Original Article

Association of metabolic syndrome with severity of coronary artery disease

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ABSTRACT

Background: South Asians are more prone to develop metabolic syndrome (MetS). The additive predictive value of components of MetS for cardiovascular diseases is still debated. We undertook this study to evaluate the association of MetS and its components with severity of coronary artery disease (CAD). **Materials and Methods:** Three hundred patients with known coronary disease above the age of 25 years were included in this study. Blood samples were collected for biochemical markers. Patients were stratified into subjects with and without MetS (International Diabetes Federation, IDF, criteria) and severity of CAD (number of vessel involved). **Results:** Mean age of the patient in the study was 60.9 ± 12.4 years (male, M: 72%; female, F: 28%). MetS was present in 64% patients. Patients with MetS had more severe CAD compared to those without MetS. Triple vessel disease (TVD) was present in 62.5% of patients with MetS compared to 34.3% among without MetS ($P < 0.0001$). The percent number of patients with TVD showed increasing trend with increasing number of components of MetS (0-0%; 1-20%; 2-27.5%; 3-47.8%; 4-72.6%; 5-78.3%; Chi square for trend <0.0001). Inflammatory markers [interleukin (IL) 6: 77.67 ± 79.48 vs. 41.21 ± 60.72 pg/ml, $P < 0.0001$; tumor nuclear factor (TNF)-α: 28.0 ± 47.49 vs 20.43 ± 24.5 pg/ml, $P < 0.0001$; high sensitive C-reactive protein (hsCRP): 14.30 ± 9.91 vs. 7.02 ± 7.18 mg/L, $P < 0.0001$], insulin resistance [homeostatic model analysis insulin resistance (HOMA-IR): 22.33 ± 23.37 vs. 10.86 ± 13.90, $P < 0.0001$] were higher and insulin sensitivity [quantitative insulin check index (QUICKI): 0.26 ± 0.03 vs. 0.30 ± 0.04, $P < 0.0001$] was significantly lower in subjects with MetS compared to subjects without MetS. Among lipids, total cholesterol were comparable but triglyceride (175 ± 42 vs. 179 ± 48 vs. 180 ± 47 mg/dl, $P < 0.0001$) was high and high-density lipoprotein (HDL; 44.72 ± 7.63 vs. 39.96 ± 8.70 vs. 36.05 ± 8.84, $P < 0.0001$) was low in subjects with TVD compared to others. Similarly, percentage of patients with diabetes (7.5% vs. 26.3% vs. 63.7%, $P < 0.0001$) and hypertension (34.3% vs. 56.6% vs. 77.7%, $P < 0.0001$) were higher in subjects with TVD compared to others. **Conclusions:** There is a strong correlation of MetS and its components with severity of CAD.

Key words: Coronary artery disease, inflammatory markers, insulin resistance, metabolic syndrome

Introduction

Metabolic syndrome (MetS) is represented by a cluster of risk factors associated with insulin resistance, subclinical inflammation, increased future risk of diabetes, and coronary artery disease (CAD).[1,2] South Asians are more prone to develop MetS because of their high percentage of body fat, abdominal obesity, and insulin resistance.[3] Despite significant controversy, most experts appear to believe that the increased cardiovascular risk seen in these subjects is probably due to the clustering of risk factors.[4,5] Many epidemiological and clinical studies have confirmed the association between MetS and increased risk CAD,[6,7] which is the leading cause of mortality worldwide. Morbidity and mortality from CAD are higher in patients with MetS; therefore, early assessment of the risk of CAD in patients with MetS is desirable because it could lead to improved patient or physician adherence to risk-reducing behaviors or interventions and improve clinical outcomes.

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There are reports in the literature on association inflammatory markers and insulin resistance with severity of disease.[8,9] There are very few studies showing association of metabolic syndrome and number of its components with severity of disease in India.[8,10]

This study was conducted with aim to evaluate the association of metabolic syndrome and its metabolic components with severity of CAD in patients with angiographically proven CAD and whether numbers of metabolic abnormalities predict the severity.

Materials and Methods

Three hundred patients with known coronary disease above the age of 25 years were included in this study. Patients, who were admitted in cardiology department for evaluation of chest pain and found angiography positive, were selected in the study consecutively as previously described (references of our studies). Exclusion criteria were presence of chronic kidney disease, hepatic dysfunction, known endocrinal or rheumatological diseases, or chronic infections. All cases were interviewed using a questionnaire, which included data on smoking, physical activity. Height, weight, waist, hip circumference were measured. Body mass index (BMI) and waist hip ratio (WHR) was calculated. Data on clinical history of hypertension (HTN), diabetes mellitus (DM), and medications (antihypertensive and oral hypoglycemic agents) was also acquired.

Nutrition assessment was done once at the time of recruitment based on previous 2-days 24-hour dietary recall. Mean of recall of 2 days was taken. Diet was assessed using a computer-based comprehensive diet assessment known as Diet soft software, verson: 1.1.7 [developed by Invincible IDeAS (www.invincibleideas.com) based on book Nutritive value of Indian Foods by C. Gopalan, B. V. Rama Sastri, and S. C. Balasubrsmanian, National Institute of Nutrition (NIN), Indian council of Medical Research, Hyderabad, India.] (Gopalan C *et al*., 2005). Questionnaires and diet assessments were administered via interview by trained staff. We have analyzed dietary carbohydrates, energy, fat, vitamins, proteins, and minerals.

Fasting blood samples were collected after 14-hour fasting. Total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol were measured by using cholesterol oxidase para aminoantipyrine (CHOD PAP), Lipase Glycerol Kinase (LIP/GK), enzymatic clearance method, respectively and LDL and VLDL were calculated by Friedewald's formula. Inter-assay 3.84% and intra-precision was 2%, respectively for all parameters. Tumor necrosis factor-α (TNF-α), interlukin-6 (IL-6), and high sensitive C-reactive protein (hsCRP) were measured by enzyme linked immunosorbent assay method with kits manufactured by Gen-probe Diaclone, France, and Biochek, CA, USA. Insulin was done by microparticle enzyme immunoassay with commercial kits supplied by Abbott laboratory, USA. Intra-assay and inter-assay precision was <5% and <10%, respectively for above parameters. Insulin resistance and sensitivity was calculated by using homeostatic model analysis insulin resistance (HOMA-IR) model [HOMA-IR = fasting insulin (μIU/ml)* fasting glucose (mmol/l)/22.5; and quantitative insulin check index (QUICKI) [QUICKI = 1/log (fasting insulin μU/mL) + log (fasting glucose mg/dl)], respectively.

Patients were divided into subjects with and without MetS according to International Diabetes Federation (IDF) criteria.[11] Patients were stratified according to number of metabolic components and severity of CAD and association with risk factors were analyzed. The study was approved by Institutional ethics committee of Deenanath Mangeshkar Hospital. Informed consent was obtained from all subjects.

Definitions

MetS were defined according to IDF criteria[11] as follows: Central obesity (waist circumference: Male > 90 cm, female > 80 cm) plus any two: Raised triglycerides (>150 mg/dl), reduced HDL cholesterol (<40 mg/dl in men or < 50 mg/dl in women), raised blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg or on treatment), or raised fasting plasma glucose (fasting plasma glucose ≥ 100 mg/dl or on treatment).

Statistical method

Statistical analysis was carried out using statistical package for social sicences (SPSS) version 20. Data were presented as mean ± standard deviation (SD), median (range), or number (%) unless specified. Significance levels were analyzed by student's *t*-test between two parameters and analysis of variance (ANOVA) test when parameters were more then two. If Bartlett's Chi-square test for equality of population variances was <0.05 then Kruskal-Wallis test was applied. All non-parametric data were analyzed by Chi-square test. A $P < 0.05$ was considered statistically significant.

Results

Mean age of the patient in the study was 60.9 ± 12.4 years, 72% were males and 28% were females. Basic characteristic

Table 1: Basic characteristics of study population

Parameters	Mean±SD (95% CI)
Age (years)	60.92±12.48 (59.50-62.34)
BMI (Kg/m^2)	27.89±3.81 (27.46-28.32)
WHR	0.92±0.06 (0.91-0.93)
Cholesterol (mg/dl)	178.76±45.66 (173.57-183.94)
Triglycerides (mg/dl)	171.16±46.28 (165.90-176.42)
HDL-C (mg/dl)	38.98±9.21 (37.93-40.02)
VLDL-C (mg/dl)	34.23±9.25 (33.18-35.28)
DM-*n* (%)	125 (41.6)
HTN-*n* (%)	188 (62.6)
Smoking-*n* (%)	111 (37.0)
Less physical activity-*n* (%)	116 (38.6)
Dyslipidemia-*n* (%)	124 (41.3)
Insulin (mU/L)	50.17±43.48 (45.23-55.11)
HOMA-IR	18.20±21.18 (15.79-20.61)
QUICKI	0.28±0.041 (0.27-0.28)
IL6 (pg/ml)	64.54±75.25 (55.99-73.09)
TNF-α (pg/ml)	25.28±40.87 (20.64-29.92)
hsCRP (mg/L)	11.68±9.66 (10.58-12.78)

BMI: Body mass index; WHR: Waist hip ratio; DM: Diabetes mellitus; HTN: Hypertension; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein; LDL: Low-density lipoprotein; HOMA-IR: Homeostatic model analysisinsulin resistance; QUICKI: Quantitative insulin check index; hsCRP: Highly sensitive C-reactive protein; IL-6: interleukin-6; TNF-α: Tumor necrosis factor-alpha

Table 2: Demographic, insulin resistance, and inflammatory markers in patients with CAD with or without MS

Parameters	MS (*n*=192)	Non-MS (*n*=108)	*P* value
Age (years)	62.5 (25-92)	61 (25-86)	0.1158
Sex	M: 132	M: 84	0.1241
	F: 60	F: 24	
BMI (Kg/m^2)	27.2 (20.02-39.4)	26.8 (19.3-37.7)	0.1744
Smoking, *n* (%)	Y: 69 (62.2)	Y: 123 (65.1)	0.7012
	N: 42	N: 66	
Less physical activity, *n* (%)	Y: 76 (65.5)	Y: 115 (62.8)	0.7294
	N: 40	N: 68	
Insulin (mU/L)	52.8 (3.5-274.8) 59.45±44.60	18.7 (2.1-213.4) 33.67±36.09	<0.0001
IL6 (pg/ml)	36.45 (0.5-253.2) 77.67±79.48	11.15 (0.4-224.9) 41.21±60.72	<0.0001
TNF- α (pg/ml)	11.8 (0-525.8) 28.00±47.49	7.95 (0.1-111.4) 20.43±24.5	<0.0001
hsCRP (mg/L)	14.7 (0.11-37.9) 14.30±9.91	3.9 (0.1-26.9) 7.02±7.18	<0.0001
HOMA-IR	16.3 (0.78-135.7) 22.33±23.37	5.7 (0.5-82.2) 10.86±13.90	<0.0001
QUICKI	0.26 (0.21-0.39) 0.26±0.03	0.29 (0.22-0.43) 0.30±0.04	<0.0001
Single vessel isease, *n* (%)	28 (14.6)	39 (36.1)	<0.0001
Double vessel disease, *n* (%)	44 (22.9)	32 (29.6)	0.2522
Triple vessel disease, *n* (%)	120 (62.5)	37 (34.3)	<0.0001

BMI: Body mass index; WHR: Waist hip ratio; HOMA-IR: Homeostatic model analysis-insulin resistance; QUICKI: Quantitative insulin check index; hsCRP: Highly sensitive C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha

of the study population is shown in Table 1. Table 2 is stratified according to presence or absence of metabolic syndrome in the study population, 64% were with MetS and 36% were without MetS. BMI was more in subjects with metabolic syndrome but not statistically significant. However, inflammatory markers (IL6, TNF-α, hsCRP), and insulin resistance (HOMA-IR) were higher and insulin sensitivity (QUICKI) was significantly lower in subjects with metabolic syndrome compared to subjects without metabolic syndrome.

Severity of triple vessel disease (TVD) increased with increase in number of metabolic abnormalities. Double vessel disease (DVD) was comparable with number of metabolic abnormalities. However, single vessel disease (SVD) decreased with increase in metabolic abnormalities. In subjects with no metabolic components, SVD was significantly high compared to DVD and TVD [Table 3 and Figure 1].

There was no age and sex difference according to severity of coronary artery disease. There was no difference in smoking and physical inactivity was comparable according to the severity of disease. BMI was found to be highest in triple vessel disease and lowest in single vessel disease [Table 4]. Dyslipidemia was more in subject with TVD. Among lipids, total cholesterol was comparable but triglyceride, VLDL, LDL were high and HDL was low in subjects with triple vessel disease. Similarly, diabetes and hypertension were significantly high in subjects with TVD. Insulin resistance and inflammatory markers increased and sensitivity decreased with the increase in severity of CAD. Dietary differences was also seen in these subjects, dietary carbohydrates, energy, fat, and

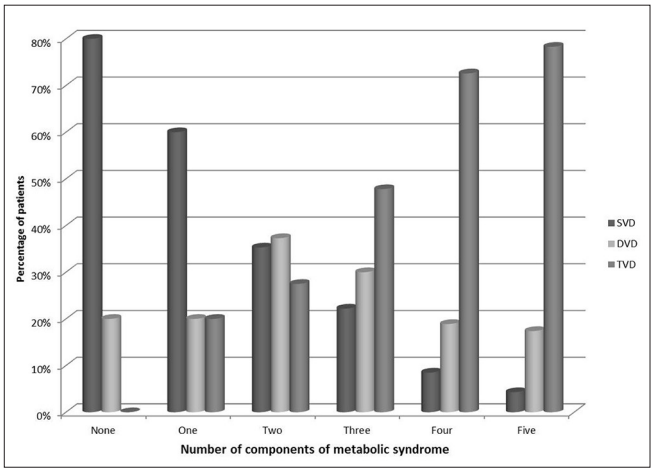

Figure 1: Severity of coronary artery disease according to components of metabolic syndrome; SVD: Single vessel disease; DVD: Double vessel disease; TVD: Triple vessel disease

vitamins were comparable in the subjects with and without metabolic syndrome but dietary proteins and minerals were significantly low in subjects with metabolic syndrome (data not shown).

Table 3: Severity of coronary artery disease according to components of metabolic syndrome

Number of metabolic components	Single vessel disease *n*: 67 (22.3%)	Double vessel disease *n*: 76 (25.3%)	Triple vessel disease *n*: 157 (52.3%)	*P* value
0	4 (80)	1 (20)	0	0.0058
1	15 (60)	5 (20)	5 (20)	<0.0001
2	18 (35.3)	19 (37.3)	14 (27.5)	0.0005
3	20 (22.2)	27 (30)	43 (47.8)	0.4458
4	9 (8.5)	20 (18.9)	77 (72.6)	<0.0001
5	1 (4.3)	4 (17.4)	18 (78.3)	0.0244
P value for trend	<0.0001	0.1341	<0.0001	

Discussion

We evaluated the association of various cardiovascular risk factors with severity of CAD in 300 subjects with angiographically proven CAD. SVD, DVD, and TVD were present in 22.3%, 25.3%, and 52.3% subjects, respectively. In a study from India by Sukhija *et al*.[12] reported SVD in 11%, DVD in 27% and TVD in 45% among 82 patients undergoing angiography. In a Korean study, individuals with the MetS had a higher prevalence of multi-vessel disease (34% vs 16%, $P < 0.001$) than those without the MetS[13] similar to our study. A lower prevalence of MetS was reported in a population based survey among Indians.[14,15] Low prevalence reported may be attributed to the different criteria used to define MetS, particularly different cut-off values for waist Circumference. Hence, the prevalence of Met S varies widely, depending upon the

Table 4: Coronary risk factors according to severity of coronary artery disease

Parameters	Single vessel disease Mean±SD (95%CI) *n*: 67 (22.3%)	Double vessel disease Mean±SD (95%CI) *n*: 76 (25.3%)	Triple vessel disease Mean±SD (95%CI) *n*: 157 (52.3%)	*P* value
Age (years)	59.24±13.59 (55.92-62.55)	60.51±13.47 (57.43-63.59)	61.83±11.45 (60.03-63.64)	0.345
Sex				
Male	18 (26.9)	17 (22.4)	49 (31.2)	0.360
Female	49 (73.1)	59 (77.6)	108 (68.8)	
BMI (Kg/m^2)	26.96±3.34 (26.14-27.77)	27.41±3.50 (26.61-28.21)	28.52±4.04 (27.88-29.16)	0.008
WHR	0.91±0.06 (0.90-0.93)	0.92±0.05 (0.91-0.94)	0.92±0.06 (0.91-0.93)	0.746
Cholesterol (mg/dl)	174.85±41.68 (164.68-185.02)	179.43±47.45 (168.59-190.28)	180.10±46.58 (172.75-187.44)	0.727
Triglycerides (mg/dl)	174.85±41.68 (164.68-185.02)	179.43±47.45 (168.59-190.28)	180.10±46.58 (172.75-187.44)	<0.0001
HDL-C (mg/dl)	44.72±7.63 (42.85-46.58)	39.96±8.70 (37.97-41.95)	36.05±8.84 (34.66-37.45)	<0.0001
VLDL-C (mg/dl)	29.06±6.80 (27.40-30.72)	31.03±8.01 (29.20-32.86)	37.98±9.11 (36.54-39.42)	<0.0001
LDL (mg/dl)	101.06±15.00 (90.09-112.04)	108.44±52.45 (96.45-120.42)	106.06±51.95 (97.86-114.25)	0.674
DM *n* (%)	5	20 (26.3)	100 (63.71)	<0.0001
HTN *n* (%)	23 (34.3)	43 (56.6)	122 (77.7)	<0.0001
Smoking	31 (46.3)	24 (31.6)	56 (35.7)	0.171
Less physical activity *n* (%)	26 (38.8)	32 (42.1)	58 (36.9)	0.752
Dyslipidemia *n* (%)	4 (6.0)	17 (22.4)	103 (65.6)	<0.0001
Insulin (mU/L)	34.53±33.61 (26.33-42.73)	46.62±38.86 (37.74-55.50)	58.57±47.29 (51.11-66.03)	<0.0001
HOMA-IR	9.72±16.17 (5.78-13.67)	12.78±9.89 (10.52-15.04)	24.44±24.85 (20.52-28.36)	<0.0001
QUICKI	0.31±0.05 (0.29-0.32)	0.28±0.03 (0.27-0.29)	0.26±0.03 (0.26-0.27)	<0.0001
IL6 (pg/ml)	31.70±58.01 (17.55-45.85)	60.74±68.19 (45.15-76.32)	80.41±80.44 (67.72-93.09)	<0.0001
TNF-α (pg/ml)	15.66±17.53 (11.38-19.94)	23.97±31.72 (16.72-31.22)	30.02±50.24 (22.10-37.94)	0.052
hsCRP (mg/L)	6.00±7.71 (4.12-7.88)	11.26±9.25 (9.14-13.38)	14.30±9.59 (12.79-15.81)	<0.0001

BMI: Body mass index; WHR: Waist hip ratio; DM: Diabetes mellitus; HTN: Hypertension; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein; LDL: Low-density lipoprotein; HOMA-IR: Homeostatic model analysis-insulin resistance; QUICKI: Quantitative insulin check index; hsCRP: Highly sensitive C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; SD: Standard deviation; CI: Cumulative incidence

type of study (hospital based vs. population based), baseline characteristics of the study population (e.g. ethnicity, age, history of ACS) and criteria used to define MetS.[14-16]

Subjects with diabetes mellitus, HTN and dyslipidemia increased with severity of coronary artery disease.[12,17-24] Multi-vesssel disease is more common in diabetic patients than in the controls, with TVD being the most common.[17,18] Rana *et al.*[19] also reported more involvement of CAD in DM versus non-DM individuals [SVD (19 vs. 14%), DVD (9 vs. 7%), and TVD (9 vs. 5%) ($P < 0.0001$ for all)]. Others have also observed similar findings.[20,21] These results support the hypothesis of a greater severity of angiographic proven CAD in diabetic than in non-diabetic patients.[22] Diabetics suffer from higher prevalence of diffuse and extensive coronary atherosclerosis.[23] Contrary to our study there was no relationship between hypertension and extent (multi-vessel involvement) of CAD (P = not significant, NS) in a study.[25]

Triglyceride and VLDL was significantly high and HDL was significantly low in TVD compared with SVD. Contrary results were obtained in some studies.[26-28] In an Iranian population, dyslipidemia (r: 0.092, *P*: 0.035) was more prevalent among those with severe coronary disease similar to our study.[29] A study observed significant difference between the severity of CAD based on presence of dyslipidemia.[30] A high statistically significant values were found for HDL present in total cholesterol (r: −0.56) and lowest correlation coefficient was found for triglyceride (r: 0.29).[31]

Severe CAD was present in significantly higher number of patients having MetS as compared to those without MetS. Similar association has been reported by other studies.[4,5,32,33] Kip *et al.*[5] reported statistically significant prevalence of severe CAD in patients with MetS (47% as compared to 25% in patients without MetS). Yavuz *et al.*[4] reported significantly higher number of patients with MetS having severe CAD as compared to patients without MetS (91% vs. 62%). Anuurad *et al.*[32] in a multicenter study also reported significantly higher prevalence of severe CAD in European American and African American patients having MetS as compared to patients without MetS (71% and 57% vs. 29% and 43%). Thus CAD tends to be more severe in patients with Met S in all populations studied and in different ethnic groups.

Severity of CAD increased with increasing number of metabolic abnormalities in this study. The MetS score was significantly associated with the extent of coronary atherosclerosis and affected vessel number in CAD.[33,34] It was found to be independently associated with coronary disease severity in patients with coronary artery disease requiring interventional treatment of stable angina.[35] Individuals with the MetS had a higher prevalence of CAD (60% vs 32%, $P < 0.001$), multi-vessel disease (34% vs 16%, $P < 0.001$), and acute coronary syndromes (49% vs 26%, $P < 0.001$) than those without the MetS.

Insulin and IR was high but sensitivity index was low in triple vessel disease. Subjects with metabolic syndrome were higher in triple vessel disease compared to single vessel disease. No difference was found between single vessel and double vessel disease. Stepwise ordinal logistic regression analysis identified in a study showed increased fasting plasma insulin concentrations in these obese subjects as a significant independent risk factor for the severity of angiographic CAD ($P < 0.0001$).[12]

Inflammatory marker (IL6, hsCRP, and TNF-α) were higher in patients with TVD compared with those with SVD. Auer *et al.*[36] suggested that the serum concentration of C-reactive protein is associated with presence, but not severity, of coronary artery disease in patients referred for coronary angiography. However, other study has reported a significant correlation of TNF-α and IL-6 with the severity of CAD as assessed by the number of obstructed coronary vessels.[37]

There are some limitations of the study. Firstly, this was a cross-sectional study among patients with CAD, hence, predictive value of each component of MetS to identify CAD risk could not be estimated. Secondly, several patients were on antihypertensive and anti-hyperglycemic drugs which could influence biochemical assessment including inflammatory cytokines. However, there were no statistically significant difference between patients who were already on drugs and those were detected new hypertension or diabetes. Lastly, we have assessed severity by the number of vessels involved, though scoring system for severity of CAD exist.[38]

Conclusions

Frequency of metabolic syndrome is high in patients with coronary artery disease and is associated with severe CAD. Severity of CAD increases with presence of increasing number of metabolic abnormality.

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