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Original Research Article

Prevalence of cardiac autonomic dysfunction in patients with metabolic syndrome: a cross-sectional, observational study

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ABSTRACT

Background: Cardiovascular autonomic neuropathy (CAN) is a distinguished disorder associated with diabetes mellitus and metabolic syndrome. The pathogenesis of CAN 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 cross-sectional observational study, total 100 consecutive cases meeting the inclusion criteria and attending the Department of Medicine in Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi were enrolled. 50 subjects who satisfied the IDF criteria of metabolic syndrome were taken as cases and remaining 50 subjects (age and gender matched) who did not satisfy the IDF criteria were taken as controls. Comparison of categorical variables was made using chi-square or Fisher's exact test. P-value <0.05 was considered as statistically significant.
Results: Majority of study population (i.e., 42%) belonged to the age group of 41-50 years. Overall prevalence of cardiac autonomic dysfunction (CAD) was 25%. Prevalence of CAD among cases and controls was 38% and 12%, respectively. 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: In this study, strong association was found 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 neuropathy (CAN) 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, hyperglycaemia, 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 CAN is complex, multi-factorial, and still remains unclear.[8] Thus, there is an extra curiosity to explore CAN 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. CAN 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 CAN 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 CAF in patients with metabolic syndrome and to correlate different parameters of metabolic syndrome with CAF.

METHODS

This is a cross-sectional observational study, performed in 100 subjects attending Department of Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. 100 subjects were randomly and equally divided into two groups: cases (n = 50; satisfying the IDF criteria of metabolic syndrome) and controls (n = 50 (age and gender matched; not satisfying the IDF criteria).

Inclusion criteria were adult subjects (>20 years of age), of either gender, fulfilling the IDF criteria for metabolic syndrome: central obesity- waist circumference ≥90 cm for men and ≥80 cm for women plus any two of the following four factors: raised TG level of ≥150 mg/dL; reduced HDL-C of <40 mg/dL in males and <50mg/dL in females; systolic BP ≥130 or diastolic BP ≥85 mmHg; and raised fasting plasma glucose (FPG) ≥100 mg/dL, or previously diagnosed type 2 diabetes.

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.

Procedure

Waist circumference of the patients were measured with the help of measuring tape. Subjects having waist circumference more than the recommended criteria were subjected to both the routine and special investigations. All the biochemical parameters were analysed with biochemistry auto-analyser Hitachi 902, 911 and 912.

Routine investigations included complete hemogram with TLC and DLC; urine routine and microscopic examination; blood glucose levels (fasting and post prandial); KFT (blood urea and serum creatinine) and LFT. Special investigations included lipid profile (serum TG, serum TC, HDL-C and LDL-C); ECG (CAF determined by heart rate variability and measured by the beat to beat R-R intervals of the cardiac cycle).

Cardiac autonomic function tests: All subjects 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.

Handgrip test: With the patients lying flat, resting diastolic BP was measured. Then, measure the maximal handgrip force by having the patient grip a semi-inflated

sphygmomanometer cuff as hard as possible. Then with a second sphygmomanometer, increase in diastolic BP was measured after a handgrip sustained for 5min. The diastolic BP should increase by>16mmHg, but in autonomic disorders it rises <10mmHg.

Deep breathing at rate of 6 breaths/min in supine position after 10minutes rest period: The average of 6 ratios between the longest R-R interval during expiration and the shortest R-R interval during inspiration for each breathing cycle, while subjects were supine and breathing deeply at a rate of 6 breaths per minute. Autonomic dysfunction is classified as an E/I ratio of ≤ 1.1.

Active standing from supine position: The ratio of longest R-R interval around 30th beat and the shortest R-R interval around 15th beat after standing from a supine position. The normal 30th:15th heart rate ratio is >1.03 and <1.0 in the presence of autonomic disturbance.

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, range and mean age of the study subjects were 21 to 79 years and 46.7±15.57 years, respectively. Majority (i.e., 42%) of the subjects belonged to an age group of 41-50 years. Age-wise distribution of the subjects in Cases and Controls groups are summarised in Table 1. This distribution of the study subjects in both the groups was not found to be statistically significant (p-value = 0.765).

Table 1: Age-wise distribution of study subjects in cases and controls groups.

Age group (years)	Cases (n = 50)		Controls (n = 50)		Total (n = 100)	
	N	%	N	%	N	%
20-30	7	14	7	14	14	14
31-40	3	6	7	14	10	10
41-50	22	44	20	40	42	42
51-60	15	30	13	26	28	28
>60	3	6	3	6	6	6
Total	50	100	50	100	100	100
#p-value	0.765					

Data expressed as absolute numbers and percentages; # - Chi-square test; p-value <0.05 was considered as statistically significant

The overall gender-wise distribution of the study subjects in different age groups are summarised in Table 2. This distribution of the study subjects according to the gender was not found to be statistically significant (p-value = 0.366).

Table 2: Gender wise distribution of study subjects in different age groups.

Age (years)	Gender			
	Male		Female	
	Frequency	Percent	Frequency	Percent
20-30	11	16.0	2	6.4
31-40	8	11.6	2	6.4
41-50	29	42.0	13	42.0
51-60	18	26.1	11	35.5
>60	3	4.3	3	9.7
Total	69	100	31	100

Data expressed as absolute numbers and percentages; # - Chi-square test; p-value <0.05 was considered as statistically significant

Table 3: Distribution of study subjects according to various parameters among cases and controls group.

Parameter	Type of patient				Total (n = 100)		#p-value
	Cases (n = 50)		Controls (n = 50)				
	N	%	N	%	N	%	
Waist circumference (cm)							
Higher than normal	50	100	17	34	67	67	<0.0001
Normal	0	0	33	66	33	33	
Fasting glucose (mg/dl)							
< 100 mg	11	22	28	56	39	39	0.01
≥ 100 mg	39	88	22	44	61	61	
Blood pressure (mm of Hg)							
Higher than normal	41	82	18	36	59	59	<0.0001
Normal	9	18	32	64	41	41	
HDL-C (mg/dl)							
Lower than normal	32	64	1	2	33	33	<0.0001
Normal	18	36	49	98	67	67	
Serum Triglyceride (mg/dl)							
Upto 150	14	28	47	94	61	61	<0.0001
>150	36	72	3	6	39	39	

Data expressed as absolute numbers and percentages; # - Chi-square test; p-value <0.05 was considered as statistically significant

Majority of the study subjects (i.e., 40%) had BMI of >30Kg/m^2. While, only 36% subjects had BMI of 18-24.9Kg/m^2. Majority of the subjects i.e. 38 (76%) in Cases group had BMI >30Kg/m^2. Whereas, majority of the subjects i.e., 32 (64%) in controls group had BMI of 18-25Kg/m^2.This distribution of subjects in cases and

control group (according to BMI) was found to be statistically significant (p-value <0.0001).

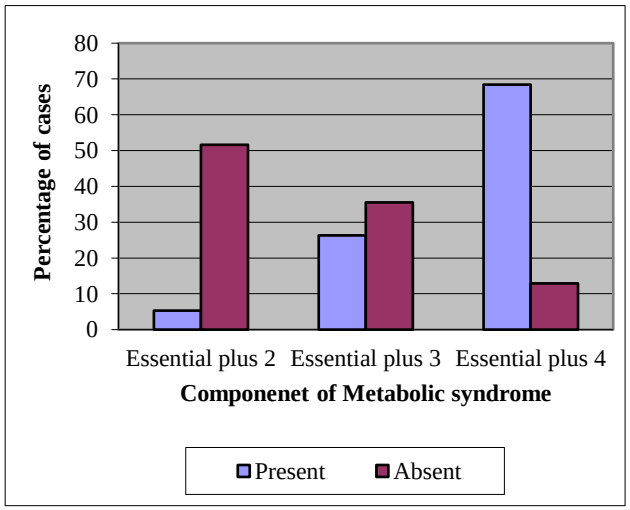
Distribution of the study subjects according to various parameters among cases and controls are summarised in Table 3. It was observed that the waist circumference (p-value <0.0001), fasting plasma sugar levels (p-value = 0.01), BP (p-value <0.0001) and serum TG levels (p-value <0.0001) were significantly greater and serum HDL-C levels (p-value <0.0001) were significantly lesser in cases as compared to Controls, respectively.

Table 4: Distribution of subjects according to type of cardiac dysfunction in cases and controls.

Type of cardiac dysfunction	Type of patient				Total		#p-value
	Cases		Controls				
	N	%	N	%	N	%	
Sympathetic dysfunction							
Present	8	16	0	0	8	8	0.0003
Absent	42	84	50	100	92	92	
Parasympathetic dysfunction							
Present	18	36	6	12	24	24	0.009
Absent	32	64	44	88	76	76	
Autonomic dysfunction							
Present	19	38	6	12	25	25	0.005
Absent	31	62	44	88	75	75	

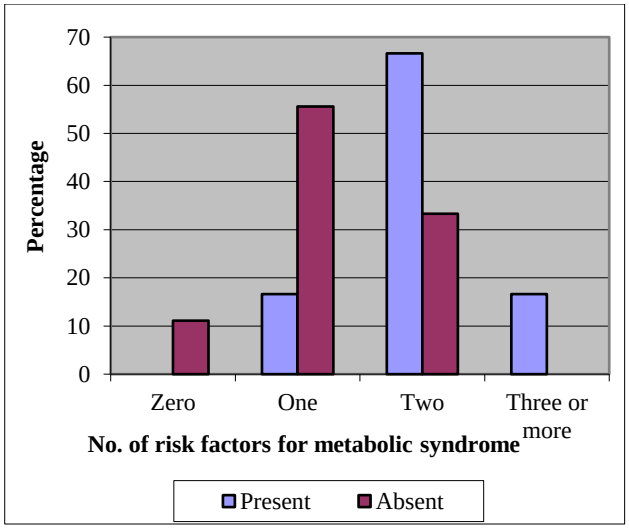
Data expressed as absolute numbers and percentages; # - Chi-square test; p-value <0.05 was considered as statistically significant

Distribution of the subjects according to the type of cardiac autonomic dysfunction in cases and controls are summarised in Table 4. It was observed that sympathetic (p-value = 0.0003), parasympathetic (p-value = 0.009) and overall, autonomic dysfunction (p-value = 0.005) was significantly greater in cases as compared to Controls.



Chi-square test; p-value <0.0001

Figure 1: Distribution of subjects according to autonomic dysfunction for various components of metabolic syndrome in cases.



P=0.01, Chi-square test; p-value = 0.01

Figure 2: Distribution of subjects according to the cardiac autonomic dysfunction in risk factor for metabolic syndrome in control group.

Table 5: Distribution of various parameters in all subjects according to cardiac autonomic dysfunction.

Parameter	Cardiac autonomic dysfunction				Total		#p-value
	Present		Absent				
	N	%	N	%	N	%	
Waist circumference (cm)							
Higher than normal	24	96	47	62.7	71	71	0.001
Normal	1	4	28	37.3	29	29	
Fasting glucose (mg/dl)							
<100	1	4	39	52	40	40	<0.0001
≥100	24	96	36	48	60	60	
Blood pressure (mmHg)							
Higher than normal	18	72	31	41.3	49	49	0.01
Normal	7	28	44	58.7	51	51	
HDL-C (mg/dl)							
Lower than normal	18	72	16	21.3	34	34	<0.0001
Normal	7	28	59	78.7	66	66	
Serum triglyceride (mg/dl)							
<150 mg/dl	8	32	54	71.1	62	62	0.001
≥150mg/dl	17	68	21	28.9	38	38	

Data expressed as absolute numbers and percentages; # - Chi-square test; p-value <0.05 was considered as statistically significant

Distribution of subjects according to CAD for various components of metabolic syndrome in Cases is depicted in Figure 1. It was noted that statistically significant number of Cases without autonomic dysfunction had no additional component of metabolic syndrome (p-value = 0.0001). Similarly, distribution of subjects according to

the CAD in risk factor for metabolic syndrome in control group is depicted in Figure 2. It was noted that statistically significant number of controls without autonomic dysfunction had no additional risk factor of metabolic syndrome (p-value = 0.01).

Distribution of various parameters in all subjects according to CAD is summarised in Table 5. It was 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.

Overall prevalence of CAD in different groups in the present study are summarised in Table 6.

Table 6: Overall prevalence of cardiac autonomic dysfunction in different groups.

Parameters	Prevalence (%)
Overall prevalence of cardiac autonomic dysfunction in this study	25%
Prevalence of cardiac autonomic dysfunction in metabolic syndrome (cases)	38%
Prevalence of cardiac autonomic dysfunction in control group	12%
Prevalence of cardiac autonomic dysfunction in subjects with impaired fasting glucose	40%
Prevalence of cardiac autonomic dysfunction in subjects with abnormal waist circumference	33.8%
Prevalence of cardiac autonomic dysfunction in subjects with high blood pressure	36.7%
Prevalence of cardiac autonomic dysfunction in subjects with low high-density lipoprotein-cholesterol	52.9%
Prevalence of cardiac autonomic dysfunction in subjects with high serum triglyceride	44.7%

Data expressed as percentages

DISCUSSION

In the present study, metabolic syndrome was present in 76% of subjects with CAD. Overall prevalence of CAD was 25%. Prevalence in Cases and Controls was 38% and 12%, respectively. 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]

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 risk factor for development of CAD.

The prevalence of CAD in subjects with central obesity was 33.8%. Among the subjects with CAD, 96% had central obesity and only 4% subjects had CAD without central obesity. Therefore, central obesity is an important risk factor for the development of CAD. According to a study in Finnish cohort by Laitinen and colleagues, the subjects with CAD and those with normal CAF had mean WC of 106±15cm and 99±11cm, respectively.[17] This finding demonstrates an association between CAD and central obesity.

The prevalence of CAD in subjects with FPG >100mg/dl and <100mg/dl was 40% and 2.5%, respectively. In subjects with CAD, 96% had FPG value higher than normal and this was found to be statistically significant. Similar findings were reported by Thiyagarajan and colleagues, who observed that the subjects with impaired FPG had altered CAF as compared to those with normal fasting glucose.[24]

The prevalence of CAD in subjects with low and normal HDL-C was 52.9% and 10.6%, respectively. The prevalence of CAD in subjects with serum TG >150mg/dl and in those with normal serum TG was 44.7% and 12.9%, respectively. This association was also found to be statistically significant. Similar to the present study, Garruti and colleagues reported a mean HDL-C levels of 39.1±10.1mg/dl and 42.5±11.3mg/dl in subject with CAD and in those with normal cardiac autonomic functions, respectively.[19] In the same study, values of serum TG reported were 167.3±92.1mg/dl and 140.9±95.8mg/dl in subjects with CAD and normal cardiac autonomic function, respectively.

The prevalence of CAD in subjects with high and normal BP range was 36.7% and 13.7%, respectively. In subjects

with CAD, 72% had BP in higher range. This finding is supported by Wu Jin-Shang and colleagues, who concluded that CAF plays a role in hypertension and altered autonomic function is already present in subjects with familial history of hypertension.[22]

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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