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Prevalence of cardiac autonomic dysfunction in patients with Metabolic Syndrome.

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ABSTRACT

Background: Cardiovascular autonomic dysfunction (CAD) is a distinguished disorder associated with metabolic syndrome. The pathogenesis of CAD in patients with metabolic syndrome still remains unclear. This study was undertaken to assess the prevalence of cardiac autonomic dysfunction in patients with metabolic syndrome and to correlate different parameters of metabolic syndrome with cardiac autonomic dysfunction. **Methods:** In this study, total 384 cases meeting the inclusion criteria and attending the Department of Medicine, Index Medical College, Indore, M.P, were enrolled. 136 (35.4%) patients satisfied the IDF criteria of metabolic syndrome were further studied for cardiac autonomic dysfunction test. Comparison of categorical variables was made using chi-square test. P-value <0.05 was considered as statistically significant.
Results: Majority of study population (32.35%) belonged to the age group of 50-59 years. 52/136 patients had CAD. So, the overall prevalence of cardiac autonomic dysfunction among MetS patients (CAD) was 38.2%. Overall distribution of various parameters like waist circumference, fasting blood glucose, blood pressure, HDL-C and serum triglycerides was assessed in all subjects with respect to CAD. Statistically significant association of these parameters was seen with CAD (p-value ≤0.01).
Conclusions: This study showed strong association between CAD and central obesity, impaired fasting glucose, high blood pressure and dyslipidemia. Thus, the metabolic disorders are good predictors of CAD.

Keywords: Cardiac autonomic dysfunction, Diabetes mellitus, Metabolic syndrome

INTRODUCTION

Cardiovascular autonomic disorder (CAD) is a grave and frequent complication associated with diabetes mellitus that is often under-recognised. As per the recent data given by the International Diabetic Federation- Diabetes Atlas (2017), approximately 425 million adults are troubled with DM and these numbers are anticipated to swell to 629 million by 2045.[1]

Diagnostic criteria for metabolic syndrome has been given by various agencies such as WHO, IDF and NCEP ATPIII.[2-4] The WHO criteria highlights the presence of insulin resistance with impaired fasting glucose (100-125 mg/dL), or impaired glucose tolerance (140-199 mg/dL), or on evaluating the homeostatic model assessment of insulin resistance (HOMA-IR) value.[2] The NCEP-ATP III criteria is amalgamation of hypertension, hyperglycemia, atherogenic dyslipidaemia, and central obesity. While, IDF stresses on the existence of central obesity, in combination with 2 or more components, even though there is lack of insulin resistance.[3,4]

According to 2015 IDF statistics, global prevalence of metabolic syndrome in all adults is around 25%.[5] Similarly, epidemiological studies in India report a prevalence of metabolic syndrome in urban communities at 22.37% and 19.52 % in North and West India, respectively.[6,7]

Pathogenesis of CAD is complex, multi-factorial, and still remains unclear.[8] Thus, there is an extra curiosity to explore CAD in pre-diabetic individuals and in individuals who are at an increased risk of type 2 diabetes mellitus (T2DM), majority of whom also suffer from metabolic syndrome. The metabolic syndrome consists of a variety of metabolic aberrations and thus, contribute to an amplified risk of cardiovascular disease (CVD) and DM.[9-12]

Autonomic dysfunction is a general term and it encompasses any disease or abnormality of the autonomic nervous system. CAD is an end product of an insult to the autonomic nerve supply to the heart.[13] Metabolic syndrome can result in initial cardiac autonomic dysfunction (CAD), particularly affecting heart rate, which can progress on to a significant cardiovascular complications including coronary artery disease, arrhythmias, myocardial infarction, orthostatic hypotension and sudden cardiac death.[14,15] Moreover, it has been demonstrated that CAD can forecast the likelihood of cardiovascular events and sudden cardiac death that is observed with heightened glycaemic control in subjects with T2DM.[16]

To best of our knowledge, prevalence of CAD has not been systematically estimated in adult Indian patients with metabolic syndrome and only few studies have examined autonomic dysfunction or its correlation within this high-risk group. Evidence suggests that abnormalities in autonomic regulation can contribute to dimensions of the metabolic syndrome and associated end-organ complications.[15,17-21] Moreover, previous studies on cardiac autonomic function (CAF) in obesity and metabolic syndrome have been performed in western world but such studies from the perspective of adult Indian population are lacking.[19,22-27]

Thus, the aims and objectives of the present study were to evaluate CAD in patients with metabolic syndrome and to correlate different parameters of metabolic syndrome with CAD.

MATERIALS AND METHODS

A total of 384 patients those attended the medicine department were included in the study. Metabolic syndrome patients will be recruited by following IDF guidelines on the basis of prevalence in the country. (15)

Inclusion criteria were adult subjects (>20 years of age), of either gender, fulfilling the IDF criteria for metabolic syndrome, The diagnosis of MetS was made when three or more of the following were present:

1. Waist circumference >102 cm in male and >88 cm in female
2. Fasting blood glucose >110 mg/dl
3. Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg
4. Fasting triglyceride (TG) >150 mg/dl
5. High density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women.

Exclusion criteria were hypo- and hyper-thyroidism; nephrotic syndrome; coronary heart disease; pregnancy; cerebrovascular disease; chronic renal failure; PCOS; and taking medications known to influence lipid profile, BP, CAF and plasma glucose.

Approval from the Institutional ethical committee was attained before conduction of the study

Cardiac autonomic function tests: All patients recruited in the study were requested to abstain from smoking and beverages containing caffeine for 12 hours prior to the testing. Only a light breakfast was permitted with a time interval of at least 2 hours prior to the testing. Postural or orthostatic hypotension was assessed by measuring both the supine and standing BP. Subjects were made to rest in supine position for 5min. BP was measured in supine and then standing position. Orthostatic hypotension was defined as a sustained decrease in systolic BP by ≥20 mmHg within 3minutes of standing from supine position.

The Parasympathetic dysfunction tests that were performed for detection of CAD were as follows:

1. **Resting heart rate**: normal is 60 to 100 beats per minute [4].
2. **Heart rate response to standing (30:15 stand ratio):** performed during the initial phase of adaptation to orthostasis i.e. immediately upon standing (first 45s), and the ratio is calculated as a quotient of the maximal (around 30th heart beat) to minimal (near 15th heart beat) RR interval in this period in the Electrocardiogram (ECG) recorded. The heart rate response to standing (30: 15 ratio) of 1.03 or more is considered to be normal parasympathetic response, 1.01-1.03 is grouped as border line and 1.00 or less is abnormal parasympathetic response.[5,20].
3. **Expiratory- Inspiratory difference (E-I difference)/heart rate response to deep breathing:** Heart rate was recorded first during normal breathing (at rest) and then during deep breathing (6/minutes, with five seconds of inhalation and five seconds of exhalation per breath). ECG was recorded and difference between the average of the largest accelerations during inspiration and the average of the largest decelerations during expiration was calculated. Value < 15 beats per minute is abnormal [5,20].
4. **The valsalva ratio:** Subjects were instructed to exhale into a mouthpiece connected to a mercury manometer and to maintain the expiratory pressure of 40 mmHg for 15 seconds. A clamp is placed on the nose and it is suddenly released after 15 seconds. ECG is recorded during the resting period and during the subsequent 40 heart beats after releasing the clamp. The ratio was calculated between the maximum R-R interval (after the release of strain) and the minimum R-R interval (during strain). Value below 1.21 is abnormal [7,20].

   Parasympathetic dysfunction was defined as abnormal result on abnormal heart rate response to standing (30:15 stand ratio) test or abnormal result on both E-I difference and Valsalva ratio tests [20].

Sympathetic function tests included:

1. **Postural hypotension/fall in SBP:** After baseline recording of SBP and heart rate in the supine position, the subject was asked to stand for at least 120 seconds. Blood pressure and heart rate were recorded immediately and 120 seconds after the standing position. Difference between the baseline supine and the minimal blood pressure after standing up was taken. More than 20 mmHg decline in SBP is abnormal [7,20].
2. **Change in DBP on sustained hand grip/isometric exercise test:** After recording basal blood pressure, subjects were asked to perform an isometric handgrip exercise. Subjects were instructed to hold the handgrip spring dynamometer in the dominant hand to have a full grip. The handles of the dynamometer were compressed by the subject with maximum effort for a few seconds. The entire process was carried out three times, with breaks in between to prevent fatigue. The mean of the three readings was referred to as maximal isometric tension (T max). Then, the subjects were instructed to perform an isometric handgrip exercise at 30% of T max for two minutes. During the test, blood pressure was recorded from the non exercising arm. Five minutes after completion of the exercise blood pressure was again recorded. Difference between the highest diastolic pressure during the examination and the average diastolic pressure at rest was taken. It should normally be higher than 10 mmHg [6,20].

   Sympathetic dysfunction was defined as abnormal result on both of the above tests of **cardiac sympathetic function [20].** Presence of either of parasympathetic or sympathetic dysfunction was defined as presence of **cardiac autonomic dysfunction(CAD)** in a subject [20].

   Normal SBP and DBP were taken as <120 mmHg and <80 mm Hg, respectively [20].

Statistical analysis

The data was collected and entered into Microsoft Excel sheet 2010 and then analyzed by SPSS version 17. Data was expressed as mean± SD for numerical variables and as absolute number and percentages for categorical variables. Comparison of categorical variables was done using chi-square or Fisher's exact test. In the present study, p-value <0.05 was considered as statistically significant.

RESULTS

In the present study, Out of the 384 cases of total study participants, males were 219 in number versus 165 numbers of females. 136 cases (136/384 = 35.41%) were identified to be having MetS. Among the 136 cases of MetS, 88 were females (88/136 = 64.7%) versus 48 males (48/136 = 35.29%). Among the male patients the prevalence of MetS was 21.9% (48/219) versus53.3% (88/165) in females. Prevalence of MetS was significantly more common in females than in males ($P < 0.05$). Among the 136 cases of MetS, maximum numbers of cases were in the age range of 50–59 years (32.35%) followed by 40–49 years (29.41%), 30–39 years (19.11%), >60 years (18.38%). Least number of cases were in <30 years age group range, i.e., (0.73%)

Among MetS patients, high obesity (95.5%), hyperglycemia was the most common accompanying disease (88.97%) followed by high blood pressure (79.41%), low HDL in 63.23% and high TG (42.64%) of cases [Table 1].

Table 1: Prevalence of components of various parameters among the subjects of metabolic syndrome (*n*=136)

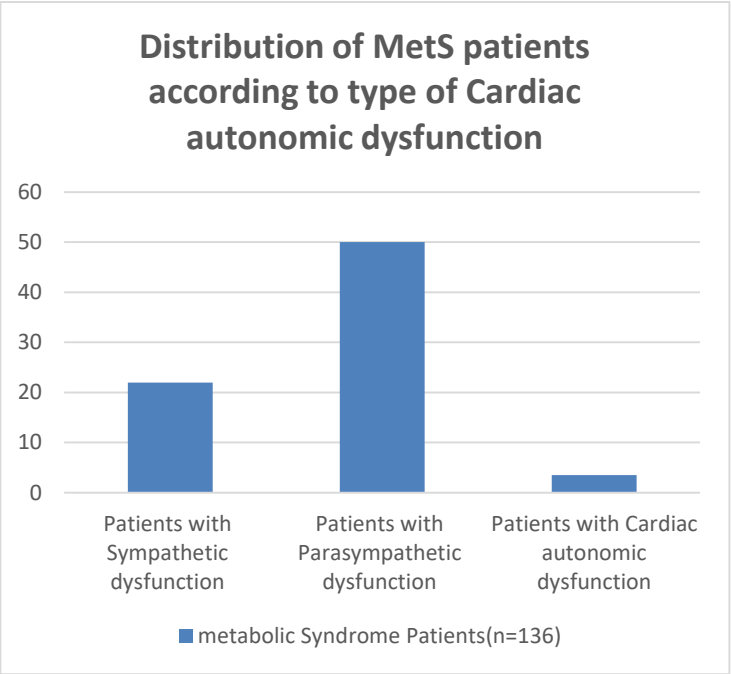
Components of MetS	Male (*n*=48), *n* (%)	Female (*n*=88), *n* (%)	Total (*n*=136), *n* (%)
Abnormal BP	39(81.25%)	69(78.4%)	108(79.41%)
Hyperglycemia	42(87.5%)	79(89.77%)	121(88.97%)
Waist Circumference(Obesity)	48(100%)	82(93.18%)	130(95.5%)
TG >150 mg/dl	13(27.08%)	45(51%)	58(42.64%)
Low HDL	31 (64.58%)	55(62.5%)	86(63.23%)

Hyperglycemia, obesity, and high TG were significantly higher prevalent in female subjects.
MetS: Metabolic syndrome; BP: Blood pressure; HDL: High density lipoprotein; TG: Triglyceride.

Table 2: Distribution of MetS patients according to type of Cardiac autonomic dysfunction

Type of cardiac autonomic dysfunction	MetS patients	Percentage (%)	p-value
Sympathetic dysfunction	22	16.17%	0.0003
Parasympathetic dysfunction	50	36.76%	0.009
Cardiac autonomic dysfunction	52	38.23%	0.005

Where, p-value <0.05 was considered as statistically significant.



Distribution of the metabolic syndrome patients according to the type of cardiac autonomic dysfunction is summarized in Table 2. It was observed that metS patient with sympathetic dysfunction was found in 22(16.17%) patients (p-value = 0.0003), metS patient with parasympathetic dysfunction in 50(36.76%) patients (p-value = 0.009) and overall, autonomic dysfunction among MetS patient was found in 52/136 (38.2%) patients (p-value = 0.005) was significant.

Distribution of various parameters in all subjects according to CAD is summarised in Table 3. It was observed that 50(96.13%) CAD patients has waist circumference higher than normal (p-value = 0.001), 49 (94.23%) patients is having fasting blood sugar levels more than 100 mg/dl (p-value <0.0001), 38 (73.07%) patients have abnormal BP (p-value = 0.01), 43 (82.69%) patients shows low serum HDL-C levels (p-value <0.0001) and 35 (67.30%) patients have high serum TG levels (p-value = 0.001).

Table 3: Distribution of various parameters in MetS patients according to Cardiac autonomic dysfunction (CAD)

Parameters	**Cardiac autonomic dysfunction (52)**	**Percentage (%)**
Waist Circumference(cm) Higher than normal	50	96.13%
Fasting glucose (mg/dl) >= 100	49	94.23%
Blood pressure (mmHg) Higher than normal	38	73.07%
HDL (mg/dl) Lower than normal	43	82.69%
Serum triglycerides (>150 mg/dl)	35	67.30%

DISCUSSION

The metabolic syndrome is characterized by clustering of risk factors, which predisposes subjects to increased risk of diabetes and cardiovascular disease (CVD) [6,7]. The main components of the syndrome are glucose intolerance, obesity, raised blood pressure and dyslipidemia. It is increasingly attracting the attention of international research institutions and scientific societies, as a major modifiable determinant of cardiovascular disease and type 2 diabetes [8-10].

The prevalence of MetS in India is increasing due to urbanization, high calorie diet and lack of physical activity. There are many criteria which have been used in various studies of MetS,[11] Depending on the study participants and criteria used, In the present study, the overall prevalence of metabolic syndrome was found to be 35.41% among individuals aged 30 years and above in the rural part of district Indore of state Madhya Pradesh. Out of the total 384 participants, 136 were found to be having metabolic syndrome. In India several studies have shown different rates of prevalence in different parts of the country [15] found the prevalence of MS in south Indian population to be 25.8% by IDF as compared to 18.3% by ATP-III Similar to the present study, Garruti G and colleagues reported the prevalence of CAN as 33.9%.[19] Laitinen and colleagues reported the prevalence of parasympathetic and sympathetic dysfunction as 25% and 6%, respectively.[17]

High prevalence of MetS in female patient has been previously documented across the globe.[23,26-31] In our study, the prevalence of MetS was significantly higher in female patients (88 in female vs. 48 in males Chi-square $P < 0.05$). The study was more close to the eastern Indian study of Prasad *et al*. where they documented the female prevalence of 52.2% versus 34.25% in males.[25] In our study, the prevalence of components of MetS in the study population was found to be in hyperglycemia (96%), high TG (46%), obesity (95.5%) high blood pressure 85.71%, and low HDL in 68.2% of cases [Table 1]. Prasad *et al*. reported the prevalence of the components: high blood pressure 63.1%, obesity 48.9%, low HDL 46.9%, triglyceridemia 46%, and hyperglycemia 31.2%.[25] The spectrum of prevalence in our study seems completely different from the above mentioned eastern Indian study.[25]

Although all the components of MetS were more prevalent in females of our study, only hyperglycemia, obesity, and high TG were significantly higher prevalence than male patients. In previous studies, it has been reported that central obesity and low HDL was more common in female patient and high blood pressure and triglyceridemia was more common in male patients, rendering the males to be more at risk for cardio vascular events.[33,34] We did not find any such differences. This probably means that females are no more at less risk than male patients in development of cardiovascular events.

In the present study, CAD was present in 38.2% of subjects with metabolic syndrome. This association was found to be statistically significant (p-value <0.001). Thus, the development of CAD is strongly associated with the metabolic syndrome as reflected by the present study, as all subjects with CAD had one or more risk factor of the metabolic syndrome. Moreover, with the addition of each of the components of the metabolic syndrome, the prevalence of the CAD had increased. Thus, CAD can be considered as the predictor of the metabolic syndrome.

Similar to the present study, Garruti G and colleagues reported the prevalence of CAN as 33.9%.[19] Laitinen and colleagues reported the prevalence of parasympathetic and sympathetic dysfunction as 25% and 6%, respectively.[17]

Prevalence of cardiac autonomic dysfunction, as reflected by various tests of sympathetic and parasympathetic function, was significantly higher in metabolic syndrome patients. Total cholesterol, LDL cholesterol, and triglycerides, were also significantly higher in metabolic syndrome patients with autonomic dysfunction than in metabolic syndrome patients without autonomic dysfunction. Parasympathetic dysfunction was found associated with BMI and triglyceride levels but not with cholesterol or HbA1c by Laitinen T et al., [8]. Higher levels of HbA1c and lipids were found in individuals with cardiac autonomic dysfunction in another study [23].

In the present study, the prevalence of CAD in the subjects with BMI of 18.5-24.9, 25-29.9 and ≥30Kg/m^2 was found to be 14.2%, 16.6% and 39%, respectively. Therefore, it can be observed that as the severity of obesity increases, the prevalence of CAD also increases. In a study by Garruti and colleagues, prevalence of CAD in subjects with BMI of 18.5-24.9, 25-29.9 and ≥30Kg/m^2 was reported to be 16.4%, 34.4% and 49.2%, respectively.[19] Thus, BMI >25Kg/m^2 is a definite riskfactor for development of CAD.

The prevalence of CAD in subjects with central obesity was 36.76%. Among the subjects with CAD, 96.32% had observed that for any waist circumference (p-value = 0.001), fasting blood sugar levels (p-value <0.0001), BP (p-value = 0.01), serum HDL-C levels (p-value <0.0001) and serum TG levels (p-value = 0.001) significant number of subjects had no CAD.

The limitations of the present study include small sample size; selection bias-by including only the patients attending the General Medicine OPD, so the Control group was not the true reflection of the healthy general population; and finally, the CAF tests performed in this study were simple bedside tests. More complicated tests are available to assess cardiac autonomic functions which can be used to diagnose CAD with more accuracy.

CONCLUSION

In the present study, strong association was observed between CAD and central obesity, impaired fasting glucose, high BP and dyslipidaemia. Therefore, the metabolic disorders are good predictors of CAD. The patients with different metabolic parameters should be screened and regularly followed up for the associated autonomic dysfunctions. This can provide a better opportunity to reorient the functional abnormalities to improved function and can prevent many serious complications.

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