Comparison of Epicardial fat volume and coronary calcification in diabetic versus non diabetic patients detected by coronary CT angiography

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Abstract:

Background: Coronary computed tomography angiography (CCTA) has evolved as a non-invasive imaging technique for evaluation of stenosis in the coronary arteries, but it is also widely used in quantitative plaque assessments. Evaluation of EFV(epicardial fat volumes) can also be performed on the same images.

Aim: To compare the relation between epicardial fat volume and coronary artery atherosclerosis in diabetic versus non diabetic patient by CT coronary angiography.

Patients and methods: We included 200 patients. They were divided into 2 groups; diabetic group, and non-diabetic group. All patients in this study have underwent full history taking, clinical examination including BMI, standard ECG, routine laboratory investigations, and multi-slice CT angiography.

Results: When comparing diabetic and non-diabetic groups, we found that Degree of stenosis in coronary artery were higher among the diabetic group compared to the non-diabetic one. Multiple vessel affection was more common among the diabetic group when compared with non-diabetic group (p<0.001). Overall, Ca total score was significantly higher among the diabetic group compared to the non-diabetic one (p<0.001). EFV was significantly higher among diabetic patients compared to the non-diabetic group (p<0.001).

EFV was significantly higher among patients with multiple vessel affection when compared with those with single vessel and normal vessels (p <0.001). Higher EFV was correlated with presence of DM more in patient longer than 5 years duration (p<0.001). It was also positively correlated with total Ca scores among our study population (r=0. 311, p=0.000).

Conclusion: A clear association was found between the DM and EFV and both presence of calcific plaques and degree of stenosis among whole study population.

Keywords: Epicardial fat volume, diabetes, coronary calcifications, coronary CT angiography.

Introduction:

Patients with diabetes mellitus type 2 (DM2) and impaired fasting glucose (IFG) suffer from a two- to four-fold higher cardiovascular mortality compared with
normoglycaemic patients. Also, patients with DM2 show a markedly increased prevalence of CAD. As both IFG and DM2 patients are reported to have higher EFV, it is of particular interest to investigate the predictive value of EFV as a risk factor for CAD in these two patient categories (1).

Considering its noninvasive technique and recent advances in temporal and spatial resolution, the measurement of epicardial fat volume by MDCT might be helpful in the prevention and treatment of coronary artery disease as it can early detect the risk factors and the sequences of these risk factors. Multidetector computed tomography (MDCT) allows simultaneous assessment of coronary artery calcium (CAC), coronary artery stenosis, coronary plaques and epicardial fat volume (EFV) without increased radiation exposure or cost (2).

This study aimed to compare the relation between epicardial fat volume and coronary artery atherosclerosis in diabetic versus non diabetic patient by CT coronary angiography.

Patients and methods:

Patients: We included 200 patients. They were divided into 2 groups;

- **Diabetic group**: Consists of 90 patients who were presenting by chest pain and referred for MSCT angiography with diabetes mellitus.
- **Non-diabetic group**: Consists of 110 patients who were presenting by chest pain and referred for MSCT angiography and didn’t have diabetes mellitus.

Patients with renal insufficiency, patients with previous history of PCI or previous CABG, patients with recent myocardial infarction, dye allergy, irregular heart rhythm like AF and frequent extra-systoles, difficulties in performing CT, like inadequate breath holding and heart failure, patients diagnosed as having acute coronary syndromes were excluded from our study.

Methods:

A. _Full history taking_ including: Age, sex, family history of ischemic heart disease (first degree relatives), smoking, hypertension and diabetes mellitus.

B. _Complete clinical examination_ including body mass index.

C. _Standard ECG_ including rhythm, rate and ischemic changes.

D. _Routine laboratory investigations_ including random Blood glucose level, serum creatinine, and complete Lipid profile.

E. _Multi-slice CT angiography:_

(1) **Imaging Technique:** All CT scans were performed on (Toshiba Aquilion prime) is source 160-slice CT scanner.

- **Patient preparation:**

  - The CT angiography was performed to all patients utilizing a dual source scanner (Toshiba Aquilion prime) and all coronary arteries was evaluated at different phases of the cardiac cycle by acquisition of thin slice sections (0.5 mm).
Heart rate of all patients was determined one hour before examination.

If heart rate is > 75 BPM, the patient was given orally beta blocker agents or calcium channel blocker.

Five milligram sublingual dose of nitroglycerin was administered just before the scan.

All scans were preceded by non-contrast enhanced scan for coronary calcium score this was done to rule out patients with dense coronary calcification (total score above 1000).

All included patients received intravenous nonionic iso-osmolar contrast medium (using the test bolus technique) a bolus of 10 ml of the contrast agent injected intravenously at a rate of (5 ml/s). Then angiography done by injecting 60 ml of the same contrast agent at a rate of 6 ml/s.

**Tomogram:**
- Taken from tracheal bifurcation to the diaphragm in a single breath-hold in the cranio-caudal direction.

**Test bolus:**
- Injection of 10 ml Iopromide 370 mg/mL followed by 50 ml saline and then acquisition of sequence of images at the level of the Aorta and Pulmonary arteries every two seconds.
- Calculation of the actual delay time from start of injection till maximum intensity of dye in the Aorta.

**CT angiography:**
- After accurate calculation of delay time and checking the ECG trigger, images acquisition is done after injection of 60 ml Iopromide 370 at flow rate 6 ml/sec followed by 60 ml saline at flow rate 6 ml/sec using power injector or infusion syringe.

**Image reconstruction:**
- The CT scanning was performed at the following settings: retrospective ECG-gated acquisition spiral mode. A three dimensional workstation was used to reconstruct axial images retrospectively at an optimal window. The image data sets were analyzed by means of Multi-planar reformatted images (vertical, long-axis, and short-axis views), curved Multi-planar reformatted images, thin-slab maximum-intensity projection images, and volume-rendered images.

- Two-dimensional reconstructions (curved Multi-planar reformation) of the coronary arteries were performed on several planes to assess patency of the vessels. These 2-dimensional images show the vessel's wall and lumen and all the surrounding tissue. They are reconstructed on at least 2 orthogonal planes, and continuity of contrast material throughout the vessel serves as an indication of patency.
(2) Measurement of plaque burden:

- Coronary segments were visually scored for the presence of coronary plaque:

a. Segment-stenosis score (SSS):

SSS was calculated as a measurement of total coronary plaque burden. Each segment was given a score from 0 to 3 [0] for normal, [1] for mild (<50%), [2] for moderate (50% to 69%), [3] for severe (≥70%) according to the degree of lumen stenosis. The summation of every segment score gives an entire score ranging from 0 to 48 (>5 points were defined as high-risk) (3).

b. Coronary Calcium Scoring:

In this test, which did not use X-ray contrast, pictures were taken of the heart to look for the presence of calcium deposits in the blood vessels of the heart or coronary arteries. Calcium deposits were a very specific sign of coronary artery disease, as cholesterol and scar tissue buildup in the arteries. While the amount of calcium in the arteries increases with age, patients who have significantly elevated amounts of calcium deposits are at increased risk to have heart attacks or ischemic heart disease and the amount of calcium deposits were measured by "agastone score " as shown in Table (3) (4).

Table 1: Relationship between CT coronary calcium score, plaque burden and probability of significant CAD.

<table>
<thead>
<tr>
<th>CT Calcium Score</th>
<th>Plaque burden</th>
<th>Probability of significant CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No identifiable plaque burden</td>
<td>Very low (generally &lt; 5% likelihood)</td>
</tr>
<tr>
<td>0 – 10</td>
<td>Minimal identifiable plaque burden</td>
<td>Very unlikely (generally &lt; 5% likelihood)</td>
</tr>
<tr>
<td>11 – 100</td>
<td>Definite (at least mild)</td>
<td>Mild or minimal coronary artery stenosis likely</td>
</tr>
<tr>
<td>101 – 400</td>
<td>Definite (at least moderate    atherosclerotic plaque burden)</td>
<td>Non-obstructive CAD highly likely, although obstructive disease possible</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>Extensive</td>
<td>High likelihood (&gt; 90%) of at least one significant coronary stenosis</td>
</tr>
</tbody>
</table>

(3) Measurement of epicardial fat volume (EFV):

- Epicardial fat was defined as the adipose tissue accumulated between the visceral layer of the pericardium and the myocardium, without a structure or fascia separating it from the myocardium and the epicardial vessels.

- Using the 3.0-mm-thick axial slices used for calcium scoring, we manually traced the parietal pericardium starting from the aortic root to the apex.

- The computer software then automatically interpolated and traced the parietal pericardium in all slices interposed between the manually traced slices to measure the EFV in cm³ as shown in patient No (4)
- The total number of slices was 30 to 40 per heart. All automatically traced slices were examined and verified for accuracy.

- Fat voxels were identified using threshold attenuation values of −30 to −250 HU.

**Statistical analysis:**

Data were coded, processed and statistically analyzed using the SPSS version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Frequencies and percentages were used to express qualitative variables. Chi square test ($\chi^2$) and Fisher exact were used to test the difference between qualitative variables as indicated. Mean and the standard deviation (SD) were used to present quantitative data. Comparison between parametric variables in 2 independent groups was done using the independent samples t-test, while non-parametric data variables were compared using the Mann Whitney U test. Receiver operating characteristic (ROC) curve analysis was established for assessing how far tested variables could predict mortality. Dependent and independent predictors of binary outcome were tested using univariate and multivariate logistic regression analysis. Statistical significance for all analyses was considered when the P value was less than 0.05.

**Results:**

About 35% of patients in this study population (70 participants) were males. Their mean age was 49.89 ± 9.79 years old. When comparing diabetic and non-diabetic groups, we found no significant difference between both groups concerning gender distribution or smoking. However, diabetic patients were significantly older and had more family history for cardiac diseases when compared to non-diabetic groups ($p=0.001$ and $0.022$ respectively).

Creatinine, triglycerides, LDL and cholesterol levels were significantly higher among diabetic group compared to the non-diabetic group ($p<0.001$ for all). While HDL serum levels were significantly lower among diabetic group compared to the non-diabetic group ($p=0.001$) (Table 1).
Table 1; showing the difference between both groups concerning laboratory findings.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic (n=90)</th>
<th>Non diabetic (n=110)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>71.68 ± 8.86</td>
<td>71.58 ± 9.3</td>
<td>0.938</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>28.97 ± 2.57</td>
<td>27.83 ± 2.71</td>
<td>0.003</td>
</tr>
<tr>
<td>Hb</td>
<td>13.8 ± 1.13</td>
<td>13.98 ± 1.21</td>
<td>0.297</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.07 ± 0.16</td>
<td>0.96 ± 0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>194.02 ± 47.1</td>
<td>155.1 ± 55.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>206.9 ± 48.86</td>
<td>172.03 ± 55.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>117.86 ± 28.3</td>
<td>94.41 ± 27.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>50.06 ± 8.72</td>
<td>54.4 ± 9.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Independent sample T test.

Mild to moderate stenosis in LM artery were higher among the diabetic group compared to the non-diabetic one (p=0.019). Mild to moderate stenosis in each of LAD, diagonal, LCX, and RCA arteries were significantly higher among the diabetic group when compared to the other one (p<0.001 for all). While the mild stenosis in OM arteries was higher among non-diabetic one compared to diabetics. However, the sever stenosis was equally present between both groups (p<0.001). Multiple vessel affection was more common among the diabetic group when compared with non-diabetic group (p<0.001).

Concerning Ca score; patients in the diabetic group could achieve higher Ca scores compared to the non-diabetic one whether in LM, LAD, LCX, RCA arteries (p<0.001, p=0.026, p=0.05 for LAD, LCX and RCA respectively). Overall, Ca total score was significantly higher among the diabetic group compared to the non-diabetic one (p<0.001). (Figure 2).
EFV was significantly higher among diabetic patients compared to the non-diabetic group (p<0.001) (Figure 3). Higher EFV was correlated with presence of DM more in patients longer than 5 years duration (p<0.001). Higher EFV was also correlated with presence of HTN among our studied patients (p<0.001). (Figure 4).
EFV positively correlated with Ca scoring among our patients ($r = 0.310$, $p<0.001$). EFV positively correlated with degree of stenosis; i.e, EFV was significantly higher among those with higher degree of stenosis ($p<0.001$).

EFV was significantly higher among patients with multiple vessel affection when compared with those with single vessel and normal vessels ($p <0.001$).

Higher EFV was reported in patients with higher degrees of stenosis in each of LAD, diagonal, LCX, OM, and RCA arteries ((p<0.001 for all). EFV increased with increase in the number of involved vessels ($p<0.001$). EFV also increased with higher degree of stenosis ($p<0.001$).

Regarding correlation of EVF with Ca scores, EVF was positively correlated with Ca scores in each of LM ($r=0.167$, $p=0.018$), LAD ($r=0.339$, $p=0.000$), LCX ($r=0.181$, $p=0.010$), and RCA ($r=0.223$, $p=0.002$), arteries. It was also positively correlated with total Ca scores among our study population ($r=0.311$, $p=0.000$).

Discussion:

We found no significant difference between both groups concerning gender distribution or smoking. However, diabetic patients were significantly older and had more family history for cardiac diseases when compared to control group ($p=0.001$ and 0.022 respectively). Despite that BMI was significantly higher among diabetic patients compared to the other group, this was statistically insignificant.

Creatinine, triglycerides, LDL and cholesterol levels were significantly higher among diabetic group compared to the non-diabetic group ($p<0.001$ for all). While HDL serum levels were significantly lower among diabetic group compared to the non-diabetic group ($p=0.001$). In contrary, when (5) compared the DM2 and IFG groups with controls, they had lower serum cholesterol values (which was due to more statin use).
According to the present study, mild to moderate stenosis in LM artery were higher among the diabetic group compared to the non-diabetic one (p=0.019). We also found mild to moderate stenosis in each of LAD, diagonal, LCX, and RCA arteries were significantly higher among the diabetic group when compared to the other one (p<0.001 for all). While the mild stenosis in OM arteries was higher among non-diabetic one compared to diabetics. However, the severe stenosis was equally present between both groups (p<0.001). Multiple vessel affection was more common among the diabetic group when compared with the other one (p<0.001). In concordance with our study, in (6) study of patients who have survived more than 45 years with T1DM without a previous diagnosis of coronary heart disease, they found a greater extent and severity of coronary atherosclerosis compared to controls. Also, both DM2 and IFG in (5) study were associated with the presence of CAD as well as the extent of CAD as determined by the involvement score.

Versteylen et al. (5) study reported that calcium scores were higher among the DM2 and impaired fasting glucose (IFG) groups were compared with controls. Similarly, we found that patients in the diabetic group could achieve higher Ca scores compared to the non-diabetic one whether in LM, LAD, LCX, RCA arteries (p<0.001, p=0.026, p=0.05 for LAD, LCX and RCA respectively). While the difference between Ca scores in both groups was insignificant in case of LM artery. Overall, we found the Ca total score was significantly higher among the diabetic group compared to the non-diabetic one (p<0.001).

We found that EFV was significantly higher among diabetic patients compared to the non-diabetic group (p<0.001). In concordance with our finding, (Versteylen et al., 2012) study reported that EAT volumes were higher among the DM2 and impaired fasting glucose (IFG) groups were compared with controls. Mean EAT volume for controls, IFG subjects, and patients with DM2. DM2 as well as IFG patients had higher EAT volumes compared with controls (P < 0.001). In contrary, (6) reported that the EAT volume did not differ between T1DM and controls. This difference can be attributed to the difference in sample sizes between the 2 studies (45 in Svanteson study vs 200 in this study). To our knowledge, EAT has not previously been associated with coronary atherosclerosis in T1DM patients, although associations of coronary atherosclerosis and EAT in patients with T2DM has been revealed (7). The inconsistent findings between T1DM and T2DM may imply that EAT potentially plays a different role between the types of DM. In T2DM metabolic syndrome, not commonly present in T1DM, has been associated with increased EAT volumes (8).

We found that EFV positively correlated with Ca scoring (p<0.001) and with degree of stenosis (p<0.001). Similar to our study, Liu et al. (9) reported that EAT was positively correlated with CAC score. Also, Versteylen et al. (5) reported that EAT was significantly associated with the extent of CAD. Linear regression analysis showed that, for each increase in 10 cm$^3$ EAT, the Agatston calcium score increased 6 units, and the involvement score increased with 0.13 segments ($P=0.009$ and $P<0.001$, respectively).

Uni-variable analysis in Versteylen et al. (5) study showed that the EAT volume predicted for the presence of any plaque on computed tomography angiography (CCTA). Also in this study, EFV was significantly higher among patients with multiple vessel affection when compared with those with single vessel and normal vessels (p <0.001). In contrary to our findings, Svanteson et al. (6) found no associations between
coronary atherosclerosis and EAT volume. This difference can be attributed to the difference in sample sizes between the 2 studies (45 in Svanteson study vs 200 in this study).

There was no significant correlation between EFV and sex, family history of cardiac disease, or dyslipidemia. While we reported higher EFV among smokers (p=0.001). Similar to our study, Liu et al. (9) reported that EAT attenuation was tightly associated with CAD risk factors, including total cholesterol.

EFV also increased with higher degree of stenosis (p<0.001). In contrast, Versteylen et al. (5) found that EFV did not independently predict the presence or extent of CAD. This difference can be attributed to the difference in sample sizes between the 2 studies (400 in Versteylen study vs 200 in the present study).

According to this study, EVF was positively correlated with each of age (r=0.429, p=0.000), SBP (r=0.417, p=0.000), DBP (r=0.334, p=0.000), and BMI (r=0.389, p=0.000). This is consistent with Djaberi et al. (10), who found associations of EAT with greater BMI. Similar to our study, Liu et al. (9) reported that EAT was tightly associated with CAD risk factors, including age.

The influence of glycemic control on EFV volume is unexplored. Darabian et al. (11) reported on a positive significant correlation between EFV and HbA1c. According to this study, higher EFV was correlated with presence of DM more in patient longer than 5 years duration (p<0.001). Higher EFV was also correlated with presence of HTN among our studied patients (p<0.001). We found that EVF was positively correlated with HBA1C (r=0.332, p=0.001), and RBS (r=0.436, p=0.000). In contrary to our finding, Svanteson et al. (6) did not find associations between EAT and HbA1c. However, in their study the participants were older, had a longer duration of T1DM and a lower BMI compared to our participants.

Finally, associations between EFV and coronary atherosclerosis are reported by multiple studies, suggesting that EFV have a role in the development of coronary atherosclerosis (12).

**Conclusion:**

A clear association was found between the EFV and diabetes also with the degree of stenosis among whole study population. EFV positively correlated with age, SBP, DBP, and BMI. EFV also positively correlated with each of serum levels of creatinine, TG, cholesterol, LDL, HDL, HBA1C, and RBS and with Ca scores among patients in this study. Multiple vessel affection and higher degrees of stenosis were more common among the diabetic group. Ca total score was significantly higher among the diabetic group compared to the non-diabetic group.

**References:**


