EPICARDIAL ADIPOSE TISSUE THICKNESS IN PATIENTS WITH METABOLIC SYNDROME AND ITS ASSOCIATION WITH CARDIOVASCULAR RISK FACTORS.

Cardiology

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ABSTRACT

INTRODUCTION: Metabolic syndrome is a constellation of several cardiovascular risk factors, and is defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria (2001) or the International Diabetes Federation (IDF) criteria (2005).^{1,2} The prevalence of metabolic syndrome varies between 24.6 - 41% in different parts of Indian subcontinent and based on different criteria for metabolic syndrome.

OBJECTIVES: To assess epicardial adipose tissue (EAT) thickness by echocardiography in patients with metabolic syndrome, and find out if there is any association between EAT thickness and different cardiovascular risk factors.

MATERIALS AND METHODS: This cross-sectional observational study was conducted in a tertiary care hospital in India among patients attending the Medicine and Cardiology out-patient department (OPD) during the study period of six months from May 2018 to October 2018. Patients satisfying the diagnostic criteria of metabolic syndrome as per the IDF criteria (2005) were included in the study, as there are separate cut off points for waist circumference for South Asian population.

Design: Cross-sectional observational study.

Setting: Single centre study in a tertiary care teaching hospital. Participants: Initially 450 patients with metabolic syndrome as per International Diabetes Federation (IDF) criteria (2005) were screened. Patients having age above 65 years, deranged liver/renal function, ischemic heart disease, heart failure, malignancy, pregnancy, ascitis, poor echo window, history of endocrine disorders like Cushing Syndrome, glucocorticoid use, having any acute illness and those not giving consent were excluded. Final sample size was 397. For defining the normal EAT thickness in this geographic region, 50 age and gender matched healthy volunteers without any conventional cardiovascular risk factors (except age in some cases) acted as controls. Study period was six months.

RESULT: The mean value of EAT thickness in the control group was 2.97 (± 0.86) mm, hence the upper reference limit of EAT thickness in this study was taken as more than mean + 2SD, i.e. 4.69mm. Mean EAT thickness in patients suffering from metabolic syndrome was 5.48 $\pm$ 0.83 mm, which was significantly increased compared to controls. Taking 4.69mm as cut off, it was seen that 311 (78.34%) patients had increased EAT thickness >4.69mm.

CONCLUSION: Further studies with larger sample size and longitudinal design are required to establish the ability of EAT thickness to predict cardiovascular risk.

KEYWORDS

INTRODUCTION

Metabolic syndrome is a constellation of several cardiovascular risk factors, and is defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria (2001) or the International Diabetes Federation (IDF) criteria (2005).^{1,2} The prevalence of metabolic syndrome varies between 24.6 - 41% in different parts of Indian subcontinent and based on different criteria for metabolic syndrome.^{3,4} It is believed that the combination of risk factors has a synergistic effect on cardiovascular risk. Increased waist circumference, i.e. abdominal obesity is a pre-requisite for the diagnosis of metabolic syndrome as per IDF criteria.² However, not only abdominal adiposity but also visceral adiposity and epicardial adipose tissue (EAT) are important factors in determining the cardiovascular risk. The severity of coronary artery disease is associated with lower adiponectin and higher interleukin 6 (IL 6) mRNA expression in EAT. It is also believed that EAT may be related to different cardiovascular risk factors, as also to different inflammatory markers. Hence, various imaging modalities to quantify EAT have been proposed. Ideal methods to measure EAT are cardiac magnetic resonance imaging (MRI), cardiac computed tomography (CT) or multi-detector CT. But these modalities are costly, not widely available and are contraindicated in some cases. EAT measurement by two dimensional echocardiography, which may be a cost-effective alternative to cardiac MRI has been tried.⁵ In this context, the present study aimed at assessing the EAT thickness by echocardiography in patients with metabolic syndrome, and finding out if there is an association of EAT thickness with different cardiovascular risk factors.

OBJECTIVES

To assess epicardial adipose tissue (EAT) thickness by echocardiography in patients with metabolic syndrome, and find out if there is any association between EAT thickness and different cardiovascular risk factors.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in a tertiary care hospital in India among patients attending the Medicine and Cardiology out-patient department (OPD) during the study period of six months from May 2018 to October 2018. Patients satisfying the diagnostic criteria of metabolic syndrome as per the IDF criteria (2005) were included in the study, as there are separate cut off points for waist circumference for South Asian population. As per the IDF criteria, a person was diagnosed as having metabolic syndrome if:

Waist circumference was ≥ 90 cm in males and ≥ 80 cm in females, measured midway between costal margin and highest point of iliac crest.

Design: Cross-sectional observational study.

Setting: Single centre study in a tertiary care teaching hospital. Participants: Initially 450 patients with metabolic syndrome as per International Diabetes Federation (IDF) criteria (2005) were screened. Patients having age above 65 years, deranged liver/renal function, ischemic heart disease, heart failure, malignancy, pregnancy, ascitis, poor echo window, history of endocrine disorders like Cushing Syndrome, glucocorticoid use, having any acute illness and those not giving consent were excluded. Final sample size was 397. For defining the normal EAT thickness in this geographic region, 50 age and gender

matched healthy volunteers without any conventional cardiovascular risk factors (except age in some cases) acted as controls. Study period was six months.

Interventions: Apart from clinical evaluation and routine blood tests, participants underwent echocardiography. Results: Upper limit of EAT thickness was calculated as 4.69mm. EAT thickness in metabolic syndrome patients was significantly more than controls. 78.34% metabolic syndrome patients had EAT thickness >4.69mm. On multivariate analysis, diabetes and high triglyceride >150mg/dL were significantly associated with increased EAT thickness. Moreover, values of EAT correlated with waist circumference in male subjects [Pearson's correlation coefficient $r=0.47$] but not in females. Significant correlation with BMI was also found [$r=0.42$].

CONCLUSIONS:

EAT thickness is increased in metabolic syndrome, and it may be associated with several cardiovascular risk factors.

Plus any two of the following:

- Triglyceride (TG) ≥ 150 mg/dL, or under treatment for this abnormality
- High density lipoprotein (HDL) <40mg/dL in males, <50 mg/dL in females
- Blood pressure (BP): systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mmHg, or under treatment for previously diagnosed hypertension
- Fasting plasma glucose ≥ 100 mg/dL, or previously diagnosed type 2 diabetes

Persons having age above 65 years, presence of deranged liver/renal function (LFT/RFT), established ischemic heart disease, heart failure or left ventricular ejection fraction (LVEF) less than 50%, malignancy, pregnancy, ascitis, poor echo window and history of endocrine disorders like Cushing Syndrome, glucocorticoid use, having any acute illness and those not giving consent were excluded from the study. After undergoing baseline investigations and anthropometric measurements, study subjects underwent echocardiography with Doppler [GE Vivid 7 Ultrasound System]. EAT was measured in parasternal long axis view, as an echo-free space immediately anterior to the right ventricle in end-systole, between the visceral and parietal layers of pericardium.⁵ A single operator with requisite qualification and experience in echocardiography took the echocardiographic measurements for each patient. Three consecutive measurements for each patient were taken and average of the three measurements was taken as final.

Required sample size for the study was calculated using the formula: $(z_{\alpha})^2 pq/L^2$, where $z_{\alpha}=1.96$, p =expected proportion of abnormal EAT thickness, L =relative precision. Taking p as 50% based on study by Mookadam et al, L as 10% of p , i.e. 5, the estimated minimum sample size came to be roughly 384.⁶

450 individuals with metabolic syndrome were screened during the specified study period. 42 patients had a poor echo window precluding precise measurement of EAT, hence excluded. Six had deranged LFT and three had deranged RFT and two patients did not give consent for the study. So after satisfying the inclusion and exclusion criteria, 397 metabolic syndrome patients were finally selected for the study. As the normal values of EAT are not standardised, 50 age and gender matched volunteers without any of the components of metabolic syndrome, having normal ECG, and echocardiogram and without any cardiological complaints or known cardiovascular risk factors (apart from age) served as controls, and normal range of EAT was estimated. The controls were chosen from family members of the study subjects.

Data analysis: The data were tabulated in Microsoft Excel version 2007 and analysed with Statistical Package for Social Sciences (SPSS) version 20. For descriptive statistics, frequency, percentage, mean and standard deviation (SD) were used. Chi square test was done for categorical variables and Student's t test for continuous variables. Logistic regression analysis was used to determine the predictors of increased EAT thickness. The study received ethical clearance from appropriate authorities [Institutional Ethics Committee; letter No MC/Ko/IEC/NON-SPON/520/02/2018, dated 20/02/2018].

RESULTS

Comparison of clinical and laboratory parameters between the

metabolic syndrome group and control group is shown in Table 1. Median age of metabolic syndrome patients was 48years [Range 29 years to 64 years]. The mean value of EAT thickness in the control group was $2.97 (\pm 0.86)$ mm, hence the upper reference limit of EAT thickness in this study was taken as more than mean + 2SD, i.e. 4.69mm. Mean EAT thickness in patients suffering from metabolic syndrome was 5.48 ± 0.83 mm, which was significantly increased compared to controls. Taking 4.69mm as cut off, it was seen that 311 (78.34%) patients had increased EAT thickness >4.69mm. The EAT values in metabolic syndrome patients ranged from 4mm to 7mm. On uni-variate analysis, it was observed that hypertension, diabetes, low HDL, high TG, hypothyroidism, LVH and presence of diastolic dysfunction in echocardiography were significant predictors of raised EAT thickness. However on logistic regression analysis by ENTER method, it was observed that diabetes and high TG were significantly associated with increased EAT thickness. [Table 2] There was good model fitness, and Nagelkerke R square was 0.406. Moreover, it was noticed that values of EAT showed moderate correlation with waist circumference in metabolic syndrome male subjects [Pearson's correlation coefficient $r=0.47$, $p<0.05$, $n=210$], but no correlation in female subjects [$r=0.02$, $p>0.05$]. Also, significant correlation with BMI was found [$r=0.42$, $p<0.05$] However, no correlation with serum uric acid levels, or left atrial size was observed.

DISCUSSION

The present study showed that metabolic syndrome was associated with increased EAT thickness compared to controls. It was also observed that the EAT thickness was associated with hyperglycemia and raised triglyceride on multivariate analysis. Moreover, the values of EAT thickness had moderate correlation with waist circumference in male subjects, and significant correlation with BMI.

Studies from different parts of the world have highlighted the importance of EAT. In the study by Calabuig A et al, EAT thickness was independently associated with metabolic syndrome, as also its individual components like low HDL, high TG and waist circumference.⁷ In menopausal women also, EAT was associated with visceral adiposity, insulin resistance and metabolic syndrome. In a study on geriatric individuals with metabolic syndrome, it was suggested that EAT more than 7.3mm was a sensitive and specific marker for diagnosing metabolic syndrome. In another study, EAT thickness was correlated with LV mass, sub-clinical myocardial dysfunction and hs CRP, which serves as an inflammatory and pro-atherogenic marker. However, hs CRP estimation was not a part of the present study protocol. Ansari MA et al have shown that EAT thickness in patients with coronary artery disease (CAD) was more than those without CAD.⁸ In HIV patients with co-existent metabolic syndrome, similar relationship with EAT has been demonstrated. EAT was also associated with intima-media thickness in patients with metabolic syndrome. EAT thickness in the present study showed positive correlation with BMI and abdominal obesity, similar to the study by Shetty R et al.⁹ In the present study, echocardiographic assessment of EAT was done. The EAT thickness derived by echocardiography correlated strongly with MRI derived thickness in one study, thus pointing out the usefulness of echocardiography in this regard.¹⁰

CONCLUSION

This study has certain limitations like single centre study with a cross-sectional study design, and hence cardiovascular risk could not be related directly to EAT thickness. But it suggests that EAT thickness is higher in metabolic syndrome patients, and it is associated with individual components of metabolic syndrome. Further studies with larger sample size and longitudinal design are required to establish the ability of EAT thickness to predict cardiovascular risk.

Table 1: Baseline parameters of the metabolic syndrome patients (n=397) compared to controls (n=50)

Parameter	Patients (n=397)	Controls (n=50)	"p"
Age (Mean $\pm$ SD) in years	48.03 $\pm$ 5.88	47.37 $\pm$ 4.92	0.45
Male: Female	210: 187	28:22	0.79
Increased waist circumference (cm)	397 (100%)	0	
SBP ≥ 130 mm Hg/ DBP ≥ 85 mmHg, or previously hypertensive	353 (88.92%)	0	
FBS ≥ 100 mg/dL or, previously diabetic	280 (70.53%)	0	

Low HDL (mg/dL)	205 (51.64%)	0	
High TG (mg/dL)	198 (49.87%)	0	
BMI (kg/m ³)	28.02 ± 2.01	21.74 ± 2.06	<0.0001
Hypothyroidism	73 (18.39%)	0	
Serum uric acid (mg/dL)	5.09 ± 0.84	4.15 ± 0.65	<0.0001
Hyper-uricemia (males>7mg/dL; females>6)	56 (14.11%)	0	
Smoker	87 (21.91%)	0	
Alcoholic	24 (6.04%)	0	
Abnormal ECG	159 (40.05%)	0	
LVEF (Simpson)	64.40 ± 3.27 (Range 55%- 74%)	65.02 ± 3.89 (Range 58%- 72%)	0.22
LVH by echocardiography	296 (74.56%)	0	
Diastolic dysfunction	318 (80.10%)	0	
EAT thickness in end- systole (mm)	5.68 ± 0.83	2.97 ± 0.86	<0.0001

Table 2: Predictors of increased EAT in patients with metabolic syndrome (n=397)

Parameter		EAT > 4.69mm (311)	Odd ratio (95% CI)	Adjusted Odd ratio(95% CI)
Age	<48 years	135	1	
	≥48 years	176	1.24(0.77-2.01)	
Gender	Male	170	1.39(0.86-2.24)	
	Female	141	1	
High BP	Absent	9	1	1
	Present	302	23.03(10.45- 50.76)	16.08(0.87- 100.56)
IFG/Diabetes	Absent	59	1	1
	Present	252	8.85 (5.19-15.07)	3.65 (2.74-17.32)
Low HDL	Absent	138	1	1
	Present	173	2.12(1.29-3.46)	1.67(0.98-4.07)
High TG	Absent	144	1	1
	Present	167	2.06(1.26-3.37)	1.78(1.12-5.98)
Smoking	Absent	243	1	
	Present	68	0.99(0.55-1.76)	
Alcoholism	Absent	296	1	
	Present	15	0.43(0.18-1.03)	
Hypothyroidism	Absent	246	1	1
	Present	65	2.58(1.18-5.60)	1.97 (0.78-10.32)
Hyper-uricemia	Absent	271	1	
	Present	40	0.65(0.34-1.22)	
LVH	Absent	36	1	1
	Present	275	23.64 (12.95-43.18)	12.86 (0.36-98.43)
Diastolic dysfunction	Absent	23	1	1
	Present	288	23.37 (12.65-43.19)	15.09 (0.63-115.23)

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