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The Association of Serum Homocysteine Levels in Coronary Artery Disease in a Tertiary Care Hospital

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Abstract **Original Research Article**

Homocysteine is metabolized in the body to convert to cysteine, oxidation of cysteine in vitro is known to be involved in atherogenesis and thrombogenesis. Cysteine is also known to decrease nitric oxide production by endothelial cells and impair endothelial functions. The present study aimed to evaluate the serum homocysteine levels in patients with established coronary artery disease Methods: This prospective cross-sectional study was conducted in the Department of General Medicine and Cardiology, Govt. Medical College and Hospital, Nalgonda. A total of n=21 male and n=16 were selected based on the angiogram evaluation of coronary artery disease they were designated as Group I (Test) group. Similar numbers of the patients in both sexes were selected who did not show any signs of CAD on angiogram they were designated as group II (controls). Serum homocysteine levels were measured with (ELISA) method. Results the angiogram profile of the patients in the test group and found that a maximum number of patients n=19 (51.35%) had a single-vessel disease. The mean serum homocysteine levels in patients with triple vessel disease were found to be maximum both in male and the females similarly the values were found to be increasing from the minor coronary artery disease to triple vessel. The mean serum levels of homocysteine in group II males was 13.56 ± 3.34 µmol/L and female was 14.5 ± 2.53 µmol/L which were significantly lower than the Test male and females mean values of 22.76 ± 1.65 and 21.41 ± 1.23 µmol/L respectively the p values were found to be significant. Conclusion: that elevated serum homocysteine is associated with severity of coronary artery disease. Hence the levels of homocysteine may be the strongest modifiable risk factor for overall morbidity and mortality due to cardiovascular disease. We recommend that the levels of serum homocysteine must be evaluated in all the patients with coronary artery disease.

Keywords: Serum Homocysteine, Coronary Artery Disease.

INTRODUCTION

Homocysteine is a sulfur-containing amino acid it is found to be increased in cases of myocardial infarction and risk of thromboembolic events irrespective of the age group [1, 2]. Hyperhomocysteinemia is usually due to deficiency of nutritional factors required for homocysteine metabolism (folate, vitamin B-12, Vitamin B6) [3, 4]. Homocystinuria is an autosomal recessive condition due to deficiency of enzyme cystathionine β synthase which is required for the conversion of homocysteine derived from dietary methionine to cystathionine [5]. Untreated homocystinuria may lead to mortality in 20% of patients before the age of 30 years [6]. These observations in patients with homocystinuria lead to the finding that homocysteine may have possibly been involved in the pathogenesis of arteriosclerosis. Several mechanisms have been proposed to explain the endothelial damage produced by homocysteine including the effects of platelets clotting factors and endothelium [7]. Homocysteine stimulated the proliferation of atherogenic smooth muscle cells by impairing the release of Nitric Oxide from endothelial cells [4, 8, 9]. Several clinical and epidemiological studies have shown a relationship between total homocysteine levels and CAD, peripheral artery disease, stroke, and venous thrombosis [10-14]. The current understanding of the pathogenesis of coronary heart disease involves a slow progression of coronary atherosclerosis, followed by unstable angina, myocardial infarction or sudden death. The acute events can be due to rupture of an atheromatous plaque with the association of thrombus formation [15]. Notably, the vascular complications reported n patients with homocystinuria are more related to thrombosis rather than atherosclerosis and the relation between total homocysteine levels and incidence of thrombotic events have been reported in patients with SLE [16]. With the

increasing incidence of CVD deaths in India especially between 35-65 years and CAD remains the highest cause of mortality in India [17, 18]. We in the present study tried to evaluate the association of serum homocysteine levels in patients with established CAD by coronary angiogram in this tertiary care hospital.

MATERIAL AND METHODS

This prospective cross-sectional study was conducted in the Department of General Medicine and Cardiology, Govt. Medical College and Hospital Nalgonda. Institutional Ethical committee permission was obtained for the study. Written consent was obtained from all the participants of the study. The study period was from September 2018 to July 2019. A total of n=25 male and n=20 female patients were initially selected however n=4 male and n=4 female was unwilling to participate in the study. Hence n=21 male and n=16 were selected based on the angiogram evaluation of coronary artery disease they were designated as Group I (Test) group. CAD is graded according to the number of involved vessels single-vessel disease, double vessel disease, and triple vessel disease. Similar numbers of the patients in both sexes were selected who did not show any signs of CAD on angiogram they were designated as group II (controls). Inclusion criteria were patients undergoing coronary angiogram in the group 36 to 65 years. Exclusion criteria were patients with thyroid disorders, pregnancy, renal disease, liver disease, cancer or those taking vitamin supplements for 3 months, those unwilling to participate in the study. A fasting blood sample was obtained in 5ml vacutainer before angiography. Serum was separated and stored at -20°C until measurement of homocysteine levels. Serum homocysteine levels were measured with (ELISA) method. The results obtained were stored in MS Excel spreadsheet and analyzed with SPSS version 17 on windows format a value of <0.05 is considered as significant.

RESULTS

The total number of patients in the group I test group with coronary artery disease (CAD) males were n=21 and females n=16. Similarly, we have taken n=21 male and n=16 female in group II as controls. In group I most of the patients were belonging to 51-55 years (21.62%), next common age was >60 years (27.02%) of patients, the age group 46-50 years contributed (13.51%) the mean age group of the group I (test) was n=53.5 years and group II (control) was n=51.5 years the male to female ratio was 1.3: 1 the other details are shown in Table-1.

Table-1: Distribution of patients based on age and sex

Age Group Years	Group I (Test I)		Total (%)	Group II (Control)		Total (%)
	Male	Female		Male	Female	
36 – 40	01	00	01 (2.7%)	01	00	01 (2.7%)
41 – 45	00	01	01 (2.7%)	00	01	01 (2.7%)
46 – 50	02	03	05 (13.51%)	02	01	03 (8.10%)
51 – 55	05	03	08 (21.62%)	05	04	09 (24.32%)
56 – 60	07	05	12 (32.4%)	07	06	13 (35.13%)
> 60	06	04	10 (27.02%)	06	04	10 (27.02%)
Total	21	16	37 (100%)	21	16	37 (100%)

The important parameters based on history were recorded, in the group, I in males 71.43% were found to be hypertensive and in females, 62.5% were found to be having hypertension. Similarly, diabetes was found in 23.8% male and 25% female patients. Alcohol consumption was found exclusively in males 9.29% and coffee consumption was seen in 71.43% males and 62.5% of females, Non-vegetarian diet were in 66.67% of male and 62.5% females. The group II parameters were recorded similarly and shown in Table-2.

Table-2: Distribution of patients in the study based on the history

History	Group I (Test)		Group II (Control)	
	Male (n=21)	Female (n=16	Male (n=21)	Female (n=16)
Hypertensive	15 (71.43%)	10 (62.5%)	12 (57.14%)	05 (31.25%)
Non Hypertensive	06 (28.57%)	06 (37.5%)	09 (42.86%)	11 (68.75%)
Diabetics	05 (23.8%)	04 (25%)	04 (19.05%)	04 (25%)
Non Diabetics	16 (76.19%)	12 (75%)	17 (80.95%)	12 (75%)
Alcoholics	02 (9.52%)	00 (00%)	03 (14.29%)	00 (00%)
Non Alcoholics	19 (90.47%)	16 (100%)	18 (85.71%)	16 (100%)
Coffee consumers	15 (71.43%)	10 (62.5%)	16 (76.19%)	12 (75%)
Non coffee consumers	06 (28.57%)	06 (37.5%)	05 (23.8%)	04 (25%)
Non vegetarians	14 (66.67%)	10 (62.5%)	13 (61.90%)	08 (50%)
Lacto vegetarians	07 (33.33%)	06 (37.5%)	08(38.09%)	08 (50%)

The mean value of the biochemical parameters like Fasting blood sugar, total cholesterol, triglycerides, HDL and LDL were compared in both the test and control group of all the parameters the HDL was found to be significantly reduced in the group I patients with Coronary artery disease shown in Table-3.

Table-3: Biochemical parameters of the patients in the study

	Group I (Test) Mean ± SD	Group II (controls) Mean ± SD	p values
Fasting Blood Sugar mg/dl	135.50 ± 5.65	112.5 ± 7.56	0.189 ^{NS}
Total Cholesterol mg/dl	180.52 ± 9.5	159.2 ± 6.57	2.5 ^{NS}
Triglycerides mg/dl	149.66 ± 10.3	121.7 ± 10.36	0.99 ^{NS}
HDL cholesterol mg/dl	31. 4 ± 2.25	37. 61 ± 1.98	0.05*
LDL Cholesterol mg/dl	110.23 ± 3.32	89.44 ± 4.68	0.23 ^{NS}

The mean fasting serum homocysteine levels were studied based on the confounding factors, in the group I (test) patients with CAD of all the factors Alcohol consumption was found to increase the serum homocysteine levels significantly the p values were found to be significant and the factors were not found to have significant impact on the serum homocysteine levels. In group II (controls) the mean serum homocysteine was found to be increased in diabetic patients when compared to the non-diabetics counterparts of the same group. The other factors did not significantly affect the mean serum homocysteine levels.

Table-4: Fasting Serum Homocysteine levels (µmol/l) based on the confounding factors in the study

	Group I (Test) Mean ± SD	p values	Group II (controls) Mean ± SD	p values
Hypertensive	24.26 ± 2.21	1.25 ^{NS}	15.37 ± 1.29	0.806 ^{NS}
Non Hypertensive	23.87 ± 1.22		13.67 ± 2.36	
Diabetics	26.6 ± 3.54	0.15 ^{NS}	16.66 ± 1.78	0.05*
Non Diabetics	22.34 ± 2.65		11.23 ± 2.1	
Alcoholics	25.51 ± 1.99	0.05 *	16.92 ± 2.7	0.125 ^{NS}
Non Alcoholics	21.5 ± 1.63		12.36 ± 1.98	
Coffee consumers	23.4 ± 2.12	1.33 ^{NS}	14.82 ± 1.47	3.65 ^{NS}
Non coffee consumers	21.5 ± 1.75		15.36 ± 1.97	
Non vegetarians	24.3 ± 2.70	0.8 ^{NS}	14.33 ± 2.01	0.566 ^{NS}
Lacto vegetarians	23.5 ± 1.88		13.78 ± 1.37	

We have done the angiogram profile of the patients in the test group and found that the maximum number of patients n=19 (51.35%) had a single-vessel disease. The mean serum homocysteine levels in patients with triple vessel disease were found to be maximum both in male and the females similarly the values were found to be increasing from the minor coronary artery disease to triple vessel disease shown in Table-5. The mean serum levels of homocysteine in group II males was 13.56 ± 3.34 and female were 14.5 ± 2.53 which were significantly lower than the control male mean values of 22.76 ± 1.65 and 21.41 ± 1.23 the pa values were found to be significant.

Table-5: Comparison of Angiogram profile of CAD patients with mean serum homocysteine levels (µmol/L) Group I (Test)

	Number (n) Male	Mean Serum Homocysteine levels (µmol/L)	Number (n) Female	Mean Serum Homocysteine levels (µmol/L)
Minor CAD	5	20.94 ± 1.35	4	19.66 ± 1.95
Single vessel disease	11	21.83 ± 2.15	8	20.14 ± 1.15
Double vessel disease	3	23.61 ± 2.25	3	22.36 ± 1.89
Triple vessel disease	2	24.66 ± 3.77	1	23.48 ± 1.63

* Significant

DISCUSSION

The methyltetrahydrofolate reductase studies have shown a significant association between serum homocysteine levels and ischemic heart disease and DVT [19]. A meta-analysis published in JAMA in 1995 involving above 4000 subjects concluded that serum homocysteine was an independent factor for CVD and they estimated that approximately 10% of the population with CVD risk is attributed to elevated

levels of homocysteine [20]. The main findings of the present study were the mean serum levels of homocysteine in group II males was 13.56 ± 3.34 µg/L and female was 14.5 ± 2.53 µg/L which were significantly lower than the control male mean values of 22.76 ± 1.65 µg/L and 21.41 ± 1.23 µg/L the pa values were found to be significant. Our results are consistent with findings of S Vihetha *et al.*, [21] who have also found elevated serum homocysteine levels in patients with coronary artery disease and the levels were correlated with the severity of the coronary artery disease. Genest JJ *et al.*, and Kang SS *et al.*, have also found a significant association ($p<0.001$) between serum homocysteine and coronary artery disease [22, 23]. Murphy chutorian *et al.*, [25] found no association between homocysteine and Coronary artery disease. Several case-control studies that have assessed the association between fasting homocysteine and CAD showed significantly higher levels of homocysteine in patients with coronary artery disease [25-28]. European studies from 19 centers concluded that plasma homocysteine levels confer independent risk for vascular disease similar to those of smoking and dyslipidemia. [26, 27] An interesting meta-analysis found that increase of homocysteine by an increment of 5µmol/L elevated the coronary artery disease risk by as much as 20mg/dl increase of cholesterol [26]. Serum homocysteine levels are now known to alter vascular endothelium and in vitro studies on homocysteine have shown to trigger the proliferation of vascular smooth muscle cells. The arterial lumen space was decreased due to the proliferation of vascular smooth muscle which an important factor for the development of CAD. They also have a role in increasing the activity of HMG CoA reductase which in turn increases the cholesterol synthesis and elevated cholesterol levels promote atherosclerosis and are risk factors for CAD [30-31]. Although the numbers of patients in this study are lesser however they were carefully chosen along with age and sex-matched controls. Our study also has shown that there was a significant decrease in HDL levels in patients with Coronary artery disease. The results of our study support the hypothesis that elevated serum homocysteine levels are related to atherothrombosis and contribute to the severity of coronary events and may also serve as a marker for prediction of future coronary artery disease.

CONCLUSION

Within the limitation of the present study, it can be concluded that elevated serum homocysteine is associated with severity of coronary artery disease. Hence the levels of homocysteine may be the strongest modifiable risk factor for overall morbidity and mortality due to cardiovascular disease. We recommend that the levels of serum homocysteine must be evaluated in all the patients with coronary artery disease.

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REFERENCES

1. Mudd SH, Levy HL, Skovby F. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic basis of inherited disease. New York: McGraw-Hill, 1995:1279–27.
2. Ueland PM, Refsum H. Plasma homocysteine as a risk factor for vascular disease: plasma levels in health, disease and drug therapy. J Lab Clin Med,1989; 114:473–01.
3. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. Jama. 1993 Dec 8;270(22):2693-8.
4. Stampfer MJ, Malinow MR. Can lowering homocysteine levels reduce cardiovascular risk? N Engl J Med, 1995; 332:328–29.
5. Mudd SH, Levy HL, Skovby G. Disorders of transsulfuration in Seriver C, Beaudet AL, Sly WS, Valle D, Eds. The metabolic basis of inherent disease, 6th Edn, Vol 1. New York: McGraw-Hill, 1989; 6936-734.
6. Mudd SH, Skovby F, Levy HL. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet, 1985; 37:1-31.
7. McCully KS. Homocysteine and vascular disease. Nat Med, 1996; 2(4):386-89.
8. Stampfer M. Rimm F. Folate and cardiovascular disease [Editorial]. JAMA, 1996:241929-30.
9. Foody J, Sprecher D. Current concepts in preventive cardiology. Clin Advisor, June 1998; 56-62.
10. Ueland PM, Refsum H, Brattström L. Plasma homocysteine and cardiovascular disease. In: Francis RB Jr, ed. Atherosclerotic cardiovascular disease, hemostasis, and endothelial function. New York: Marcel Dekker, 1992:183-36.
11. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA, 1995; 274:1049-57.
12. Verhoef P, Stampfer MJ. Prospective studies of homocysteine and cardiovascular disease. Nutr Rev, 1995; 53:283-88.
13. Brattström L. Vitamins as homocysteine-lowering agents. The Journal of nutrition. 1996 Apr 1;126(suppl_4):1276S-80S.
14. Den Heijer M, Koster T, Blom HJ, Bos GM, Briët E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. New England journal of medicine. 1996 Mar 21;334(12):759-62.

15. Fuster V. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. Circulation, 1994; 90:2126-46.
16. Petri M, Roubenoff R, Dallal GE, Nadeau MR, Selhub J, Rosenberg IH. Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. Lancet 1996; 348:1120-24.
17. Upadhyaya RP. An overview of the burden of non-communicable diseases in India. Iran J Public Health. 2012; 41(3):1–8.
18. Goyal A, Yusuf S. The burden of cardiovascular disease in the Indian subcontinent. Indian J Med Res, 2006; 124(3):235–44.
19. Brattstrom L, Wilcken DEL, Ohrvik J, Brudin L. Common methylene- tetrahydrofolate reductase gene mutation leads to hyperhomocysteine- mia but not to vascular disease. Circulation, 1998; 98:2520-26.
20. Nygård O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, Ueland PM, Kvåle G. Total plasma homocysteine and cardiovascular risk profile: the Hordaland Homocysteine Study. Jama. 1995 Nov 15;274(19):1526-33.
21. Shenoy V, Mehendale V, Prabhu K, Shetty R, Rao P. Correlation of serum homocysteine levels with the severity of coronary artery disease. Indian Journal of Clinical Biochemistry. 2014 Jul 1;29(3):339-44.
22. Genest JJ, McNamara JR, Salem DN, Wilson PW, Schaefer EJ, Malinow MR. Plasma homocyst (e) ine levels in men with premature coronary artery disease. Journal of the American College of Cardiology. 1990 Nov 1;16(5):1114-9.
23. Kang SS, Wong PW, Cook HY, Norusis M, Messer JV. Protein-bound homocyst (e) ine. A possible risk factor for coronary artery disease. The Journal of clinical investigation. 1986 May 1;77(5):1482-6.
24. 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. Journal of the American College of Cardiology. 1985 Oct 1;6(4):725-30.
25. Verhoef P, Stampfer MJ, Buring JF, Gaziano JM, Allen RH, Stabler SP, Reynolds RD, Kok FJ, Hennekens CH, Willett WC. Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate. American journal of epidemiology. 1996 May 1;143(9):845-59.
26. Graham IM, Daly LE, Refsum HM, Robinson K, Brattström LE, Ueland PM, Palma-Reis RJ, Boers GH, Sheahan RG, Israelsson B, Uiterwaal CS. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. Jama. 1997 Jun 11;277(22):1775-81.
27. Schwartz SM, Siscovick DS, Malinow MR, Rosendaal FR, Beverly RK, Hess DL, Psaty BM, Longstreth Jr WT, Koepsell TD, Raghunathan TE, Reitsma PH. Myocardial infarction in young women in relation to plasma total homocysteine, folate, and a common variant in the methylenetetrahydrofolate reductase gene. Circulation. 1997 Jul 15;96(2):412-7.
28. Verhoef P, Kok FJ, Kruyssen DA, Schouten EG, Witteman JC, Grobbee DE, Ueland PM, Refsum H. Plasma total homocysteine, B vitamins, and risk of coronary atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 1997 May;17(5):989-95.
29. Bilsborough W, Green DJ, Mamotte CDS, van Bockxmeer FM, O'Driscoll GJ, Taylor RR. Endothelial Nitric Oxide synthase gene polymorphism, homocysteine, cholesterol, and vascular endothelial function. Atherosclerosis, 2003; 169(1):131–38.
30. Kanani PM, Sinkey CA, Browning RL, Allaman M, Knapp HR, Haynes WG. Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocysteinemia in humans. Circulation, 1999; 100(11):1161–68.
31. Cavalca V, Cighetti G, Bamonti F, Loaldi A, Bortone L, Novembrino C, De Franceschi M, Belardinelli R, Guazzi MD. Oxidative stress and homocysteine in coronary artery disease. Clinical chemistry. 2001 May 1;47(5):887-92.