Research Article

Association of Epicardial Fat with Metabolic Syndrome in Indian Population

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Abstract

Introduction: Visceral obesity and dyslipidemia are the two most commonly occurring components of the metabolic syndrome. Epicardial fat is a true visceral adipose tissue deposited around the heart and has characteristics of a high insulin-resistant tissue.

Material and methods: The study included 66 subjects (33 cases and 33 controls). Epicardial fat thickness was measured by echocardiography on the free wall of the right ventricle from both parasternal long- and short-axis views and anthropometric and biochemical parameters were recorded.

Results: Range of epicardial fat thickness varied between 0.8 to 7.3 mm. The normal cutoff value is considered to be between 1 to 4 mm. The mean epicardial fat thickness was found to be 4.3 ± 1.83 mm (mean ± standard deviation) in females and 3.5 ± 1.18 mm in males amongst the cases, and 2.4 ± 1.33 mm in females and 2.2 ± 1.02 mm in males in the control group. Epicardial fat thickness was higher in the patients with metabolic syndrome as compared to controls. There was a statistical significant correlation between epicardial adipose tissue and body mass index (BMI), fasting plasma glucose, triglycerides and homeostasis model for assessment of insulin resistance (HOMA IR).

Conclusion: 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. Epicardial adipose tissue measurement could be an important tool to increase the knowledge of metabolic syndrome on epidemiological basis.

Keywords: Metabolic syndrome, Epicardial fat, Echocardiography, Indian population.

Introduction

The metabolic syndrome is a constellation of clinical and metabolic abnormalities including abdominal obesity, hypertension, dyslipidemia and impaired glucose tolerance.[1] Visceral adipose tissue (VAT) is most strongly associated with the metabolic syndrome.[2] Epicardial fat is one of the components of VAT.[3] The echocardiographic measurement of epicardial fat is a non-invasive and objectively quantifiable method.[4] The relationship between epicardial fat and metabolic syndrome is still not much explored in the Indian population; hence the aim of the study was to explore relationship between epicardial fat and anthropometric, clinical and biochemical parameters of metabolic syndrome.

Lately, epicardial adipose tissue, a type of visceral fat surrounding heart, has developed a strong clinical and scientific interest.[5] In the adult heart, fully differentiated, white adipose tissue can be commonly found in the atrioventricular and inter ventricular grooves extending to the apex. Minor foci of fat are also located sub epicardially in the free walls of the atria and around the two

appendages.[7] Physiological functions of epicardial fat are based on observational data and include: buffering coronary arteries against the torsion induced by the arterial pulse wave and cardiac contraction, facilitating coronary artery remodeling, regulating fatty acid homeostasis in the coronary microcirculation and providing fatty acids to cardiac muscle as a local energy source in times of high demand.[3,8] Epicardial adipose tissue expresses a wide range of inflammatory mediators and has comparatively higher expression of inflammatory cytokines (interleukin-1β, interleukin-6 and interleukin-6 soluble receptor, and tumor necrosis factor-α) and chemokines (monocyte chemotactic proteins) than subcutaneous fat. On the basis of these observations, *Mazurek et al* proposed that adipocyte-derived tumor necrosis factor-α acts in an autocrine way, impairing signaling via the insulin receptor and increases lipolysis[18]. The subsequent release of nonesterified fatty acids might contribute to insulin resistance in peripheral tissues, such as adipose and muscle tissue, the liver and the heart.[9,11,18]

Higher number of inflammatory cells in epicardial fatty tissue could indicate an analogy to the inflammatory infiltrates in perivascular regions and adventitia adjacent to advanced atherosclerotic lesions.[18,19] A study done by *Iacobilis et al* has shown that epicardial adipose tissue measured by echocardiography is related to the main anthropometric and clinical parameters of metabolic syndrome.[15] A statistical significant correlation has been found between epicardial adipose tissue and waist circumference, diastolic blood pressure, fasting plasma insulin, Low density lipoprotein (LDL) cholesterol, and plasma adiponectin. A relationship between epicardial fat thickness and coronary artery disease has been also reported.[6,13,20]

True VAT measurement can be obtained by echocardiography; avoiding the possible confounding effect of increased subcutaneous abdominal fat thickness.[14,15] Echocardiographic calculation of epicardial fat is easily reproducible, has shown an excellent reliability with the CT and MRI epicardial and visceral adipose tissue measurements.[10,14] Echocardiographic assessment of visceral fat could be an easy method to indicate patients with high cardiovascular risk.

Material and Methods

This observational study was conducted at a tertiary care center during November 2012 to February 2014 and enrolled 66 subjects (33 cases and 33 controls) prospectively. The sample size was kept limited as echocardiography was overwhelmed. The subjects were selected on convenience sampling.

Subjects: Both males and females of age above 25 years who fulfilled all inclusion and exclusion criteria were selected and labeled as cases. The control group included subjects, age and sex matched, who didn't have metabolic syndrome.

Inclusion criteria: Subjects of age above 25 years who were newly diagnosed and fulfilling three or more of the ATP III criteria with IDF country specific waist circumference modification were selected. The ATP III criteria are as follows.

The 2001 ATP III Definition:[16]

In 2001, a new definition of the metabolic syndrome was proposed - the ATP III definition. This definition was designed to facilitate diagnosis in clinical practice and therefore does not include a measurement of insulin resistance.[16]

The ATP III guidelines state that metabolic syndrome may be diagnosed when a patient has three or more of five clinically identifiable risk factors:

1. Central obesity (Waist circumference) Men- Equal to or greater than 102 cm (90 cm for
   a. Indians) Women- Equal to or greater than 88cm (80 cm for Indians)
2. Elevated triglycerides: Equal to or greater than 150 mg/dl
3. Reduced High density lipoprotein (HDL) cholesterol: Men- less than 40 mg/dl;
   a. Women- less than 50 mg/dl.
4. Elevated blood pressure (BP): Equal or greater than 130/85 mmHg.
5. Elevated fasting plasma glucose (FPG): Equal to greater than 110 mg/dl.

International Diabetes Federation proposed country/ethnic-specific values for waist circumference, according to which in South Asians central obesity was defined as waist circumference >90cm in males and > 80 cm in females.[17]

Exclusion criteria: involved valvular heart disease, congenital heart disease, pericardial effusion, inadequate transthoracic echocardiographic window, pregnant females and ascites. All of these factors have

interfered with the measurement of epicardial fat. Furthermore patients on beta-blockers, diuretics, insulin, statins, fibrates, niacin, orlistat, metformin, thiazolidinediones and hormone replacement therapy were also excluded as the drugs could have an effect on fat composition of the body.

The patients were enrolled in the study after informed consent. All study details including documentations and ethical issues were reviewed and approved by ethical committee of our institution.

As per predesigned proforma, detailed history was taken and physical examination was done. Indirect auscultatory arterial blood pressure was measured by standard clinical sphygmomanometer and stethoscope by the same observer. Precautions were taken by creating standard conditions of blood pressure recording as per WHO recommendations. Standing height was measured to the nearest 0.1 cm without shoes; the back against the wall, eyes looking straight ahead (visual axis being horizontal with the top of the external auditory meatus in level with the inferior margin of the bony orbit), with a set square 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 costal margin and iliac crest. Hip circumference was measured at the inter-trochanteric level using a measuring tape.[21]

Laboratory Investigations-

After about eight hours of fast, venous samples were collected with the patient lying supine. Blood glucose was determined by the enzymatic method using the reagent kit-Randox, Gluc-PAP, HITACHI.

The serum cholesterol was measured by the enzymatic method using the reagent kit-Randox Diagnostics. HDL cholesterol was determined using the enzymatic clearance assay.[22,23] Serum triglycerides were determined using the enzymatic fully automated calorimetric method. The very low density lipoprotein (VLDL) cholesterol content was calculated according to the method of Friedewald WT in which the triglycerides content of the plasma was divided by five. The LDL cholesterol was also derived by the Friedewald's method: LDL cholesterol = total cholesterol – (measured HDL cholesterol + calculated VLDL cholesterol).[24]

Glycated haemoglobin (HbA1c) was tested by the Bio-Rad in2it (I) analyzer using venous blood collected in EDTA vial. Serum insulin levels were obtained from the biochemistry lab using Mercodia insulin ELISA machine by standard techniques.

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 three cycles of two-dimensional parasternal long-and short-axis views recorded by experienced cardiologist following standard echocardiography guidelines.[12] 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.[3,14] The values were averaged and a mean calculated which was the thickness of epicardial fat. Homeostasis model assessment of insulin resistance (HOMA IR) was used to assess insulin resistance.[25]

HOMA-IR formula = [Fasting Glucose (mg/dl) x fasting Insulin (µIU/ml)]/405

Correlation between thickness of epicardial fat and following parameters was calculated: waist circumference, body mass index (BMI), blood pressure (BP), fasting plasma glucose (FPG), glycated haemoglobin (HbA_1C), fasting serum insulin levels, HOMA IR, and lipid profile: total cholesterol, triglycerides, HDL, LDL and VLDL cholesterol.

Statistical Analysis

The analysis was carried out with Microsoft Excel 2010 and SPSS software version 17. Statistical significance of outcomes with different variables was determined by chi-square/Fisher exact test. A p-value of ≤0.05 was taken as level of statistical significance Pearson's test was used for determination of correlation.

Results

Mean age of study population was 44.6 ± 10.29 years. Mean age of cases was 44.7 ± 10.18 years and that of controls was 44.4 ± 10.55 years. Demographics of the study subjects are shown in table 1. 87.8% of patients had central obesity, 81.2% of cases had raised blood pressure, 72.73% had raised fasting plasma glucose, 84.8% had reduced HDL values and 45.4% had raised triglycerides. This implies that a metabolic score of four was present in more than 80% of cases and a score of three in 20%.

Table 1.Anthropometric and Clinical Parameters in Males and Females (Mean ± Std Deviation)

	Cases		Controls	
Parameters (mean ± SD)	**Males(n=17)**	**Females(n=16)**	**males(n=19)**	**Females(n=14)**
Age (years)	44.9 ± 10.31	44.5 ± 10.37	45.5 ± 10.85	42.9±10.34
BMI (Kg/m^2)	28.7 ± 2.62	31.1 ± 6.12	24.1 ± 2.10	24.8± 6.53
Waist Circumference (cm)	93.1 ± 8.89	92.6 ± 10.30	86.3 ± 2.53	77.5±1.45
FPG (mg/dl)	133.4 ± 27.69	135.6 ± 35.12	95 ± 9.03	92.3±9.65
Epicardial Fat (mm)	3.5 ± 1.18	4.3 ± 1.83	2.2 ± 1.02	2.4 ± 1.3
Systolic BP (mm Hg)	137.2 ± 11.09	140 ± 15.83	120.7 ± 6.8	122.7 ± 6.30
Diastolic BP (mm Hg)	83.4 ± 5.18	86 ± 6.96	77.3 ± 4.47	79.1 ± 3.00
HDL (mg/dl)	36.5 ± 4.01	38.3 ± 5.68	44.2 ± 5.05	52.2 ± 2.45
Triglycerides mg/dl)	154.7 ± 60.34	146.2 ± 61.01	105.5 ± 44.28	123.9 ± 52.52
HbA1c (%)	6.6 ± 0.61	6.6 ± 0.82	5.3 ± 0.53	5.4 ± 0.52
HOMA IR	3.56 ± 1.94	4 ± 1.79	1.34 ± 0.85	1.52 ± 0.78

Mean epicardial fat thickness in females in cases was 4.3 ± 1.83 mm and in controls was 2.4 ± 1.33 mm. Mean epicardial fat thickness in males in cases was 3.5 ± 1.18 mm and in controls was 2.2 ± 1.02 mm. Higher mean value of epicardial fat thickness was seen in the females as compared to males in both cases and controls. Range of epicardial fat is shown in table 2. Epicardial fat thickness was divided into three groups and subjects were classified in each group: less than 2.5 mm; 2.5 to 3.5 mm; more than 3.5 mm.

Table 2.Range of Epicardial fat thickness

Epicardial Fat	Controls (in mm)	Cases (in mm)
Lowest value	0.8	1.4
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

Amongst the cases, 54.5% of the subjects were in the third group (epicardial fat thickness above the range of 3.5). 24.2% subjects were in the second group (2.5-3.5) and 21.2 % subjects were in the first group (<2.5). Amongst the controls, 66.7% subjects were in the first group (<2.5). 21.2% subjects came under the second group (2.5-3.5) and 12.1 % subjects were in the third group (>3.5). It clearly depicts that epicardial fat thickness is less in the control population as compared to cases. Multivariate regression analysis done on the parameters showed significance in fasting plasma glucose and triglycerides with p value of 0.003 and <0.001 respectively. Correlation of epicardial fat thickness with various parameters of metabolic syndrome is shown in table 3.

Table 3.Correlation of epicardial fat thickness with various parameters in cases (in mm)

Parameters	R (Correlation)	P-Value
BMI	0.40	0.02
Waist circumference	0.19	0.27
BP Systolic	0.14	0.43
BP diastolic	0.15	0.38
FPG	0.69	<0.001
HbA1C	0.59	0.014
HOMA IR	0.53	0.001
Triglycerides	-0.07	<0.001
HDL	-0.008	0.96

Discussion

In our study we found that the range of epicardial fat thickness varied between 0.8-7.3 mm. This is considerably less as compared to the western data (1.8-16.5 mm).[4] This could be attributed to the ethnic and racial differences in the visceral fat thickness. It was observed that females had a higher amount of epicardial fat as compared to males. The mean value of epicardial fat thickness was found to be 4.3mm in females and 3.5mm in males amongst the cases and 2.7mm in females and 2.2mm in males in the control

group. There was no significant correlation with the age of the subjects. Our data showed that epicardial adipose tissue measured by echocardiography is related to a number of anthropometric and clinical parameters of metabolic syndrome. There was a statistical significant correlation between the epicardial fat thickness and the following parameters: BMI (r=0.4, p= 0.02), FPG (r = 0.69, p = 0.001), HbA1c (r= 0.59, p = 0.014), HOMA IR (r = 0.53, p = 0.001) and triglyceride levels (r=-0.070 p =<0.0001).

The biochemical properties of epicardial adipose tissue suggest its possible role as a cardiovascular and metabolic risk indicator and correlation with deranged lipid profile is demonstrated in many studies, we found no significant correlation with the levels of LDL and HDL cholesterol. The relationship of epicardial fat to fasting plasma glucose, HOMA IR and HbA1c strongly suggests that it should be considered a highly insulin- resistant adipose tissue.

Ethnic differences in echocardiographic epicardial fat thickness have also been reported recently and the result obtained in the current study shows that the range of epicardial fat thickness is lower in Indian population as compared to western data.[3,4] Threshold values of high-risk epicardial fat thickness may therefore vary among different populations and ethnic groups. It can be also postulated that the cutoff values could be different if they aimed to predict metabolic syndrome or coronary artery disease. Although the majority of the studies have found positive relationships between epicardial fat and cardiovascular risk, a few studies have questioned this association. Our study shows a positive correlation with body mass index, blood pressure, fasting plasma glucose HbA1c, and HOMA IR level with epicardial fat thickness.

Epicardial adipose tissue calculation by echocardiography requires very little time and can be easily applied during an 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 VAT prediction.

Limitations of the Study

Although the research study was conducted carefully and has reached its aim, 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.

Recommendations

Our study shows that epicardial fat could well be considered as a risk factor in the development of metabolic syndrome and should be looked as a parameter during routine 2 D echocardiography. Further investigations should be encouraged to confirm or refute a physiologic mechanism or explanation for a relationship between epicardial fat and cardiometabolic risk. Future studies in these directions seem to be warranted.

Conflict of Interest: None

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