial function, promoting thickening of the intima and oxidative damage of low density lipoprotein.[12] The hyperhomocysteinemia was reported in 40% of patients with vascular disease[8] and lowering plasma homocysteine level would reduce the risk of CAD by 16%.[13] Additionally, some studies showed hyperhomocysteinemia may have prognostic value in mortality of patients with CAD.[14] The role of elevated homocysteine level in CAD seems to be complex and further studies are needed to clarify the relationship of homocysteine and atherosclerosis. Moreover, some studies demonstrated that there is difference in prevalence and importance of homocysteine in CAD in different ethnic groups.[15,16] There are a few studies in Iran evaluating the extent of impact of hyperhomocysteinemia on CAD risk in our population.[17,18] The aim of the present study was to determine the relationship between

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hyperhomocysteinemia and CAD in Iranian population.

Materials and Methods

The consecutive patients admitted to the Department of Angiography of Noor, Sina and Chamran hospitals of Esfahan for evaluation of CAD and undergone coronary angiography in the year of 2010 were included in the study. Based on angiography results, the patients were divided into two groups. Those who had stenosis of ≥ 75% in at least one of their major coronary arteries were considered as CAD or case group and other patients served as non-CAD or control group. The patients with diabetes, hypertension, thyroid dysfunction, chronic renal failure, hyperlipidemia and obesity and other CAD risk factors were excluded from the study. Forty five patients with CAD were compared with forty five subjects that had normal coronary arteries in angiography, matched for age and gender. The level of homocysteine was measured in two groups using immunoturbidimetry method. Samples for plasma tHcys were placed on ice, serum was separated whitin 1 hour and was stored at -70°C. Statistical analyses were carried out using $SPSS_{13}$. Homocysteine and continuous variables reported as mean ± SD, were compared using student t test. Comparison of frequencies was carried out using X^2 test or Fishers extract test as appropriate.

Results

Table 1 shows demographic characteristics of cases and controls. Mean age of participants in CAD and control groups were 50.8±5.2 and 47.7±8.3 years, respectively. CAD group had significantly higher level of homocysteine than those in the control group (17.1±5.3 versus 14.2±3.8 micromol/lit, respectively, P= 0.004). Totally, 16 (35.6%) vs. 4 (8.9%) subjects in control and CAD groups, respectively, suffered from stable angina. Prevalence of MI and unstable angina were significantly higher in CAD group (P = 0.001). Homocysteine levels were higher in men than in women (16.7± 5.2 and 14.3±3.9 micromol/lit, respectively, P=0.019).

Discussion

In spite of multiple studies, the role of hyperhomocysteinemia as a risk factor of CAD is still disputed. Boushey et al.[19] estimated that 10% of general population CAD risk is attributed to homocysteine. They found that a 5-mumol/lit increment in tHcy increases odds ratio for CAD as great as 1.6 for men and 1.8 for women. Nygard et al.[14] found a strong association between elevated tHcy concentration and overall mortality in CAD patients. Consistent graded relationship between plasma tHcy concentration and CAD risk were found both in the British BUPA cohort and Tromso study.[20,21]

Although almost all retrospective and most of prospective studies have confirmed the role of homocysteine as an independent risk factor of CAD, some studies suggest that hyperhomocysteinemia may be secondary to preclinical vascular disease.[22,23] Additionally, several studies demonstrated that hyperhomocysteinemia is a causal risk factor for CAD.[8,24] In other words, elevated level of homocysteine interacts with other conventional risk factors and in combination with these factors increases the risk of atherothrombotic vascular disease. A case-control study demonstrated that hyperhomocysteinemia had more effect on CAD risk in hypertensive patients, smokers and patients with hypercholesterolemia than in normal population.[8] Donner et al. excluded the patients with other risk profiles from their study and concluded that

Table 1. Demographic and clinical characteristics of study population

Risk factors		Coronary artery disease (CAD)	Controls	P value
Sex (male/female)	N (%)	30/45 (66.7%)	22/45 (48.9%)	0.09
Age (years)	(mean ± SD)	50.8±5.2	47.7±8.3	0.06
tHcy (micromol/lit)	(mean ± SD)			
Men		18±5.9	14.9±3.4	0.27
Women		15.3±3.5	13.6±4.1	0.11
Total		17.1±5.3	14.2±3.8	0.004
Myocardial infarction (mean ± SD)		5 (11.1%)	0 (0%)	0.001
Stable Angina (mean ± SD)		4 (8.9%)	16 (35.6)	0.001
Unstable Angina (mean ± SD)		36 (80%)	29 (64.4%)	0.001

SD; Standard deviation

hyperhomocysteinemia is not associated to premature CAD in patients without diabetes, hypertension, hyperlipidemia.[24] A metaanalysis demonstrated homocysteine level was less strongly associated to ischemic heart disease and stroke in general population than has been reported.[25] The American multiple risk factor intervention trial (MRFIT)[26] and Finnish North Karelia project[27] failed to find any association between hyperhomocysteinemia and CAD. On the contrary, in Framingham[28] heart study a strong association between elevated level of homocysteine and CAD even after adjustment of other coronary risk factors was found. A prospective study carried out by Whincup[29] had the same result. In the present investigation, we excluded subjects with other cardiovascular risk factors from our study. We found a strong association between plasma tHcy and CAD independent of other conventional CAD risk factors.

Differences in design, statistical approach and power may partly explain variations in results of different studies but other causes of erratic results may be nutritional and large interethnic genetic variations.

The major determinants of plasma homocysteine level are B vitamins and folate intake and genetic factors.[30-32] Methylene tetrahydrofolate reductase (MTHFR) is an enzyme required for conversion of homocysteine to methionine. Polymorphism of MTHFR in individual with the TT genotype leads to reduced enzyme activity and increased homocysteine concentration.[33] The frequency of polymorphism of MTHFR varies in different racial and ethnic groups.[34-36] Investigations showed that almost 12% of Asian population is homozygote for T allele (T/T) and up to 50% of them are heterozygote for it (C/T).[36] Moreover, studies of Japanese population showed a significant association between TT genotype and CAD risk.[37-39] It is denoted that in addition to geographical variation in dietary folate intake, geographical variation in the frequency of genetic polymorphism may be important in impact of hyperhomocysteinemia on CAD risk. There are a few studies evaluating relationship between plasma tHcy and CAD in Middle East especially in Iran and adjustment of other cardiovascular risk factors was not carried out by any of these studies. One study performed on samples of male adults in the south west of Iran found significant association between high plasma homocysteine and CAD.[17] Kazemi et al. study[40] showed the patients with abnormal angiography reports had higher levels of homocysteine compared with the patients with normal angiography reports and it was concluded that the increased level of homocysteine is an independent risk factor of CAD. In contrast, in Namazi et al. study,[41] lowering the homocysteine concentration with folic acid therapy showed no significant effect on in-stent restenosis after PTCA. Our study suggested that elevated level of plasma tHcy was associated to an increased risk of CAD in Iranian population. A great advantage of our study was exclusion of patients with other confounding risk factors from our study, and then, this relationship seems to be independent of other CAD risk factors.

Conflict of Interests

Authors have no conflict of interests.

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