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Homocysteine Level According to Some Cardiac Risk Factors and Extent of Coronary Disease

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ABSTRACT

Hyperhomocysteinemia is accompanied by many cardiovascular risk factors. However it's relation with other cardiac risk factors and with extent of coronary artery disease (CAD) is still a controversial issue. This study was designed to investigate the relationship between total plasma homocysteine (tHcy) levels and other cardiovascular risk factors and the severity of CAD. Fasting plasma tHcy levels were measured in 60 patients with angiographically documented CAD and compared to 56 control subjects matched for age, sex, and smoking habits. Also patients were classified into two groups of low risk (with two or few risk factor) and high risk (with three and more risk factor) according to their major risk factors. Mean of tHcy levels were significantly higher in high risk patients compared to low risk patients (p=0.013). Also hyperhomocysteinemia rate was higher in the high risk patients compared to low risk patients, OR=5 (CI 95%=1.6-16).There was relationship between coronary risk factors and severe coronary artery disease (three vessels disease) but this relationship was statistically significant only in smokers (P=0.012) and diabetic patients (P=0.035) . Plasma tHcy level was an independent risk factor for high risk patients.

1 . Introduction

Iranian people have high prevalence rate of CAD.[1] It is reported that ischemic cardiovascular disease is a multifactorial cause disease. In an attempt to identify patients with high cardiovascular risk, lots of epidemiological studies were done by researchers all over the world to determine new cardiovascular risk factors. Among many studied risk factors inflammatory factors including fibrinogen, homocysteine, lipoprotein(a) (Lp(a)), and C-reactive protein (CRP) are investigated extensively. It was proved that high levels of homocysteine are linked with vascular disease [4;5], thus hyperhomocysteinemia is considered to be an in depended risk factor for CAD.[6;7] Factors which influence the levels of homocystein include age, genetics, and nutrition.[8;9] As nutrition and genetic background is different among populations, it is necessary to study the homocystein levels in different ethnic groups. Hyperhomocysteinemia is accompanied by many cardiovascular risk factors. However it's relation with other cardiac risk factors and with severity of coronary

artery disease (CAD) is still a controversial issue. This study was designed to investigate the relationship between total plasma homocysteine (tHcy) levels and other cardiovascular risk factors and extent of CAD.

2. Materials and Methods

In this study 116 consecutive subjects of both sexes underwent diagnostic coronary angiography in Beheshti hospital from Sep 2005 to Dec 2006. The number of case and control subjects was 60 and 56 respectively. Exclusion criteria were, history of utilization of nicotinic acid, clofibrat, ionized, vitamin B6, B12, folic acid, age>65 years old, thyroid, psychiatric disease, pregnancy and megaloblastic anaemia in two groups.

2.1. Patient group

Patients with one or more stenosis of at least 50% of the vessel diameter in any of main coronary arteries are included in our study. Angiographic findings were classified according to segmental assortment (CASS: Coronary Artery Surgery Study).[10] The assessment of stenosis severity was done in a visual method. One experienced cardiologist who was unaware of the patient's tHcy levels and risk profile assessed the angiograms. The severity of coronary artery involvement was graded according to following findings: 1. Normal coronary: with no coronary lesions or lesions <10% stenosis 2. One vessel disease (1VD): the lesions >50% stenosis in one coronary artery or one of its main branches 3. Two vessels disease (2VD): the lesions >50% stenosis in two coronary arteries 4. Three vessels disease (3VD): the lesion >50% stenosis in three coronary arteries.[10]

2.2. Controls

The control group had angiographically normal coronary arteries besides their sex, age and smoking habits were matched with case group. Information about hypertension, smoking, history of angina, and previous myocardial infarction (MI) on, was obtained from all subjects through a questionnaire.

2.3. Parameter definition

Major risk factors for CAD were determined. A sustained blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic or the use of antihypertensive drugs at the time of investigation was defined as hypertension. Hypercholesterolemia was defined as plasma total cholesterol level ≥200mg/dL. Hypertriglyceridemia was defined as a plasma total triglyceride level ≥200mg/dL. Diabetes mellitus was considered to be present if there was fasting blood sugar ≥126 mg/dL. The normal fasting levels of homocysteine are between (5-15) µmol/L and hyperhomocysteinemia was defined as total homocysteine level>15. Smoking was defined as the use of one cigarette daily at least for a year. Patients were classified into two risk groups according to their major risk factors; low risk (with two or few risk factors) and high risk (with three and more risk factor).

2.4. Biochemical measurements

Venous blood was obtained after a 12 h overnight fast the day after the coronary angiogram. Serum was prepared by centrifugation at 1000 g, for 30 min at 4˚C after collection. Triglyceride and total cholesterol concentrations were measured enzymatically with colorimetric methods (Pars Azmun CO. Iran) by automatic analyzer (Selectra II analyzer, Netherland). Plasma samples for measurement of homocysteine levels were stored at -70˚C until analysis. Then total L-homocysteine levels were quantified using the AXIS homocysteine enzyme immunoassay (EIA).[11]

2.5. Statistical analysis

Primary analysis compared tHcy levels in case and control groups. Secondary analysis evaluated the relationship of tHcy with conventional cardiovascular risk factors and the extent of coronary disease. All analyses were performed using the SPSS version 11.5, by Mann-Whitney test, Student t-test, chi square and Odd`s ratio estimation.

2.6. Ethic

The study protocol was approved by the ethics committee of Zanjan University of medical science.

3. Results

The patients' characteristics have been summarized in Table I. The mean age of patients with CAD was higher than control group (56.8±6.9 vs. 54.2±8.1, respectively). The majority of risk factors leading to CAD were higher in the CAD group compared to the control.

Table 1- Demographic characteristics and cardiovascular risk factors in case-control group.

Variables	Case	Control	P
Age, year	56.8±6.9	54.2±8.1	0.2
Gender, Male/Female	30/30	27/29	0.8
Smoking,%(n)	30(18)	21(13)	0.4
Diabetes Mellitus,%(n)	33(20)	17(10)	0.035
Hypertension,%(n)	55(33)	56(34)	0.8
Hypercholesterolemia,%(n)	45(27)	30(18)	0.09
Hypertriglyceridemia,%(n)	20(12)	13(8)	0.41

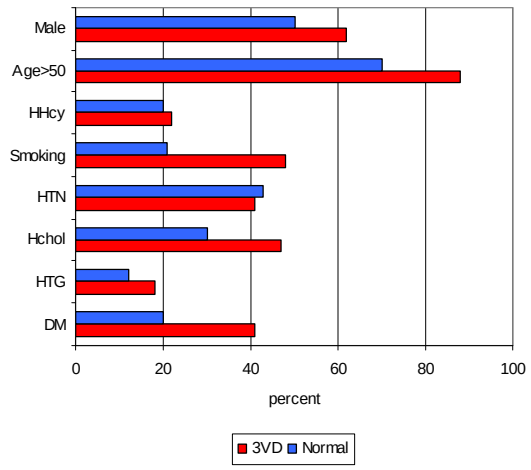
Mean tHcy level was higher in high risk patients compared to low risk patients and this difference was significant statistically (14.7±10.5 vs 10±8.5) (p=0.013). Also hyperhomocysteinemia (tHcy >15µmol/L) rate was higher in the high risk patients compared to low risk patients, OR=5 (CI 95%=1.6-16). The mean tHcy levels were higher in the patients with CAD compared to the control but this difference was not significant statistically (13.6±11 vs. 12±9, P=0.38 respectively). Also hyperhomocysteinemia rate was higher in case group compared to the control group but it was not statistically significant 15 (25%) vs. 12 (20%) (P=0.6 respectively) (Table2).

Table 2- The comparison of tHcy level and hyperhomocysteinemia rate in case- control groups.

Variables	Case(60)	Control(56)	P
tHcy level	13.6±11	12.0±9	0.38
HHcy,%(n)	25(15)	20(12)	0.6

HHcy: Hyperhomocysteinemia
tHcy : Total Homocysteine

There was a relationship between coronary risk factors and severe coronary artery disease (three vessels disease) but this relationship was only statistically significant in smokers (P=0.012) and diabetic patients (P=0.035) (figure 1).
Hyperhomocysteinemia in men was more than women, OR=3 (CI 95%=1-7.5).



Hcy: Hyperhomocysteinemia, **HTN**:Hypertension
HChol: Hypercholestrolemia, **HTG**:Hypertriglyceride

Fig 1 - The comparison between coronary risk factors with coronary artery involvement.

4. Discussion

The main finding of this study was that the mean tHcy level was higher in high risk patients compared to low risk patients and this difference was statistically significant. Total homocysteine level has no independent association with severity of CAD after adjustment for major risk factors. However patients with CAD showed a trend towards higher median tHcy levels compared to control subjects. Our results are consistent with two of four cross-sectional angiographic studies, where the fasting plasma tHcy levels were measured and the association of tHcy and CAD was evaluated. Murphy-Chutorian et al [12] and Amalial-Bufidou et al [13] found no association between tHcy and CAD. In contrast, the other two studies demonstrated a significant (P<0.001) univariate association between tHcy and CAD.[14,15] These later two studies were conducted in the USA; the first included 170 male patients, while the second included 241 patients (173 males) with CAD. Ten out of 13 studies that assessed the association between fasting tHcy level and CAD showed significantly higher levels of tHcy in patients with CAD compared to those without CAD[16-27]. However, some case- control and prospective studies reported that there is not relationship between tHcy and CAD.[13, 28-31] In our study, the mean tHcy levels were higher in the patients with CAD compared to the control but this difference was not statistically significant. Also hyperhomocysteinemia rate was higher in the patients with CAD compared to the control group but again it was not statistically significant. However, the patients with CAD showed a tendency towards higher

tHcy levels. Our results are consistent with Amalial-Boufidou et al.[13] However in our study 25% of the patients had tHcy levels above 15μmol/L compared to 20% of controls. Thus, it might be that severe rather than borderline hyperhomocysteinemia is a predictor of CAD, at least in our population. Donner, et al [29] have found that in low risk patient groups and patients under the age of 50 the incidence of hyperhomocysteinemia was not significantly high. They concluded that the CAD and hyperhomocysteinemia relationship reported in other studies was actually a result of other primary risk factors. In our study such relationship in high risk and low risk subgroups was not seen but tHcy levels were higher in high risk group compared to low risk group and this difference was statistically significant. Some studies showed that there was no relationship between age and tHcy levels[17, 32] which were similar to our study. It is known that in males the tHcy levels are 11-12% higher than in females. [33, 34] In our study such relationship was seen, too. Also hyperhomocysteinemia had a strong relationship with male sex. In a study conducted in Turkey in 2003, weak relationship between tHcy levels with smoking was found[17] but in our study this relationship was not observed. Although most studies failed to recognize a relationship between hypertension and lipid profiles with tHcy,[32,33,35-37] some epidemiologic studies reported the existence of this phenomenon [38,39]. In our study there was not significant relationship between tHcy levels with lipid profile and hypertension. In recent years, it has been reported that level of tHcy may be related to the number of vessels involved in CAD and this may be important in the progression of disease.[32,40] A prospective study based on a definition of 50% stenosis showed that tHcy level was weakly related with vessel score.[35] Montulescot ,et al [40] accepted >75% stenosis as the criteria for a diagnosis of CAD and found a weak but significant relationship between the number of vessels involved and the level of tHcy. Wilcker et al[41] who took the CAD criteria to be 50% stenosis reported there was no relationship between tHcy level and disease severity similar to our study that there was not any relationship between tHcy levels and the number of vessels involved in CAD patients. The major limitation of our study is the relative small sample size, this underlines the need for larger prospective and intervention studies.

5. Acknowledgements

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Ethical issues

The study was approved by the Ethical Committee of the University.

Conflict of interests

No conflict of interest to be declared.

References

1.Sarraf-Zadegan N, Sayed-Tabatabaei FA, Bashardoost N, Maleki A, Totonchi M, Habibi HR, Sotodehmaram E, Tafazoli F, Karimi A. The prevalence of coronary artery disease in an urban population in Isfahan, Iran. ***Acta Cardiol*** 1999;54:257-263.

2.Gotto AM Jr. Management of dyslipidemia. ***Am J Med*** 2002; 112: 10S-18S.

3.Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. ***N Engl J Med*** 2002;347:1557-1565.

4.Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, Graham I. Hyperhomocysteinemia: an independent risk factor for vascular disease. ***N Engl J Med*** 1991;324:1149-1155.

5.Murphy-Chutorian D, Alderman EL. The case that hyperhomocysteinemia is a risk factor for coronary artery disease. ***Am J Cardiol*** 1994;73:705- 707.

6.Guba SC, Fink LM, Fonseca V. Hyperhomocysteinemia. An emerging and important risk factor for thromboembolic and cardiovascular disease. ***Am J Clin Pathol*** 1996;106:709-722.

7. Okada E, Oida K, Tada H, Asazuma K, Eguchi K, Tohda G, Kosaka S, Takahashi S, Miyamori I. Hyperhomocysteinemia is a risk factor for coronary arteriosclerosis in Japanese patients with type 2 diabetes. ***Diabetes Care*** 1999;22:484-490.

8.Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. ***Am J Med*** 1994;96:239-246.

9.Stabler SP, Marcell PD, Podell ER, Allen RH, Savage DG, Lindenbaum J. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. ***J Clin Invest*** 1988;81:466-474.

10.Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R, Kennedy JW, Fisher L, Judkins MP, Mock MB, Killip T. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). ***Circulation*** 1981;64: 360-367.

11.Karabiber H, Sonmezgoz E, Ozerol E, Yakinci C, Otlu B, Yologlu S. Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B12, and folic acid. ***Brain Dev*** 2003;25:113-115.

12.Murphy-Chutorian DR, Wexman MP, Grieco AJ, Heininger JA, Glassman E, Gaull GE, Ng SK, Feit F, Wexman K, Fox AC. Methionine intolerance: a possible risk factor for coronary artery disease. ***J Am Coll Cardiol*** 1985; 6: 725-730.

13.Boufidou AI, Makedou AD, Adamidis DN, Karvounis HI, Gourassas JT, Kesidis HT, Makedou KG, Papadopoulos CE, Parharidis GE, Louridas GE. Association between plasma homocysteine levels and coronary artery disease: a population-based study in northern Greece. ***Curr Med Res Opin*** 2004;20:175-180.
14.Genest JJ Jr., McNamara JR, Salem DN, Wilson PW, Schaefer EJ, Malinow MR. Plasma homocyst(e)ine levels in men with premature coronary artery disease. ***J Am Coll Cardiol*** 1990;16: 1114-1119.
15.Kang SS, Wong PW, Cook HY, Norusis M, Messer JV. Protein-bound homocyst(e)ine. A possible risk factor for coronary artery disease. ***J Clin Invest*** 1986;77:1482-1486.
16.Aamir M, Sattar A, Dawood MM, Dilawar M, Ijaz A, Anwar M. Hyperhomocysteinemia as a risk factor for ischemic heart disease. ***J Coll Physicians Surg Pak*** 2004;14:518-521.
17.Bozkurt E, Keles S, Acikel M, Islek M, Atesal S. Plasma homocysteine level and the angiographic extent of coronary artery disease. ***Angiology*** 2004;55:265-270.
18.Dalery K, Lussier-Cacan S, Selhub J, Davignon J, Latour Y, Genest J. Homocysteine and coronary artery disease in French Canadian subjects: relation with vitamins B12, B6, pyridoxal phosphate, and folate. ***Am J Cardiol*** 1995;75:1107-1111.
19.Foody JM, Milberg JA, Robinson K, Pearce GL, Jacobsen DW, Sprecher DL. Homocysteine and lipoprotein(a) interact to increase CAD risk in young men and women. ***Arterioscler Thromb Vasc Biol*** 2000;20:493-499.
20.Geisel J, Hennen B, Hubner U, Knapp JP, Herrmann W. The impact of hyperhomocysteinemia as a cardiovascular risk factor in the prediction of coronary heart disease. ***Clin Chem Lab Med*** 2003;41:1513-1517.
21.Israelsson B, Brattström LE, Hultberg BL. Homocysteine and myocardial infarction. ***Atherosclerosis*** 1988;71:227-233.
22.Sipahi E, Taskin G, Kumbasar D, Halloran M, Yildirimkaya M, Nadirler F, Yildirir A, Berkalp B, Laleli Y. Hyperhomocysteinaemia and coronary artery disease in the Turkish population. ***Acta Cardiol*** 2002;57:415-420.
23.Skibińska E, Sawicki R, Lewczuk A, Prokop J, Musiał W, Kowalska I, Mroczko B. Homocysteine and progression of coronary artery disease. ***Kardiol Pol*** 2004;60:197-205
24.Ubbink JB, Vermaak WJ, Bennett JM, Becker PJ, van Staden DA, Bissbort S. The prevalence of homocysteinemia and hypercholesterolemia in angiographically defined coronary heart disease. ***Klin Wochenschr*** 1991;69:527-534.
25.Von Eckardstein A, Malinow MR, Upson B, Heinrich J, Schulte H, Schönfeld R, Köhler E, Assmann G. Effects of age, lipoproteins and hemostatic parameters on the role of homocyst(e)inemia as a cardiovascular risk factor in men. ***Arterioscler Thromb*** 1994;14: 460-464.
26.Wilcken DE, Reddy SG, Gupta VJ. Homocysteinemia, ischemic heart disease, and the carrier state for homocystinuria. ***Metabolism*** 1983;32:363-370.
27.Wu LL, Wu J, Hunt SC, James BC, Vincent GM, Williams RR, Hopkins PN. Plasma homocyst(e)ine as a risk factor for early familial coronary artery disease. ***Clin Chem*** 1994;40:552-561.
28.Chacko KA. Plasma homocysteine levels in patients with coronary heart disease. ***Indian Heart J*** 1998;50:295-299.
29.Donner MG, Klein GK, Mathes PB, Schwandt P, Richter WO. Plasma total homocysteine levels in patients with early-onset coronary heart disease and a low cardiovascular risk profile. ***Metabolism*** 1998;47: 273-279.
30.Montaño-Loza A, Meza-Junco J, Valles V, Castillo-Martínez L, Orea-Tejeda A. [Plasma homocysteine concentrations in Mexican patients with ischemic heart disease]. ***Rev Invest Clin*** 2004;56:580-585.
31.Sastry BK, Indira N, Anand B, Kedarnath, Prabha BS, Raju BS. A case-control study of plasma homocysteine levels in South Indians with and without coronary artery disease. ***Indian Heart J*** 2001; 53: 749-753.
32.Yoo JH, Park JE, Hong KP, Lee SH, Kim DK, Lee WR, Park SC. Moderate hyperhomocyst(e)inemia is associated with the presence of coronary artery disease and the severity of coronary atherosclerosis in Koreans. ***Thromb Res*** 1999;94: 45-52.
33.Chao CL, Tsai HH, Lee CM, Hsu SM, Kao JT, Chien KL, Sung FC, Lee YT: The graded effect of hyperhomocysteinemia on the severity and extent of coronary atherosclerosis. ***Atherosclerosis*** 1999;147: 379-386.
34. Senaratne MP, MacDonald K , De SD. Possible ethnic differences in plasma homocysteine levels associated with coronary artery disease between south Asian and east Asian immigrants. ***Clin Cardiol*** 2001; 24:730-734.
35. Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. ***N Engl J Med*** 1997;337: 230-236.
36. Whincup PH, Refsum H, Perry IJ, Morris R, Walker M, Lennon L, Thomson A, Ueland PM, Ebrahim SB. Serum total homocysteine and coronary heart disease: prospective study in middle aged men. ***Heart*** 1999;82: 448- 454.
37. Rodríguez JF, Escobales N, Cruz D, Banch H, Rivera C, Altieri PI. [Total plasma homocysteine concentrations in Puerto Rican patients with ischemic heart disease]. ***Rev Esp Cardiol*** 2001; 54: 1411-1416.
38. Jacques PF, Bostom AG, Wilson PW, Rich S, Rosenberg IH, Selhub J. Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. ***Am J Clin Nutr*** 2001;73:613-621.
39. Nygård O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, Ueland M, Kvåle G. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. ***JAMA*** 1995;274: 1526-1533.
40. Montalescot G, Ankri A, Chadefaux-Vekemans B, Blacher J, Philippe F, Drobinski G, Benzidia R, Kamoun P, Thomas D. Plasma homocysteine and the extent of atherosclerosis in patients with coronary artery disease. ***Int J Cardiol*** 1997; 60:295-300.
41. Wilcken DE, Wang XL, Sim AS, McCredie RM. Distribution in healthy and coronary populations of the methylenetetrahydrofolate reductase (MTHFR) C677T mutation. ***Arterioscler Thromb Vasc Biol*** 1996;16:878-882.