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Original Research Article

Study of role of homocysteine as a risk factor in patients with acute vascular events

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Abstract

Background: Evidence from retrospective and prospective clinical studies indicates that elevated levels of homocysteine are associated with increased risk of CAD, Ischemic stroke and peripheral vascular disease. Present study was aimed to study role of Homocysteine as a risk factor in patients with Acute Vascular Events.
Material and Methods: Present study was prospective, observational study, conducted in patients with age above 18 years, either gender, admitted for Ischemic heart disease, peripheral vascular disease, Deep Vein Thrombosis and Pulmonary Thromboembolism.
Results: In this study most of the cases are between the age group of 60-69 years (55%). Youngest patient in this study is 20 year old. This is a male dominated study with males comprising 72% of the study group. In this study Dyslipidemia (62%) is the most common risk factor followed by Smoking (53%). Hypertension (50%) and Diabetes mellitus (41%) are observed. Family h/o CAD (20%) is present and only (14%) patient was alcoholic. Overweight is present among 41% of patients. In this study significant number of patients (72%) have hyperhomocysteinemia. 47% of patients are moderate and 23% are intermediate. Only 2 patients have severe hyperhomocysteinemia. Mean plasma homocysteine level is 11±3µmol/L and is statistically significant. The mean plasma homocysteine was high among smokers when compared to non-smokers difference was highly significant. No much significant difference was noted in mean values of homocysteine among patients with other high risk factors, such as alcohol consumption, diabetic, dyslipidemia, BMI, family history of CAD. Hyperhomocysteinemia is seen in 38 out of 51 patients with Cerebrovascular Disease, 32 out of 42 patients with Cardiovascular Disease, one of 4 patients with Peripheral arterial Disease and one with Deep vein thrombosis.
Conclusion: Plasma homocysteine should be considered as an independent risk factor for the development of future acute vascular event.

Keywords: Plasma homocysteine, vascular disease, acute vascular event, hyperhomocysteinemia

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Introduction

Arterial disease [1], usually due to atherosclerosis, is the most prevalent chronic disease in the developed world [2, 3], and is rapidly increasing in importance in the developing world [4, 5]. Although atherosclerotic arterial disease can cause stable or slowly progressive clinical syndromes, such as stable angina and intermittent claudication, the main clinical burden consists of acute, usually ischemic, vascular events. Acute arterial vascular events are the leading cause of premature death and disability in the developed world [2, 3].

Increasing recognition [12] that as many as 30-50% of patients with established CVD lack the traditional risk factors has led to search for additional new risk factors that may predispose individuals to coronary artery disease over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for atherothrombotic vascular disease, the growing list of new and emerging risk factors include elevated blood levels of homocysteine [6].

Major risk factors are sedentary life style, cigarette smoking, alcohol, hypertension, high LDL cholesterol and diabetes mellitus. Evidence from retrospective and prospective clinical studies indicates that elevated levels of homocysteine are associated with increased risk of CAD, Ischemic stroke and peripheral vascular disease [7]. Present study was aimed to study role of Homocysteine as a risk factor in patients with Acute Vascular Events.

Material and Methods

Present study was prospective, observational study, conducted in department of general medicine, at Basappa Memorial Hospital, Mysore, India. Study duration was of 2 years (July 2018 to June 2019). Study was approved by institutional ethical committee.

Inclusion criteria

- Patients with age above 18 years, either gender, admitted for Ischemic heart disease, peripheral vascular disease, Deep Vein Thrombosis and Pulmonary Thromboembolism willing to participate in study.

Exclusion criteria

- Patients associated with diseases such as renal failure, hypothyroidism, psoriasis, any malignancies and psychiatric disorders.
- Patients taking drugs such as Methotrexate, oral contraceptive pills-dopa, Nicotinic acid and Theophylline.
- Patients taking folic acid or any vitamin supplement.
- Patients not willing to participate.

Study was explained & written consent was taken for participation. A detailed history and thorough clinical examination was done as per the proforma and were investigated further, cardiac enzymes-CKMB, Blood urea, Serum creatinine & Coagulation Profile were done in all patients.

Fasting plasma homocysteine

Estimation was done by Fluorescence polarization immunoassay (FPIA-ABBOTT-AXSYM-USA). Plasma homocysteine level greater than 15μmoles/L is considered as hyperhomocysteinemia. Whenever required Echocardiography, Computed Tomography Head

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and Thorax, Magnetic Resonance Imaging Brain, Carotid and Vertebral Doppler Study, Doppler of Peripheral Vessel, Angiogram & Venogram were done.
The following parameters were studied

1. **Smoking:** In terms of pack years, smoking index.
2. **Diabetes mellitus**

1) Known diabetics on treatment.
2) Newly detected DM satisfying WHO criteria.

a) Symptoms of diabetes mellitus with random blood glucose >200 mg%.
b) Fasting plasma glucose > 126 mg%.
c) 2hr plasma glucose > 200 mg%.

3. **Hypertension**

1) Known hypertensive on treatment.
2) Newly detected hypertension according to JNC VII criteria.

4. Family history of Ischemic heart disease.
5. **Obesity:** Patients were classified as overweight and obese based on body mass index.
6. BMI = Weight (kg)/height (mt2).
7. Dyslipidemia: According to NCEP-ATP III guidelines, patients were considered to have dyslipidemia when.

1) Total cholesterol > 200 mg%.
2) HDL < 40 mg%.
3) LDL > 130 mg%.
4) Triglycerides > 150 mg%.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

In this study most of the cases are between the age group of 60-69 years (55%). Youngest patient in this study is 20 year old. This is a male dominated study with males comprising 72% of the study group. In our study homocysteine levels are high in vegetarians when compared to mixed (veg & non veg) which is statistically significant.

Table 1: General characteristics

Age	Number of cases	Percentage	P value
20-29	4	4	Chi-square-142.56 P-value-0.00
30-39	4	4	
40-49	16	16	
50-59	21	21	
60-69	55	55	
Sex			
Male	72	72	P-value-0.000
Female	28	28	
Food habits			Chi-square-23.04 p value-0.00 highly significant
Veg	74	74	
Mix	26	26	

In our study, 44% of patients have weakness in limbs followed by others (40%), which include discolorations of the toes, swelling of the limbs, giddiness, ataxia, seizures, vomiting and sweating. 39% have chest pain followed by difficulty in speech (23%), breathlessness (14%), headache (4%) and palpitation (1%), which is statistically significant.

Table 2: Symptoms at the time of admission

Symptoms	Number of cases	Percentage	Chi-square	P value
Chest pain	39	39	4.840	0.028
Breathlessness	14	14	51.840	0.000
Palpitation	01	01	96.040	0.000
Headache	04	04	84.640	0.000
Difficulty in speech	23	23	29.160	0.000
Weakness in limbs	44	44	1.440	0.230
Others	40	40	4.000	0.046

In this study Dyslipidemia (62%) is the most common risk factor followed by Smoking (53%). Hypertension (50%) and Diabetes mellitus (41%) are observed. Family h/o CAD (20%) is present and only (14%) patient was alcoholic. Overweight is present among 41% of patients.

Table 3: Comparison of risk factors among patients

Risk factors	Cases	Percentage	Chi-square	p-value
Diabetes mellitus	41	41	3.240	0.072
Hypertension	50	50	0.000	1.000
Smoking	53	53	0.360	0.549
Alcohol	14	14	51.840	0.000
Family h/o CAD	20	20	36.000	0.000
Dyslipidemia	62	62	5.760	0.016

In this study significant number of patients (72%) have hyperhomocysteinemia. 47% of patients are moderate and 23% are intermediate. Only 2 patients have severe hyperhomocysteinemia.

Table 4: Homocysteine levels

Homocysteine	Number of cases	Range (µmol/L)
Moderate	47	15-30
Intermediate	23	30-100
Severe	02	>100
Total	72	

Chi-square-42.250 p value-0.000

In this study mean plasma homocysteine level is 11±3µmol/L and is statistically significant.

Table 5: Mean plasma homocysteine in patients

Risk factor	Mean value
Homocysteine (5-15µmol/L)	11.13±3.09µmol/L
>15µmol/L	32.0±19.5µmol/L

P value-0.000 highly significant

The mean plasma homocysteine (30.9 ± 22.3µmol/L) was high among smokers when compared to non-smokers (20.8 ± 12.9µmol/L) difference was highly significant. No much

significant difference was noted in mean values of homocysteine among patients with other high risk factors, such as alcohol consumption, diabetic, dyslipidemia, BMI, family history of CAD.

Table 6: Comparison of mean plasma homocysteine among smokers and non-smokers

High risk factors		Plasma homocysteine level	Family h/o CAD
Smoking	Smokers	30.9±22.3µmol/L	0.008
	Non-smokers	20.8±12.9µmol/L	
Alcohol	Non-alcoholic	24.85±17.56µmol/L	0.087
	Alcoholic	34.27±26.12µmol/L	
Diabetes mellitus	Diabetic	23.71±14.58µmol/L	0.286
	Non-diabetic	27.88±21.66µmol/L	
Hypertension	Hypertensive	24.96±14.95µmol/L	0.531
	Non-hypertensive	27.37±22.60µmol/L	
Lipid abnormality	Dyslipidemia	26.88±18.0µmol/L	0.635
	Normal	25.0±20.94µmol/L	
BMI	Normal	25.50±15.78µmol/L	0.679
	Overweight	27.12±23.26µmol/L	
Family h/o CAD	No family history	27.77±20.30µmol/L	0.093
	Family h/o CAD	19.74±11.56µmol/L	

In our study, hyperhomocysteinemia is seen in 38 out of 51 patients with Cerebrovascular Disease, 32 out of 42 patients with Cardiovascular Disease, one of 4 patients with Peripheral arterial Disease and one with Deep vein thrombosis.

Table 7: Percentage of Homocysteine in Acute Vascular Event

Acute vascular event	Cases	Percentages
CAD (MI & US)	42	42
CVD	51	51
PAD	4	4
DVT & PTE	3	3

Chi-square-75.600 p value-0.000

Discussion

Although acute coronary, cerebrovascular, and peripheral vascular events share the same underlying pathologies, risk factors and preventive treatments, they are rarely studied concurrently.

Only about two-thirds of all episodes of symptomatic atherothrombotic vascular disease in developed countries can be attributed to established genetic and environmental vascular risk factors [8]. An additional causal vascular risk factor may be raised plasma levels of homocysteine (hyperhomocysteinaemia). Although 30 years have elapsed since hyperhomocysteinaemia (and homocystinuria) were first associated with an increased risk of atherothrombotic vascular disease [9], it is only recently that sufficient evidence has mounted to suggest that the association is independent and dose-related and it remains to be established whether it is causal and modifiable.

WHO and World Bank data indicate that in India deaths attributed to Coronary and Cerebrovascular disease have increased markedly with the expanding population and will continue to increase [10].

However hyperhomocysteinemia is not considered to be a major risk factor for atherosclerosis by the AHA and NCEP ATP III. This may be due to the low incidence of hyperhomocysteinemia, just 5-7% in the American population [11]. In contrast to the west,

among Indians, the incidence of hyperhomocysteinemia is higher at 52-84%. In view of this increased incidence, it is felt that hyperhomocysteinemia may be an important risk factor for cardiovascular disease and stroke for Indians [6].

The sex distribution in this study is male dominant of 72% when compared to other studies. Hyperhomocysteinemia is common in men compared to female. This can be attributed to the protective effects of oestrogen in premenopausal females. Similar findings were noted by R Abraham *et al*.[12], A Puri *et al*.[13] & Dr. Venkata Madhav *et al*. [14].

In this study dyslipidemia is a common risk factor present in 66% of the patients. In other studies similar findings were noted in Puri *et al*. Smoking (53%) is the second most common risk factor which was comparable with other studies. Other risk factors like hypertension, Diabetes mellitus and family history of CAD were present in a few patients.

Study done by Boushey *et al*. [15] based on meta-analysis of 27 studies indicated that an elevation in homocysteine levels >15µmol/L was associated with an increased risk of CHD, peripheral arterial disease, stroke and venous thromboembolism

Mean plasma homocysteine is high among smokers (30.92±22.33µmol/L) when compared to the non-smokers (20.81± 12.90µmol/L). Statistically the difference is highly significant. Study by Puri *et al*., [13] noted high homocysteine levels among non-smokers (30.24±14.16µmol/L) compared to smokers (25.41±11.88µmol/L). Study by Rajashekar Reddy [16] also shows high mean plasma homocysteine in smokers (24.11±5.6µmol/L) when compared to non-smokers (18.79±7.7µmol/L).

Mean plasma homocysteine is high among alcoholics (34.27±26.12µmol/L) when compared to the non-alcoholics (24.85±17.56µmol/L), but is statistically not significant. Study by K. Rajashekar Reddy *et al*. [16] was noted high mean plasma homocysteine among non-alcoholics (26.13± 7.54µmol/L) compared to alcoholics (19.11± 6.65µmol/L) and was statistically significant. Craro ML *et al*. [17], mean homocysteine was twice as high as in chronic alcoholic, than in non-alcoholic.

Patients with dyslipidemia has higher mean plasma homocysteine (26.88±18.03µmol/L) compared to patients with normal lipid levels (25.0±20.94µmol/L) but statistically not significant. K Rajashekar Reddy [16] noted high mean homocysteine level among patients with dyslipidemia (23.34 ± 8.02µmol/L) when compared to a patients with normal lipids (17.81 ± 5.5µmol/L). Other studies like Puri *et al*. [13] and Dr. Venkata Madhav M *et al*. [14] also had high homocysteine level among patients with dyslipidemia than in normal lipid levels.

Mean plasma homocysteine level is high among patients with BMI >25 (27.12±23.26µmol/L) when compared to patients with normal BMI (25.50±15.78µmol/L) but statistically not significant. K Rajashekar Reddy [16] noted high homocysteine level among patients with BMI>30 (19.69 ± 6.94µmol/L) when compared to patients with normal BMI (18.54 ± 6.5µmol/L).

High level of homocysteine is noted among patients with non-hypertension, non-diabetic and no family history of CAD but is not statistically significant. In our study homocysteine levels are high in vegetarians when compared to mixed (veg & non-veg). Yajnik CS *et al*. [18] noted that Vegetarians had 4.4 times higher risk of low vitamin B12 concentrations and 3.0 times higher risk of hyperhomocysteinemia compared to those who ate non-vegetarian foods frequently.

Novel risk factor like homocysteine is elevated among the patients with acute vascular disease when compared to normal levels. In the present study higher level of homocysteine is found in smokers, which is highly significant. However, there is no significant association between hyperhomocysteinemia and other conventional risk factors like alcohol, dyslipidemia, Diabetes mellitus, Hypertension and family history of CAD.

Further large scale randomized multicentered studies are yet to be done to understand the proper association between homocysteine and conventional risk factors in an individual with acute vascular event.

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Conclusion

Plasma homocysteine should be evaluated in all patients of vascular disease especially in the absence of traditional risk factors and it should be considered as an independent risk factor for the development of future acute vascular event.

Conflict of interest: None to declare.

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