The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/18.4912

ORIGINAL PROF-4912

ACUTE MYOCARDIAL INFARCTION;

FREQUENCY OF ELEVATED HOMOCYSTEINE LEVELS IN PATIENTS PRESENTING WITH ACUTE MYOCARDIAL INFARCTION

Rana Muhammad Suhail Khan[1], Sabeen Farhan[2], Fahad Aman Khan[3]

1. MBBS, FCPS (Medicine)
Assistant Professor
Department of Medicine
Allama Iqbal Medical College, Lahore.
2. MBBS, FCPS (Medicine)
Associate Professor
Department of Medicine
Gujranwala Medical College
Gujranwala.
3. MBBS, FCPS (Medicine)
Assistant Professor
Department of Medicine
Allama Iqbal Medical College, Lahore.

Correspondence Address:
Dr. Rana Muhammad Suhail Khan
House No.10 Ismaeel City, Ismaeel Road, (Daewoo Road) Faisalabad.
Drsuhail.rana@yahoo.com

Article received on:
27/04/2018
Accepted for publication:
25/07/2018
Received after proof reading:
02/10/2018

ABSTRACT... Objectives: To determine the frequency of elevated homocysteine level in patients presenting with acute myocardial infarction. **Design:** Cross-sectional. **Place and Duration:** Coronary Care Unit of Allied hospital Faisalabad, from 25-11-09- to 24-05-2010. **Material and Methods:** A total of 164 patients fulfilling the inclusion criteria were selected. Demographic details, history and examination findings of the patients were recorded. Blood sample were collected in fasting state for estimation of plasma glucose, serum LDL, serum cholesterol and serum total homocysteine level. **Data Analysis:** Descriptive statistics like mean with standard deviation were applied on age. Frequency of elevated homocysteine levels was calculated in acute myocardial infarction with other conventional risk factors for coronary artery disease. Male to female ratio was calculated. Frequency of elevated homocysteine levels was calculated in acute myocardial infarction. **Results:** Out of 164, 53.9% (n=88) were male patients and 76 46.08% (n=76) were females. Average age was 60.90±10.19. Among conventional risk factors, the frequency of elevated homocysteine levels was high (82%) in smokers. The frequency of elevated homocysteine levels was 55% in acute myocardial infarction and it was 61% in males and 39% in females respectively. The frequency of elevated homocysteine levels was highest (73%) among age group between 40-50 years. **Conclusion:** Frequency of elevated homocysteine levels was high among the patients with acute myocardial infarction. Moderate elevated homocysteine levels were associated with smoking.

Key words: Acute Myocardial Infarction, Cardiovascular Disease, Homocysteine, Smoking.

Article Citation: Khan RMS, Farhan S, Khan FA. Acute myocardial infarction; frequency of elevated homocysteine levels in patients presenting with acute myocardial infarction. Professional Med J 2018; 25(10):1450-1457.
DOI:10.29309/TPMJ/18.4912

INTRODUCTION

Atherosclerotic disease involving coronary arteries contributes to be a major health problem in adult population both in developed and developing countries. Control of conventional risk factors like smoking, hyperlipidemia, hypertension and diabetes mellitus has brought decline in incidence of coronary artery disease(CAD). Even with aggressive control of risk factors in general population, it is not possible to prevent progression of CAD in all patients. Homocysteine (Hcy) recently has emerged as a risk factor for atherosclerotic vascular disease and hypercoagulability states.

Total homocysteine (tHcy) is the term used to describe combination of homocysteine, homocysteine thiolactone and homocysteine mixed disulfide in the serum. Elevation of plasma total Hcy level is multifactorial. It is elevated by increasing dietary intake of methionine, heritable enzyme deficiency and cofactors deficiencies.[1]

The two pathways which metabolize Hcy are trans-sulfuration and re-methylation. When excess tHcy is present in the blood a major by-product is formed which is homocysteine thiolactone, which reacts with low density lipoprotein (LDL) to form LDL homocysteine thiolactone aggregate. These are taken up by macrophages and subsequently incorporated into foam cells in early atherosclerotic plaques, within these plaques homocysteine thiolactone acylates proteins. This modifies the oxidative process in the vessel which promotes atherosclerosis thrombosis. In addition auto-oxidation of homocysteine results in the

formation of superoxide and hydrogen per oxide. These oxygen-derived molecules contribute to oxidation of LDL and endothelial dysfunction, which promote proliferation of vascular smooth muscle cells.

Many studies have been done to assess the role of homocysteine as an independent risk factor for atherosclerosis. These studies have showed that moderately high levels of plasma tHcy are associated with increased risk of CAD independent of other coronary risk factors.[2] Normal range of homocysteine is 5-15 μ mol/L. A two fold increase in likelihood of CAD among persons with tHcy concentration more than or equal to 15 μ mol/L has been noted in a national representative survey in the United States.[3] High plasma tHcy level, low folate and low vitamin Cyanocobalamine (B12) are associated with increased risk of extra cranial carotid artery stenosis in the ederly.[4] Elevated Hcy level is an independent risk factor for stroke and deep vein thrombosis in the general population.[5,6]

Age, gender, serum folate, vitB12, vitB6, serum creatinine and enzyme deficiencies, are all important determinants of the plasma Hcy concentration. Some drugs e.g. phenytoin, carbamazepine, methotrexate and penicillamine also increase Hcy level. Advancing age increases Hcy level due to impairment of renal function. Gender difference in plasma Hcy level may be because of fact that it is more formed in men than women in combination with more creatinine synthesis in men.[7] It has been showed that high plasma Hcy level can be reversed with vitamins supplementation.[8]

Plasma elevated Hcy level is a strong predictor of mortality in patients with angiographically confirmed CAD.[9] A case-control study was conducted in 551 cases (294 European and 257 Asian) in European. Those showed that the Asians with CAD had elevated Hcy level and 40% higher mortality as compared to European.[10] At the same time studies were conducted on smaller number of patients in Asians. Those did not show any significant difference in Hcy level.[11,12] Sastry et al. did not find significant difference in plasma Hcy levels between controls and cases with CAD in South Indian population.[13]

The relationship of elevated Hcy level and CAD has not been studied extensively in Pakistani population. Only few studies have been conducted on smaller number of patients. The aim of my study is to find out the frequency of elevated Hcy level in the local population and their association with other risk factors (hypertension, smoking, dyslipidemias and diabetes mellitus) in the patients with CAD presenting with acute coronary syndrome (ACS).

Elevated Hcy level is an easily modifiable risk factor. Pharmacological intervention with vitB6, vitB12 and folic acid will result in reduction of Hcy level. This treatment is inexpensive in developing countries like Pakistan. Reduction in elevated Hcy level will result in reduction of the patients with CAD presenting with ACS. Modification of this culprit causing CAD will reduce the morbidity and mortality of patients with CAD.

MATERIALS AND METHODS

The study was conducted in Coronary Care Unit of PMC and affiliated Hospital Faisalabad. The study was completed over a period of 06 months from 25-11-2009 to 24-05-2010. The study was conducted on 164 patients of acute myocardial infarction.

Sampling technique use was non-probability consecutive sampling.

Inclusion Criteria

All patients of either sex, irrespective of their age with acute myocardial infarction (confirmed by fulfilling two of the following three criteria i.e. classical history of ischemic cardiac pain ≥30 minutes[14], ECG findings (ST segment elevation ≥2 mm in precordial leads, ≥1mm in limb leads.[14] ST segment depression ≥ 1.2mm or T inversion ≥ 6mm or LBBB[15], positive cardiac troponin T.[15]

Exclusion Criteria

- All patients having renal failure, leukemia and megaloblastic anemia.
- Patients taking drugs e.g. phenytoin,

carbamazepine, methotrexate and penicillamine.

Data Collection Procedure

164 patients with acute myocardial infarctions admitted in Coronary Care Unit of PMC and affiliated hospital fulfilling the inclusion criteria of acute myocardial infarction were included in study after approval from hospital ethical committee and taking informed consent. This was followed by history of anterior chest discomfort in patients and performing ECG on them. Cardiac troponin T was measured by using Sensitive Rapid Assay and serum homocysteine level measured by using Fluorescein Polarization Immunoassay. Serum cardiac troponin T > 1ng/ml and serum homocysteine level ≥ 15 μmol/L of all the patients would be considered positive. A proforma was developed to record physical and biochemical findings of all patients.

Data Analysis

Data was analyzed with SPSS-12. Descriptive statistics were calculated. Quantitative variables like age were presented as mean±SD. Qualitative variables like homocysteine level were presented as percentage.

RESULTS

164 patients of acute myocardial infarction were enrolled from coronary care unit and medical wards of Allied hospital Faisalabad. The mean age of the patients was 60.90±10.19 years. Descriptive statistics of age is depicted in Table-I. Gender distribution of patients is shown in Table-II. Frequencies of characteristics like smoking, hypertension, diabetes and LDL levels are shown in Table-III. Relation of tHcy levels with smoking, hypertension, diabetes and LDL is shown in Table-IV,V,VI and VII respectively. Table-VIII depicts the relation of cholesterol with Hcy. Lastly Tables-IX and X depict the frequencies of hyperhomocystinemia according to gender and age respectively.

Minimum=40
Maximum=90
Range= 50

Age		Fre-quency	Percent	Valid Percent	Cumulative Percent
Valid	40-50	37	22.56	22.56	22.56
	51-60	70	42.9	42.9	65.46
	61-70	33	20.10	20.10	85.56
	71-80	16	9.9	9.9	95.46
	81-90	08	4.8	4.8	100.0
	Total	164	100.0	100.0	
Mean ±SD		60.90±10.19			

Table-I. Distribution of patients by age (n=164)

		Fre-quency	Percent	Valid Percent	Cumulative Percent
Valid	Male	88	53.9	53.9	53.9
	Female	76	46.1	46.1	100.0
	Total	164	100.0	100.0	

Table-II. Distribution of patients by sex (n=164)

	N/Frequency	%Age
Sex		
Male	88	53.9
Female	76	46.1
Total	164	100
Hcy		
No	74	45
Yes	90	55
Total	164	100
Smoking		
No	90	55
Yes	74	45
Total	164	100
Hypertension		
No	85	52
Yes	79	48
Total	164	100
Diabetes Mellitus		
No	129	78
Yes	35	22
Total	164	100
LDL		
No	138	84
Yes	26	16
Total	164	100
Cholesterol		
No	144	88
Yes	20	12
Total	164	100

Table-III. Clinical characteristics n= 164

	Hcy		Total
	<15	15+	
Smoking			
No	62	28	90
	69.55%	30.45%	100.00%
Yes	13	61	74
Total	17.30%	82.70%	100.00%
	75	89	164
	45.00%	55.00%	100.00%

Table-IV. Frequency of elevated tHcy Level with smoking in AMI patients n=164

	Hcy		Total
	<15	15+	
Hypertension			
No	38	47	85
	45.20%	54.80%	100.00%
Yes	35	44	79
	44.80%	55.20%	100.00%
Total	73	91	164
	45.00%	55.00%	100.00%

Table-V. Frequency of elevated tHcy Level with hypertension in AMI Patients n=164

	Hcy		Total
	<15	15+	
Diabetic			
No	34	51	85
	40.40%	59.60%	100.00%
Yes	49	30	79
	61.50%	38.50%	100.00%
Total	83	81	164
	45.00%	55.00%	100.00%

Table-VI. Frequency of elevated tHcy with diabetes mellitus in AMI patients n=164

	Hcy		Total
	<15	15+	
LDL			
<160	58	80	138
	42.00%	58.00%	100.00%
160+	16	10	26
	60.00%	40.00%	100.00%
Total	74	90	164
	45.00%	55.00%	100.00%

Table-VII. Frequency of elevated tHcy level with LDL in AMI patients n=164

	Hcy		Total
	<15	15+	
Cholesterol			
<260	60	84	144
	41.50%	58.50%	100.00%
260+	14	6	20
	71.40%	28.60%	100.00%
Total	74	90	164
	45.00%	55.00%	100.00%

Table-VIII. Frequency of elevated HCY Level with cholesterol in AMI patients n=164

Presence of Hyperhomo-cystinemia	M n=88	Per-cent	F n=76	Per-cent	Total n=164	Per-cent
Yes	55	61	35	39	90	55
No	33	44	41	66	74	45

Table-IX. Distribution of hyperhomocystinemia according to gender

		hyperhomocystinemia		Total
		Yes	No	
Age Group	40-50	27(73%)	10(27%)	37
	51-60	40(57%)	30(43%)	70
	61-70	15(45%)	18(55%)	33
	71-80	6(37%)	10(63%)	16
	81-90	2(25%)	6(75%)	8
Total		90(55%)	74(45%)	164

Table-X. Distribution of frequency of hyperhomocystinemia according to age (n=164)

DISCUSSION

Atherosclerotic cardiovascular disease accounts for about half of all premature deaths among the men in the developed as well as developing countries.[16] Hypertension, cigarette smoking, diabetes mellitus and dyslipidemias are important risk factors for 50-75% of coronary artery disease.[17] There has been much recent interest in search for new risk factors which are emerging and revolutionizing. Among them the role of the elevated tHcy level is growing in pathogenesis of atherosclerosis.

Over the past three decades, the association between elevated serum tHcy level and risk of cardiovascular disease has grown from an obscure hypothesis to a major current topic in preventive cardiology. Many studies have demonstrated that moderately elevated tHcy level is associated with increased risk of CAD, independent of

other coronary risk factors. A two fold increase in likelihood of CAD among the persons with tHcy level more than or equals to 15μmol/L has been noted in national representative in United States (US).[3] More than 20 prospective and 30 retrospective studies on tHcy level have been published. In meta-analysis of 14 case-control studies, Bousely and colleagues found that an increment of 5 μmol/L of tHcy level above the normal was associated with 60% increase of odds of CAD in men and 80% increase of odds of CAD in women.[18] An increase of 5 μmol/L above the normal was estimated to increase the risk of CAD by as much as 20mg /dl cholesterol. It has been reported that increase in 3 μmol/L of elevated tHcy level above normal, equals a 35% increase in myocardial infarction.[19] Matetzkyt et al, showed in their prospectus study that patients with elevated tHcy level>20μmol/L had higher recurrent coronary events as compared to those with <20μmol/L.[20] Evidence supports the hypothesis that elevated tHcy level is an independent risk factor for MI and it should be screened early like triglyceride and cholesterol.[21]

It is estimated that 5-10% of population have a tHcy concentration >15μmol/L[22] and may be as high as 30-40 % in elderly population.[23] Meta-analysis also has estimated that approximately 10% of CAD in general population could be attributed with hyperhomocystinemia. Framingham study showed that plasma tHcy level was >15.8μmol/L in 25% elderly participants.[22] In another prospective cohort study carried out in United States involving 14,914 US males' physicians without prior MI; it was found that those physicians having serum tHcy level 12% above the normal had threefold increased risks of MI as compared to those who had lower levels even after adjustment of traditional risk factors.[2]

Cigarette smoking is an independent risk factor for CAD and its cession reduces the incidence of CAD. Smoking plays an important role for elevated tHcy level by interfering enzyme pyridoxal phosphate which is important for conversion of Hcy to cystathione by cystathione beta synthetase.[23] In Hordaland study in Norway revealed that increased habit of cigarette smoking was associated with increased tHcy level.[10] Studies examined the role of elevated tHcy level and revealed an additive coronary risk factors (hyperlipidemias and smoking) effect.[24] In my study the observations show that elevated tHcy level is associated with smoking in patients presenting with acute myocardial infarction. Muhammad Naeem Aslam and Colleagues at Faisalabad conducted a study and showed that smokers were more prone to have ACS due to increased level of serum tHcy level.[25] These finding are consistent with the observations of my results. Muhammad Aamir and Colleagues at Rawalpindi conducted a study and showed that elevated tHcy level was associated with smoking (p-0.04) and subsequently CAD[19] J.R Faria-Neto and Colleagues revealed that elevated tHcy level was associated with smoking but not with CAD in Brazilian population.[26] My results are also comparable with study done by Gulbahar and Colleague in Iran at Shiraz. They concluded that serum elevated tHcy level had relation with smoking in CAD patients.[27] Cigarette smoking is the most prevalent both in low and high socioeconomic society. Poor people use it as cheap leisure activity due to lack of awareness and education, whereas rich for status symbol. Our population need awareness that smoking greatly increases the risk of CVD and therefore be offered intensive advice to help them cease it. It will reduce the elevated tHcy level which is culprit of CVD. None of the patient has tHcy level >100 μmol/L which is severe hyperhomocystinemia. It is due to enzyme deficiencies that usually manifests with early age in the form of thromboembolism. In my study, average age was 50 year. It is unlikely that elevated tHcy level is due to enzyme deficiency.

Hypertension is also a notorious risk factor for causing CAD but the association between elevated tHcy level and hypertension has not been studied extensively. One study showed that an elevated serum tHcy level was positively correlated with hypertension and heart rate in patients of myocardial infarction but mechanism behind this relationship was not known. Another study showed that when hypertension was taken into consideration, tHcy levels were

not significantly different in normotensive as compared to hypertensive CAD patients. When they were segregated on the basis of coexistence of hypertension and diabetes, those were found with low levels.[28] Elevated tHcy level impairs vasodilatory mechanism, which can support that correlation.[29] Results of my study show that an elevated tHcy levels are not associated with hypertension. These results are comparable to the study conducted by Muhammad Aamir and Colleagues at Rawalpindi (Pakistan).[19] Results are also comparable with the studies done in India by Mehta and Colleagues, where association between elevated tHcy level and hypertension had not been observed.[28] The observations of my study also have matched with the results of Monta A and Colleague, where no association has been found between elevated tHcy level and hypertension in CAD patients in Mexican (USA) population.[30] More studies are needed with adjustment other coronary risk factors for clarification the possible influence of elevated tHcy level with hypertension. Hypertension accounts for about 50% of CAD. If elevated tHcy level is associated with hypertension, then early screening of it should be carried out to prevent the CVD.

Diabetes mellitus is also a major risk factor for CAD. Its causal effect for atherosclerosis is multifactorial. The mean plasma tHcy level is usually low or normal in diabetic patients except in diabetic nephropathy due to higher glomerular filtration rate. Although diabetes and hyperhomocystinemia are strong risk factors for CAD, but association between them were not seen.[28] Hoffmann et al reported that hyperhomocystinemia was more common in type-1 DM with nephropathy.[31] Deepa et al did not reveal any significant increase of tHcy level in DM or DM with CAD.[18] Results of my study show that elevated tHcy level is not associated with diabetic patients (p-0.176). These results are comparable to the study conducted by Muhammad Aamir and Colleagues in Rawalpindi (Pakistan).[19] Another study was done by Mehta and Colleagues in Ahmedabad, India, and showed that mean tHcy level in DM patients were 14.4μmol/L whereas nondiabetic had 30 μmol/L.[28] Monta A and Colleague conducted a study and revealed that Mexican (USA) population had not any association between elevated tHcy level and diabetes mellitus.[30] These patients develop glomerular hyper filtration before the onset of diabetic nephropathy which leads to more excretion of tHcy in urine, resulting in lower level. More studies and more number of the patients with long trials, adjusting of others coronary risk factors are needed to see exact relationship between elevated tHcy and diabetes mellitus in ACS patients.

Dyslipidemias is also major coronary risk factor. It accounts for 40% of CAD. The association between elevated tHcy level and dyslipidemias has not been studied extensively. Some studies have established relationship between them while others rejected it. The observations of one study showed that elevated tHcy level had strong association with dyslipidemias. This might be explained by the fact that synthesis of tHcy and lipids were related.[24] In Hordaland study in Norway revealed that increased cholesterol and triglycerides were associated with elevated tHcy level.[10] Studies examined the role of hyperhomocystinemia in patients with CAD risk factors and demonstrated an additive risk factors (dyslipidemias and smoking) effect.[21] Results of my study show that an elevated tHcy level is not associated with dyslipidemias (LDL P-0.296, cholesterol P-0.135 which is not statistical significant). These results are comparable to the study conducted by Muhammad Aamir and Colleagues at Rawalpindi (Pakistan).[19] In Iran Gulbahar and Colleague showed that elevated tHcy level was not associated with dyslipidemias.[27] Monta A and Colleague conducted a study and revealed that elevated tHcy level was not associated with dyslipidemias in Mexican (USA) population.[30] The observations from my study are statistical insignificant due to smaller number of dyslipidemic patients encountered (LDL patients n=10, and hypercholestoremic patients n=7). More studies and more number of patients are needed for clarification the possible influence of elevated tHcy level with dyslipidemias in ACS patients.

Moreover elevated tHcy level is potential modifiable risk factor with folic acid, vitB6 and vitB12. Treatment of elevated tHcy level is inexpensive in developing countries. A regimen of folic acid 1 mg, vitB6 10mg and vitB12 400 μgram significantly reduced cardiovascular events in patients undergoing angioplasty. In USA tHcy level has decreased by fortification of cereals flour with folic acid in coronary artery disease. Mishra et al in their study of an urban population have observed an association between elevated tHcy level and low intake of folic acid and vitB12.[1] Folic acid in dose of 400 μgram/day reduces elevated tHcy level 25% and with addition of vitB12 further reduces it 7%. Demographic factors play a role in explaining the variability in the impact of folic acid on elevated tHcy level e.g. food fortification with folic acid is done in USA while this practice is not present in European and Asian. The supplementation has influence on elevated tHcy level.

CONCLUSION

Elevated homocysteine level is associated with cigarette smoking but not with other traditional coronary risk factors in patients presenting with acute myocardial infarction. Therefore, smokers are more prone to have CVD due to increased level of homocysteine. Smokers should be offered intensive advice to help them stop the cigarette smoking habit. This will result in reduction in elevation of homocysteine level, which is synergistic culprit in pathogenesis of coronary atherosclerosis. Moreover elevated homocysteine level is easily and potentially modifiable coronary risk factor. Its treatment is inexpensive with folic acid, vitamin B6, and vitamin B12. Modification of this novel and new emerging coronary risk factor will lead to decrease of morbidity and mortality in patients due to CVD. More studies and more number of patients are required to assess the possible influence of elevated homocysteine level with other traditional coronary risk factors.

REFERENCES

1. Scott JM, Weir DG. **Folic acid, homocysteine and one carbon metabolism: A review of the essential biochemistry.** J Cardiovasc Risk 1998; 5:223-7.
2. Stampfer MJ, Malinow MR, Willett WC, Newcomer LM, Upson B, Vllmann D, et al. **A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians.** JAMA 1992; 268:877-81.
3. Wayne HG, Janet B, Greelund K. **Association between total homocysteine and the likelihood for history of acute myocardial infarction by race and ethnicity.** Am Heart J 2000; 139:446-53.
4. Sehlub J, Jacques PF, Bosten AG. **Association between plasma homocysteine concentration and extracranial carotid artery stenosis.** N Engl J Med 1995; 332: 286-91.
5. Perry J, Refsum H, Morris RW, Ebrahim SB. **Prospective study of total homocysteine concentration and risk of stroke in middle aged British men.** Lancet 1995; 346:1395-8.
6. Den M, Henk TK, Boss GM. **Hyperhomocysteinemia as a risk factor for deep vein thrombosis.** N Engl J Med 1996; 33 4:759-62.
7. Brattstrom E, Lindgren A, Israilsson B, Andersson A, Hultberg B. **Homocysteine and cysteine: determinants of plasma level in middle aged and elderly subjects.** J Intern Med 1994; 236:633-41.
8. Malinow A. **Homocysteine and arterial occlusive diseases.** J Intern Med 1994; 236:603-17.
9. Nygard O, Volloset SE, Refsum H, Stenvoald I, Tverdal A, Nordrehaug JE. **Plasma homocysteine levels and mortality in patients with coronary artery diseases.** N Eng J Med. 1997; 337:230-36.
10. Chambers JC, Obeid OA, Refsum H, Ueland P, Hacket D, Hooper J, et al. **Plasma homocysteine concentration and risk of coronary artery disease in UK Indian Asian and European men.** Lancet 2000; 160:422-34.
11. Chacko KA. **Plasma homocysteine levels in patients with coronary artery disease.** Indian Heart J 1998; 50: 295-9.
12. Gheye S, Lakshmi, Krishna TP. **Fibrinogen and homocysteine levels in patients with coronary artery diseases.** Indian Heart J 1999; 51: 499-502.
13. Sastry BKS, Indira N, Anand B. **A case-control study of plasma homocysteine levels in South Indians with or without coronary artery disease.** Indian Heart J 2001; 53: 749-53.
14. Awtry EH, Loscalzo J. **Coronary artery disease. In: Carpenter CC, Criggs RC, Loscalzo J, editors. Cecil essentials of medicine.** 6th ed. Philadelphia: Elsevier Saunders; 2004. p. 87-108.

15. Cannon C, Braunwald E. **Unstable angina and non-ST-elevation myocardial infarction. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease.** 7th ed. Philadelphia: Elsevier Saunders; 2005. p. 1243-67.

16. American Diabetes Association. **Report of the expert committee on the diagnoses of diabetes mellitus.** Diabetes Care 1997; 20: 1183-201.

17. **The fifth report of the Joint National Committee on the detection, evaluation and treatment of high blood pressure.** Arch Intern Med 1993; 153: 154-83.

18. Boushey C, Beresford S, Omenn G. **A quantitative assessment of plasma homocysteine as a risk factor for vascular diseases: probable benefits of increasing folic acid intakes.** JAMA 1995; 274: 1049-57.

19. Amir M, Sattar A, Dawood MM, Dilawar M, Ijaz A, Anwer M. **Hyperhomocysteinemia as a risk factor for ischemic heart disease.** J Coll Physicians Surg Pak 2004; 14: 518-21.

20. Matetzky S, Freimark D, Ben-Ami S, Goldenberg I, Leor J, Doolman R. **Association of elevated homocysteine levels with higher risk of recurrent coronary events and mortality in patients with acute myocardial infarction.** Arch Intern Med 2003; 163: 1933-7.

21. **Relationship of total homocysteine, cholesterol, triglyceride in the serum and diastolic blood pressure of patients with myocardial infarction.** Iran Biomed J 2001; 5: 97-101.

22. Selhub L,Jacques PF, Wilson PW, Rush W, Rosenberg IH. **Vitamin status intakes as primary determinants of homocysteinemia in an elderly population.** JAMA 1993; 270:2693-8.

23. Abraham R, John MJ, Calton R, Dhanoa J. **Raised serum homocysteine level in the patient of coronary artery disease and the effects of vitamin B12 and folic acid on its concentration.** Indian J Clin Biochem 2006; 21: 95-100.

24. Elia M. Nutrition. In: Kumar P,Clarke M, editors. **Kumar and Clark clinical medicine.** 6th ed. London: Elseveir Saunders; 2005.p. 229-64.

25. Aslam MN, Malik FA, Javad H, Anwar E, Awan JA, Khan YH, et al. **Relation of smoking and elevated homocysteine in patients presenting with acute coronary syndrome.** Pak J Cardiol 2006; 17:48-56.

26. Faria-Neto JR, Chagas ACP, Bydlowski SP, Lemos Neto PA, Chamone DA, Ramirez JAF, et al. **Hyperhomocysteinemia in patients with coronary artery disease.** Braz J Med Biol Res 2006; 39: 455-63.

27. Gulbahar J, Rezaian GR. **Association of hyperhomocysteinemia with coronary artery disease in Southern Iran.** J Med Sci 2004; 29: 116-9.

28. Vita J, Treasure C, Nebal E. **Coronary vasomotor response to acetylcholine relates to risk factors for coronary arteries diseases.** Circulation 1990; 81: 491-7.

29. Chambers J, Obade O, Kooner J. **Physiological increment in plasma homocysteine induce vascular dysfunction in normal human subjects.** Arterioscler Thromb Vas Biol 1999; 19: 2922-7.

30. Monta A, Loza A. **Plasma homocysteine concentrations in Mexican patients with ischemic heart disease.** Rev Invest Clin 2004; 56:580-5.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Rana M. Suhail Khan	Formatting of the article as per manuscript requirements & origional research.	
2	Sabeen Farhan	Formtting of the article as per manuscript requirement.	
3	Fahad Aman Khan	Data analysis.	