Epicardial fat thickness and severity of coronary heart disease in patients with diabetes mellitus type II

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Abstract

BACKGROUND: Clinical imaging studies have demonstrated a strong direct correlation between epicardial fat and abdominal visceral adiposity. There are several studies about positive correlation of epicardial fat and atherosclerotic coronary disease in general population. This study aimed to evaluate the association of epicardial fat thickness with atherosclerotic coronary disease in patients with diabetes mellitus type II.

METHODS: This cross-sectional observational study involved 80 patients with diabetes mellitus type II. The patients were chosen using simple sampling method from patients with diabetes mellitus who were referred for angiography because of suspected coronary artery disease. The severity of coronary atherosclerotic lesions was evaluated using modified Gensini scoring system. Epicardial fat thickness was measured by transthoracic echocardiography within 90 days after coronary angiography. Multiple linear regression method was used to evaluate the association between mean epicardial fat thickness and Gensini score.

RESULTS: After adjustment for the effects of body mass index (BMI), age, angina, and sex, there was a significant association between Gensini score and epicardial fat thickness (β = 0.825; P < 0.001). Patients with higher blood pressure and higher body mass index also had a higher Gensini score (P < 0.010).

CONCLUSION: In patients with diabetes mellitus type II, there is a positive association between epicardial fat thickness and severity of coronary artery disease. So, by echocardiography evaluation of epicardial fat thickness, we could have an estimation of the severity of coronary arteries diseases before using more invasive techniques.

Keywords: Body Fat, Coronary Artery Disease, Stenosis, Diabetes Mellitus

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Introduction

Obesity is an important risk factor for the development of all features of metabolic syndrome and atherosclerotic cardiovascular disease.1-6 Clinical imaging studies have demonstrated a strong direct correlation between epicardial fat and abdominal visceral adiposity. Epicardial fat covers 80% of the heart’s surface and constitutes 20% of total heart weight.7 Epicardial fat is three to four folds more associated with the right than the left ventricle.7

There is a lot of publications about the physiological and metabolic importance of epicardial adipose tissue. Both the epicardial fat thickness and volume have strong association with obesity, impaired fasting glucose, insulin resistance, metabolic syndrome, hypertension, diabetes mellitus, and atherosclerosis.8 An association between insulin resistance and central adiposity, and clinical parameters of cardiovascular risk including low-density lipoprotein (LDL) cholesterol and blood pressure had been shown in previous studies.9

Epicardial fat is independently associated with coronary artery disease (CAD). This correlation may be explained by systemic inflammation induced by visceral fat including epicardial fat.10

Epicardial adipose tissue (EAT) mediates inflammatory process within the atherosclerotic plaque.11 The paracrine or vasocrine secretion of
epicardial inflammatory adipokines, such as tumor necrosis factor alpha, plasminogen activator inhibitor-1, interleukin-6, interleukin-1β, monocyte chemo-attractant protein-1, and resistin contribute to the metabolic and inflammatory milieu that promotes atherogenesis and insulin resistance. This mechanism may explain the positive relationship between the amount of fat surrounding the heart and vessels and several components of the metabolic syndrome and diabetes mellitus type II. There are few studies about the association of epicardial fat thickness and severity of CAD in subgroup of patients with diabetes mellitus. In this study, we aimed to determine the relationship between the epicardial fat thickness and severity of CAD in patients with diabetes mellitus type II.

Materials and Methods

This cross-sectional observational study was performed in Chamran hospital, Isfahan University of Medical Sciences, Iran. Eighty five patients with diabetes mellitus type II aged 40 to 80 years took part in this study. The cases were chosen via simple sampling method, from the patients with diabetes mellitus type II, who were referred for coronary angiography because of suspected CAD during August 2015 to May 2016.

All the patients underwent detailed history, clinical examination, anthropometric measurement, routine biochemistry, electrocardiography (ECG), and transthoracic echocardiography.

Patients who had chest deformities, chronic lung disease, poor echo window, pericardial and/or pleural effusion on transthoracic echocardiography, previous coronary artery bypass graft (CABG) surgery, and percutaneous coronary intervention (PTCA) were excluded from study. Patients with chronic kidney disease defined by rise in creatinine or albuminuria, patients with any kind of metastatic chronic kidney disease, poor echo window, pericardial and/or pleural effusion, patients with any kind of metastatic on non-metastatic cancer, and patients with increased liver enzyme were also excluded.

Blood pressure was measured from right hand after 10 minutes of rest. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or requirement of antihypertensive medication. Body mass index (BMI) was calculated as body weight in kilograms divided by height squared. Obesity was defined as having a BMI ≥ 30 kg/m². Diabetes mellitus type II was defined according to the criteria of the American Diabetes Association. These criteria included:

1. Symptoms of diabetes plus random blood glucose concentration over 200 mg/dl
2. Fasting blood glucose over 126 mg/dl
3. Glucose over 200 mg/dl during glucose tolerance test
4. Glycated hemoglobin (HbA1c) over 6.5%

Hyperlipidemia was defined as total cholesterol higher than 220 mg/dl or triglycerides ≥ 150 mg/dl.

In a fasting state, coronary angiography was performed using the Judkins’ technique, by the femoral or radial artery approach. The severity of coronary atherosclerotic lesions was evaluated from at least 3 projections in all the patients by modified Gensini scoring system. According to this scoring system, coronary arterial system was divided into 8 segments and the most severe luminal narrowing in each coronary segment was graded with 1 to 4 points (between 1% and 49%, 1 point; 50% and 74%, 2 points; 75% and 99%, 3 points; 100%, 4 points). Each patient was evaluated with a total score between 0 and 32 points. Each point was multiplied with separate coefficients based on vessel and its segments; these coefficients were 5 for left main coronary artery, 2.5 for proximal left anterior descending (LAD), 1.5 for middle LAD, 1.5 for distal LAD, 1 for diagonal LAD, 2.5 for proximal circumflex artery, 1 for marginal obtuse and posterolateral branch, 1.5 for right proximal coronary, 1 for posterior descending artery, and 0.5 for others. The points were added and total Gensini points were calculated for each patient.

Epicardial fat thickness was measured using transthoracic echocardiography within 90 days of coronary angiography. Echocardiographies were performed by a single cardiologist with a GE Vivid 3 instrument (Providian Medical, LLC, USA) according to standard techniques, with subjects in the left lateral decubitus position. Cardiologist that performed echocardiography was not aware of angiography results.

The epicardial fat thickness was measured perpendicularly on the free wall of the right ventricle at end-systole for 3 cardiac cycles. The measurement was performed at a point on the free wall of the right ventricle where the fat thickness was highest. All data were analyzed via SPSS software (version 15, SPSS Inc., Chicago, IL, USA).

Continuous data were demonstrated as mean and standard deviation. Categorical data were shown as absolute number and percent. The normality of data was evaluated via Kolmogorov-Smirnov test. Independent t test was used for continuous data and chi-square test for categorical data analysis. Multiple linear regression was used to evaluate the relationship between means of epicardial thickness and modified Gensini score.
Table 1. Demographic characteristic of patients and comparing between the two groups based on the median of epicardial fat thickness

| Variables                  | Equal or less than 0.7 mm (n = 45) | More than 0.7 mm (n = 40) | P       | Total (n = 85) |
|----------------------------|-------------------------------------|---------------------------|---------|---------------|
| Sex (Men)                  | 25 (55.6)                           | 20 (55.0)                 | 0.610   | 45 (52.9)     |
| History of Heart failure   | 6 (13.3)                            | 11 (27.5)                 | 0.100   | 17 (20.0)     |
| Smoking                    | 13 (28.9)                           | 18 (45.0)                 | 0.120   | 31 (36.5)     |
| Hypertension               | 33 (73.3)                           | 33 (82.5)                 | 0.310   | 66 (77.6)     |
| Dyslipidemia               | 15 (33.3)                           | 8 (20.0)                  | 0.160   | 23 (27.1)     |
| History of MI              | 9 (20.0)                            | 21 (52.5)                 | 0.002   | 30 (35.0)     |
| History of angina          | 39 (86.7)                           | 35 (87.5)                 | 0.910   | 74 (87.0)     |
| Age (year)                 | 58.20 ± 8.34                        | 62.60 ± 7.83              | 0.014   | 60.31 ± 8.36  |
| Weight (kg)                | 73.30 ± 11.40                       | 79.20 ± 8.85              | 0.010   | 76.09 ± 10.62 |
| Height (cm)                | 168.90 ± 7.69                       | 167.20 ± 6.57             | 0.280   | 168.14 ± 7.20 |
| Body mass index (BMI)      | 25.60 ± 3.24                        | 28.40 ± 3.44              | < 0.001 | 26.93 ± 3.60  |
| Duration of diabetes (year)| 7.44 ± 2.88                         | 8.57 ± 3.42               | 0.100   | 7.97 ± 3.18   |
| Modified Gensini score     | 12.10 ± 4.98                        | 24.40 ± 5.45              | < 0.001 | 17.89 ± 8.04  |

All continuous variables reported as mean ± standard deviation (SD) and categorical variables reported as absolute number (percent). MI: Myocardial infarction

Results

Eighty five patients took part in this study, 45 men (53%), and 40 women (47%). Participants were divided into two group according to median (7 mm) of epicardial fat thickness (EFT). The patients with EPT of over 7 mm were significantly older (62.6 ± 7.83 vs. 58.2 ± 8.34; P = 0.014) and fatter (28.4 ± 3.44 vs. 25.6 ± 3.24; P < 0.001), and had more severe CAD (mean Gensini score of 24.4 ± 5.45 vs. 12.1 ± 4.98; P < 0.001) (Table 1).

After adjustment the roles of BMI, age, angina history, and sex, multiple linear regression analysis revealed a significant association between modified Gensini score and epicardial fat thickness (Crude Model: 0.83, Adjusted Model: 0.72; P < 0.001 for both). One millimeter increase of mean epicardial fat thickness was associated with 0.82 unit of modified Gensini score (Figure 1).

Discussion

In this study, we found a correlation between the severity of CAD calculated by modified Gensini method and echocardiographic epicardial fat thickness in patients with diabetes mellitus type II. We also found that there was a relationship between obesity and hypertension with the severity of CAD; but this relationship was not linear.

Patients divided into two groups of below and above the median of Gensini score and mean z. The difference between the 2 groups was evaluated using t-test. P-value lower than 0.050 was considered significant.

Figure 1. Association of modified Gensini score and epicardial fat thickness

Magnetic resonance imaging (MRI) and computed tomography (CT) scan are currently gold standards for measuring epicardial fat; but these are expensive, and are not routinely performed in a typical cardiac patient. So, we used echocardiography for measurement of epicardial fat thickness, which is an estimation of epicardial fat content.

There are a lot of studies about the epicardial fat thickness and atherosclerotic diseases of CAD; but, there are few studied in the subgroup of patients with diabetes mellitus. In a recent study on 123 patients with CAD, echocardiographic epicardial fat thickness was significantly correlated with the presence and severity of angiographically detected CAD. They used Gensini scoring system for measurement of the severity of CAD. In another study on 110 patients, epicardial fat thickness in men and women was not statistically different and coronary artery lesions...
measured by Gensini score showed linear association with severity of CAD, and epicardial fat thickness.\(^{20}\) Nakazato et al. measured epicardial fat volume by CT scan instead of echocardiography, and found that epicardial fat valium was independently and linearly associated with existence of CAD and its severity.\(^{21}\)

The location of lipid accumulation around the heart may be important in increasing the probability of coronary stenosis. In a study on 157 patients with diabetes mellitus type II and without CAD history, left atrioventricular groove epicardial adipose volume was an independent predictor of CAD.\(^{22}\)

Cystatin C, a 13-kD endogenous cysteine proteinase inhibitor, is ubiquitously expressed, mainly in the brain, testis, lung, spleen, and adipose tissue.\(^{23}\) Recently, a strong association between epicardial fat and cystatin C in patients with diabetes type II is founded. This means that epicardial fat accumulation may bring an essential role in cystatin C secretion, that contributing to atherosclerosis risk in these patients.\(^{24}\)

There is a decreased expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and uncoupling protein 1 (UCP1) mRNA in epicardial fat tissue of patients with CAD and diabetes mellitus type II that may be caused by a loss of brown-like fat features. There is a higher prevalence of CAD in patients with decreased expression of PGC1α in epicardial adipose tissue.\(^{25}\)

Besides, its effect on coronary artery pericardial fat is related to other cardiac conditions such as heart failure calcification of coronary arteries, coronary artery spasm, etc. Ng et al. found that in with patients mellitus, epicardial fat is independently associated with impaired myocardial systolic function despite preserved 3 dimensional (3D) left ventricular ejection fraction and absence of obstructive CADs. They measured epicardial fat using 3D echocardiography.\(^{26}\)

Coronary artery calcium score is associated with epicardial fat thickness, too. A cohort study showed that progression of coronary artery calcification was correlated with epicardial fat thickness, and this score also had significant correlation with systemic inflammation markers.\(^{27}\)

A 5-year CT scan follow-up study by Hwang et al. showed that greater amount of epicardial fat at baseline CT scan independently predicted the development of non-calcium coronary plaque in asymptomatic individuals.\(^{28}\) The development of coronary artery calcification may be mediated by epicardial fat volume via the activation of local inflammatory cytokines.

Epicardial fat is related to the presence of coronary artery calcification but not to aortic valve or ascending aorta calcification. These findings support a local paracrine effect of epicardial fat in mediating coronary atherosclerosis.\(^{29}\)

Epicardial fat volume also correlated with atherosclerotic plaque vulnerability. There was an association between epicardial fat volume and development of coronary atherosclerosis and the most dangerous types of plaques in Ito et al. study.\(^{30}\) Ergonovine-induced epicardial coronary artery spasms is also related to epicardial fat valum.\(^{31}\) So, increased epicardial fat thickness may predict the probability of angina attack in patients with non-significant coronary stenosis.

**Conclusion**

In conclusion, this study showed significant correlation between epicadial fat and the severity of CAD; epicardial fat also related to other cardiac conditions including left ventricular dysfunction, myocardial fibrosis, coronary artery calcification, and coronary spasm. It needs new studies finding best solution to prevent and treat this condition.

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**Conflict of Interests**

Authors have no conflict of interests.

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