Comparison of epicardial fat thickness in diabetic patients compared to non-diabetics with acute myocardial infarction and ST-segment elevation (AMI-STEMI)

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Abstract

Introduction: Visceral fat has deleterious metabolic effects and has been associated with myocardial ischemia. Objective: To compare epicardial fat thickness in diabetic versus non-diabetic patients with acute myocardial infarction with ST-segment elevation. Material and methods: We performed a cross-sectional study in 60 patients with acute myocardial infarction with ST-segment elevation (30 diabetic and 30 non-diabetic). Cardiovascular risk factors and Thrombolysis in Myocardial Infarction (TIMI) score were registered. Using echocardiography, left ventricle ejection fraction and epicardial fat measured in the interventricular septum, right ventricle outflow tract, apex, and right ventricle free wall was evaluated. Results: Epicardial fat at the apex (6.1 vs. 5.8 mm; p = 0.038) and in the interventricular septum (7.0 vs. 5.7 mm; p = 0.033) was higher in diabetic versus non-diabetic patients. In diabetic patients, plasmatic glucose correlated with TIMI score (R: 0.49; p = 0.005) and body mass index (R: –0.50; p = 0.004). The TIMI score (4.5 vs. 3.4; p = 0.04), body mass index (29.3 vs. 26.4; p = 0.008), epicardial fat in the interventricular septum (6.8 vs. 4.7; p = 0.000004) and in the right ventricle outflow tract (6.8 vs. 5.0; p = 0.000042) were higher in patients with fat in apex ≥ 6 mm. Conclusions: In diabetic patients with acute myocardial infarction with ST-segment elevation, interventricular septum and apex epicardial fat was higher compared with non-diabetic patients.

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Introduction

Diabetes mellitus (DM) global prevalence is rapidly increasing as a result of population ageing, urbanization and lifestyle-associated changes. World-wide, estimated number of diabetic people for the year 2035 will be 592 million, which accounts for 8.7% of adult population¹. Cardiovascular conditions are the main cause of death in diabetic patients, with a risk 2-4-fold higher than in the general population².

On the other hand, visceral adiposity has acquired relevance owing to its association with pathologies such as coronary artery disease and type 2 diabetes mellitus (type 2 DM) and, recently, extra-abdominal regional visceral fat deposits, including epicardial adipose tissue. In physiological conditions, epicardial adipocytes...
appear smaller than abdominal adipocytes, their protein content is higher, the rate of glucose utilization is lower and the synthesis of fatty acids and their subsequent degradation is higher than in other visceral adipocytes, suggesting that this tissue exerts a buffer effect that protects the heart from exposure to high levels of circulating fatty acids and the ensuing cardiotoxicity thereby generated, in addition to being considered a possible energy source for the myocardium. However, adipocytes can be an important source of anti-inflammatory and inflammatory adipocytokines, which might cross the coronary arteries wall, or be directly released into the vasa vasorum and then transported within the arterial wall by a vasocrine signaling mechanism. In pathological conditions, as in obesity and diabetes, there is deterioration of the adipocyte buffer, which determines lower free fatty acids uptake by the adipocyte and higher cardiolipotoxicity. In addition, inflammatory transcriptors are activated at the level of the adipocyte, such as the nuclear factor kappa beta, which induces the formation of inflammatory mediators such as the tumor necrosis factor alpha, interleukin 1 and 6, visfatine and C-reactive protein.

Pericardial fat thickness can be measured with bi-dimensional transthoracic echocardiography, and it is identified as the space between the external wall of the myocardium and the visceral layer of the pericardium. It is a non-invasive, reliable and easily reproducible study and is a direct measurement of the heart’s visceral fat with little intra- and inter-observer variability. The purpose of this study was to compare the epicardial fat thickness in patients with ST segment elevation acute myocardial infarction (STEAMI) between diabetic and non-diabetic subjects, as well as to find out if there is a relationship between epicardial fat thickness and the Thrombolysis in Myocardial Infarction (TIMI) score in these patients.

### Material and methods

We conducted a comparative cross-sectional study in patients admitted to the high specialty medical unit hospital UMAE EH No. 1 León Bajío with a diagnosis of STEAMI, of either gender, older than 18 years and younger than 75. In all cases the acute myocardial infarction (AMI) was corroborated by 12-lead electrocardiogram and all patients signed the consent form to participate in the study after having understood the purpose and type of the study they were to undergo. In the group of diabetic patients, only those with an established diagnosis of type 2 DM with any time of evolution were included. In the group of non-diabetic patients, only those who, in addition to not knowing if they had this condition, showed fasting or any period glucose levels outside the ADA ranges at discharge. Patients were not included in case of having a history of pericardial surgery, a diagnosis of end-stage renal failure or of any type of cancer except for localized basal cell or squamous cell malignancies. Subjects with an echocardiographic window not suitable for epicardial fat measurement or patients with pericardial effusion were excluded. Fasting blood glucose levels were determined and the TIMI risk was calculated in all patients.

Epicardial fat measurement was carried out by Dr. Miguel Ángel Carillo Torres, a cardiologist specialized in echocardiography, member of the National Society of Echocardiography. A General Electric Vivid S6 equipment was used. The measurement was performed in the left lateral decubitus position, with the parasternal long axis projection, in the space comprised between the myocardial outer wall and the pericardial visceral layer, with measurements made at end of systole on three cardiac cycles, at the free wall, apex and right ventricular outflow tract and interventricular septum, according to the methodology previously described by Iacobellis. The left ventricular ejection fraction was also measured using Simpson’s method.

| Table 1. Clinical and biochemical characteristics of diabetic and non-diabetic patients with ST segment elevation acute myocardial infarction |
|---------------------------------|-----------------|-----------------|-----|
| Variable                        | No DM (n = 30)  | DM (n = 30)     | p   |
| Gender M/F                      | 23/7            | 24/6            | 0.82|
| Age (years)                     | 64.6 ± 11.4     | 59.7 ± 8.6      | 0.06|
| SAH n (%)                       | 13 (43.3)       | 22 (73.3)       | 0.04|
| Dyslipidemia n (%)              | 14 (46.6)       | 17 (56.6)       | 0.51|
| Smoking n (%)                   | 20 (66.6)       | 17 (56.6)       | 0.51|
| Obesity n (%)                   | 10 (33.3)       | 17 (56.6)       | 0.07|
| BMI (kg/m²)                     | 27.6 ± 4.1      | 29.2 ± 3.9      | 0.13|
| Glucose (mg/dl)                 | 100.0 (100.2 ± 121.1) | 173.5 (152.2 ± 224.7) | 0.0005|
| TIMI                            | 3.9 ± 2.3       | 3.6 ± 1.3       | 0.64|
| LVEF (%)                        | 49.0 ± 11.0     | 46.8 ± 10.4     | 0.43|

Values shown as the mean ± SD or median (95% CI) for variables with normal and skewed distribution, respectively.
The treatment established for ischemic heart disease was left at the discretion of the treating physician and there was no intervention of the research group.

**Sample size**

To detect an epicardial mass thickness difference of 2 mm between diabetic and non-diabetic subjects, with a SD of 3 mm for diabetics and 2 mm for non-diabetic subjects, with 80% power and 95% one-tailed significance, a total of 27 patients per group was determined in the Medcalc statistical program, version 14.0, with inclusion of 30 patients per group being decided.

**Statistical analysis**

Descriptive statistics was used to identify the data distribution. Continuous variables between the groups of patients with and without DM were compared with Student’s t-test or Mann-Whitney U-test according to normal or skewed data distribution, respectively. The chi-square test was used for the comparison of proportions. The association between epicardial fat measurement and left ventricular ejection fraction, glucose levels and TIMI risk was assessed using Pearson’s or Spearman’s correlation tests according to the distribution of variables. A p-value < 0.05 was considered to be significant. The analysis was made using the Statistica software, version 6.0.

**Results**

Diabetic patients showed a tendency to be younger, but to have higher levels of glucose and a higher proportion of hypertension as a comorbidity. However, no difference was observed in left ventricular ejection fraction and the TIMI score (Table 1).

Epicardial fat thickness was higher in the apex and interventricular septum regions in patients with DM in comparison with non-diabetic subjects, with a maximum epicardial fat thickness of 7 mm at the interventricular septum in diabetic patients. A trend for total, right ventricular free wall and right ventricular outflow tract epicardial fat thickness to be higher was observed in this same group (Table 2).

No correlation of clinical or biochemical variables with epicardial fat was observed in non-diabetic patients. In contrast, in diabetics, glucose had a positive correlation with infarction seriousness according to the TIMI score \( (R = 0.49; \ p = 0.005) \) and an inverse correlation with the body mass index \( (BMI) \) \( (R = -0.50; \ p = 0.004) \).

When the patients were pooled according to those with apex epicardial fat above or below the mean \( (6 \ mm) \), higher scores were found in the TIMI scale \( (4.5 \ vs. 3.4; \ p = 0.04) \), higher BMI \( (29.3 \ vs. 26.4; \ p = 0.008) \), and more fat at the intraventricular septum \( (6.8 \ vs. 4.7; \ p = 0.000004) \) and left ventricular outflow tract \( (6.8 \ vs. 5.0; \ p = 0.000042) \) in those patients with apex fat > 6 mm than in those with < 6 mm.

Among all patients, only 1 death was reported in the group of diabetic patients, a 41-year old man with a previous extensive infarction and TIMI 5; the record of his epicardial fat was higher at the apex and interventricular septum, with 6-mm thickness and left ventricular ejection fraction \( (LVEF) \) of 39%.

**Discussion**

In our study group, the male gender around the 6th decade of life was predominant, which is consistent with widely reported data; for example, in the RENASC study conducted in Mexico in 2010, which included 2,389 patients with ischemic heart disease admitted to tertiary care hospitals of the National Institute of Social Security (IMSS – Instituto Nacional del Seguro Social), 71% of registered patients were males\(^\text{10}\).

In both groups, smoking and dyslipidemia were observed in more than half the population, and diabetic subjects showed systemic arterial hypertension more frequently, as well as a trend to be more obese. This is in line with previous reports of multicenter studies,
where up to 41% of diabetic patients have combined hypercholesterolemia and hypertension, exponentially increasing cardiovascular risk\(^1\). Patients with DM and STEAMI showed higher epicardial fat thickness in comparison with non-diabetic subjects in some specific sites and there was a trend towards higher total epicardial fat. According to a recent study, which included 50 diabetic patients, epicardial fat was established to be an independent measure of hospital-acquired cardiac complications and showed direct association with the SYNTAX score\(^1\). Epicardial fat in the Mexican diabetic population that attended our hospital showed a mean of 6.6 ± 1.3, similar to figures published in other countries, where epicardial thickness of 7 mm is reported in males and 6.5 mm in females\(^1\). Insulin resistance and hyperinsulinemia, frequently observed in these patients, exert multiple potentially deleterious effects, such as sodium retention, free calcium intra-cytoplasmic accumulation, increased sympathetic activity and proto-oncogene expression, effects that participate in the pathophysiology of arterial hypertension, cardiac hypertrophy and atherosclerosis\(^1\). However, whether they have any participation in epicardial fat accumulation and its consequences is not known; in addition, epicardial fat measurement is not yet recommended for general population screening.

In previous studies\(^1\), elevated plasma glucose has been shown to entail a somber prognosis with regard to normoglycemia in AMI. In our study, we were able to confirm that plasma glucose is correlated with the TIMI score in the diabetic population.

The sites where the highest measurements of epicardial fat were found were the apex and interventricular septum. Apex-located epicardial fat in our population was generally correlated with age, with the TIMI score and with epicardial fat thickness in other locations; therefore, measurement at this site could be routinely used for diabetic patients with acute coronary syndrome (ACIS).

In recent literature, cardiac fat was post-mortem analyzed in diabetic patients, and epicardial fat was shown to be found in both ventricles, in the atrioventricular and interventricular grooves until the apex and along the coronary arteries. In addition, epicardial fat covering the right ventricle was found to likely be up to 3-fold higher than the fat covering the left ventricle, and could be measured in new locations such as the right ventricle right lateral and posterior walls, with either being associated with higher cardiovascular risk\(^1\).

Although some studies have demonstrated a relationship between alterations in adipokine secretion from epicardial fat in diabetic patients and ventricular dysfunction\(^1\), in our study, the presence of higher levels of epicardial fat was not related to the percentage of LVEF or the TIMI score. Adipose tissue of patients with obesity, type 2 DM and cardiovascular disease is characterized by alterations in the secretion of adipokines, which suggests a continuous state of low-grade inflammation. The most important adipokines include the fatty acid-binding protein 4, which has been shown to suppress the contractile function in vitro in rat-isolated cardiomyocytes and, in addition, it produces alterations in the shortening of the sarcomere, the cytosolic calcium and the SERCA receptors in myocytes, with all this contributing to the appearance of cardio-suppressant effects and negative inotropic effect\(^1\). In a recent study, an association was found between epicardial fat thickness and subclinical markers of atherosclerosis. Patients with thickness larger than 7 mm had greater carotid intima-media thickness and carotid artery sclerosis\(^2\). Additionally, in a study conducted in women, a relationship was found between epicardial fat and low coronary reserve. This suggests that epicardial fat thickness might be a predictor of coronary reserve in women with normal epicardial arteries by catheterization\(^2\). In contrast, in other study, no correlation was found between epicardial fat and the presence of severity in coronary lesions\(^2\).

One limitation of our study is the sample size, which precludes the formation of risk or disease severity strata, as well as comparisons by gender. Moreover, a normal value for epicardial fat thickness has so far not yet been established, and further studies are required to consider pericardial fat as a cardiovascular risk indicator.

**Conclusion**

In diabetic patients with STEAMI, epicardial fat was higher with regard to non-diabetic patients at the interventricular septum and the apex. There was no correlation between epicardial fat and LVEF or the TIMI score.

**References**