A Study on Metabolic Syndrome in the South Indian Population with Coronary Artery Disease Proven By Angiography.

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ABSTRACT

Background: The prevalence of metabolic syndrome is increasing in Indian population, predisposing an increased risk for the development of diabetes mellitus and cardiovascular diseases. **Methods:** A case control study was conducted to assess the prevalence of MS and the association between the components of MS in 250 patients, diagnosed by angiography to have CAD (125 patients) as cases and no CAD (125 patients) as control group. MS was diagnosed based on the modified ATP III guidelines, if three or more of the following were present: abdominal obesity, hypertension, glucose intolerance, hypertriglyceridemia or low HDL-C levels. SPSS Version 15 was used for statistical analysis and Chi-square analysis was used to estimate the prevalence of MS with respect to the severity of CAD, family history of CAD and smoking history. The association between individual risk factor and outcome was estimated using univariate logistic regression. The multivariate logistic regression analysis was used to estimate the components of MS as a risk factor for CAD, controlling the other confounders. A P value of <0.05 was considered as statistically significant. **Results:** The prevalence of MS was higher in CAD (70.4%) than in subjects without CAD (66.4%). Diabetic subjects with (88.24%) and without (87.93%) CAD had significantly higher % of MS when compared with non-diabetic subjects with CAD (49.12%) and without CAD (47.76%) (P < 0.001). Of 125 patients with CAD, 3% patients had no functional markers of MS; 11.2 % had an expression of one; 20 % had two; 32 % had three and 33.8% had four functional markers of MS. The level of MS mounted high with the increasing severity of CAD when compared with normal coronary arteries but was not statistically significant (P=0.176). The percentage of MS was higher in patients with family history of CAD (78.18%) which was statistically significant (P<0.001) and was comparatively lower in non-smokers (46.7%) and ex-smokers (62.2%) than smokers (65.2%). **Conclusion:** A higher prevalence of MS was observed in diabetics with and without CAD. This is suggestive of an increased risk of CAD in diabetic patients with MS than in non-diabetic patients.

Keywords: metabolic syndrome, CAD, diabetes.

INTRODUCTION

Metabolic syndrome (MS) comprises of a cluster of metabolic risk factors such as central obesity, hypertension, glucose intolerance (type 2 diabetes, impaired glucose tolerance or fasting glycemia), Insulin resistance (IR), atherogenic dyslipidemia characterized by low high density lipoproteins (HDL-C) and high triglycerides which predispose the individual to increased risk for development of diabetes mellitus and cardiovascular diseases.[1-3] It serves as a valuable tool in the identification of individuals at risk for diabetes and CAD. Epidemiological studies have reported a high prevalence of MS and cardiovascular mortality among non-resident Indians settled abroad.[4-6] Lifestyle factors appear to play an important role as BMI, especially abdominal obesity, and dyslipidaemia worsen with urbanization and migration.[7,8]

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The increasing prevalence of BMI and a longer life expectancy are predisposing factors for a rising incidence of type 2 diabetes mellitus coupled with CAD globally.[9] Patients with Insulin resistance are at an increased risk of developing MS, a major contributor of heart disease and dyslipidemia.[10] Although environmental factors such as diet and physical activity, coupled with still largely unknown genetic factors, clearly contribute to the genesis of MS, the exact pathogenesis is still enigmatic.[11] IR is considered as the chief underlying pathophysiology in MS and is found to

be associated with cardiovascular disease, in a family study,[12] in community based samples[13,14] and in primary preventive settings[15,16]. The aforementioned observations paved way for the inclusion of MS identification in guidelines for the prevention of cardiovascular diseases in clinical practice.[17]

Different definitions of MS have been framed by the WHO, European Group for the Study of Insulin Resistance (EGIR) ATP III, American Association of Clinical Endocrinologists (AACE), and recently the International Diabetic Federation (IDF). Even though most of these agree on fundamental components namely glucose intolerance, obesity, hypertension and dyslipidemia, they vary with respect to the cut-off points for the criteria of each component of the cluster and the mode of combining them to characterize MS. Moreover, most of the prior reports on MS have been derived from studies on Europeans. Asian Indians have very higher rates of DM[18] and premature CAD with high severity[19]; keeping these distressing observations in mind, special waist cut-off have been proposed for Asians.[20] The IDF and WHO have called for more studies employing different criteria for MS in diverse ethnic inhabitants and population-based national studies on prevalence of MS and its risk for DM and angiographically proven CAD among urban South Indians are currently lacking. Hence case-control study was proposed to estimate the prevalence of MS in angiographically confirmed CAD and non-CAD subjects and also to associate the various components of MS with the severity of CAD, family history and smoking, adopting Adult Treatment Panel-III guidelines.

MATERIALS AND METHODS

This study evaluated the association between the components of MS in 250 patients between the age group of 35-65 years, admitted with a suspicion of CAD, in the cardiac care centre of a 1750 bedded South Indian tertiary care teaching hospital, after obtaining approval from the Institutional ethics committee and the consent of the patients. The patients who were angiographically proven to have CAD (125 patients) were categorized as cases and those with no CAD (125 patients) by angiography were categorized as control. MS was diagnosed based on the modified ATP III guidelines[21], if three or more of the following were present: abdominal obesity (definition of abdominal obesity was modified using Asia-Pacific WHO guidelines as waist circumference $\geq$ 90 cm for males and $\geq$ 80 cm for females [20], hypertension (subjects who were on antihypertensive medication and/or had systolic pressure $\geq$ 130mmHg and / or $\geq$ 85mmHg), glucose intolerance (fasting blood glucose $\geq$110mg/dl), hypertriglyceridemia (fasting TG $\geq$ 150mg/dl) or

low HDL-C levels (males: HDL-C cholesterol < 40 mg/dl, females: HDL-C < 50 mg/dl) and Insulin resistance as calculated using Homeostasis assessment (HOMA-IR) model (using the formula: Fasting insulin (μIU/ml) x fasting glucose (mmol/litre) / 22.5).[22] Descriptive statistics was used to summarize the clinical findings, risk factors, and coronary angiographic findings of patients. Chi-square analysis was used to estimate the prevalence of MS with respect to the severity of CAD, family history of CAD and smoking history. The association between individual risk factor and outcome was estimated using univariate logistic regression. The multivariate logistic regression analysis was used to estimate the components of MS as a risk factor for CAD, controlling the other confounders. SPSS Version 15 was used for statistical analysis and a value of P<0.05 was taken as significant.

RESULTS

In the current study, among 125 patients angiographically diagnosed with CAD (cases), 91 (73%) patients were males and 34 (27 %) were females. In angiographically proven control population 71 (57%) were females and 54 (43%) were males. Among cases 34 (27.2%), 35 (28%) and 56 (44.8%) had single vessel disease (SVD), double vessel disease (DVD) and triple vessel disease (TVD) respectively. 73 (58.4%) subjects had type 2 DM with CAD and 52 (41.6%) had CAD without type 2 DM. Among the control subjects, 64 (51.2%) subjects had type 2 DM and 61 (48.8%) had no type 2 DM. In the total study population, 111(44.4%) subjects had positive family history of CAD while 139 (55.6%) subjects had no family history of CAD. Among the above study population 198 (79.2%) were non smokers. 37 (14.8%) were smokers and 15 (6%) were ex-smokers.

Table 1 shows characteristics of subjects with CAD and without CAD included in the case control study such as, age, body mass index (weight in kg / height in m2), waist hip ratio and waist circumference, systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), glycated hemoglobin (%), total serum cholesterol (mg/dl), serum triglycerides (mg/dl), total serum cholesterol (mg/dl), serum triglycerides (mg/dl), LDL-C (mg/dl), HDL-C (mg/dl). We found that subjects with CAD when compared without CAD had higher systolic blood pressure (139 vs.128 mm Hg, P < 0.01), diastolic pressure (87 vs. 82 mm Hg, P < 0.01), fasting plasma glucose (144 vs. 127 mg/dl, P < 0.05) and glycated hemoglobin (7.0 vs. 6.5 %, P < 0.05). However, waist hip ratio (WHR) (94.4 vs. 93.2 cm, P < 0.368), LDL-C (109 vs. 107 mg/dl, P= 0.550) and HDL-C (40 vs. 41 mg/dl, P= 0.213) levels were not statistically significant between the subjects with CAD and without CAD.

The prevalence of components of MS in CAD subjects (n=125) was higher (70.4%) than subjects without CAD (66.4%). Among the components of MS, waist circumference of >90 cm was found in 67(67.05%) in males diagnosed with CAD and 36 (34.95%) with no CAD; while in contrast waist circumference of > 80 cm was observed in 21 (25%) in females patients diagnosed with CAD and 63 (75%) patients with no CAD; a blood pressure of ≥ 130/85 mmHg was observed in 75(63.56%) patients with CAD and 43(36.44%) patients with no CAD; a

fasting blood sugar of ≥ 110mg/dl was found in 75(53.19%) patients with CAD and 66(46.81%) patients with no CAD; a triglyceride levels of ≥ 150mg/dl was found in 78(55.71%) patients with CAD and 62(44.29%) patients with no CAD; an HDL-C of ≤ 40mg/dl was found in 52(65.82%) males with CAD and 27(34.18%) males with no CAD and HDL-C levels of ≤ 50mg/dl was found in 20 (23.81%) females with CAD and 62(44.29%) females with no CAD.

Table 1: General Characteristics of Study Subjects.

Variables*	Subjects without CAD (n = 125)	Subjects with CAD (n = 125)	P value**
Age (years)	51 ± 8	55 ± 8	<0.01
BMI (kg/m^2)	26.5 ± 4.3	26.2 ± 4.0	0.333
Waist circumference (cm)	93.2 ± 11.4	94.4 ± 11.1	0.368
Systolic blood pressure (mm Hg)	128 ± 16	139 ±19	<0.01
Diastolic blood pressure (mm Hg)	82 ± 9	87 ± 9	<0.01
HOMA – IR	3.6 ₊1.5	5.4 ₊1.7	<0.01
Fasting plasma glucose (mg/dl)	127 ± 51	144 ± 66	<0.05
Glycated haemoglobin (%)	6.5 ± 1.4	7.0 ±1.6	<0.05
Total serum cholesterol (mg/dl)	166 ± 42	172 ± 39	0.187
Serum triglycerides (mg/dl)	159 ± 86	185 ± 83	< 0.01
LDL cholesterol (mg/dl)	107 ± 30	109 ± 30	0.550
HDL cholesterol (mg/dl)	41 ± 7	40 ± 7	0.213

* Data is presented as mean± SD;
 **A P value of 0.05 was considered statistically significant

Diabetic subjects with (88.24%) and without (87.93%) CAD had significantly higher % of MS when compared with non-diabetic subjects without CAD (47.76%) and non-diabetic subjects with CAD (49.12%) (P <0.001). An inclination in level of MS was observed with the increasing severity of CAD: SVD (58.82%) < TVD (73.21%) <DVD (77.14%), when compared with normal coronary arteries (NCA) (No CAD) (66.4%) but was not found to be

statistically significant (P=0.176). An attempt was made to correlate the extent of myocardial ischemia in subjects with CAD as computed by Gensini scoring system[23] with the MS. Among 125 CAD patients, 88 had MS while 37 patients had no MS. The Gensini scores (Mean ± SEM) in patients having MS was higher (47.44±3.22) when compared to patients having no MS (36.62±3.19).

Table 2: Multiple Logistic Regression Analysis Using Cad as Dependent Variable.

Parameter	Odds Ratio [OR]	95% Confidence Interval [CI]	P value
Independent variable: Metabolic syndrome			
Model 1: MS - Unadjusted	1.2	0.68 – 2.13	0.49
Model 2: [Model 1 + adjusted for age and gender]	1.86	1.012 – 3.457	0.045
Model 3: [Model 2 + FBS]	2.34	1.21 – 4.51	0.011

*A P value of 0.05 was considered statistically significant

In the total study population (n=250), percentage of MS-a strong determinant risk factor of CAD was higher in patients with family history of CAD (78.18%) in contrast to patients having no family history of CAD (50.86) which was statistically significant (P < 0.001). Also the prevalence of MS was comparatively lower in non-smokers (46.7%) and ex-smokers (62.2%) than smokers (65.2%). These findings suggests that patients having MS coupled with positive family history of CAD and smoking history can become highly vulnerable subjects to develop premature CAD.

The functional markers to diagnose MS include three or more of the following: dyslipidemia with low serum HDL-C, elevated TG and total cholesterol; higher abdominal obesity (waist circumference), blood pressure, and fasting glucose. In the present study on 125 patients with CAD, 3% patients had no functional markers of MS (0 MS); 11.2 % had an expression of one functional marker (1 MS); while 20 % had two functional markers of MS. 32 % had three (3 MS) and 33.8% had four (4 MS) functional markers of MS respectively. A mounting trend in the percentage of markers of MS occurrence in study

population with CAD substantiates the fact that MS is a strong predisposing factor of CAD.

Multivariate logistic regression analysis was carried out to find the independent association of MS with CAD (Table 2). Areas under the curve of Model 1 (MS – Unadjusted), Model 2 (Model 1 + adjusted for age and gender), and Model 3 (Model 2 + FBS) of regression model were 1.2 (95% CI, 0.68 – 2.13, P = 0.49), 1.86 (95% CI 1.012 – 3.437, P=0.045) and 2.34 (95% CI 1.21 – 4.51, P=0.011), respectively. The logistic regression model incorporating with age, gender and other major risk factors of atherosclerosis may be useful for screening CAD in patients with type 2 DM. In this case, MS showed a strong association with CAD and diabetes, even after adjusting for age, gender and fasting blood sugar.

DISCUSSION

The occurrence of MS in various ethnic groups - including Caucasians, Africans, Latin Americans, Asian Indians, Chinese and Aboriginal Australians has been substantiated in numerous epidemiological studies. In developing countries, the lifestyle changes as a result of rapid industrialization and rural-urban migration, is chiefly associated with reduced levels of physical activity and increased intake of energy. The consequent rise in obesity rates has led to a massive increase in prevalence of MS in developing regions. However clear-cut statistics for its prevalence are unavailable. This can be partly explained due to the lack of an internationally accepted definition for MS. Different definitions have been formulated by WHO, US National Cholesterol Education Program Adult Treatment Panel III and IDF.[24] People with MS are twice as likely to die from, and three times as likely to develop, MI or stroke when compared to people without MS.

Multiple factors such as blood pressure, BMI, LDL-C, waist circumference, TGL and fasting glucose plays a prominent role in an increased risk of CAD. An aberrant lipoprotein phenotype characterized by increased blood pressure (≥130/85mmHg) and BMI (>30kg/m2), decreased HDL-C and an accumulation of small dense LDL-C particles with the levels of LDL-C being often normal is commonly associated with both MS and type 2 diabetes.[25] Various lipid related parameters have been used to predict the risk of CAD. According to Grover, et al.,[26], high blood pressure and LDL-C were shown to be more accurate predictors of coronary heart disease, where as the evaluation of either BMI or fasting glucose is the best related predictor of future cardiovascular events.

BMI plays a key role in the development of type 2 DM and atherosclerosis and contribute to the pathogenesis of MS by promoting inflammation, hypertension and dyslipidemia.[27] Moreover, hypertension is considered as a strong risk factor for

CAD.[28] Abdominal fat which is associated with BMI, a characteristic feature of the MS, is a major source of the excessive flux of free fatty acids which are known to have pro-arrhythmic properties. The prolonged release of free fatty acids is implicated in the development of type 2 DM, since it promotes IR and the associated loss of pancreatic-cell function.[29] Diabetic patients with MS has a significant increase in fasting glucose, BP and the BMI when compared to the type 2 DM patients without MS, which poses them to be at a higher risk for CAD.[30] A multifactorial intervention addressing all the associated cardiovascular risk factors is the need of the hour for clinical management.

In the present study, MS was found in 70.4% patients diagnosed with CAD and 66.4% in patients without CAD based on modified ATP III guidelines. This guideline was particularly preferred as it is widely used globally with proven validity.[31] The prevalence of MS was higher in diabetic subjects with and without CAD when compared with non-diabetic subjects. More over MS proved to be an independent risk factor for CAD even when adjusted for confounding variables like age, gender and fasting blood sugar. The ICMR task force collaborative study reported the prevalence of MS to be 30 per cent in urban areas of Delhi and 11 per cent in rural Haryana using ATP-III criteria.[32] Mishra, et al.,[33], reported 30 per cent prevalence among the urban slum population in Delhi. Ramachandran et al.,[34], reported a prevalence of 41 per cent in urban area of Chennai using modified ATP-III criteria among adults aged 20 to 75 years. They also reported that prevalence was higher in women than men (46.5 vs. 36.4%) and in older people. In contrast, Sarkar, et al.,[7] reported 30-50 per cent prevalence in Bhutia tribe, with no rural-urban difference. Among the Toto tribe, the rural community prevalence was low 4-9 per cent. The prevalence of MS among Asian Indian males is higher than that reported among African Americans but similar to Non-Hispanic Whites and Mexican Americans.[35] The differences may be attributed to the variations in study areas, and the different definitions of MS used. Waist circumference of ≥ 90cm in males and ≥ 80cm in females, a fasting blood glucose of ≥ 110mg/dL, triglyceride levels of ≥ 150 mg/dL and HDL-C levels of ≤ 40mg/dL in males and ≤ 50mg/dL in females were observed to be major components of MS in patients with CAD and no CAD in the present study. A blood pressure of ≥ 130/85mmHg was found in majority of patients with CAD (63%); where as 62 % of patients with no CAD had a blood pressure of ≤ 130/85 mmHg.

Furthermore, there was a higher prevalence of MS among the smokers (65.2%), in patients having FH-CAD (79.8%, P<0.001) and high degree of coronary artery stenosis (DVD (77.14%); TVD (73.21%)). The causes of the MS are likely to reflect the inter-play of genetic and environmental factors. Current

study confirms that genetic factors contribute to the concentration of the MS and its components within family groups.

CONCLUSION

The higher prevalence of MS in diabetics with and without CAD than non-diabetic patients depicts that those patients with type 2 DM with MS are at a greater risk for CAD. MS showed a strong association with CAD and diabetes, even after adjusting for age, gender and fasting blood sugar, hence may be a useful screening tool CAD in patients with type 2 DM. The magnitude of MS was higher among urban subjects of South India as compared to reported values in rural areas. An additional goal of CAD screening program should be the earlier identification of high-risk individuals with MS, having smoking history (who can be targeted for smoking cessation) and family history of CAD.

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