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Research Paper Medicine

Homocysteine-A Novel Risk Factor For Atherovascular Disease

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ABSTRACT

Background: Presence of mild to moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis in the coronary, cerebral, and peripheral vasculature, and for vascular disease. Several traditional risk factors are associated with total Homocysteine.

Objectives: To evaluate S .Homocysteine level as a risk factor for atherovascular disease and to assess correlation between traditional risk factors and S. Homocysteine level.

Methods: Patients with atherovascular disease admitted in medical wards were enrolled. Traditional risk factors along with S. Homocysteine level were measured and studied.

Results: Incidence of Homocysteinemia is found in 84% of cases, among which 69%of patient have moderate rise and 31% of patient have intermediate rise in Homocysteine level. Homocysteine concentrations were higher in men than in women and increased with age. Several traditional risk factors are associated with total Homocysteine. Homocysteine has more than a multiplicative effect on traditional risk factors.

Conclusion: Homocysteine level should be measured routinely in every patient who is suspected of having atherosclerosis.

KEYWORDS : Homocysteine, Atherovascular disease, Traditional risk factors

Introduction

Atherosclerosis is the leading cause of mortality in developed words. Clinical manifestations depend on particular part involved. For example, coronary artery disease, Ischemic stroke, Peripheral vascular disease, mesenteric ischemia, renal artery stenosis etc. Risk factors for atherosclerosis are classified in Traditional and Novel risk factors. Traditional risk factors are again classified in Non modifiable and Modifiable risk factors. Non Modifiable risk factors are age group, gender, heredity, race etc. Modifiable risk factors are hypertension, smoking, Dyslipidemia, DM, Obesity etc. Novel risk factors include S. Homocysteine, Fibrinogen, Lipoprotein(a), Markers of inflammations(hs-CRP, ICAM1, IL 6).

Homocysteine was first described by Butz and du Vigneus in 1932.In 1969, McCully described various vascular pathological events in patient with homoctsteinuria.

The term Homocysteine refers to both the oxidised and the reduced forms. In the plasma traces of Homocysteine are encountered as reduced Homocysteine (1%), in combination with albumin (70%), and the remaining 29% as low molecular weight disulphides, mainly cysteine. The total of all kinds of Homocysteine is described by the term "total Homocysteine."[1]

Factors affecting S. Homocysteine level are Genetic (Homozygous defect for CBS, Homozygous defect for MTHFR , Cobalamin mutations , Down's syndrome , Heterozygous defect for CBS , Heterozygous defect for MTHFR), Drugs (Folate antagonists (methotrexate) , Vitamin B6 antagonists , Vitamin B12 antagonists , Antiepileptic drugs , Contraceptives , Aminothiols (penicillamine, acetylcysteine) ,Others (niacine, cholestyramine, L-dopa) Clinical conditions(Folate deficiency , Vitamin B12 deficiency , Vitamin B6 deficiency , Renal failure ,Hypothyroidism, Neoplasms) Lifestyle(Vitamin intake ,Smoking , Coffee ,Alcohol, Exercise) Other factors(Increasing age , Male sex , Increased muscle mass).[1]

Reference Ranges:[2]

Normal Adult	5-15 µM/L
HyperHomocysteinemia	>15 µM/L
Moderate	15-30 µM/L
Intermediate	30-100 µM/L
Severe	>100 µM/L

Homocysteinemia is associated with endothelial cell injury, platelet dysfunction (increase turnover and adhesiveness of platelet, increase production of thromboxane, modulation of platelet endothelial interaction), hypercoagulation (stimulation of procoagulant factor and inhibition of anticoagulant, impaired fibrinolysis), smooth muscle proliferation, oxidative modification of LDL, alteration in endothelial and leukocyte interaction.[1]

All the large meta-analyses conducted during the last decade yield consistent results: Homocysteine can be considered as an independent risk factor for cardiovascular disease (CVD).[3]The first large meta-analysis published in 1995 pointed out that Homocysteine is strongly associated with vascular disease, arguing that an increment in total Homocysteine by 5 mmol/L is equivalent to the elevation in CAD risk induced by a 20 mg/dL increase in plasma cholesterol.[3]Furthermore, it was suggested that Homocysteine accounts for up to 10% of the population's CAD risk.[3] Hyperhomocysteinemia confers an increased risk of coronary artery disease stroke and deep vein thrombosis and is a strong predictor of mortality among patients with ischemic heart disease.

Material & Method

I studied 50 patients who were admitted in General medical wards with different manifestations of athero-vascular disease.

Inclusion Criteria

Age 15-45 Years

Patients with Ischemic heart disease, Ischemic Stroke, Peripheral vascular disease.

Exclusion Criteria

Age <15 or >45

Hemorrhagic and venous stroke

Stroke associated with Vasculitis, Dissection, Fibromuscular dysplasia, Cardio embolic stroke.

Informed consent of all patients enrolled in study taken.

After admission detailed medical history, General examination and systemic examination done. Special attention was given to palpation of carotid artery and peripheral arteries, and auscultation of carotid bruit.

Routine blood investigations including complete hemogram, Random Blood Sugar, Creatinine, Electrolytes, Fasting lipid Profile and Fasting Homocysteine level carried out.

Specific Investigations like 12 lead ECG, 2D Echo with Doppler, CT

Scan Brain, MRI Brain, Carotid Doppler and peripheral arterial Doppler done as per requirement.

Cerebral angiography, MR angiography, 4 vessels Digital Substraction Angiography are rare form of investigation done in specific situations.

Observation and Discussion

Table 1
Incidence of Atherosclerosis Disease according to Age Group

Age Group (Years)	No. of Cases	Incidence
15-25	6	12%
26-35	16	32%
36-45	28	56%

Earliest lesion of atherosclerosis is present at age of 10 years. Risk of atherosclerosis increase with age. Usually the atherovascular disease manifest after the age of 45 in men and after the age of 55 in female. [4]

In present study, age limit is 15-45 years, so highest incidence was found with age group 36-45.

Table 2
Incidence of Atherovascular Disease According to Sex

Sex	No. of Cases	Incidence	Male: Female
Male	40	80%	4:1
Female	10	20%	

Overall incidence of atherovascular disease is more in male as compared to female. Estrogens in female have multiple protective effects on lipid, nitric oxide, and vascular tone and antioxidant properties.[4]

In present study, incidence is four times higher in male as compared to female.

Table 3
Incidence of Different manifestations of athero-vascular disease

Etiology	No. of Cases	Incidence
Coronary artery disease	34	68%
Cerebrovascular disease	15	30%
Peripheral vascular disease	1	2%

Atherosclerosis leads to end organ manifestations in form of coronary artery disease, cerebrovascular disease, peripheral vascular disease, renal artery stenosis, mesenteric ischemia etc.

In selected group of atherovascular disease incidence of coronay artery disease are significantly higher. Among coronary artery disease, 32 patients had myocardial infarction and 2 had unstable angina. 30% had cerebovascular ischemia and only one patient had peripheral vascular disease.

Table 4
Incidence of Traditional Risk factors in atherovascular disease

Risk Factors	No. of Cases	Incidence
Hypertension	17	34%
DM	8	16%
Dyslipidemia	44	88%
Smoking	20	40%

Risk factors for atherosclerosis are classified in Traditional and Novel risk factors. Traditional risk factors are Non modifiable and Modifiable risk factors. Non Modifiable risk factors are age group, gender, heredity, race etc. Modifiable risk factors are hypertension, smoking, Dyslipidemia, DM, Obesity etc.

In present study highest association found with dyslipidemia followed by smoking.

Table 5
Incidence of Hyperhomocysteinemia in atherovascular disease

S. Homocysteine level	No. of Cases	Incidence
High	42	84%
Normal	8	16%

Reference range for normal Homocysteine level is 15µmol/L. In present study 86% of patients with atherovascular disease had S. Homocysteine level > 15µmol/L. Homocysteinemia is considered as an independent risk factor for atherovascular disease.

Homocysteinemia is associated with endothelial cell injury, platelet dysfunction (increase turnover and adhesiveness of platelet, increase production of thromboxane,modulation of platelet endothelial interaction),hypercoagulation (stimulation of procoagulant factor and inhibition of anticoagulant,impaired fibrinolysis),smooth muscle proliferation, oxidative modification of LDL, alteration in endothelial and leukocyte interaction.[1]

Homocysteinemia is considered as an independent risk factor for atherovascular disease.

Table 6
Incidence of Hyperhomocysteinemia according to Age Group

Age Group (years)	No. of Cases	Incidence
15-25	5	83.33%
26-35	13	81.25%
36-45	24	85.71%

In present study highest incidence found in age group 36-45 years.

There is significant positive correlation between plasma Homocysteine and age.[1] Homocysteine level usually increase with increasing age and it is independent of vitamin B level. The exact reason is not yet known but possible causes may include increase in serum creatinine and urea level, poor glycemic control, total cholesterol level, hypertension and smoking.

Table 7
Incidence of Hyperhomocysteinemia according to Sex

Sex	No. of Cases	Incidence	Male: Female
Male	33	82.5%	3.6:1
Female	9	90%	

In this study males had higher incidence of Homocysteinemia as compared to females.

The reason for this gender predominance is yet not known.

These observations could be attributable to differences in vitamin levels and to the effect of sex hormones.[1,5] Homocysteine levels typically increase after menopause. The difference between the sexes could involve the formation of Homocysteine in relation with creatine/ creatine synthase, which is proportional to the difference in muscle mass and is consequently higher in men than in women.[1,5]

Table 8
Incidence of Hyper Homocysteinemia according to etiology

Etiology	No. of Cases	Incidence

Coronary artery disease	28	82.34%
Cerebrovascular diseas	13	81.25%
Peripheral vascular disease	1	100%

In present study 82.34% cases of Homocysteinemia were associated with coronary artery disease, 81.25% cases were associated with cerebrovascular disease.

It is now well accepted that increase in Homocysteine level is strong, graded and independent risk factor for stroke, MI and other vascular disease.

In a metaanalysis of 27 trials, comparing patient with Homocysteine level above 90th percentile to the rest, risk ratio for coronary artery disease 1.7, carebrovascular disease 1.7, and peripheral vascular disease 6.8. An increment in total Hcy by 5 mmol/L is equivalent to the elevation in CAD risk induced by a 20 mg/dL increase in plasma cholesterol.[6]

The strongest association observed for cerebrovascular disease. 80% of all arterial strokes has raised in Homocysteine in The Ruby Hall Study (Largest Indian Study).[6]

Table 9
Severity of Hyperhomocysteinemia according to etiology

Etiology	S. Homocysteine Level (micromole/L)			
	Normal	Moderate	Intermediate	High
Coronay artery disease	6	19	9	-
Cerebrovascular disease	2	9	4	-
Peripheral vascular Disease	-	1	-	-

The first large meta-analysis published in 1995 pointed out that Hcy is strongly associated with vascular disease, arguing that an increment in total Hcy by 5 mmol/L is equivalent to the elevation in CAD risk induced by a 20 mg/dL increase in plasma cholesterol.[3] Thus more the Homocysteinemia, more chances of manifestation of atherovascular disease.

But recent study suggests that both mildly and markedly elevated circulating Homocysteine levels are associated with increase in rise of vascular occlusion. Markedly rise in Homocysteine occur in 20-30% of patient with atherosclerosis.

Table 10
Incidence of Traditional Risk Factor with Homocysteinemia

Risk Factors	No. of Cases	Incidence
Hypertension	15	35.70%
DM	8	19.03%
Dyslipidemia	38	90.48%
Smoking	16	38.02%

This study showed that the patients with higher level of Homocysteine level are also associated with other traditional risk factors in order of severity as following dyslipidemia, smoking, hypertension and DM.

Table 11
Correlation between S. Homocysteine level and other Traditional Risk Factors

S. Homocysteine level	Hypertension	DM	Dyslipidemia	Smoking
Normal	2	1	7	5
Moderate	11	7	25	10
Intermediate	4	1	13	6
High	-	-	-	-

Some prospective studies showed weak or no relation between total Homocysteine and other risk factors for atherosclerosis. Several traditional risk factors are associated with total Homocysteine and may confound relation between Homocysteine and CVD. There is increasing evidence that Homocysteine is proximate risk factor provoking acute event and it strongly interact with traditional risk factors.[7]

Homocysteine has more than multiplicative effect on risk in smoker, hypertension, and dyslipidemia.[7]

Recent observations suggest that plasma Homocysteine is not related to CAD in patient without conventional risk factors.[7]

Conclusion:
It is accepted that increase in Homocysteine level is strong, graded and independent risk factor for stroke, MI and other vascular disease.

The risk of atherovascular disease increases with increase in age. Atherovascular disease is more common in middle to older age group, but it can occur at any age group.

Atherovascular disease have a wide spectrum of risk factors particularly traditional risk factor like hypertension, diabetes, dyslipidemia, smoking and novel emerging risk factors like Homocysteine.

Males are predominantly affected than female.

Among atherovascular disease, coronary artery disease is the most common manifestation. Incidence of Homocysteinemia is found in 84% of cases, among which 69%of patient have moderate rise and 31%of patient have intermediate rise in Homocysteine level.

Homocysteine concentrations were higher in men than in women and increased with age.

Both mildly and markedly elevated circulating Homocysteine levels are associated with increase in rise of vascular occlusion.

Markedly rise in Homocysteine occur in 20-30% of patient with atherosclerosis.

Several traditional risk factors are associated with total Homocysteine. Homocysteine has more than a multiplicative effect on traditional risk like smoker, hypertension, and dyslipidemia.

Limitation of Study:
This is a unicentric study including relative small number of participants. Multicentric study with large number of participants is required to make the data applicable to community.

Abbreviations:
DM : Diabetes Mellitus

HsCRP : Highly sensitive C reactive protein

ICAM 1 : Intercellular adhesion molecule 1

IL 6 : Interleukin 6

CBS : Cysteine B synthase

MTHFR : Methyle tetra hydro folate reductase

LDL : Low density lipid

CAD : Coronary artery disease

CT scan : Computerised tomography scan

MRI : Magnetic Resonance Imaging

MI : Myocardial Infarction

CVD: Cerebrovascular Disease.

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