Association Of Epicardial Fat Thickness In Coronary Artery Disease (CAD) Patients With Metabolic Syndrome

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Background: Epicardial fat is getting more attention for its involvement in cardiovascular complications due to its close proximity with heart tissue. Epicardial fat plays a significant role in the development and progression of coronary atherosclerosis. Quantification of epicardial fat noninvasively, has emerged as a potentially useful tool for CVD risk stratification in clinical practice.

Aim: The aim of this study was to evaluate the epicardial fat (EF) thickness in CAD patients and Non CAD participants with or without metabolic syndrome.

Materials & Methods: We selected study patients who were referred to coronary angiography due to typical chest pain or atypical chest pain with a positive pre-test result for coronary artery disease (CAD). After coronary angiography, 346 patients with significant coronary lesion (≥ 50% stenosis) served as the CAD group, 220 patients with non-significant coronary lesion (< 50% stenosis) and/or a coronary plaque served as the non-significant CAD group. All patients underwent transthoracic echocardiographic examination.

Results: The present study observed a significant difference in CAD and Non CAD groups for lipid profile, BMI and Waist circumference. It was significantly higher in the coronary lesion (≥ 50% stenosis) group, 7.2 ± 1.15 mm compared to the coronary lesion (< 50% stenosis) group 3.6± 0.83 mm. A significant difference was observed for Epicardial fat thickness in CAD and Non CAD group (7.2 ±1.15 mm / 3.6± 0.83 mm) and CAD-with metabolic syndrome Vs CAD without metabolic syndrome (6.29 ±(1.09) mm / 5.15(± 1.28) mm).

Conclusions: Our study reported a significant correlation of epicardial fat thickness with WC in CAD patients with metabolic syndrome.
INTRODUCTION:
Epicardial fat (EF) is a visceral fat, located between the heart and the pericardium. It is anatomically close to myocardium and shares the same microcirculation. EF is one of the most important metabolically active endocrine organs that produce several factors, which play a crucial role in cardiac function and morphology. Severity of CAD increases with presence of increasing number of metabolic syndrome predisposing factors. Visceral obesity and insulin resistance have been projected as the main underlying mechanism in metabolic syndrome. [1-3]

Severity of CAD increases with presence of increasing number of metabolic syndrome predisposing factors. Visceral obesity and insulin resistance have been projected as the main underlying mechanism in metabolic syndrome. [4]

The exact role of epicardial fat and its expansion is not really very well understood and not many studies were done on Indian population regarding epicardial fat and its role in heart diseases The exact physiological and pathological functions of EF were also not clear. The thickness of EF increases with increase in other visceral fat depots. Echocardiographic epicardial fat thickness clearly reflects visceral adiposity rather than general obesity. A study has been shown that Frequency of metabolic syndrome is high in patients with coronary artery disease and is associated with severe CAD. Severity of CAD increases with presence of increasing number of metabolic abnormality. [5]

The aim of the present study is to study the Epicardial fat thickness and evaluate its association with metabolic syndrome parameters. Metabolic Syndrome is a component of several cardio metabolic risk factors and associated with cardiovascular disease. Incidence of metabolic syndrome is high in patients with coronary artery disease and is associated with severe CAD. Epicardial fat thickness is generally recognized as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium and is measured vertically on the free wall of the right ventricle at end-systole. EF is able to produce an echo-free space that can be mistaken for pericardial fluid. Occasionally, it appears as hyperechoic space, if in large amount (> 15 mm). Echocardiographic epicardial fat thickness clearly reflects visceral adiposity rather than general obesity. It correlates with metabolic syndrome, insulin resistance, diabetes mellitus, coronary artery disease, and subclinical atherosclerosis, and therefore it might serve as a simple tool for cardiometabolic risk prediction (Meenakshi 2016). It correlates with metabolic syndrome, insulin resistance, diabetes mellitus, coronary artery disease, and subclinical atherosclerosis, and therefore it might serve as a simple tool for cardiometabolic risk prediction. A study observed that epicardial fat is independently and linearly associated with CAD and its severity. [6, 7]

Epicardial has various physiological and beneficial roles of as immune barrier, myocardial and coronary artery protection, local fatty acid source for the myocardium. Under physiological conditions, EF acts as a buffer that protects the heart from lipotoxicity and provides the myocardium the energy by oxidation of fatty acids by β-oxidation, in addition to its mechanical protective effect. But its expansion can be pathological; hence its increase may be hazardous which actively secretes some of the proinflammatory markers. Under pathological conditions, as in metabolic syndrome, EF dysfunction occurs, leading to the loss of its cardioprotective effect. [8]

Substantial increases of epicardial fat might pack the space between the visceral pericardium and myocardium surface and even cover the entire epicardium surface. Small amounts of epicardial fat can also grow inside myocardium and typically go with the intramyocardial branch of coronary artery. [9]

Measuring the amount of EF might represent a novel parameter that is inexpensive and quantify epicardial fat noninvasively which is safe as well helpful in cardiovascular risk stratification. However, the relationship between epicardial fat and determinants of coronary artery disease is not well established. A significant difference has been observed in various studies as some of these investigators measured EF at end-systole while others used end-diastolic frames and this may explain differences between them.

MATERIALS & METHODS:
This study was a prospective observational case control study that was conducted at a tertiary care hospital. The present study included 346 CAD patients (with >50% stenosis) and 220 participants (with < 50% stenosis). All the study participants were examined clinically and anthropometric measurements were recorded. Routine biochemical
investigations like blood glucose and lipid profile were carried for all study participants. Both the groups underwent an Echocardiography test for assessment of cardiac profile. Epicardial fat thickness is measured as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium and is measured perpendicularly on the free wall of the right ventricle at end-systole for 3 cycles. The study was approved by institutional ethics committee. The written consent was obtained from all the study participants. Extremes of age (less than 18 or more than 70 years), patients with debilitating diseases, patients with poor acoustic windows, patients with normal coronaries despite having previously documented ischemic insult, patients with acute coronary syndromes, patients refusing to participate were excluded from the study.

Statistical analysis was done using SPSS 23.0 software. Continuous variables were expressed as means ± SD and categorical variables as absolute numbers and percentages. Descriptive statistics was expressed as a mean and standard deviation for continuous variables and as frequencies and percentages for categorical variables and used to summarize baseline patient characteristics. Continuous variables were compared using Student's t-test. An independent sample t-test was used to comparisons of continuous variables. Pearson's correlation test was used to determine the correlation between continuous variables.

RESULTS:
The present study observed a significant difference in CAD and NCAD groups for lipid profile and BMI, Waist circumference. A significant difference was observed in both CAD groups for Epicardial fat thickness (7.2 ±1.15 mm / 3.6± 0.83 mm).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAD</th>
<th>Non CAD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>58.51 (±5.66)</td>
<td>54.53 (±7.79)</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>27.44 (±2.57)</td>
<td>25.65 (± 2.51)</td>
<td>0.000</td>
</tr>
<tr>
<td>WC cm</td>
<td>95.36 (± 6.07)</td>
<td>91.16 (± 7.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>FBS mg/dL</td>
<td>199.3 (± 20.8)</td>
<td>103.5 (± 10.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglyceride mg/dL</td>
<td>180.86 (±43.64)</td>
<td>163.06 (±32.63)</td>
<td>0.000</td>
</tr>
<tr>
<td>T. cholesterol mg/dL</td>
<td>202.41 (±35.96)</td>
<td>175.02 (±22.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL cholesterol mg/dL</td>
<td>131.12 (±36.94)</td>
<td>97.72 (±22.43)</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL cholesterol mg/dL</td>
<td>38.87 (±6.34)</td>
<td>44.69 (±6.12)</td>
<td>0.000</td>
</tr>
<tr>
<td>Epicardial fat Thickness (EFT) mm</td>
<td>7.2 (±1.15)</td>
<td>3.6 (± 0.83)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Further it was observed that a moderate statistical difference is persistent in subgroups of CAD-with and without metabolic syndrome. A significantly higher values were observed in patients with CAD-with metabolic syndrome for Epicardial fat thickness than CAD without metabolic syndrome (6.29 ± (1.09) mm / 5.15(± 1.28) mm).

When observed the correlation, it was noted that BMI, WC, TAG and HDL were shown a statistically significant positive correlation with EF thickness.
especially in CAD with metabolic syndrome. It was observed that WC was more closely correlated than BMI. WC ($r=0.479$, $P=0.000$) and BMI ($r=0.202$, $P=0.002$) in patients CAD with metabolic syndrome.

**Table 2: Baseline characteristics and Lipid profile in subgroups of CAD- based on presence of Metabolic Syndrome**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAD With Metabolic Syndrome n=219</th>
<th>CAD Without Metabolic Syndrome n=127</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>59.15($±5.72$)</td>
<td>57.08($±5.26$)</td>
<td>0.350</td>
</tr>
<tr>
<td>BMI kg/m$^2$</td>
<td>28.73($±4.2$)</td>
<td>23.55($±2.9$)</td>
<td>0.001</td>
</tr>
<tr>
<td>WC cm</td>
<td>93.8($±6.4$)</td>
<td>85($±7.8$)</td>
<td>0.000</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>159.98 ± 49.44</td>
<td>113.43 ± 25.85</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglyceride mg/dL</td>
<td>188.34($±45.65$)</td>
<td>164.13($±33.32$)</td>
<td>0.001</td>
</tr>
<tr>
<td>T. cholesterol mg/dL</td>
<td>203.58($±48.65$)</td>
<td>199.81($±28.57$)</td>
<td>0.000</td>
</tr>
<tr>
<td>LDL cholesterol mg/dL</td>
<td>140.43($±55.50$)</td>
<td>126.96($±2.46$)</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL cholesterol mg/dL</td>
<td>38.5($±6.42$)</td>
<td>36.92($±6.20$)</td>
<td>0.001</td>
</tr>
<tr>
<td>EF mm</td>
<td>6.29($±1.09$)</td>
<td>5.15($±1.28$)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Further it was also observed that age and WC showed a significant correlation with epicardial fat thickness in CAD patient without metabolic syndrome also WC ($r=0.396$, $P=0.000$) and BMI ($r=0.301$, $P=0.001$). No statistical correlation has been noted with any of the variable from lipid profile with epicardial fat thickness in CAD group.

**Table 3: Correlation of Epicardial fat thickness with anthropometric and lipid profile**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAD Patients with metabolic syndrome</th>
<th>CAD Patients without metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient (r)</td>
<td>$p$-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.110</td>
<td>0.852</td>
</tr>
<tr>
<td>BMI</td>
<td>0.201</td>
<td>0.002*</td>
</tr>
<tr>
<td>WC</td>
<td>0.479</td>
<td>0.000*</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.108</td>
<td>0.092</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.170</td>
<td>0.008*</td>
</tr>
<tr>
<td>T. cholesterol</td>
<td>0.054</td>
<td>0.389</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.031</td>
<td>0.632</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.127</td>
<td>0.047*</td>
</tr>
</tbody>
</table>

**DISCUSSION:**
We evaluated the association of anthropometric measurements, lipid profile and epicardial fat thickness in 346 CAD subjects (with >50% stenosis) and 220 Non CAD participants (with < 50% stenosis). Our study showed a significant difference between CAD and Non
CAD study participant’s Epicardial fat thickness (7.2 ±1.15 mm / 3.6± 0.83 mm). The present study observed consistent results like other studies carried out in the past. Epicardial fat thickness may possibly influence by age, gender, and race. The timeframe of measurement of epicardial fat is also important to get consistent results-end-systole or -diastole. Epicardial fat thickness, which is easily and non-invasively evaluated by transthoracic echocardiography, can be an adjunctive marker to classical risk factors for the prediction of CAD. [10] The components of metabolic syndrome (MetS), like visceral obesity, are associated with a low-grade systemic inflammatory state. The study assessed the relationship between echocardiographic epicardial fat thicknesses (EF), MetS, the components of MetS, and a special inflammatory marker -high sensitivity C-reactive protein (hs-CRP) levels in patients with MetS. A study observed highest levels of hsCRP in CAD patients with unstable angina and considered them as the most risky group amongst the CAD patients. [11] Further it was also observed that increased EF was associated with low-grade systemic inflammation, might play a role in the pathogenesis of atherosclerosis in MetS patients. [12, 13] Epicardial fat may release factors that promote harmful coronary artery and myocardial changes. A body of evidence shows that epicardial fat is an extremely active organ that produces several bioactive adipokines and cytokines. [14, 15] Further it have been observed that EF volume was larger in the presence of obstructive CAD and non-calcified plaques and suggested that the association of EF thickness in the development of coronary atherosclerosis and in potentially dangerous types of plaques. [16] A cross talk between the inflammatory and anti inflammatory molecules in epithelial fat may be involved in pathogenesis of atherosclerosis. [17]

CONCLUSION:
Our data indicated that EF thickness is associated with waist circumference and BMI. Visceral obesity may be associated with epicardial fat thickness which plays an important role in pathogenesis of coronary atherosclerosis. The measurement of Epicardial fat thickness by Echocardiography can be used as one of the cost effective, convenient and easy tool to assess the risk of CAD.

STUDY LIMITATIONS:
The study population consisted entirely of Indian patients from a tertiary care hospital, so the relevance of this study to patients other racial backgrounds awaits further research. Though CT and MRI have better image quality and can carry out volumetric measurements, they are disappointing due to high costs, low accessibility and complexity of measurement compared to 2 D Echo. The study results may not be applicable to symptomatic subjects or subjects with known CAD, but are rather more representative of the general asymptomatic population. The study population consisted entirely of Indian patients, so the findings of this study may not be relevant to patients of other ethnic backgrounds.

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