

To evaluate the thickness of epicardial fat by 2-D echocardiography and its correlation with various parameters of metabolic syndrome

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Abstract

Introduction: There is increase in prevalence of metabolic syndrome in younger population in India. Epicardial fat is one of the components of visceral adipose tissue. There is little evidence to suggest that the extent of epicardial fat is strongly related to overall adiposity. The relationship between epicardial fat and metabolic syndrome is still unexplored. Hence the hypothesis of the study is to evaluate whether epicardial adipose tissue is related to anthropometric, clinical and biochemical parameters of metabolic syndrome.

Materials and Methods: The present study is a case control study which included 66 subjects- 33 cases (patients who fulfilled the NCEP ATP III criteria for metabolic syndrome) and 33 Controls. Detailed clinical history and physical examination (including blood pressure, height, weight, waist/hip circumference) along with biochemical examination (blood glucose, HbA1c, HOMA IR, serum insulin levels, fasting lipid profile) was done. Each subject underwent transthoracic two dimensional M-mode echocardiogram in left lateral decubitus position on Philips Sonos 5500 echocardiography machine to evaluate epicardial fat thickness.

Results: In our study we found a strong positive correlation between the epicardial fat thickness and the following parameters in patients of metabolic syndrome: BMI: $r = 0.52$, $p = 0.02$; HOMA IR; $r = 0.58$, $p < 0.001$; FPG; $r = 0.79$, $p < 0.00$; HbA1c, $r = 0.59$, $p < 0.001$; Triglyceride levels; $r = 0.75$, $p < 0.001$

Conclusion: Our study show a positive correlation with body mass index, blood pressure, fasting plasma glucose HbA1c, HOMA IR and Serum triglyceride level with epicardial fat thickness. We suggest that echocardiographic epicardial adipose tissue could be applied as an easy and reliable imaging indicator of cardiometabolic risk.

Keywords: Epicardial fat, Metabolic syndrome, HOMA IR.

Introduction

The metabolic syndrome is a constellation of chemical and metabolic abnormalities including abnormal obesity, hypertension, dyslipidemia and impaired fasting glucose or impaired glucose tolerance.¹ All these manifestations are surrogate marker of insulin resistance which is the crux abnormality associated with metabolic syndrome.

The incidence of coronary disease along with carotid atherosclerosis is higher in patients with metabolic syndrome along with mortality from all such cases. Similarly in individuals with cardiovascular disease there is recent evidence that the presence of each feature of syndrome is associated with greater absolute risk or recurrent cardiovascular event.²

Epicardial fat is one of the components of visceral adipose tissue.^{3,4} In the adult heart fully differentiated white adipose tissue can be commonly found atrioventricular and interventricular grooves extending to the apex. As the amount of epicardial fat increases, it progressively fills the space between the ventricles, sometimes covering the entire epicardial surface.⁴

There is little evidence to suggest that the extent of epicardial fat is strongly related to overall adiposity. Because of the close anatomical relationship to the heart and the absence of fascial boundaries, epicardial adipose tissue may locally interact and modulate the coronary arteries and myocardium through paracrine effects and direct secretion of anti-inflammatory and

proinflammatory adipokines.^{4,5} It has also been implicated in development of coronary atherosclerosis and might serve as a marker of cardio metabolic risk, even superior to subcutaneous fat and total body adiposity.

Magnetic resonance imaging (MRI) and computed tomography scan (CT scan) estimate visceral fat accurately but are expensive. Echocardiographic epicardial fat thickness clearly reflects visceral adiposity rather than general obesity.⁶ The echocardiographic measurement of epicardial fat is a non-invasive and objective qualification method.⁷

Lacunae in Existing Knowledge: The relationship between epicardial fat and metabolic syndrome is still unexplored. Hence the hypothesis of the study is to evaluate whether epicardial adipose tissue is related to anthropometric, clinical and biochemical parameters of metabolic syndrome.

Aims and Objectives

1. To evaluate the thickness of epicardial fat by two dimensional echocardiography.
2. To evaluate the correlation of thickness of epicardial fat with various parameters of metabolic syndrome.

Materials and Methods

The study was conducted in the department of medicine and biochemistry in LLRM Medical College Meerut.

The study included 66 subjects (33 cases and 33 Controls).

Study Design: The present study is a case control study in which cases were the patients who fulfilled the criteria for metabolic syndrome and meet the exclusion criteria. Controls were the subjects who don't have any feature of metabolic syndrome but meet the exclusion criteria.

Table 1: The NCEP ATP III criteria as mentioned was used for inclusion criteria

Central obesity	Waist circumference ≥ 90 cm (male) ≥ 80 cm (female) for south Asians }
Raised triglycerides	1.7 mmol/l (150 mg/dl)
Reduced HDL cholesterol	< 1.03 mmol (40 mg/dl) in males < 1.29 mmol/l (50 mg/dl) in females
Raised blood pressure	Systolic ≥ 130 mmHg Or Diastolic ≥ 85 mmHg
Raised fasting plasma glucose	Fasting Plasma glucose > 6.1 mmol/l (110 mg/dl)

Subjects: Both males and females of age ≥ 25 years with obesity, diabetes or hypertension visiting the medicine OPD/IPD, Medical college Meerut who fulfilled all inclusion and exclusion criteria for metabolic syndrome were selected and labeled as cases. The control group included subjects, age and sex matched, who visited the medicine OPD/IPD, Medical college Meerut and didn't have any of the features of metabolic syndrome.

Inclusion Criteria: Any subject of age above 25 years who is having 3 or more of the following criteria (ATP III criteria).

1. Increase waist circumference: Men > 102 cm, Women > 88 cm
2. Raised triglycerides: ≥ 150 mg/dL (1.7 mmol/L)
3. Reduced HDL Cholesterol < 40 mg/dl (1.03 mmol/L) in males, < 50mg/dL (1.29 mmol/L) in females.
4. Raised blood pressure symbolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg
5. Raised fasting plasma glucose (FPG) > 100mg/dL (5.6 mmol/L)

Exclusion Criteria are as follows

1. Valvular heart disease
2. Congenital heart disease
3. Pericardial effusion
4. Inadequate transthoracic echocardiographic window
5. Pregnant females
6. Ascites
7. Patients on drugs like beta-blockers, diuretics, insulin, statins, fibrates, niacin, orlistat, metformin, thiazolidinediones and hormone replacement therapy.
8. Patients objecting to consent.
9. Febrile illness

The patients were enrolled for the study after informed consent. All the issues including ethical issues of the study had been evaluated by the Institutional review board and approved.

As per predesigned proforma, detailed history was taken. Indirect auscultatory arterial blood pressure was

measured by standard clinical sphygmomanometer and stethoscope by the same observer. Precautions were taken in creating standard conditions of blood pressure recording as per WHO recommendations.

Blood Pressure: The pressure cuff (cuff off size 14 cm x 42 cm) with its lower border 2-3 cm above the anti-cubital space was applied to the right arm. The cuff was applied early and left in place during the interview and physical examination. The same cuff size was used throughout the study. A sitting position for adults was chosen only because of its convenience. The arms was comfortably supported, with the lower edge of the cuff at mid arm level. The cuff was rapidly inflated to a pressure 20 mm Hg above the systolic, as recognized by disappearance of the radial pulse. The bladder was deflated as the rundown of mercury was started at rate of 2 mm Hg every second. The systolic pressure was recorded by the first perceptible of sound (first korotkoff sound). The diastolic pressure (fifth Korotkoff sound) was determined by perception of disappearance of sound. The cuff was deflated to zero pressure and reading tabulated to nearest 2 mm Hg. Mean of three readings was taken after 1 minute intervals.

Standing Height was measured to the nearest 0.1 cm, without shoes, against the wall tape, eyes looking straight ahead (visual axis being horizontal with the top of the external auditory meatus in level with the inferior margin of bony orbit) resting on the scalp and against the wall.

Weight was measured in normal indoor clothing and without shoes.

Waist circumference was taken as the smallest girth between between coastal margin and iliac crest.

Hip circumference was measured at the inter trochanteric level using a steel tape as per recommended methodology.

Laboratory Investigations: After about 8 hours fast, venous samples were collected with the patient lying supine.

Blood Glucose: Blood glucose was determined by the enzymatic method using the reagent kit (Randox Gluc-PAP HITACHI). Whole blood was used for

determination of blood glucose immediately after collection. Post prandial venous samples were taken 2 hrs after meals.

Conversion of blood glucose to plasma glucose is done as Blood glucose x 1.14

Serum Cholesterol: Serum Cholesterol was measured by the enzymatic method using the reagent kit (Randox Diagnostics). Since the posture of the subjects has an effect on measured level of serum cholesterol, samples of all patients were taken in supine position. (Desirable range < 200 mg/ dl).

HDL cholesterol was determined using the enzymatic clearance assay. (Target level > 45 mg/dl).

Serum Triglycerides: Serum triglycerides were determined using the enzymatic fully automated calorimetric method. (Target level < 150 mg/dl).

VLDL and LDL: The VLDL cholesterol content is calculated according to the method of Friedewald WT in which the triglycerides content of the plasma is divided by 5. The LDL cholesterol is also derived by the Friedewald's method.

LDL Cholesterol = total cholesterol – (measured HDL cholesterol + Calculated VLDL cholesterol)

Desirable range < 100 mg/dl & 8 hours fasting sample was tested.

Glycated Haemoglobin (HbA1c): The Bio-Rad in2it (I) system allows the in vitro quantitative determination of HbA1c in whole venous blood collected in EDTA vial. The in2it test uses the well established method of boronate affinity chromatography to separate the glycated fraction from the non-glycated fraction. The in 2 it (I) Analyser is a single wavelength (440nm) photometer designed as a fully automated system. (Desirable range < 7%).

Serum Insulin Levels: Serum insulin levels are obtained from the biochemistry lab using Mercodia insulin ELISA machine by standard techniques. Homeostasis model assessment of insulin resistance (HOMA IR) was used to assess insulin resistance

$$\text{HOMA-IR formula} = \frac{\text{Fasting Glucose (mg/dl)} \times \text{fasting insulin } (\mu\text{U/ml})}{405}$$

405

Echocardiography: Each subject underwent transthoracic two dimensional M-mode echocardiogram in left lateral decubitus position on Philips Sonos 5500 echocardiography machine.

The echocardiographic study included recording of 3 cycles of two dimensional parasternal long and short axis views. Reader was blinded to subjects anthropometric features. Epicardial fat thickness was measured on the free wall of the right ventricle from both parasternal long and short axis views, using the aortic annulus as anatomic reference for the parasternal long axis view and the papillary muscles for the short – axis view. The value were averaged and a mean calculated which is the thickness of epicardial fat.

Epicardial fat thickness was divided into three groups and subjects were classified in each group

1. < 2.5 mm
2. 2.5 -3.5 mm
3. > 3.5 mm

Correlation between thickness of epicardial fat and following parameters was measured.

1. Waist circumference
2. BMI
3. Blood pressure
4. Fasting blood glucose
5. Glycosylated haemoglobin (HbA1c)
6. Fasting serum insulin levels
7. HOMA IR
8. Lipid profile; total cholesterol triglycerides HDL, LDL and VLDL

Statistical Analysis: The analysis was carried out in Microsoft Excel 2010, and SPSS software version 24. Statistical significance of outcomes with different variables was determined by chi-square/ fisher exact test. A p –values of ≤0.05 was taken as level of statistical significance. Pearson's test was used for determination of correlation.

Results

A total of 66 subjects were analyzed which included 33 cases and 33 controls. There were total 37 males and 29 females.

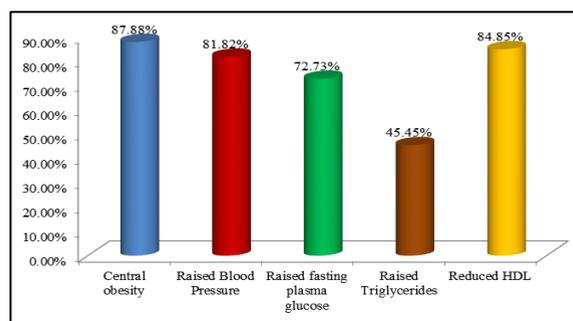


Fig. 1: Shows Percentage of cases fulfilling ATP III criteria for metabolic syndrome

Table 2: shows mean values and standard deviation of the anthropometric, clinical and biochemical characteristics of the subjects

Parameters	Cases (mean ± SD)	Controls (mean ± SD)
Age	44.72 ± 10.5	44.45 ± 10.5
BMI	29.9 ± 4.73	24.3 ± 2.14
Waist circumference	138.5 ± 13.45	82.57 ± 4.9
BP Systolic	85.09 ± 6.26	21.6 ± 6.57
BP diastolic	92.93 ± 9.45	78.12 ± 3.96
FPG	135.18 ± 30.71	93.3 ± 9.26
HbA1c	6.60 ± 0.71	5.34 ± 0.55
HOMA IR	3.78 ± 1.84	1.42 ± 0.81

Triglycerides	190.48 ± 54.6	106.39 ± 32.21
HDL	38 ± 5.48	47.6 ± 5.22

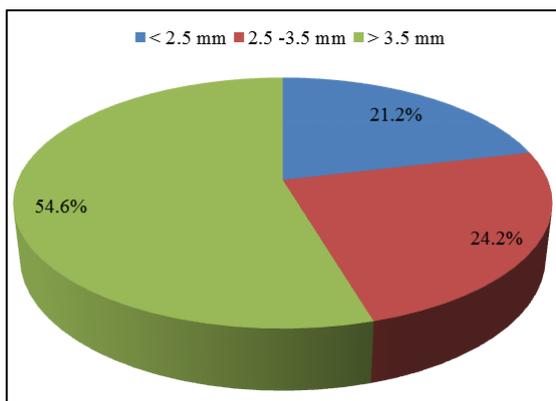


Fig. 2: Distribution of epicardial fat thickness in cases

Table 3: Distribution of epicardial fat thickness in controls

S. No.	Epicardial Fat Thickness	Percentage of cases
1	< 2.5 mm	66.7
2	2.5 - 3.5 mm	21.2
3	> 3.5 mm	12.1

Table 4: Range of epicardial fat thickness

Epicardial Fat	Controls	Cases
Lowest value	0.8	14
Highest value	6.3	7.3
Median	2	3.9
95% CI for the median	1.6822 to 2.5767	3.0000 to 4.3589

Correlation of epicardial fat thickness with parameters of metabolic syndrome in cases: Pearson's correlation test is applied for calculation of regression r - the correlation coefficient p - the significance level. The P value of less than 0.05 is considered to be significant.

Table 5: Mean epicardial fat thickness in subjects, cases, and controls

S. No.	Subjects (n=66)	Epicardial Fat Thickness (Mean ± SD)
1	Cases (n=33)	3.900 ± 1.584
2	Controls (n=33)	2.263 ± 1.150
3	Total subjects (n=66)	3.08 ± 1.604

Table 3-4: and Fig. 2: Shows that epicardial fat thickness was higher in the patients suffering from metabolic syndrome as compared to controls

Table 6: Correlation of epicardial fat thickness with various parameters in cases

Parameters	r	p
BMI	0.52	0.002
Waist circumference	0.27	0.11
BP Systolic	0.18	0.29
BP diastolic	0.16	0.35
FPG	0.79	<0.001
HbA1c	0.59	<0.001
HOME IR	0.58	<0.001
Triglycerides	0.73	<0.001
HDL	-0.19	0.27

According to table 6 it is observed that the epicardial fat thickness is positively correlated to BMI, FPG, HbA1c, HOMA IR and triglycerides with significant p value (< 0.05). There is negative correlation between epicardial fat thickness and HDL however it is not significant. There is no significant correlation between epicardial fat and systolic or diastolic BP and waist circumference.

Table 7: Correlation of epicardial fat thickness with various parameter in controls

Parameters	r	P
BMI	0.13	0.44
Waist circumferences	-0.05	0.78
BP Systolic	-0.09	0.58
BP diastolic	0.15	0.402
FPG	0.26	0.13
HbA1c	-0.3	0.086
HOME IR	0.6	<0.001
Triglycerides	0.7	<0.001
HDL	0.23	0.26

Table 7 shows that the epicardial fat thickness is correlated to HOMA IR and triglycerides with significant p value (< 0.05). There is no significant correlation between epicardial fat thickness and systolic or diastolic BP, FPG, BMI and waist circumference.

Our data showed that epicardial adipose tissue measured by echocardiography is related to the main anthropometric and clinical parameters of metabolic syndrome which was the objective of our study.

Discussion

The mean age in the study population in found to be 44.6 years. In the control group it is 44.7 years and in cases, it is 44.45 years, which is almost similar to the mean age in the study done by Iacobellis et al.⁷

Amongst the subject the sex distributions was found to be equitable in cases with 51.5% males and 48.5% females. In controls, the proportion of males was slightly higher with 57.6% males and 42.4% females.

Mean waist circumference in cases around 92.9 cm which was substantially less as compared to the above mentioned study (104-107 cm).

Fasting plasma glucose and triglyceride level were found to be higher in our subjects as compared to other studies.

Cut off values for insulin resistance was found to be 1.21 -1.45 by HOMA in western studies.⁸⁻¹⁰ Indian cut off value for HOMA IR is greater and found to be as high as 3.6 in a study done on teenagers.¹¹ In our study the mean HOMA IR is found to be 3.78 in cases and 1.42 in controls.

In our study we found the range of epicardial fat thickness to be 0.8- 7.3 mm this is less as compared to the western data (1.8-16.5 mm) the mean value was found to be 4.3 mm and 3.5 mm in females and males respectively in cases, and 2.7 mm and 2.2 mm in females and males respectively in controls. This could be due to the ethnic and racial differences in the visceral fat thickness.

Amongst the cases, 54.5% of the subjects were in the third group (epicardial fat thickness above the range of 3.5 mm). 24.2% subjects were in the second group (2.5 -3.5 mm) and 21.2% subjects were in the first group (<2.5mm).

Amongst the controls, 66.7% subjects were in the first group (<2.5mm) 21.2% subjects came under the second group (2.5-3 5mm) and 12.1 % subjects were in the third group (3.5mm). It clearly depicts that epicardial fat thickness is less in control population as compared to cases.

In a study showing correlation of epicardial fat with anthropometric measurements in Indians done by Goel A et al,¹² showed that epicardial fat thickness correlated well with weight ($r=0.399$, $p<0.001$) abdominal circumference ($r =0.522$, $p<0.001$) and BMI ($r=.471$, $p<0.001$). Epicardial fat also correlated with age ($r=0.559$, $p<0.001$).

In a study done by Iacobilis et al⁷ and Musteliet al¹³ very good correlation between epicardial adipose tissue and waist circumference, diastolic blood pressure, fasting plasma insulin, LDL cholesterol was found.⁷

Study done by D Tok et al¹⁴ demonstrates that Epicardial fat thickness (EFT) is higher in patients with metabolic syndrome (MetS), and that MetS and highly sensitive CRP (hsCRP) are independent predictors of this increased EFT. Increased EFT which is associated with low- grade systemic inflammation may play a role in the pathogenesis of atherosclerosis in MetS patients.

In our study we found a strong positive correlation between the epicardial fat thickness and the following parameters in patients of metabolic syndrome BMI: $r = 0.52$, $p = 0.02$; HOMA IR; $r = 0.58$, $p = < 0.001$; FPG; $r = 0.79$, $p = < 0.001$; HbA1c, $r = 0.59$, $p = < 0.001$; Triglyceride levels; $r = 0.75$, $p = < 0.001$

In a study done by Yorgun H et al,¹⁵ the mean epicardial fat thickness (EFT) was significantly increased in patients with metabolic syndrome (MetS) compared in those without it (8.49 ± 1.43 mm VS 7.39 ± 2.10 mm. $p<0.001$) Additionally there was a graded

relationship between increasing number of MetS components and mean total EFT. But in our study we couldn't find a graded relationship between components of metabolic syndromic and epicardial fat.

Echocardiography is a relatively simple and inexpensive method, but the accuracy and reproducibility should be further tested.

Limitations of the Study

There were some unavoidable limitations. First, due to time limitation the research was conducted on a small sample size. Mean age of study population was a bit higher, metabolic syndrome in younger population also need to be investigated and risk factors are to be determined for an early prevention. In addition as epicardial adipose tissue has a 3 dimensional distribution, 2-dimensional echocardiography may not completely assess the total amount of epicardial adiposity. Sometimes it is difficult to differentiate between epicardial and pericardial fat by echocardiography. Hence further study will be necessary.

Conclusion

Echocardiographic evaluation of epicardial fat thickness is an inexpensive, reproducible, and direct measure of visceral fat. It may have an important role in predicting and stratifying cardiometabolic risk in both clinical care and the research setting.

Our study show a positive correlation of body mass index, blood pressure, fasting plasma glucose HbA1c, HOMA IR and Serum triglyceride level with epicardial fat thickness.

Epicardial adipose tissue calculation by echocardiography require very little time and can be easily applied during and examination for evaluation of morphological and functional cardiac parameters in patients with obesity, diabetes, and hypertension. Hence, transthoracic echocardiography could be an accurate, easy and reliable imaging method for prediction of visceral adiposity. The possible association of epicardial adipose tissue measurement with anthropometric clinical, metabolic and biochemical parameters is shown by many studies as well as our study. However, more robust and convincing evidence is necessary to evaluate whether echocardiographic epicardial fat thickness may have these diagnostic and predictive properties and really become a routine way of assessing cardiovascular risk in a clinical setting.

Recommendations

We suggest that echocardiographic epicardial adipose tissue could be applied as an easy and reliable imaging indicator of cardiometabolic risk. Further investigation with a larger population will be necessary to create threshold values of mild and severe visceral fat deposition and to confirm or refute a physiologic

mechanism or explanation for a relationship between epicardial fat and cardiometabolic risk.

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