



Original Article

Evaluation and Consideration of Metabolic Syndrome, Associated Factors and Homocysteine Levels- A Cross-Sectional Study

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ABSTRACT

Introduction: The metabolic syndrome is associated with prevalence and incidence of CHD, stroke. The Metabolic Syndrome is a modern-day epidemic which predicts total and cardiovascular diseases (CVD) mortality; the incidence and progression of carotid atherosclerosis and sudden death independent of other cardiovascular risks. Subjects with metabolic syndrome have three-fold risk of a heart attack or stroke, two-fold risk of CVD or dying from such events, and five-fold greater risk of developing type 2 diabetes mellitus in both sexes when compared to people without it. Day by day the incidences of metabolic syndrome, diabetes and cardiovascular disease increases in urban as well as rural areas, rich and poor communities because of life style changes, imbalance nutrition and easy availability of cheap fast food. India which is considered diabetic capital of world needed to be explored in direction of insulin resistance and metabolic syndrome and associated diseases. The relationship among insulin resistance, MetS, and cardiovascular (CV) morbidity and mortality has now been well established. Elevated plasma homocysteine, have been identified as a separate risk factor for hypertension and thus cardiovascular disease. Homocysteine aggravates hypertension by promoting vascular remodeling, oxidative stress, and endothelial dysfunction **Materials and methods:** We studied 50 healthy and 50 metabolic syndrome patients, with matched for age and. criteria fulfilling metabolic syndrome subjects taken as metabolic syndrome patients. selected from medical, paramedical staff and general public who were around 40 to 60 year of age. All subjects were belonged to the Latur district of Marathwada region. Patient belonging to group II were selected after attending medicine OPD of MIMSR Medical College, Latur detailed history, blood pressure, diabetes, dyslipidaemia, waist circumference etc. were taken and diagnosed as metabolic syndrome. Fasting blood sample were collected and blood glucose and lipid profile, homocysteine were determined. **Results:** In the control group I mean values of total cholesterol were 179.9 ± 22.60 mg %, serum triglycerides were 105.16 ± 22.53 mg %, and in the group II serum total cholesterol were 198.10 ± 25.56 mg %, triglycerides 181.1 ± 28.20 mg % and were significantly increased as compared to group I. The serum HDL-c in group II 39.14 ± 3.46 mg % were significantly decreased as compared to group I (45.92 ± 3.48 mg %). Triglyceride /HDL-c ratio were significantly increased in group II as compared to group I. In the control group I homocysteine were 12.04 ± 3.5 μ m/L and in the group II 19.41 ± 6.27 μ m/L which were significantly increased as compare to group I. This difference is statistically significant ($P < 0.0001$) suggestive of strong association between homocysteine & metabolic syndrome. **Conclusion:** From the results of this study, we conclude that dyslipidemia is a common feature of metabolic syndrome, and a large number of patients had more than one individual lipid abnormality. Evaluation of lipid profile indicates that HDL-c is decreased and triglycerides, and VLDL-c are increased in metabolic syndrome patients. Increased ratio of triglycerides/HDL-c is a feature of

metabolic syndrome, insulin resistance and an important predictor or marker of it. There was a strong association between homocysteine and metabolic syndrome. Changed life style and dietary pattern are related factors in genesis of metabolic syndrome, elevated homocysteine and other metabolic abnormalities through insulin resistance and other mechanisms are pointer to the need of routine screening of homocysteine test in patients with metabolic syndrome. Routine screening for homocysteine in patients not only with metabolic syndrome but also in patients suffered from IHD OR MI and vice versa can be helpful in estimating the magnitude of overlap between two conditions, help in early detection and prompt intervention of any of the two conditions, so as to design the holistic strategies of management And also to prevent end organ damage at other places of arteries.

Keywords: Central Obesity, dyslipidaemia, Hypertension, Cardiovascular morbidity, Inflammation, Insulin resistance, metabolic syndrome, homocysteine.

INTRODUCTION

The metabolic syndrome is a combination of risk factors of metabolic origin that are accompanied by increased risk for cardiovascular disease and type 2 diabetes. It is basically a combination of central obesity, dyslipidemia (hypertriglyceridemia and low HDL-c) hypertension, and impaired glucose tolerance.[1,2] Recent researches in India shows that about one third of urban population in major cities has metabolic syndrome.[3] The majority of persons with metabolic syndrome have insulin resistance. Insulin resistance and associated hyperinsulinemia are believed to be the direct cause of other metabolic syndrome risk factors.[4]

Different guidelines given by World Health Organization (WHO), National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP-III) and International Diabetes Federation (IDF) are used to identify metabolic syndrome in clinical practice.[5] Irrespective of the criteria used metabolic syndrome is associated with increased risk of developing Type 2 Diabetes Mellitus, elevated blood pressure Coronary Artery Disease (CAD), altered homocysteine metabolism cerebrovascular diseases, sleep apnoea and .[6] Among the various studies conducted among Indians of different age groups, using different criteria, NCEP ATP III definition was found to be a better tool for screening, than definitions provided by WHO and IDF.[7,8]

This study is concentrated around the metabolic syndrome, visceral fat, dyslipidaemia insulin resistance, metabolic syndrome hypertension and homocysteine levels. Insulin resistance occurs when cells of liver, skeletal muscle and adipose tissue become less sensitive and eventually resistant to insulin, the hormone which is produced by the beta cells in the pancreas to facilitate glucose absorption. Glucose can no longer be taken by the cells but remains in the blood, triggering hyperinsulinemia; this over burdens the pancreatic beta cells and which eventually wears out leads to clinical diabetes .[9]

There is association between insulin resistance and hyperinsulinaemia.[10] Although hyperinsulinemia may compensate for insulin resistance to some biological actions of insulin, i.e. maintenance of normoglycemia in some tissues, it may cause over expression of insulin activity in normally sensitive tissues. This traces the some insulin actions coupled with resistance to other actions of insulin results in the clinical manifestations of metabolic syndrome.[11] Hyperinsulinemia stimulates sodium reabsorption and activates sympathetic system causing hypertension. Hyperinsulinemia have additional effects on growth and development as well as on carbohydrate, protein and lipid metabolism which might promote atherosclerosis.[12] Chronic stimulus to beta cells of pancreas & high levels of insulin secretion will eventually exhaust the beta cells of the pancreas, increasing the likelihood of a functional deficit of these tissues, resulting in adult onset diabetes mellitus. India leads the world with largest number of diabetic patients earning the dubious distinction of being called the “diabetes capital of the world”. According to the recent projections of World Health Organization (WHO), India already leads the world with the largest number of diabetic subjects (nearly 40 million) and it is predicted that this number would reach almost 80 million by the year 2030.[13]

The International Diabetes Federation (IDF) estimates the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2027 unless urgent preventive steps are taken. India and China contribute to 75% of total diabetic patient load of world. India faces a serious health care burden because of the high prevalence of type-2 diabetes and its complication like cardiovascular disease, retinopathy, nephropathy, and neuropathy.[13,14] The Metabolic Syndrome is a modern day epidemic which predicts total and cardiovascular diseases (CVD) mortality.[15] The incidence and progression of carotid atherosclerosis.[16] and sudden death independent of other cardiovascular risks.[17] Metabolic syndrome increases three-fold risk of a heart attack or stroke, two-fold risk of CVD or dying from such events, and five-fold greater risk of developing type 2 diabetes mellitus in both gender when compared to people without it.[18]

Homocysteine a sulphur containing non-essential amino acid, is the byproduct in the conversion of methionine to cysteine. For the metabolism or recycling of methionine the B complex vitamins like vitamin B12, vitamin B6, folic acid are necessary, the deficiency of which leads to elevated homocysteine. Methionine takes S adenosine from ATP to form S adenosyl methionine. The methyl group of SAM transferred to a variety of acceptor molecule and this leads to the production of S-adenosylhomocysteine from SAM from which homocysteine is released. Which is again recycled or catabolized in the presence of sufficient amount of B complex vitamins. Serum blood homocysteine levels $>15 \mu\text{mol/L}$ is defined as Hyperhomocysteinemia [19]. In 1976, Wilcken and Wilcken [7] first provided evidence for an association between elevated homocysteine levels and atherosclerosis. A meta-analysis of 29 epidemiologic studies shown considerable evidence that elevated homocysteine levels were associated with an increased risk of arteriosclerotic vascular disease [8]. Large number of researches confirmed the association of homocysteine with CVD & CVD mortality [22-26]. A recent large trial of homocysteine reduction in hypertensive patients without a history of stroke or myocardial infarction in China resulted in a 21% reduction of stroke risk, suggesting that homocysteine level reduction could be considered as primary prevention for CVD [27]. Abdominal obesity has been associated with variety of metabolic disorders such as type 2 diabetes, hypertension cardiovascular diseases, and total mortality [28-29]. Recent studies reported a association between abdominal obesity and homocysteine and changes in body composition especially abdominal obesity predicting homocysteine [30-32]. These studies suggest a possibility that abdominal obesity and homocysteine may have the synergistic effects on the risk of MetS and CVD mortality. Hyperhomocysteinemia has been regarded as a new modifiable risk factor for cardiovascular disease (CVD) can cause low-density lipoprotein cholesterol (LDL-C) peroxidation and thrombosis activation [33,34]. Previous studies also established that there was a possible link among homocysteine, dyslipidemia and atherosclerosis. Homocysteine might also increase the risk of CVD in dyslipidemia patients [36-37]. Several studies shown elevated homocysteine disturb or impair HDL-C metabolism and can reduce circulating HDL-C via inhibiting Apolipoprotein A-I protein synthesis and enhance HDL-C clearance [38, 39]. Hypertension, a major contributor to cardiovascular morbidity and mortality, continues to pose significant global health challenges. As of recent estimates, nearly 1.3 billion adults worldwide are affected by hypertension, with its prevalence steadily increasing in both developed and developing countries [40]. Beyond traditional risk factors such as age, obesity, and sedentary lifestyle, dietary pattern are emerging evidence highlights the role of metabolic disturbances, including lipid abnormalities and hyperhomocysteinemia, in the pathogenesis of hypertension [41]. These revelations highlight how crucial it is to understand how lipid metabolism and homocysteine levels interact in hypertension. Elevated plasma homocysteine, have been identified as a separate risk factor for hypertension and thus cardiovascular disease. Homocysteine aggravates hypertension by promoting vascular remodeling, oxidative stress, and endothelial dysfunction [42]. Research has indicated that increasing homocysteine levels are linked to reduced nitric oxide bioavailability and increased arterial stiffness, both of which raise blood pressure [43]. Recent research suggested that hyperhomocysteinemia is an independent predictor for CVD. [44-45] A recent study revealed that elevated insulin can disturb the metabolism of homocysteine and cause elevated homocysteine levels. Insulin resistance in metabolic syndrome is marked by high insulin levels. That is homocysteine levels metS and CVD are associated with one another. Obesity and overweight, salty diet, lack of physical activity, smoking, alcohol abuse and associated hyperhomocysteinemia are modifiable factors. Not every patient with chronic heart disease presents classic risk factors. That is why the assessment of the level of homocysteine may be helpful in the prediction of heart failure. It has been proven that only hyperhomocysteinemia, with no other risk factors, might be responsible for 10% of heart failures. Other 90% cases are bound with classic risk factors. It is known that coexistence of two or more risk factors increases their unfavorable mechanism. It has been confirmed that hyperhomocysteinemia increases proatherogenic influence of hypertension and smoking. There is association between elevated homocysteine and dyslipidaemia. Homocysteine assessment is important test for early risk stratification, ideally in midlife or before the onset of overt vascular disease, rather than as a late-stage therapeutic target. [46]. But it should not be neglected as it can damage other part of arteries and organs. Since the available studies show conflicting causal relationship between these two common conditions, and homocysteine increased incidence of CVD need was felt for carrying out research to reestablish cause and reconsideration of homocysteine. Decreased homocysteine levels and B complex vitamins may have role in regression of atherosclerotic plaque, decrease stiffness of arteries and thus prevents plaque formation at other places, also maintain or regress preformed plaques. With this background we decided to start a pilot project to find out the relation between, visceral fat (obesity), metabolic syndrome and lipid profile, homocysteine levels to predict insulin resistance, risk of diabetes & hypertension, leading to CVD

MATERIALS AND METHODS

We studied 50 healthy (control) subjects and 50 metabolic syndrome patients, with matched for age and criteria fulfilling metabolic syndrome subjects taken as metabolic syndrome patients. Subjects were selected from medical, paramedical staff and general public who were around 40 to 60 year of age. All subjects were belonged to the Latur district of Marathwada region. Patients belonging to group II were selected after attending medicine OPD of MIMSR Medical College, Latur and diagnosed as metabolic syndrome. The healthy subjects (control) were nonsmokers, non obese non alcoholic and free from any disease and not taking any drugs that alter lipid and carbohydrates metabolism. Research protocol was approved by the Institutional Ethics Committee. All subjects after taking informed consent was interrogated and detailed examination was done. All Criteria for diagnosis of metabolic syndrome were fulfilled i.e. blood pressure examination, waist circumference (central obesity) visceral fat measurement and blood glucose and dyslipidaemia. Then

patients included in study. Blood samples drawn after an overnight fast. After serum separation the analysis was done on the same day and for serum homocysteine the samples were sent to Metropolis laboratory Mumbai. Maharashtra India. We estimated blood glucose by GOD method (Autopack Siemens kit) serum triglycerides by enzymatic method (Autopack Siemens kit), total cholesterol by enzymatic methods (Autopack Siemens kit) and HDL-c measured by phosphotungstate method (Autopack Siemens kit). LDL-c and VLDL-c values were calculated by Friedwald's equation.

- Homocysteine normal range 5-15 $\mu\text{m/L}$
- All patients belonging to group II had metabolic syndrome.
- Criteria for diagnosis of metabolic syndrome,

Following are the criteria used for the selection of subjects belonging to group 2 (metabolic syndrome)

1) The major criterion for selection of subject was central obesity. (Waist Circumference (WC) \geq 80 Cm for female and WC \geq 90 Cm for male which is ethnic specific value for Indians). This criterion was based on international diabetes federation's definition of metabolic syndrome. The IDF consensus worldwide definition of the metabolic syndrome (2006) contains Central obesity (defined as waist circumference $>$ 90 cm for male, $>$ 80 cm for female, with ethnicity specific values)

2) Systolic BP \geq 130 or diastolic BP \geq 85 mm Hg or treatment of previously diagnosed hypertension (FPG) \geq 100mmHg.

3) Raised fasting plasma glucose (100 mg/dL i.e.5.6 mmol/L) or previously diagnosed type 2 diabetes.

4) Dyslipidaemia;

5) Visceral fat measurement. Visceral fat was measured by Omron Karda scan model HBF-362. For healthy subject results $<$ 9 % and for metabolic syndrome $>$ 10 %, were included in the study. The HBF-500 CAN estimates the body fat percentage by the Bioelectrical Impedance (BI) method. Muscles, blood vessels and bones are body tissues with high water content that conduct electricity easily. Body fat is tissue that has little electric conductivity. The HBF- 362 sends an extremely weak electrical current of 50 kHz and less than 500 μA through our body to determine the amount of each tissue. This weak electrical current is not felt while operating the HBF-362. Visceral fat or abdominal fat also known as organ fat or intra-abdominal fat is located inside the abdominal cavity, packed between the organs (stomach, liver, intestines, kidneys, etc. Visceral fat is composed of several adipose depots, including mesenteric, epididymal white adipose tissue and perirenal depots. An excess of visceral fat is known as central obesity. The association between central obesity and cardiovascular disease and diabetes is strong. There are studies reporting that visceral fat is associated with diabetes, insulin resistance, inflammatory diseases, and other obesity-related diseases.[40,41]

Primary outcome was to study the association between homocysteine and MetS .

RESULT

Table 1: Serum Triglycerides and other Biochemical Parameter in Normal Healthy Subjects (Group I) and metabolic syndrome patient (Group II)

PARAMETER	GROUP-I (n=50)	GROUP-II (n=50)
TOTAL CHOLESTEROL	• 179.9 \pm 22.60	• 198.1 \pm 25.56
TRIGLYCERIDE	*105.16 \pm 22.53	*181.1 \pm 28.2
HDL-c	*45.92 \pm 03.48	*39.14 \pm 3.46
LDL-c	#112.57 \pm 22.84	#122.75 \pm 26.06
VLDL-c	*21.03 \pm 4.5	*36.20 \pm 5.6
TG / HDL-c	*02.31 \pm 0.56	*04.68 \pm 0.84
Homocysteine	*12.04 \pm 3.5	*19.41 \pm 6.27

*= $P < 0.0001$ The values are extremely statistically significant.

•= P is 0.0003 The value are highly statistically significant.

#= P is 0.04 The value are statistically significant.

In the control group I mean values of total cholesterol were 179.9 \pm 22.60 mg %, serum triglycerides were 105.16 \pm 22.53 mg %, and in the group II serum total cholesterol were 198.10 \pm 25.56 mg %, triglycerides 181.1 \pm 28.20 mg % and were significantly increased as compared to group I. The serum HDL-c in group II 39.14 \pm 3.46 mg % were significantly decreased as compared to group I (45.92 \pm 3.48 mg %). Triglyceride /HDL-c ratio were significantly increased in group II as compared to group I. In the control group I homocysteine were 12.04 \pm 3.5 $\mu\text{m/L}$ and in the group II 19.41 \pm 6.27 $\mu\text{m/L}$

which were significantly increased as compared to group I. This difference is statistically significant ($P < 0.0001$) suggestive of strong association between homocysteine & metabolic syndrome.

DISCUSSION

In the group II metabolic syndrome total cholesterol, triglycerides, TG/HDLc ratio significantly increased and HDLc level significantly decreased. Similar finding also shown in earlier study [47] This finding corresponds with the risk factors for metabolic syndrome. Impaired glucose tolerance, total cholesterol, triglycerides, waist circumference, high blood pressure are risk factors for metabolic syndrome, but HDLc serves as a protective factor against metabolic syndrome [47]. As hypertension, diabetes mellitus, and dyslipidemia were highly prevalent in the metabolic syndrome group. Importantly, we noted a statistically significant increase in homocysteine levels in the metabolic syndrome group. Because of these our result and various researches, we are tracing about the association between homocysteine levels and metabolic syndrome.

There was an increase in impaired glucose tolerance, central obesity, high blood pressure, dyslipidaemia as homocysteine levels increased. The same results were also shown in previous studies [48-50] however, HDL had a reverse relationship with homocysteine levels, which was also noted in a previous study [51]. The proportion of chronic diseases, including hypertension and diabetes mellitus, which have a strong relationship with metabolic syndrome, also increased as homocysteine levels increased, and also earlier researches support these findings. According to the results of our study, which indicated a strong relationship between homocysteine levels and metabolic syndrome. This result confirmed that homocysteine levels are an independent risk factor for metabolic syndrome.

As its elevated levels, dyslipidaemia, oxidation of cholesterol, insulin resistance (elevated ratio TG/HDLc, dyslipidaemia are indicator of insulin resistance), all are sufficient for new plaque formation and to increase stiffness or narrowing of arteries. These effects are amplified if the homocysteine not recycled or catabolized due to B complex deficiencies. [52]. Indian diet is rich in carbs, vegan diet increase the requirement of B complex vitamins. Indians have B12 and folic acid deficiencies which may be precipitated by genetic factors. That may be reason for Indians have higher levels of homocysteine as compared with western and other countries.

Metabolic syndrome has become a global health issue. In Metabolic syndrome group 70% had hypertension which can further increase total cholesterol and decrease in HDLc. In this cases persistent hypercholesterolaemia cholesterol may get oxidized by homocysteine even in normal concentration, leads to stiffness of arteries formation of plaques at various places. This is one of cause of end organ damage. Diabetic dyslipidaemia, increase in triglyceride total cholesterol and lowers HDLc, which increase insulin resistance (increase TG/HDLc ratio), which can also leads to stiffness of arteries and plaque formation as discussed above. This is also equally important in ischemic heart disease, coronary heart disease, and myocardial infarction patients.

Metabolic syndrome is a problem of epidemic proportions, increasing the risk for dyslipidemia, diabetes mellitus type 2, atherosclerosis, cardiovascular diseases, and other chronic diseases [53,54-56]. Chronic inflammation in metabolic syndrome is closely related to adipose tissue and are involved in the development of atherosclerosis and cardiovascular disease (CVD) [57]. Researches shown that, 20–30% of the global population has metabolic syndrome [58] which increases the risk of cardiovascular mortality and the risk of myocardial infarction or stroke [59,60]. This shows there is association metabolic syndrome, homocysteine and CVD.

Homocysteine is considered a potentially harmful substance affects arteries macrocirculation and microcirculation [61]. Numerous studies have revealed the association between endothelial dysfunction and homocysteine, which increases oxidative stress and injures the vascular endothelium [62]. Homocysteine decreases the level of nitrogen oxide, increases the proliferation of vascular smooth cells, and alters the elastic property of the vascular wall [63]. The compromised vascular wall contributes to the development of hypertension [64]. Additionally we found that hypertension was related to hyperhomocysteinemia in our study.

In our study, we found that participants with high homocysteine levels tended to have metabolic syndrome, hypertension, diabetes mellitus, and a greater waist circumference. Adipocytes, the cells responsible for insulin resistance and hyperinsulinemia, are often excessive in individuals with larger waist circumferences, diabetes mellitus, and metabolic syndrome. The results of our study support this mechanism, which may explain the association of metabolic syndrome with cardiovascular disease. Additionally, we confirmed that homocysteine levels were an independent risk factor for metabolic syndrome, even after considering all related factors in our study.

CONCLUSION

There was a strong association between homocysteine and metabolic syndrome. Changed life style and dietary pattern are related factors in genesis of metabolic syndrome, elevated homocysteine and other metabolic abnormalities through insulin resistance and other mechanisms are pointer to the need of routine screening of homocysteine test in patients with metabolic syndrome. Routine screening for homocysteine in patients not only with metabolic syndrome but also in patients

suffered from IHD OR MI and vice versa can be helpful in estimating the magnitude of overlap between two conditions, help in early detection and prompt intervention of any of the two conditions, so as to design the holistic strategies of management And also to prevent end organ damage at other places of arteries..

Ethical approval: Approved by Ethical committee of MIMSR Medical College Latur.

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