HYPERHOMOCYSTEINEMIA AS A CARDIOVASCULAR RISK FACTOR IN YOUNG SOUTH INDIAN POPULATION

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CERTIFICATE

This is to certify that the dissertation entitled **"HYPERHOMOCYSTEINEMIA AS A CARDIOVASCULAR RISK FACTOR IN YOUNG SOUTH INDIAN POPULATION"** submitted by **Dr.P.ABEESH** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of Doctor of Medicine, is a bonafide work carried out by him under my guidance and supervision during the academic year 2006-2007. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

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DECLARATION

I**, Dr.P.ABEESH, solemnly** declare that the dissertation titled "**HYPERHOMOCYSTEINEMIA AS A CARDIOVASCULAR RISK FACTOR IN YOUNG SOUTH INDIAN POPULATION**" has been prepared by me.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch I (General Medicine)

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

Place: Madurai
Date:

Dr.P.ABEESH

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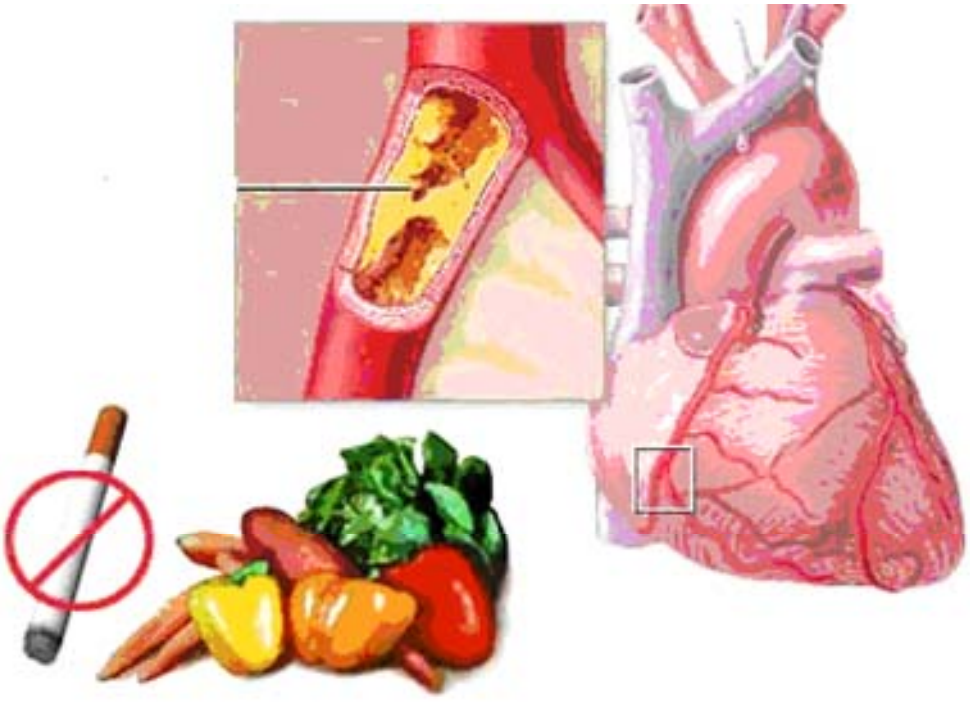
CONTENTS

ABBREVIATIONS

CAD	**-**	**Coronary Artery Disease**
DM	**-**	**Diabetes Mellitus**
Hcy	**-**	**Homocysteine**
tHcy	**-**	**Total homocysteine**
h/o	**-**	**History of**
MI	**-**	**Myocardial Infarction**



INTRODUCTION

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The second half of the 20th century has witnessed a global spread of Coronary Artery Disease (CAD) especially in developing countries, including India. Major risk factors are sedentary life style, cigarette smoking, hypertension, high LDL cholesterol and diabetes mellitus.

However, there are a substantial number of cases who do not have these traits and habits and yet they suffer at a young age and have very advanced coronary atherosclerosis. To explain this enigma, numerous newer coronary risk factors like hyperhomocysteinaemia, heredofamilial factors, socioeconomic factors and psychosocial stress have been implicated in the pathogenesis of coronary artery disease.

Hyperhomocysteinemia has received increasing attention during the past decade and has joined smoking, dyslipidemia, hypertension and obesity as an independent risk factor for cardiovascular disease. In addition, elevated Homocysteine levels have been implicated in a number of other clinical conditions including renal failure, rheumatoid arthritis, alcoholism, osteoporosis, neuropsychiatric disorders, diabetes mellitus and complications of diabetes.

Observations in patients with homocysteinemia led to the idea that tHcy may be involved in the pathogenesis of atherosclerosis. This concept prompted a large number of epidemiological studies that assessed the relation between moderately elevated tHcy levels and coronary artery disease.

Observations in approximately 80 clinical and epidemiological studies suggested that elevated tHcy is a risk factor for atherosclerotic vascular disease and for arterial and venous thromboembolism.

The aim of the present study is to evaluate the role of Homocysteine as a predictor of MI in young South Indian patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Ischaemia refers to lack of oxygen due to inadequate perfusion of the myocardium, which causes an imbalance between oxygen supply and demand. The most common cause of myocardial ischaemia is obstructive atherosclerotic disease of the epicardial coronary arteries.

EPIDEMIOLOGY OF CORONARY ARTERY DISEASE

Incidence in Developed Countries

Coronary artery disease causes more deaths and disability and incurs greater economic costs than any other illness in the developed countries. A high fat and energy rich diet, smoking and a sedentary lifestyle are associated with emergence of coronary artery disease. In the Western World it is growing amongst the poor rather than the rich (who are adopting more healthful lifestyles) while primary prevention has delayed the disease to later life in all economic groups. Obesity, insulin resistance and type II Diabetes are increasing and are powerful risk factors for CAD.

CAD in South Asians

While death rates of CAD have been declining over past three decades for the population as a whole, a disturbing trend has been noted among the persons of the South Asian origin. With urbanization in developing countries the prevalence of risk factors for CAD is increasing rapidly in these regions.

(a) Prevalence among immigrant South Asians[2]

The term 'South Asians' includes persons who originated from nations of the Indian subcontinent – India, Pakistan, Bangladesh, Nepal, Bhutan and Srilanka.

For the approximately 16 million Asian Indians living outside India, prevalence of risk factors including hypertension, dyslipidemia, central obesity and diabetes, is not only higher in this population, but is also rapidly increasing.

(b) Prevalence among immigrant Indians[3]

The prevalence of CAD among immigrant Indians is about three-fold higher than in comparable indigenous population. On an average, a three-fold-higher prevalence of CAD has been noted among Indians when compared to the respective native inhabitants. CAD tends to occur earlier in life among people of Indian descent. Mortality attributable to CAD is substantially higher among Indian immigrants across all age groups and is remarkably pronounced in the young.

(c) Prevalence of CAD in native Indians[2]

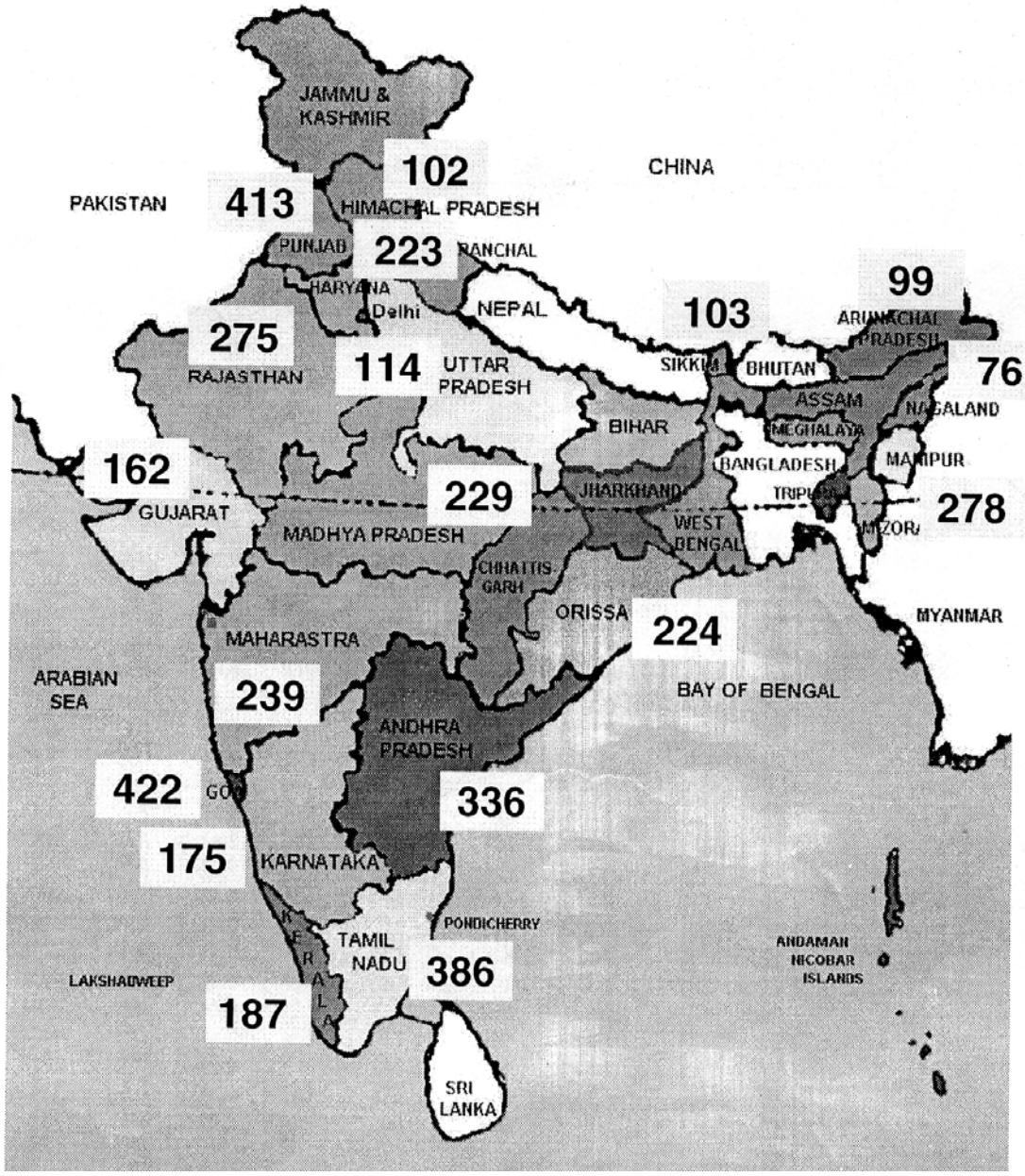
Prevalence of CAD among Indians living in India has also been shown to be high in multiple cross-sectional studies. Of the 2.78 million deaths caused by cardiovascular diseases, ischaemic heart disease caused 1.51 million deaths. Assessment of disease burden using the disability adjusted life years (DALYs) methodology revealed that cardiovascular diseases contributed to 30.5 million DALYs of which the major share was ischaemic heart disease (15.1).

It is apparent that cardiovascular diseases especially coronary heart disease are major cause of death in India and absolute mortality due to coronary heart disease shall increase from 1.59

million/year in the year 2000 to 2.03 million in 2010 and 2.58 million by the year 2020[2].

However, the prevalence of CAD among native Indians is less than among immigrant Indians and there's a definite urban-rural gradient in disease prevalence. Overall, the prevalence estimates obtained from the studies performed in the last decade range between 7.6% and 12% for urban population and 3.1 to 7.4 for rural population[3]. The rates appear to be higher in South India with highest in Kerala[12].

Cardivascular disease mortality in different Indian states (rates/100,000)[40]



Although the large epicardial coronary arteries are capable of constriction and relaxation in healthy persons, they serve as conduits and are referred to as **conductance vessels**, while the intramyocardial arterioles normally exhibit changes in

and are therefore referred as **resistance vessels**. Abnormal constriction (Prinzmetal angina) or failure of normal dilation of the coronary resistance vessels can cause ischaemia.

The normal coronary circulation is dominated and controlled by the heart's requirement of oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Intramyocardial resistance vessels demonstrate an immense capacity for dilatation. For example, the changing oxygen need for the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium. The coronary resistance vessels also adapt to physiological alteration in blood pressure in order to maintain coronary blood flow at levels appropriate to myocardial needs (auto-regulation)

By reducing the lumen of coronary arteries atherosclerosis limits its appropriate increase in perfusion when the demand for flow is augmented, as occurs during exercise or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Epicardial coronary arteries are the major sites of atherosclerotic disease.

MAJOR RISK FACTORS FOR ATHEROSCLEROSIS:

- Cigarette smoking
- Hypertension (BP≥140/90)
- Low HDL cholesterol
- Diabetes mellitus
- Family history of premature CAD
    - CAD in male first degree relatives <55yrs
    - CAD in female first degree relative <65yrs
- Age (men≥45yrs, women≥55yrs)
- Life style risk factors
    - Obesity (BMI≥30kg/m^2)
    - Physical inactivity
    - Atherogenic diet
- Emerging risk factors
    - Lipoprotein(a)
    - Homocysteine
    - Prothrombotic factors
    - Proinflammatory factors
    - Impaired fasting glucose
    - Subclinical atherogenesis

These risk factors for atherosclerosis disturb the normal functions of vascular endothelium. These functions include local control of vascular tone, maintenance of anti-coagulant surface and defense against inflammatory cells.

The loss of these defences leads to inappropriate constriction, luminal clot formation and abnormal interaction with blood monocytes and platelets. The latter results in the subintimal collections of fat, smooth muscle cells, fibroblasts and intercellular matrix(atherosclerotic plaques) which develops at irregular rates in different segments of the epicardial coronary tree and lead eventually to segmental reduction in cross sectional area. When a stenosis reduces the cross sectional area by 75% full range of increase in flow to meet increased myocardial demand is not possible. When the luminal area is reduced ≥80%, blood flow at rest may be reduced and further minor decreases in the stenotic orifice can reduce coronary flow dramatically and cause myocardial ischaemia.

Segmental atherosclerotic narrowing of epicardial coronary arteries is most commonly by the formation of a plaque, which is subject to fissuring, erosion, haemorrhage and thrombosis. Any of these events can temporarily worsen the obstruction, reduce coronary blood flow and cause clinical manifestations of myocardial ischaemia. The location of the obstruction influences the quantity of myocardium rendered ischaemic and determines the severity of clinical manifestations.

HOMOCYSTEINE[14]

Homocysteine is an aminoacid produced in the human body by the chemical conversion of methionine, a compound regularly consumed within the diet. When methionine-rich foods such as fish are eaten, the methionine is taken into the blood stream and into cells where a methyl group (one carbon and three hydrogen atoms) is removed to produce Homocysteine.

Homocysteine sits at the juncture of two critical metabolic pathways: the remethylation/transmethylation and trans-sulphuration pathways. Remethylation converts Homocysteine to methionine and requires folate and cobolamin (vitamin B_{12}). The trans-sulphuration pathway requires pyridoxine (vitamin B_6) as a cofactor and condenses Homocysteine with serine to form glutathione and finally cysteine.

Hence, Homocysteine perform a necessary function in the body by converting itself to glutathione - the body's best anti-ageing agent (and also works as detoxifier) and other beneficial compounds such as ATP, S-adenosyl methionine, creatinine, choline part of RNA & DNA messengers and epinephrine.

The main sites of metabolism are in the kidney and the liver and optimal levels of folic acid are needed to keep Homocysteine low.

EPIDEMIOLOGY OF HOMOCYSTEINEMIA[14]

1. Genetic defects

Many enzymes or catalysts are involved in the complete metabolism of Homocysteine. If any of these enzymes is defective or functions inefficiently due to a mutated or defective gene, the body is less able to successively process Homocysteine.

2. Age

Children before puberty have low levels (about 6 μmol/lit). During puberty, levels increase to a greater extent in boys than in girls.

By age 40-42, the average concentration of Homocysteine is about 11 and 9 μmol/L in men and women respectively.

In the elderly, higher Homocysteine levels may be caused by many factors including physiological age-related changes. Reduced appetite may lead to inadequate consumption of vitamins and when combined with slower metabolism, this could lead to elevated Homocysteine levels.

3. Pregnancy

During pregnancy, Homocysteine concentrations are reduced by up to 50% possibly due to increased metabolism and also higher plasma volume.

4. Life style factor which increase Homocysteine levels include

a. Diet – A low diet with deficiency of nutrients particularly B-6, B-12, and folic acid.

b. Smoking

c. Alcohol – high alcohol intake reduce the absorption of vitamins.

d. Lack of physical exercise and excessive stress.

e. Obesity.

f. Drugs such as Oral contraceptive pills, L-Dopa, Methotrexate, Nicotinic acid, Theophylline, etc.

g. Renal failure, hypothyroidism, psoriasis and malignancies.

THE EFFECT OF HYPERHOMOCYSTEINEMIA

High levels of Homocysteine have been linked to the development of a number of common conditions. Homocysteine has also been shown to play a crucial role as a key marker for disease development determining longevity and health throughout a person's life.

1. Pregnancy and new borns[16, 18]

Women with high Homocysteine levels find it harder to conceive, are at risk from repeated early miscarriages and are over twice as likely to experience pregnancy complications.

2. The middle years

a. Coronary Heart Disease[17, 18, 19]

Homocysteine is believed to be a causal influence on the development of cardiovascular disease and the subsequent likelihood of myocardial infarction. Homocysteine has the ability to change cholesterol into a far more sinister version which attacks arterial walls. Homocysteine also results in increased coagulability of blood leading to coronary artery occlusion.

b. Stroke[18]

Like CAD, strokes are also greatly influenced by high Homocysteine levels.

c. Diabetes[18]

People with diabetes are at risk of having high Homocysteine levels.

d. Osteoporosis[18]

Osteoporosis, a condition where the density of bone-mass decreases leading to fragile, weakened bones, has been strongly linked to homocysteinuria and associated with high Homocysteine levels.

e. Alzheimer's Dementia[20]

After 80 years of age, 20% of people develop dementia, the most common form being Alzheimer's disease. As Homocysteine levels increase, brain undergoes oxidative stress and lessens the chance of repairing damaged DNA. Over time, memory loss increases as more and more cells die.

MEASUREMENT OF HOMOCYSTEINE – THE SCALE OF HEALTH[21]

Homocysteine is measured in micromole per litre of blood (μmol/L).

There is really no healthy level for Homocysteine but generally the lower, the better. A 'safe zone' is normally considered to be below 10 μmol/L.

Normal range: 5 – 15 μmol/L.

Hyperhomocysteinemia:

Mild : 15 – 20 μmol/L

Intermediate : 25 – 50 μmol/L

Severe : Above 50 μmol/L

REDUCING THE RISK[14]

a. A 3 μmol/L drop in Homocysteine lessens the likelihood of MI by 16%, strokes by 24% and deep vein thrombosis by 25%.
b. A 5 μmol/L decrease in Homocysteine reduces the risk of death from all causes by 49%, death from cardiovascular disease by 50% and death from cancer by 26%.

MANAGEMENT OF HYPERHOMOCYSTEINEMIA

Once elevated Homocysteine has been diagnosed, the next step is a simple examination of diet. A healthy balanced diet containing at least five servings of fruits and vegetables a day will help to lower the Homocysteine level and keep within the ideal range.

Folic acid and vitamins B-6 and B-12 have been shown to have the greatest effect at breaking down harmful Homocysteine from within the body[14].

Foods rich in folic acid include:

a. Green leafy vegetables such as spinach, cabbage, etc.
b. Citrus fruits particularly orange and grape fruits.
c. Pulses such as black-eyed beans and chick peas.
d. Whole grain cereals.

Maintaining low plasma Homocysteine is also easily achieved through vitamin supplementation. Patients with elevated Homocysteine (> 14 μmol/L with no other risk factors, or > 11 μmol/L for patients with more than 2 risk factors) can be treated effectively with multivitamins containing 400 μg of folic acid supplemented with an additional 400 to 1000 μg of folic acid. After 6 to 8 weeks of vitamin supplementation, Homocysteine should be repeated. Continued elevated Homocysteine should be treated with increased doses of supplemental folic acid up to 5mg/d.[15]

For many people, the daily intake of 500 μg TMG (Trimethyl glycine), 800 μg of folic acid, 1000 μg of vitamin B_{12} and 250 mg of choline, 250 mg of inositol, 30mg of zinc and 100mg of vitamin B_6 will keep Homocysteine levels in the normal range.

HOMOCYSTEINE AND CORONARY ARTERY DISEASE:

Homocysteine is a thiol containing amino acid derived from the metabolism of methionine that circulates in plasma in 3 forms : as a single free amino acid (1%), as Homocysteine or cysteine-Homocysteine disulfides (20% to 30%) or bound to plasma proteins (70% to 80%). Together, these account for the total plasma Homocysteine (tHcy). Inborn errors of metabolism arising from a deficiency of Hcy-metabolizing enzymes result in extremely high tHcy concentrations and are associated with atherosclerosis and premature thrombosis.

Case-control studies have reported stronger associations than prospective studies in which some but not others claim that Hyperhomocysteinemia is a risk factor for future stroke development.

A prospective, cohort, 10-year follow-up study on plasma Homocysteine levels and prognosis in patients with previous premature myocardial infarction was done in Akershus University Hospital. A total of 247 patients (193 men and 54 women) in stable clinical phase after premature MI were included as subjects. The primary end point measured was total mortality and the secondary end-point was cardiac death. The third end-point was major cardiac events: a combination of cardiac death, MI and cardiac arrest. A long-term increase in risk of death was observed with increasing tHcy, suggesting that tHcy is a predictor of cardiac death in relatively young stable CHD patients.[21]

An epidemiological study on plasma Homocysteine levels and atherosclerosis was done in Japan by use of carotid ultrasonography.

In 1111 cases (452 men and 659 women) aged 63 $\pm$ 10 years old, recruited from a population-based survey, fasting plasma total Homocysteine levels were measured and bilateral carotid B-mode ultrasound was performed. It was found that for the total population, the mean Homocysteine level was 10.9 μmol/L. Total Homocysteine levels were higher in men than in women and increased with ageing. It was concluded that plasma total Homocysteine levels in Japan are similar to those reported in western countries. Mild Hyperhomocysteinemia is an independent factor for increased carotid artery wall thickness in Japan as well.[22]

A case-control study of plasma Homocysteine levels in South Indians with and without coronary artery disease was done in Hyderabad. In the study, plasma Homocysteine levels were estimated in 565 subjects of whom 221 were cases and 344 were controls. Of the 221 clinically defined cases, 112 underwent coronary angiography while 107 of the 344 controls had angiographically proven normal coronary arteries. Fluorescent polarization immunosorbent assay was used to measure plasma Homocysteine levels. It was found that the mean plasma Homocysteine level was 18.30 $\pm$ 10.08 μmol/L in clinically defined cases and 18.04 $\pm$ 10.69 μmol/L in controls. Similarly, in angiographically proven coronary artery disease patients, the mean plasma Homocysteine level was 18.49 $\pm$ 10.04 μmol/L and in individuals with angiographically normal coronary arteries, it was 19.16 $\pm$ 11.38 μmol/L. It was concluded that there is no statistically significant difference in plasma Homocysteine levels between controls and cases with coronary artery disease.[23]

A cohort follow-up study on plasma Homocysteine levels and mortality in patients with coronary artery disease was done in Norway. 587 patients with angiographically documented coronary disease were studied between February 1991 and June 1992. Angiogram was interpreted and stenoses of at least 50% were considered significant. After median follow-up of 4.6 years, overall mortality was 11.1% among men and 10.1% among women with a strong, graded dose-response relationship to Homocysteine levels. It was found that patients with higher plasma Homocysteine levels at baseline had a higher mortality. However, Homocysteine did not correlate with the degree of coronary disease. Furthermore, serum lipids, which correlate with the extent of coronary disease, did not correlate well with mortality. Thus it was concluded that Homocysteine has a role in the development of thrombotic events, where as the role of lipids is more in the development of atherosclerosis.[24]

A case-control study on the role of Homocysteine and lipoprotein (a) in coronary artery disease was done to look at the possible role of some nontraditional risk factors for premature coronary artery disease and assess the presence of the relationship between these factors and the traditional cardiovascular risk factors. The study subjects (n=45) were divided into three groups comprising 15 premature CAD patients without traditional cardiovascular risk factors, 15 premature CAD patients with one or more traditional cardiovascular risk factors and 15 healthy normal control subjects, matched for age and sex. Estimation of plasma Homocysteine was performed by enzyme-linked immunosorbent assay.

Results showed a significant association between elevated Hcy and low folate levels and premature CAD in both patient groups.

It was concluded that Hcy and folic acid might serve as independent risk factors for premature CAD in patients, both with and without traditional risk factors. However, Lp (a) might confer an additional coronary risk factor only in presence of traditional risk factors.[25]

A prospective, case-control study was conducted to assess the risk of incident ischemic stroke conferred by serum total Homocysteine among patients with pre-existing stable coronary artery disease. With a nested case-control design, the baseline total Homocysteine concentration was measured in sera of matched case-control pairs: patients who developed ischemic stroke during a mean follow-up of 8.2 years (cases) and age and sex-matched controls without subsequent cardiovascular events. It was found that an increase of 1 natural log unit in Homocysteine concentration was associated with a > 3-fold increase in relative odds of incident ischemic stroke. It was concluded that serum total Homocysteine concentration is a strong predictor of incident ischemic stroke among patients at increased risk because of chronic CHD.[26]

A prospective, multicenter study was conducted to examine changes in Homocysteine in the acute phase after an incident stroke. Blood samples were collected at days 1, 3 5, 7 and between 10 and 14 days after the stroke. Seventy six participants (51 men) were enrolled. Mean age was 65.6 years, and subjects had at least two Homocysteine measurements.

The estimated mean Homocysteine level at baseline was 11.3 ± 0.5 μmol/L which increased consistently to a mean of 12.0 ± 0.05, 12.4 ± 0.5, 13.3 ± 0.5 and 13.7 ± 0.7 μmol/L at days 3, 5, 7 and 10 to 14 respectively. The magnitude of the change in Homocysteine was not affected by age, sex, smoking status, and alcohol use, history of hypertension or diabetes or Rankin Scale Score. Thus these data suggest that clinical interpretation of Homocysteine after stroke and the eligibility for clinical trials assessing treatment for elevated Homocysteine levels require an adjustment in time since stroke to properly interpret the observed Homocysteine levels.[27]

The **Zutphen Elderly study** was a longitudinal population-based cohort, 10-year follow-up study that investigated the association of serum Homocysteine and risk of coronary artery disease and cerebrovascular disease in Elderly men. Serum Homocysteine levels in 878 elderly men were investigated (mean age at baseline, 71.5 years; range, 64 to 84 years). After adjustment for other major risk factors, high Homocysteine levels at baseline were associated with an increased baseline prevalence of myocardial infarction and with a marginally significant increase in the risk of coronary artery disease but not with an increased risk of first-ever myocardial infarction. Thus it was concluded that in a general population of elderly men, a high Homocysteine level is common and is strongly associated with the prevalence of coronary artery disease and cerebrovascular disease.[28]

The **Northern Manhattan study** is a population-based cohort study that investigated the association between Homocysteine and the risk of ischemic stroke, myocardial infarction and vascular death in a Triethnic cohort.

Baseline values of tHcy and methylmalonic acid were measured among 2939 subjects (mean age, 69 ± 10; 61% women, 53% Hispanics, 24% blacks and 20% whites). Cox proportional models were used to calculate hazard ratios (HRs) and 95% CIs in tHcy categories after adjusting for age, race, education, renal insufficiency, B_{12} deficiency, and other risk factors. The adjusted HR for a tHcy level of15 μmol/L was compared with < 10 μmol/L and was greatest for vascular death followed by combined. Vascular events (HR = 2.27; to Ischemic stroke (HR = 2.01; and nonvascular death (HR = 2.02; 95%). The effect of tHcy was stronger among whites and Hispanics, but not a significant risk factor for blacks. Thus it was concluded total Hcy elevations above 15 μmol/L are an independent risk factor for ischemic stroke, where as mild elevations of tHcy of 10 to 15 μmol/L are less predictive. The vascular effects of tHcy are greatest among whites and Hispanics and less among blacks.[29]

A case-control study was done in the United Kingdom on the plasma Homocysteine concentration in the acute and convalescent periods of Atherothrombotic stroke. The fasting plasma Homocysteine concentrations of one hundred six patients (59 men and 47 women, mean age 57.2 (25 to 70) and 56.5 (26 to 69 years, respectively) were measured immediately after atherothrombotic stroke and in the convalescent period. It was found that the Median tHcy in the acute phase of stroke was not significantly higher than in matched control subjects. Median plasma concentrations increased significantly in the convalescent period and were then significantly higher than in control subjects in both men and women, (P = 0.03 and 0.05 respectively, Mann-Whitney U test).

Thus the data did not support the hypothesis that raised plasma Homocysteine concentrations predate atherothrombic stroke.[30]

A longitudinal, prospective study on Homocysteine and risk of recurrent stroke was done in Denmark to investigate whether elevated total Homocysteine (tHcy) measured within 24 hours of acute stroke was an independent risk factor for recurrent stroke and to compare levels of tHcy in groups of patients with diagnosis of ischemic and hemorrhagic cerebrovascular events. Fasting tHcy was measured in 1039 stroke patients (mean age, 75 years). It was found that serum Homocysteine was significantly higher in the 105 patients who experienced a stroke recurrence during the follow up period than in patients without recurrence. At the index event, serum Homocysteine was significantly higher in 909 patients with ischemic cerebrovascular events than in 30 patients with intracerebral hemorrhage. It was concluded that elevated tHcy is an independent risk factor for recurrent stroke.[31]

A cross-sectional population based study was done in Northern Greece to examine the association between plasma Homocysteine levels and coronary artery disease. Plasma fasting tHcy levels were measured in 42 patients with angiographically documented CAD and compared to 42 age-and sex-, BMI-, and smoking habit-matched control subjects. Plasma vitamin B_{12}, folic acid and lipoprotein levels and conventional risk factors for CAD were also estimated. It was found that in univariate analysis, tHcy levels were higher in patients compared to controls. Multivariate analysis of conventional risk factors showed that tHcy levels were not an independent risk factor for CAD.

However, tHcy levels were significantly higher in patients with a previous history of myocardial infarction

compared to patients without such a history and to controls. It was concluded that in Northern Greece, plasma tHcy levels may not be an independent risk factor for angiographically documented CAD patients.[32]

A prospective, population-based study on Hyperhomocysteinemia as a cardiovascular risk factor was done in Mumbai to assess Homocysteine, vitamin B_{12} and folic acid concentration in resident Indian women and to study their correlation with traditional risk factors of coronary artery disease. The study included 137 consecutive women who attended a health care program for women and above 40 years of age. It was found that prevalence of Hyperhomocysteinemia was 24.2%. No correlation was found between plasma Hcy and blood sugars, lipids, age, body mass index and menopausal status. The CAD risk was assessed using Framingham risk score, and this too did not show a correlation with plasma Hcy. Hence, it was concluded that a large number of women from the present study had hyperhomocysteinemia and were deficient in vitamin B_{12}. A significant negative correlation between vitamin B_{12} and plasma Hcy levels was found in these older women. Most Indian studies including the present one do not show a positive correlation between elevated Hcy levels and CAD inspite of a large percentage of persons showing elevated Homocysteine levels.[33]

A prospective study was done in India on raised serum Homocysteine levels in patients of coronary artery disease and the effect of vitamin B12 and folate on its concentration.

This study included 70 cases and 70 controls presenting with acute coronary symptoms.

It was found that mean Homocysteine levels in patients (22.81 ± 13.9) were significantly higher than the controls (7.77 ± 9.3). However no statistically significant correlation could be reduced between Homocysteine vitamin B12 and folate. Cumulative analysis have indicated an increase in Homocysteine levels among patients with CAD with every additional risk factor.[44]

A prospective study on hyperhomocysteinemia and risk of ischemic stroke among young Asian adults was done in Singapore. The study included 109 consecutive young (<50 years) first-ever hospitalized ischemic stroke patients and 88 age/gender-matched hospital-based controls during a period of 18 months. Prevalence of vascular risk factors was assessed; fasting Homocysteine, vitamin B_{12}, and folate were assayed. Stroke mechanisms were sub typed using TOAST study criteria. It was found that mean fasting Homocysteine levels were significantly higher in cases (13.7 μmol/L) than controls (10.8 μmol/L). Mean vitamin B_{12} levels were significantly lower in cases than control. Folate levels were not significantly different. Mean Homocysteine levels were significantly elevated in large-artery strokes, but not other stroke subtypes compared with controls. It was concluded that hyperhomocysteinemia is an independent risk factor for ischemic strokes in young Asian adults.[45]

HOMOCYSTEINE AND OTHER DISEASE

Elevated Homocysteine levels have been implicated in a number of clinical conditions other than cardiovascular diseases such as diabetes mellitus, renal failure, neuropsychiatric disorders, rheumatoid arthritis and osteoporosis.

A cross-sectional study on distribution of serum total Homocysteine and its association with diabetes and cardiovascular risk factors of the insulin resistance syndrome in Mexican American men was done in USA. Analysis were restricted to Mexican American men aged 40-74 years with data on glycated hemoglobin (%), body mass index (BMI), body fat distribution HDL cholesterol, fasting serum insulin, serum TG and fasting serum tHcy concentrations. It was found that log serum tHcy was not associated with prevalence of diagnosed diabetes mellitus or glycated hemoglobin percent or other risk factors other than age. Log serum tHcy concentration showed borderline significant (P = 0.049) positive association with fasting serum insulin concentration independent of age and BMI only in men aged 60-74. Thus it was found that no consistent association of tHcy with diabetes prevalence or variables of the insulin resistance syndrome were found in Mexican American men aged 40-74 years.[34]

A case-control study on plasma Homocysteine levels in obese and non-obese subjects with or without hypertension and its relationship with oxidative stress and copper was done in Turkey.

Non-obese normotensive subjects (n: 25), non-obese hypertensive subjects (n: 25), obese normotensive subjects (n: 35), and obese hypertensive subjects (n: 45) participated in the study. Plasma tHcy were determined by an enzyme immunoassay method. Plasma lipid peroxidation levels were measured by spectrophotometric methods. Plasma levels of copper and insulin were measured by atomic absorption spectrophotometer and electrochemiluminescence method respectively. It was found that plasma tHcy; copper and insulin levels did not differ in non-obese normotensives. Plasma lipid levels were significantly increased in non-obese hypertensives when compared to non-obese normotensives. Plasma tHcy, lipids, copper and fasting insulin levels were significantly higher in obese normotensives and hypertensives than in nonobese normotensives and hypertensives respectively. There was a significant difference in plasma tHcy, lipid peroxide and copper levels between obese subjects with or without hypertension. Thus it was concluded that in the presence of other traditional risk factors, Hcy may have a permissive role in the endothelial damage even within the normal range and this role may be related to free radical generating systems. Therefore, modest elevation of plasma Hcy may causally be involved in the pathogenesis of atherosclerosisticcardiovascular disease.[35]

A prospective study on increasing production of Homocysteine and neopterin and degradation of tryptophan with older age was done in Austria. Serum concentrations of neopterin, Homocysteine, tryptophan (trp) and kynurenine (kyn) and of vitamins folate and B_{12} were measured in 43 healthy individuals (21 females, 22 males) aged 34-93 years. Comparing three age groups of similar size (34-60, 61-71 and 72-93 years), neopterin and Homocysteine concentrations as well as kyn/trp ratio were found to increase with older age.

Folate concentrations were lower in the middle aged group and vitamin B_{12} concentration did not differ between groups. It was concluded that the strong association between Homocysteine and neopterin concentrations and kyn/try implies that immune activation is related to the development of moderate hyperhomocysteinemia in the elderly.[36]

HOMOCYSTEINE AND FOLIC ACID IN VASCULAR DISEASE

Lower Homocysteine levels are associated with lower rates of coronary artery disease and stroke. Folic acid and vitamin B_6 and B_{12} lower Homocysteine levels.

An analytical, case-control study was done in Iran on Homocysteine, Vitamin B_{12} and folate levels in premature coronary artery disease. The aim of the study was to assess folate and vitamin B_{12} deficiency in the development of premature CAD. The study included 294 individuals less than 45 years (225 males and 69 females). It was found that the level of Homocysteine measured in the plasma of the male participants was significantly high. However there was no significant difference in Homocysteine levels of females. Based on the mean plasma level of folic acid it was found that 10.7% of the study group had folate and vitamin B_{12} deficiency. It was concluded that hyperhomocysteinemia is an independent risk factor for CAD in young patients especially in men and Vitamin B12 deficiency is a preventable cause of hyperhomocysteinemia.[37]

A randomized, double-blind, placebo-controlled trial was done on Homocysteine lowering with folic acid and B vitamins in Hamilton to assess whether vitamin supplementation reduced the risk of major cardiovascular events in patients with vascular disease.

5522 patients 55 years of age or older who had vascular disease or diabetes were randomly assigned to daily treatment either with the combination of 2.5 mg of folic acid, 50 mg of vitamin B_6 and 1 mg of vitamin B_{12} or with placebo for an average of five years. The primary outcome was a composite death from cardiovascular equal MI and stroke. It was found that mean plasma Homocysteine levels decreased by 2.4 μmol/L in the active treatment group and increased by 0.8 μmol/L per liter in the placebo group. Primary outcome events occurred in 519 patients assigned to active therapy and 547 assigned to placebo. As compared with placebo, active treatment did not significantly decrease the risk of death from cardiovascular causes and MI. Thus it was concluded that supplements combining folic acid and vitamin B_6 and B_{12} did not reduce the risk of major cardiovascular events in patients with vascular disease.[38]

CORONARY ARTERY DISEASE AND PREVALENCE

Coronary artery disease is the number one killer in developed nations. While death rates of CAD have been declining over past three decades for the population as a whole, a disturbing trend has been noted among the persons of South Asian origin. Asian Indians have considerably higher prevalence of premature coronary artery disease and standardized mortality rates for CAD compared with Europeans.

An epidemiological study involving two residential areas in Chennai in South India was done to assess the prevalence and risk factors for CAD in native urban South Indian population. Of the total of 1399 eligible subjects (age 20 years), 1,262 (90.2%) participated in the study.

The study subjects underwent a glucose tolerance test and were categorized as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or diabetes. ECG was performed. CAD was diagnosed based on previous medical history. It was found that the overall prevalence rate of CAD is 11.0% (age standardized, 9.0%). The prevalence rates of CAD were 9.1%, 14.9% and 17% in those with NGT, IGT and diabetes respectively. Prevalence increased with an increase in total cholesterol. It was concluded in the study that the prevalence of CAD is rising rapidly in urban India. Lifestyle changes and aggressive control of risk factors are urgently needed to reverse this trend.[39]

An epidemiological study on correlation of regional cardiovascular disease mortality in India with lifestyle and nutritional factors were done from the mortality data obtained from the Registrar General of India and life style data from national surveys. The main aim was to determine the significance of various nutritional factors and other lifestyle variables in explaining the difference in cardiovascular disease mortality in different Indian states. Major differences in cardiovascular disease mortality rates in different Indian states were reported varying from 75-100 in Nagaland, Meghalaya, Himachal Pradesh and Sikkim to a high of 360-340 in Andhra Pradesh, Tamil Nadu, Punjab and Goa. There was a significant positive correlation of cardiovascular disease mortality with prevalence of obesity and dietary consumption of fats, milk and its products and sugars and negative correlation with green leafy vegetable intake. It was concluded that there are large disparities in cardiovascular disease mortality in different Indian states. This can be epidemiologically explained by difference in dietary consumption of fats, milk sugar and green-leafy vegetables and prevalence of obesity.[40]

CORONARY ARTERY DISEASE AND RISK FACTORS

The major conventional coronary risk factors are smoking, hypertension, sedentary life style, high LDL cholesterol heredofamilial factors and diabetes mellitus. The newer coronary risk factors are lipoprotein (a), psychosocial stress, etc.

A cohort, prospective study on coronary artery disease in the young; Heredofamilial or faulty life style or both was done in India. The study comprised 70 young (≤ 40 years) CAD patients. There were 56 males and 14 females, mostly belonging to 36-40 age groups. More than half of the patients were from low socioeconomic group. It was found that 61.42% were chronic smokers and all of them were males. 18.8% gave history of CAD in their first degree relatives. Hypertension was detected in 51.42% cases, obesity in 35.71% cases and underweight in 14% subjects. Hypercholesterolemia was observed in 41.66% cases. Low HDL was the next most common dylipidemia. 7.14%cases were diabetic. Most ominous combination was smoking, low socioeconomic status, increased waist-hip ratio (WHR), dyslipidemia and hypertension. The study reported that both heredofamilial as well as faulty life style risk factors contribute to the development of CAD in young people.[41]

A case control study to assess the association of lipoprotein (a) [(Lp (a)] with CAD was conducted in Andhra Pradesh. 151 consecutive patients with clinical and angiographic evidence of CAD and 49 healthy controls were drawn for the study. Triglycerides, VLDL-C, total-cholesterol/high density cholesterol (HDL-C) ratio, low density cholesterol (LDL-C)/HDL-C ratio, and Lp (a) were found to be higher in patients than controls.

In female sex and in those with family h/o CAD, higher total and LDL cholesterol levels were observed to be associated with higher Lp (a) levels. Significant difference in Lp(a) levels were observed between normal coronaries Vs single and triple vessel disease and also between single vs double and triple vessel disease. The findings suggested that a cut-off level of 25mg/dl for the determination of risk of CAD.[42]

A case-control study to determine the relationship between plasma lipoprotein (a) levels and their phenotypes in a group of South Indian patients with coronary artery disease was done in CMC, Vellore. A total of 104 patients with angiographically proven coronary artery disease were compared with 104 age and sex-matched controls with no risk factors. Lipoprotein (a) levels were measured by ELISA method and its phenotyping was done by SDS agarose gel electrophoresis. Plasma lipoprotein (a) levels were significantly elevated in patients with coronary artery disease as compared to controls Lipoprotein (a) phenotyping showed that low-molecular weight isoforms were found only in 19.2% of the patients with coronary artery disease and their plasma lipoprotein (a) levels were significantly elevated compared to CAD patients with higher molecular weight isoforms. It was concluded that plasma lipoprotein (a) levels are significantly elevated in CAD patients and the commoner phenotype in a south Indian population is the larger apolipoprotein (a) in which the lipoprotein (a) levels are lower.[43]

A case-control study on the comparative account of serum lipids, lipoproteins and Apolipoprotein–B in patients of coronary artery disease was done in Punjab. Serum total lipids (cholesterol and triglycerides), lipoproteins (VLDL, LDL and HDL) and Apolipoprotein-B levels of normal healthy individuals (n=25) and coronary artery disease patients (n=25) were estimated.

The objective of the present study was to ascertain the role of apo-B in causation and inheritance of CAD. It was observed that on an average serum total cholesterol and triglyceride more than 200mg/dl bring the individuals to a risk of CAD irrespective of the age. CAD patients achieved this value at an early age (35-45 years). Similarly VLDL and LDL levels were found to be raised and HDL levels were found to be lower in CAD patients compared to age-matched controls. Serum apo-B levels were significantly raised in CAD patients and patient with positive family history of CAD. A positive coefficient of correlation was between serum apo-B and LDL levels suggesting that more the number of Apo-B particles, more will be the synthesis of atherogenic particles (LDL). The study concluded that elevated apo-B levels turn out to be a genetic factor responsible for causative factor of coronary artery disease.[7]

A prospective, case-cross over study was done in Israel on negative emotions, anger and sudden changes in posture as independent triggers for ischemic stroke. 200 consecutive patients hospitalized with an ischemic stroke or a transient ischemic attack were interviewed one to four days after stroke onset using a validated questionnaire. Reported exposure to potential triggers, such as negative and positive emotions, anger, sudden postural changes in response to a starting event, strenuous physical exertion, heavy eating and sudden temperature changes during a two-hour period prior to stroke onset were compared with the same period during the preceding day and to average exposures in the previous year. Anger and other negative emotions were rated on a seven-point scale and were said to be present if the score was 5 or higher. During 2 hours before stroke 76 patients experienced at least one of the study triggers. Thus the study demonstrated that apart from the conventional risk factors, there are factors that may trigger the premature onset of stroke and this is an important area of potential invention.[8]

AIM OF STUDY

AIM OF STUDY

The aim of the present study is

- **to estimate the plasma Homocysteine levels in young patients presenting with myocardial infarction**

- **to assess the possible role of Homocysteine as non-traditional risk factor in these patients**

- **to study the association of Homocysteine with traditional risk factors.**

STUDY PLAN

STUDY PLA N

The present study was planned to estimate the plasma Homocysteine in young patients presenting with MI, and to associate with Homocysteine with non-traditional risk factor and finally to assess the role of Homocysteine as a new predictor of MI in young patients with signs of myocardial infarction, admitted in the Government Rajaji Hospital, Madurai as outlined below :

- Selection of patients based on inclusion criteria.
- Study of demographic and disease presenting characteristics and correlation with MI.
- Collect patient family history and family medication history and to associate with the diagnosed indications.
- Estimation of Homocysteine levels in MI patients and compare it with healthy subjects.
- To study the association of Homocysteine and disease.
- To explore the possible influence of Homocysteine on traditional risk factors.

MATERIALS AND METHODS

MATERIALS AND METHODS

Setting

Department of Medicine and Department of Cardiology, Government Rajaji Hospital, Madurai.

Study design

This is a cross-sectional, cohort study carried out in young MI patients.

Study protocol

Patients admitted in Intensive Care Unit of Government Rajaji Hospital, Madurai for MI were enrolled in the study. Patients were interviewed and a designed questionnaire was used to collect demographic details, previous history of MI, presenting symptoms, the earlier medication and food supplementation used.

Ethical Committee Approval

The study protocol was duly approved by the Ethics Committee of Government Rajaji Hospital, Madurai.

Collaborating Department

1. Department of Medicine and Department of Cardiology, Government Rajaji Hospital, Madurai.

2. Sai Labs, Madurai.

Study Criteria

Selection of patients:

Inclusion Criteria:

The following categories of patients from cardiology department are included in the study.

- Inpatients admitted for myocardial infarction.
- Patients with age 45 years and below only.

Exclusion criteria:

- Patients with age above 45 years.
- Patients suffering from diseases such as renal failure, hypothyroidism, psoriasis, any malignancies and psychiatric disorders.
- Patients taking drugs such as Methotrexate, oral contraceptive pills, L-dopa, nicotinic acid and Theophylline.
- Patients taking folic acid or any vitamin supplement.

SOURCE OF DATA

Department of Cardiology, Government Rajaji Hospital, Madurai. The data were obtained from

- Patient interview
- Treatment chart
- Prescriptions

METHOD OF COLLECTION OF DATA

This is a cross-sectional, cohort study carried out from June 2006 to Dec 2006, to analyze the Homocysteine levels in young MI patients and its association with other risk factors.

Proforma was prepared as an aid for collecting the demographic data. Model of Proforma is given in Appendix.

ESTIMATION OF HOMOCYSTEINE

Estimation of Homocysteine was performed by automated immuno assay analyzer – IMX ABBOTT System (USA).

DATA ANALYSIS:

Graph-Pad software was used for statistical analysis.

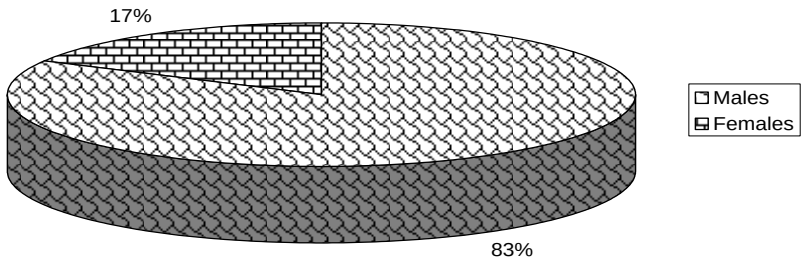
OBSERVATIONS AND RESULTS

OBSERVATION AND RESULTS

The study included 35 cases presenting with MI and 6 healthy subjects as controls.

1. Sex distribution:

Of the 35 patients with MI, 29 (82.85) were males and 6 (17.14) were females.

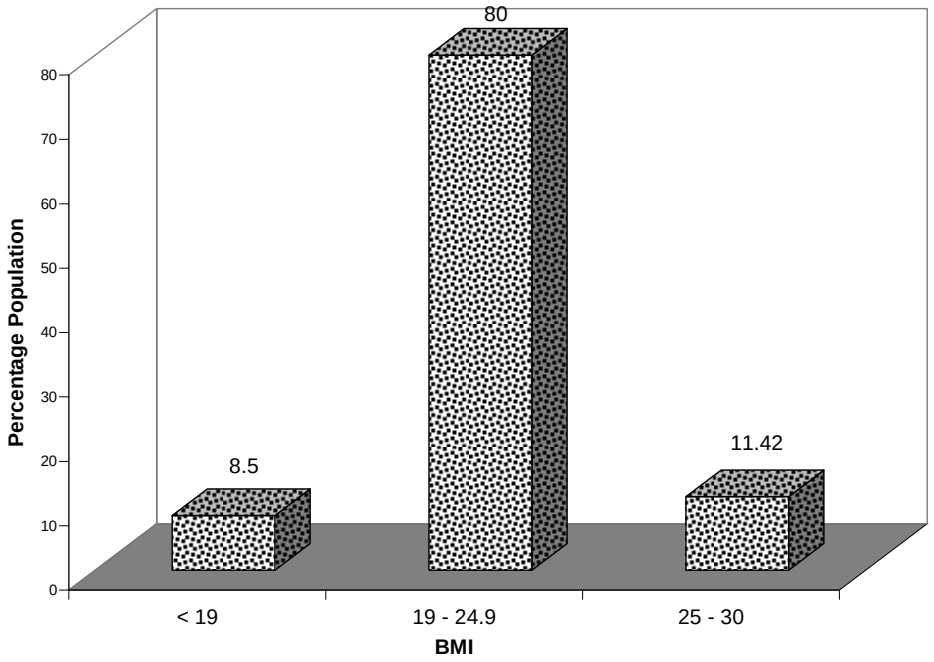


1.1. Comparison of mean sex and Homocysteine:

Sex	Mean ± SEM	SD
Male	15.9517 ± 2.167	11.667
Female	13.866 ± 0.9591	2.347

2. BMI:

Of the total study population with 35 MI patients, 3 (8.5%) were underweight, 28 (80%) were normal and 4 (11.42%) were overweight.

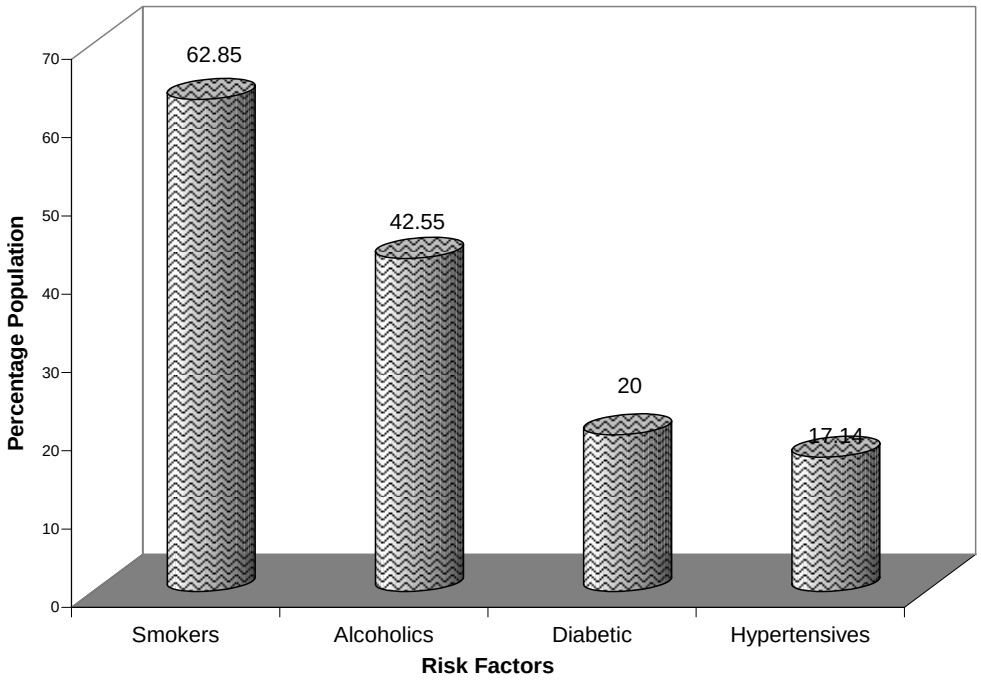


2.**1Comparison of mean BMI**

BMI	Mean ± SEM	S.D
Underweight	**17.166 ± 5.656**	**9.796**
Normal	**15.8928 ± 2.176**	**11.481**
Overweight	**12.325 ± 2.185**	**4.369**

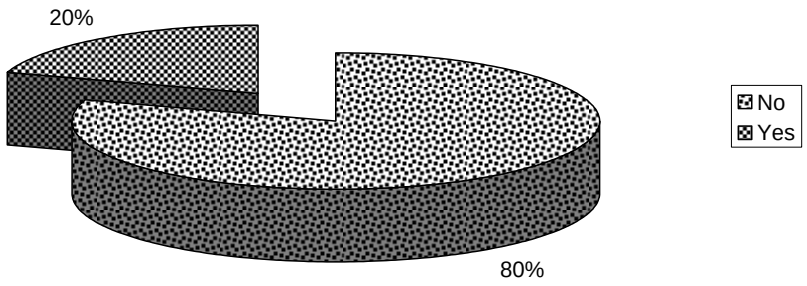
3. **Risk Factors:**

Of the 35 patients with MI, 22 (62.85%) were smokers, 15 (42.85%) were alcoholics, 7 (20%) were Diabetics and 6 (17.14%) were hypertensives.



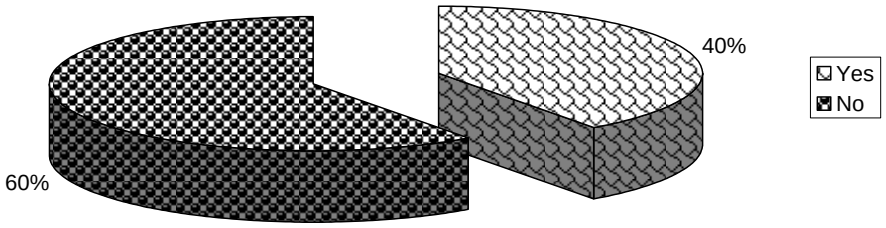
4. **Family history of MI:-**

Of the 35 patients with MI, 7 were having family history of MI and 28 were not having any family history of MI.



5. Previous history of MI:-

Of the total study population of 35 patients with MI, 14 had previous history of MI and 21 did not have.

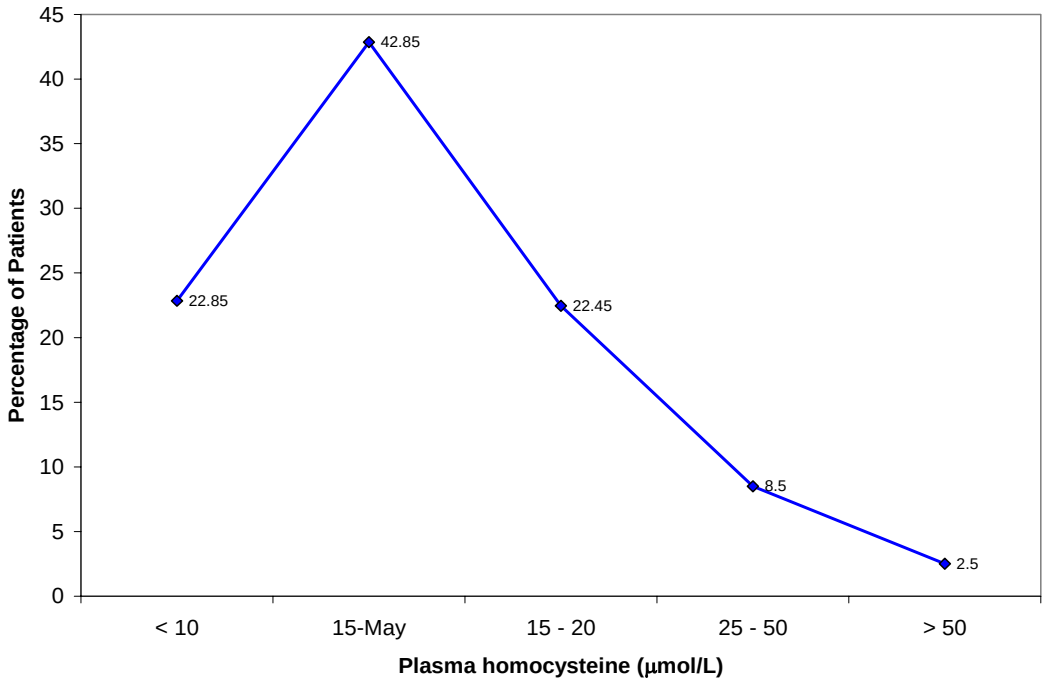


6. Baseline characteristics of study participants

Characteristics	Cases	Control
Men	29 (82.85)	-
Diabetes mellitus	7 (20%)	-
Hypertension	6 (17.1%)	-
Current smoking	22 (62.85%)	-
Alcoholics	15 (42.85%)	-
Previous myocardial infarction	14 (40%)	-
Diastolic blood pressure, mm Hg	81.7142 ± 2.005	78.33 ± 2.108
Systolic blood pressure, mm Hg	120.8571 ± 3.185	122.6 ± 8.803
Total cholesterol mg/dL	166.5428 ± 5.824	111.83 ± 3.330
HDL cholesterol, mg/dL	40.628 ± 0.324	45.66 ± 0.321
LDL cholesterol, mg/dL	81.8571 ± 0.54	93.33 ± 0.431
VLDL cholesterol, mg/dL	42.3485 ± 1.321	26 ± 1.336
Triglycerides, mg/dL	200.685 ± 18.741	124.166 ± 4.729
Serum creatinine	0.9878 ± 0.3364	0.9714 ± 0.321
Blood urea	26.54 ± 1.464	26.48 ± 1.324

7. Plasma Homocysteine:

Of the 35 MI patients, 8 (22.85%) were having desirable plasma Homocysteine levels, 15(42.85%) were having normal but undesirable Homocysteine levels, 8 (22.85%) had mild hyperhomocysteinemia, 3(8.5%) were intermediate and 1(2.5%) had severe hyperhomocysteinemia.



7.1. Comparison of mean Homocysteine between group A (case) and group C (control)

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
A	15.5942 ± 1.801	10.656

Unpaired t-test **P value = 0.0377**

There is a significant difference in Homocysteine levels between case and control suggesting an association between Homocysteine and MI in both groups.

8. Association of plasma Homocysteine and other risk factors of MI:

The major conventional risk factors of MI are smoking, alcoholism, hypercholesterolemia, hypertension and diabetes mellitus. From the study, it is found that of the 35 patients with MI, 22 were smokers, 15 were alcoholics, 7 were diabetics 6 were hypertensives, 7 had family history of MI and 14 had previous history of MI. The new risk factor Homocysteine is associated with the conventional risk factors.

8.1. Comparison of mean homocysteine of smokers (S1) and Patients without smoking (S0) with control group C

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
S1	15.64545 ± 2.189	10.267
S0	11.8384 ± 1.046	3.771

Unpaired t-test

When Homocysteine levels of group S1 was compared with that of group C, the P value was 0.0339 and the result was found to be significant.

Comparison of Homocysteine levels of group S0 with group C was shown to be not significant with P value of 0.0755.

8.2. Comparison of mean Homocysteine of alcoholics (A1) and without alcohols (A0) with group C.

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
A1	17.22166 ± 2.860	11.078
A0	14.37 ± 2.335	10.444

Unpaired t-test

Comparison of Homocysteine levels of group A1 with group C showed a significant result with P value of 0.261

When Homocysteine levels of group A0 were compared with that of group C, P value was 0.0746 and the result was found to be very not significant.

8.3. Comparison of mean Homocysteine levels of patients with diabetes mellitus (D1) and without diabetes mellitus (D0)

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
D1	11.085 ± 3.812	10.086
D0	16.73 ± 2.187	11.572

Unpaired t-test

When Homocysteine levels of patients with group D1 was compared with group C, P value was 0.0042 and the result was found be very significant.

Comparison of mean Homocysteine value of group D0 with group C gave a P value 0.0367 and result was considered to be significant

8.4. Comparison of plasma Homocysteine levels of patients with hypertension (H1) and without hypertension (H0) with controls

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
H1	12.35 ± 1.358	3.327
H0	16.2656 ± 2.143	11.541

Unpaired t-test

Comparison of mean Homocysteine levels of patients with group H1 with group C was considered to be very significant with P value of 0.0012.

Comparison of mean Homocysteine levels of group H0 with group C was considered to be very significant with P value of 0.0445.

8.5. Comparison of mean Homocysteine of patients without family history of MI (FH_0) and with family history MI (FH_1) with group C.

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
FH_O	15.2214 ± 2.067	10.939
FH_1	17.0857 ± 3.812	10.086

Unpaired t-test

When Homocysteine levels of FH_O was compared with group C, the result was found to be not quite significant with P value of 0.0530.

Comparison of Homocysteine levels of FH_1 with group C was found to be significant with P value of 0.0231

8.6. Comparison of mean Homocysteine of patients without previous history of MI (PH_O) and with previous history of MI (PH1) with group C

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
PH_O	15.4333 ± 2.177	9.978
PH_1	11.987 ± 3.209	11.987

Unpaired t-test

When Homocysteine levels of PH_O was compared with group C, the P value was < 0.001 and the result was extremely significant.

When Homocysteine levels of PH_1 were compared with group C, the result was not quite significant with P value of 0.668.

8.7. Comparison of mean Homocysteine of patients with (T1) and without hypercholesterolemia (T0) and group C

Group	Mean Homocysteine ± SEM	S.D
C	6.1333 ± 0.2765	0.6772
T1	14.7217 ± 1.878	9.007
T0	17.466 ± 3.873	13.417

Unpaired t-test

Comparison of Homocysteine levels of group T1 with group C was found to be significant with the P value of 0.0292.

Comparison of Homocysteine levels of group T0 with group C gave P value 0.0621 and was considered to be not quite significant.

9. Effects of risk factors on Homocysteine

Group	Risk factors	Number	Hcy mean ± SEM
A	CAD alone (C_0)	2	15.585 ± 6.355
B.	CAD + any one risk factor (HTN / DM/SMOKING/HYPERCHOLESTEROLAEMIA / ALCOHOLISM) (C_1)	7	15.585 ± 6.355
C.	CAD + any two risk factors (C_2)	89	17.566 ± 4.307
D.	CAD + any three risk factors (C_3)	8	16.3375 ± 3.377
E.	CAD + any four risk factors (C_4)	5	15.44 ± 0.98111
F.	CAD + all five risk factors (C_5)	54	11.3 ± 1.85

9.1. Students - Newmann-Keuls Multiple comparison test:

Comparison	**Mean**	**P value**
C_5 Vs C_2	-6.267	ns p > 0.05
C_5 Vs C_3	-5.030	ns p > 0.05
C_5 Vs C_1	-4.286	ns p > 0.05
C_5 Vs C_4	-4.140	ns p > 0.05
C_5 Vs C_0	-1.450	ns p > 0.05
C_0 Vs C_2	-4.817	ns p > 0.05
C_0 Vs C_3	-3.588	ns p > 0.05
C_0 Vs C_1	-2.836	ns p > 0.05
C_0 Vs C_4	-2.690	ns p > 0.05
C_4 Vs C_2	-2.127	ns p > 0.05
C_4 Vs C_3	-0.8975	ns p > 0.05
C_4 Vs C_1	-0.1457	ns p > 0.05
C_1 Vs C_2	-1.981	ns p > 0.05
C_1 Vs C_3	-0.7518	ns p > 0.05
C_3 Vs C_2	-1.229	ns p > 0.05

10. Comparison of mean BMI of control and patients

Group	Mean BMI ± SEM	S.D
Control BMI	21.90725 ± 0.4430	1.085
Patient BMI	22.14668 ± 0.4832	2.740

Comparison of BMI of case and control was found to be not significant with P value 0.8352.

11. Comparison of total cholesterol and triglycerides of case and control

Group	Mean ± SEM	S.D	P value
1. Total cholesterol Control Case	 157.64 ± 6.753 166.54 ± 5.824	 16.54 34.452	 0.5130
1. Triglycerides Control Case	 134..333 ± 3.490 200.6857 ± 18.741	 8.548 110.87	 0.1551

Unpaired t-test

Comparison of total cholesterol and triglycerides of control and case was not found to be significant.

DISCUSSION

DISCUSSION

Prevalence of risk factors is higher and rapidly raising in Indian population. This predisposition to accelerated atherosclerosis seems to have genetic predisposition but is being enhanced by changing lifestyle, dietary and cultural preferences, and suboptimal application of health care. The activation of "thrifty" gene is associated with the development of obesity and metabolic syndrome. Even though the environmental and behavioral responses to urbanization and westernization appear to be consistent across cultures, the genetically determined metabolic response to these environmental changes and resulting CAD risk profiles may vary in different ethnic groups.[55] Ethnicity is a strong surrogate for gene-environment interactions and it may underlie the tendency to develop obesity and atherosclerosis due to selection of the "thrifty gene", that increases efficiency of fat storage. The extent to which these variations in different ethnic groups are due to genetic or environmental factors remains unclear.[56]

According to the Indian studies, the prevalence rate of CAD was 9.7% in Delhi, 3.5% in Rajasthan and 11% in urban population of South India.[46]

Among all the ethnic groups studied, the standard mortality ratio for men born in the Indian subcontinent and aged between 20 and 69 years was by far the highest.[47]

In the analysis by Balarajan, the excess mortality seen among immigrants from the subcontinent steadily increased with decreasing age. Men in the age group 20-29

and 30-39 years had SMRs of 313 and 210, respectively. The rate of first MI was five times higher among Indian men compared to the Europeans in the study.[48]

Further, the mean age at first MI was about 5 years lower for the Indian men (50.2 v 55.5 years). Indians also suffered larger infarcts as estimated from peak creatine kinase (CK) levels and degree of left ventricular dysfunction. Lowry et al., found a small increase in the atheroma score among South Asian patients when compared to the Europeans in the study. More South Asian patients (38% v. 22%) were found unsuitable for surgery because of extensive disease. CAD tends to occur earlier in life among people of Indian descent.[49]

In addition to the conventional risk factors such as smoking, HT, DM, hypercholesterolemia, obesity and reduced physical activity Hyperhomocysteinemia was found to be independent risk factor of CAD.

Identification of new markers such as homocysteine associated with an increased risk of CAD may provide a better insight into the pathology of coronary atherosclerosis and facilitate the development of preventive and therapeutic measures.

Normal values of plasma total homocysteine are between 5 and 15 μ mol/L. In our study, the mean plasma homocysteine in healthy subjects was 6.133 ± 0.2765 and in CAD patients, the total plasma homocysteine was 15.5942 ± 1.801 ($P = 0.0377$) indicating that homocysteine level is an independent marker of CAD. A two fold increase in likelihood of MI among persons with a total Hcy concentration more than or equal to 15 μ mol/L has been noted in an United States study.[50]

An Indian study which gave a mean value of 22.81 ± 13.9 in cases and 7.77 ± 7.3 in controls showed a significant difference of homocysteine values between the two groups and hence showed increased homocysteine levels among patients with coronary artery disease.[44]

However, another Indian study with a mean homocysteine value of four cases as 18.30 ± 10.08 μ mol/L and control 18.04 ± 10.65 reported a negative association between homocysteine with MI.[23]

Homocysteine and Smoking:

CAD patients who were smokers had a mean Hcy level of 15.65 ± 2.189 as compared to 11.84 ± 1.046 in CAD patients who are non-smokers. This higher level of Hcy may be due to the influence of smoking in homocysteine metabolism. Among secondary causes of hyperhomocysteinemia, smoking plays an important role by interfering with the synthesis of pyridoxal phosphate, which is important for the conversion of homocysteine to cystathione by the enzyme cystathione b synthase.[51]

Homocysteine and alcoholism:

Alcoholic intake increases the absorption of vitamins and interferes with the metabolism of homocysteine, leading to hyperhomocysteinemia. In our study mean Hcy of alcoholics was found to be 17.22 ± 2.86 as compared to 14.37 ± 2.335 in non-alcoholics.

Homocysteine and Hypertension:

A number of studies have shown a correlation between hyperhomocysteinemia and HT.

This was confirmed in our study too, where; mean Hcy value of 16.26 in hypertensives and 12.35 in non hypertensives. However, a contradictory report was obtained from a western study with a mean value of tHcy 10.4 ± 53 in hypertensives.[29]

Homocysteine and Diabetes Mellitus:

Varied results were observed among diabetes as well. **Munshi et al.** demonstrated elevated homocysteine levels in non-insulin dependent diabetes subjects compared to age matched controls[52] and **Hoffman et al,** reported that hyperhomocysteinemia is more common in type 1 diabetic patients with nephropathy.[53] **Deepa et al.** did not reveal any significant increase in homocysteine level in diabetes with CAD.[54] In our study population, there was a small difference in Hcy levels among diabetes and non diabetes patients (17.085 and 16.72).

Homocystiene and hypercholesterolaemia

In the **Hordaland study** in Norway, increasing plasma levels of cholesterol, triglycerides and smoking were associated with increasing levels of homocysteine. In our study, homocysteine levels were actually less (14.721) in CAD patients with hypercholesterolemia when compared to CAD patients (17.45) without this risk factor. Lowered Hcy may be due to change in life style adopted by patients as part of treatment for high cholesterol. In addition majority of our patients were manual workers, not having sedentary life style pattern.

HDL was comparatively less in patients (40.6) as compared to controls (45.66). VLDL was relatively high in patients (42.3) as compared to controls. These results help to confirm the fact that hyperhomocysteinemia along with conventional risk factors give rise to CAD and MI in young individuals. Alarmingly, out of 35 patients studied (65.7%) 23.5 had hypercholesterolemia.

Homocysteine and Stroke:

Hyperhomocysteinemia is an independent risk factor for ischemic strokes in young Asian adults. The relationship between increasing Hcy and stroke is strong and significant. The association with large-artery strokes suggests that hyperhomocysteinemia may increase stroke risk via a proatherogenic effect. The burden of stroke arises largely from the elderly population. However, there remains a small but significant subset of younger patients with ischemic stroke, in whom conventional vascular risk factors play a smaller role.[45]

Homocysteine is believed to cause atherogenesis and thrombogenesis via endothelial damage, vascular smooth muscle proliferation and coagulation abnormalities. High Hcy levels are associated with increased risk of cardiovascular and cerebrovascular diseases.[35] Our study findings are consistent with these reports : CAD patients with stroke showed a very high homocysteine value 53 μ mol/litre compared to other CAD patients without such complications.

Hcy is postulated to cause ischemic stroke via various mechanisms. It may promote atherogenesis by damaging the vascular matrix, increasing oxidative injury to arterial endothelium and enhancing proliferation of vascular smooth muscle. High levels of Hcy have been associated with extra-cranial carotid disease. It may also be

prothrombotic and impair vasomotor regulation Hcy is thus a biologically plausible factor in the pathogenesis of ischemic stroke, in particular large-artery strokes. Total Hcy concentration is a strong predictor for incident ischemic stroke among patients at increased risk because of CAD. The graded association observed is independent of traditional risk factors in inflammatory markers and indicates the importance of homocysteine levels in patients with preexisting vascular diseases.[45] In the present study; we provide evidence consistent with a strong graded association between total homocysteine concentration and incident ischemic stroke in patients with preexisting atherosclerotic vascular disease

Homocysteine and Obesity:

None of the patients in our study were found to be obese, 8.5% were underweight with a Hcy value (17.166), 80% normal body weight with Hcy value (15.8928) and 11.42% over weight patients with 12.325 Hcy. Elevated levels of Hcy in underweight subjects could be due to malnutrition and its impaired effect on Hcy metabolism.

Homocysteine and family history of CAD:

It is also interesting to note that Hcy levels were higher (17.08) in patients with a family history of MI in comparison of patients without such risk factor (Mean Hcy 15.22).

Homocysteine and previous history of CAD:

Many studies have shown that patients with MI had significantly elevated tHcy levels compared to patients without such history as well as to controls.[32, 24]

However, in our study it was found that tHcy of patients with previous history was lower that of patients with previous history of MI (11.987 ± 3.20 Vs 15.43 ± 2.17).

This may be due to the effects of administration of lipid lowering agents following the previous MI events. It has been reported in a study that lower levels of tHcy were observed amongst patients taking lipid-lowering agents.[21]

Homocysteine and gender:

In this study, no significant difference was found in the total homocysteine levels of men (15.95 ± 2.167) and women (13.8 ± 0.9291).

The study matched with an Indian study where large number of women had high total homocysteine and were deficit in vitamin B12.[33]

Hyperhomocysteinemia as a risk factor for MI may have profound public health implications because total homocysteine can be lowered inexpensively and easily by modification of dietary patterns and vitamin supplements. But a Western study had shown that vitamins did not reduce the risk of major cardiovascular events in patients with vascular disease.[38]

The results of ongoing clinical trials to determine the effect of multivitamin therapy on CAD are awaited. If casually related, our findings suggest that young people with high risk of MI may particularly benefit from interventions that lower total homocysteine concentrations.

CONCLUSION

CONCLUSION

At the threshold of this millennium, CAD is looming large as the new epidemic afflicting Indians at a relatively younger age. Of the 35 MI patients, 8(22.85%) were having desirable plasma homocysteine levels (<10µmol/L), 15(42.85%) were having normal but undesirable homocysteine levels (10-15µmol/L), 8(22.85%) had mild hyperhomocysteinemia (15-20µmol/L), 3(8.5%) were intermediate (20-50 µmol/L) and 1 (2.5%) had severe hyperhomocysteinemia (>50%).

In the study, homocysteine was identified as a nontraditional risk factor for MI. Among the study population of MI it was found that 77.14% had higher homocysteine than control. In the study, the mean plasma homocysteine level in healthy subjects was 6.13±0.28µmol/l and in CAD patients the total plasma homocysteine was 15.6±1.8µmol/l(P=0.0377) indicating that homocysteine level is an independent marker of CAD.

It was also found that homocysteine levels were higher in patients who had additional conventional risk factors when compared to patients without such risk factors except hypercholesterolemia.

However, as the study was limited to a small population due to financial constraint, analysis of a larger group would definitely give an insight into the various causative factors leading to hyperhomocysteinemia and its role in CAD amongst the young Indian population.

As such Asian Indians are genetically predisposed to CAD. Hence it is mandatory to determine homocysteine levels in people after thirties so that preventive measures such as vitamin supplementation and life style modifications could be undertaken and thus reduce the incidence and mortality due to CAD..

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APPENDIX

PROFORMA

Name of the patient :

Age : **Sex:**

Marital Status :

Body Weight (in kg) : **Height (in cms.):**

BMI :

Food habits : **Veg:** **Non-veg:**

If non-veg, how frequently?

SYMPTOMS:

- **Giddiness**
- **Palpitation**
- **Chest discomfort**
- **Headache**

Habits : *a. Smoker*

If yes, how long? :

Number of cigarettes/day :

If discontinued, whether after MI:

b. Alcoholic

If yes, how long? :

Frequency (mild/moderate) :

If discontinued, whether after MI:

Concomitant disease:

Kidney failure :

Psoriasis :

Hypothyroidism :

Diabetes Mellitus :

Hypertension :

CAD :

FAMILY HISTORY:

Diabetes mellitus :

CAD :

HYPERTENSION :

CKD :

Drug history

a. Oral contraceptive pills :

b. L-Dopa :

c. Methotrexate :

d. Nicotinic acid :

e. Theophilline :

f. Exposure to nitrous oxide :

Any folic acid / vitamin being taken :

General examination:

Pallor

Jaundice

Pedal edema

External markers of hyperlipidemia

PR:

BP:

Systemic examination:

CVS :

RS :

ABDOMEN:

CNS :

Diagnosis :

Investigation:

Haemoglobin% :

ESR :

Blood sugar :

Serum creatinine :

Serum urea :

Lipid profile :

i. Total Cholesterol :

ii. Triglycerides :

iii. HDL :

iv. VLDL :

v. LDL :

ECG

ECHO :

PLASMA HOMOCYSTEINE :

MASTER CHART

CASES

S.No.	Age	Sex	Smoking	Alcohol	FH	PH	HT	DM	BMI	TC	HDL	LDL	TGL	HOMOC
1	32	M	N	Y	N	N	N	N	23.6	149	40	87	110	12
2	40	M	Y	Y	N	Y	N	N	19.6	181	49	102	151	14.2
3	43	M	N	N	N	N	N	N	22	140	42	75	114	12.8
4	43	F	N	N	N	Y	N	Y	24.1	184	42	105	185	12.7
5	40	F	N	N	Y	N	Y	N	28.1	189	40	111	192	16.2
6	40	M	Y	N	Y	Y	N	N	23.7	226	40	138	238	16
7	44	M	N	N	N	N	N	N	23.5	201	40	125	180	18.2
8	42	M	Y	Y	N	N	Y	N	23.6	180	42	125	130	10
9	35	M	Y	N	N	Y	Y	N	28.1	183	40	130	128	12.4
10	30	M	Y	Y	N	N	N	N	18.3	155	42	72	203	14.2
11	42	M	Y	N	N	Y	N	Y	20.3	184	40	92	278	16.2
12	40	M	Y	N	N	N	N	N	18.1	207	40	151	78	28.4
13	45	F	N	N	N	Y	N	Y	23.4	147	46	74	179	14.5
14	45	F	N	N	N	Y	N	N	20.8	209	38	78	230	09.8
15	45	M	N	N	N	N	N	N	23.8	152	38	90	120	12.7
16	45	F	N	N	N	N	Y	Y	21.4	181	40	103	191	14.2
17	31	M	Y	Y	N	N	N	N	23.4	181	42	104	174	29
18	42	M	N	N	N	Y	N	N	21.5	204	40	110	260	7.8
19	45	M	N	N	N	N	N	Y	21.9	146	44	83	106	5.9
20	39	M	Y	N	Y	N	N	N	17	143	40	68	176	10.4
21	39	M	Y	Y	N	Y	Y	N	23.9	214	42	136	220	6.2
22	28	M	Y	Y	N	N	N	N	19.5	138	42	68	161	16.9
23	42	M	Y	Y	N	N	N	Y	27.6	202	40	130	108	19.2
24	26	F	N	N	N	Y	N	N	24.4	188	38	128	110	15.8
25	45	M	Y	Y	N	Y	Y	Y	22.4	211	40	130	207	7.6
26	44	M	N	N	Y	N	N	N	24.6	217	40	130	239	16.2
27	37	M	Y	Y	N	N	N	N	26.6	132	42	71	97	10.3
28	42	M	Y	N	Y	N	N	N	21.5	252	40	170	199	12.3
29	31	M	Y	N	Y	Y	N	N	24.5	188	40	110	193	16
30	41	M	Y	Y	N	N	N	N	21.6	200	36	130	180	11
31	35	M	Y	Y	N	N	N	N	21	137	42	79	80	38
32	37	M	Y	Y	Y	Y	N	N	23.4	194	42	124	120	52.8
33	36	M	Y	N	N	N	N	N	23	216	40	140	114	6.8
34	42	M	Y	Y	N	Y	N	N	22	134	40	73	105	12.7
35	45	M	Y	Y	N	N	N	N	23.4	124	40	64	133	6.8

CONTROLS

S.No.	Age	Sex	Smoking	Alcohol	FH	PH	HT	DM	BMI	TC	HDL	LDL	TG	HOMOC
1	32	M	Y	N	N	N	N	N	21	126	42	65	126	6.8
2	30	F	N	N	N	N	N	N	20	130	38	70	150	5.6
3	40	F	N	N	N	N	N	N	19	154	40	90	119	6.7
4	35	M	N	Y	N	N	N	N	22	132	44	70	105	5.8
5	38	F	N	N	N	N	N	N	23	149	40	75	128	9
6	35	F	N	N	N	N	N	N	23	130	38	75	118	6

HT – HYPERTENSION
DM- DIABETES MELLITUS
BMI- BODY MASS INDEX
TC- TOTAL CHOLESTROL
PH – PAST HISTORY OF IHD
HDL – HIGH DENSITY LIPOPROTEINS
LDL- LOW DENSITY LIPOPROTEINS
TG-TRIGLYCERIDES
HOMOC-HOMOCYSTEINE
FH- FAMILY HISTORY OF IHD