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Journal of Cardiovascular Emergencies 2016;2(1):11-18
DOI: 10.1515/jce-2016-0003

ORIGINAL RESEARCH

Prognostic Value of Epicardial Fat Thickness as a Biomarker of Increased Inflammatory Status in Patients with Type 2 Diabetes Mellitus and Acute Myocardial Infarction

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ABSTRACT

Introduction: The prognostic value of epicardial fat thickness (EFT) and inflammatory biomarkers such as hs-CRP have not been fully investigated in patients with acute myocardial infarction (AMI) and type 2 diabetes mellitus (DM). The study aim was to assess the correlation between the EFT, the persistence of elevated circulating levels of hs-CRP at 7 ± 2 days after an AMI and the amplitude of the left ventricular (LV) remodeling, in patients with type 2 DM. **Methods:** The study included 98 patients (45 with type 2 DM and 43 with no DM): Group 1 included 22 low-to-intermediate risk patients (hsCRP <3 mg/l) and Group 2 had 23 high-risk, (hsCRP >3 mg/l) patients. EFT, LV function and remodeling were assessed at baseline and at six months after AMI in both groups. **Results:** In the diabetic population, the EFT was significantly higher in patients who developed ventricular remodeling as compared with those who did not (8.02 ± 1.80 mm vs. 6.65 ± 2.17 mm, p = 0.02) and significantly correlated with the circulating levels of hsCRP (r = 0.6251, p <0.0001). The levels of circulating hs-CRP, at baseline, significantly correlated with the RI at six months (r = 0.39, p <0.001). Also, in the diabetic population, the epicardial fat thickness was significantly higher in patients who developed ventricular remodeling as compared with those who did not (8.02 ± 1.80 mm vs. 6.65 ± 2.17 mm, p = 0.02). The epicardial adipose tissue thickness significantly correlated with the circulating levels of hsCRP (r = 0.6251, p <0.0001), while in the non-diabetic population, EFT was not significantly higher in patients who developed ventricular remodeling as compared with those who did not (71.38 ± 9.09 vs. 67.4 ± 10.17, p = 0.23). Multivariate analysis identified the hs-CRP values (OR: 4.09, p = 0.03) and the EFT (OR: 6.11, p = 0.01) as significant independent predictors for LV remodeling in diabetic population. **Conclusions:** A larger EFT is associated with a more severe remodeling and impairment of ventricular function in patients with type 2 DM and AMI.

Keywords: inflammation, remodeling, ventricular function, postmyocardial infarction

ARTICLE HISTORY

Received: 15 October, 2015
Accepted: 20 January, 2016

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INTRODUCTION

The leading cause of mortality and morbidity in diabetic patients is represented by coronary artery disease, and the majority of the deaths in these patients are caused by an acute myocardial infarction (AMI).[1] Among the multiple factors that may influence the prognosis following an AMI, a major contributor is the degree of the left ventricular (LV) remodeling process, which in turn is directly correlated with the scale of the inflammatory reaction in the post-infarction phase.[2] Low-grade inflammation is recognized as playing a significant role in the pathogenesis of type 2 diabetes mellitus (DM) and its complications, but the potential role of this inflammation in intensifying the remodeling process following an AMI is still uncertain. Studies have indicated that elevated circulating levels of highly-sensitive C-reactive protein (hs-CRP), a protein expressing an increased inflammatory status.[3] are associated with the amplitude of the LV remodeling.[4] However, the prognostic value of hs-CRP in the subset of AMI patients, presenting different comorbidities which express a persistent inflammation, is still under debate.[5–7]

Epicardial adipose tissue is a metabolically active visceral adipose tissue, which has been shown to be involved in the pathogenesis of coronary artery diseases progression through secretion of pro-inflammatory cytokines.[8,9] It has been suggested that a significant increase in mean epicardial fat thickness is present in patients with metabolic syndrome.[10]

Moreover, it has been proposed that the inflammatory cytokines released by the epicardial fat surrounding coronary arteries may have a significant contribution to atherosclerosis progression via modulation of coronary artery function.[9]

The aim of this study was to assess the correlation between several markers expressing an increased inflammatory status in a diabetic population, such as (1) persistence of elevated circulating levels of hs-CRP, as determined at 7 ± 2 days after an AMI and (2) the epicardial fat thickness, as determined by 2D echocardiography, and the evolution of the condition following an acute myocardial infarction, expressed by: (1) the evolution of ejection fraction and (2) the amplitude of the LV remodeling at 6 months post-infarction.

The Null hypothesis that was tested in this study was that there are no differences between the groups with respect to:

1. Persistence of elevated circulating levels of hs-CRP, as determined at 7 ± 2 days after an AMI;
2. The epicardial fat thickness, as determined by 2D echocardiography;
3. The evolution of the condition following an acute myocardial infarction, expressed by the evolution of ejection fraction and the amplitude of the LV remodeling at 6 months post-infarction.

At the same time, the aim was to assess the prognostic value of a new imagistic marker, the epicardial fat thickness, in predicting the evolution after an AMI in diabetic population.

METHODS

The study included 98 patients (45 with DM and 43 non-diabetic) presenting with an acute myocardial infarction 4 [± 2] days prior to the inclusion in the study.

All the patients received primary PCI with post-procedural TIMI 3 flow, followed by medication including statins, dual antiplatelet therapy, ACE inhibitors and cardioselective beta-blockers in optimal adjusted doses.

STUDY GROUPS

In all patients, hs-CRP levels were determined within 4 [± 2] days following the infarction and the patients were divided into the following two groups according to the risk categories[11] and to their hs-CRP levels in the post-acute phase:

- Group 1 was comprised of 43 low-to-intermediate risk patients (22 diabetic and 28 non-diabetic) with hsCRP levels below 3.0 mg/l;
- Group 2 was comprised of 48 high-risk patients (23 diabetic and 25 non-diabetic), with hs-CRP levels above 3.0 mg/l.

The echocardiographic assessment included determination of the left ventricular end-diastolic (LVED) and end-systolic volumes, and calculation of the left ventricular ejection fraction (EF) and the remodeling index (RI).

Epicardial fat thickness was measured at day 4 [± 2] following the infarction and repeated at six months, using the echocardiographic parasternal long-axis view (Philips Sonos 7500, Eindhoven, Netherlands) at end-systole.

The remodeling index was calculated as the difference between the LVED volume at six months and the LVED at baseline divided by the baseline LVED volume. A RI >20% classified the patients as positive remodeling patients. All patients provided written informed consent prior to be included in study.

TABLE 1. Baseline characteristics of study population

	Diabetic population			Non-diabetic population		
	Group 1 low–to-intermediate risk, hsCRP <3.0 mg/l n = 22 (48.88%)	Group 2 high risk, hsCRP >3.0 mg/l n = 23 (51.12%)	p value	Group 1 low–to-intermediate risk, hsCRP <3.0 mg/l n = 28 (65.11%)	Group 2 high risk, hsCRP >3.0 mg/l n = 15 (34.89%)	p value
Age, years	60.59 ± 8.7	61.30 ± 10.70	0.8	61.85 ± 9.3	59.4 ± 11.13	0.4
Gender, male	16 (68.18%)	13 (56.5%)	0.3	19 (67.85%)	9 (60%)	0.7
Hypertension	16 (68.18%)	19 (82.6%)	0.76	22 (78.57%)	8 (53.33%)	0.16
Hyperlipidemia	14 (63.3%)	15 (65.2%)	1	15 (53.57%)	4 (26.66%)	0.11
Obesity (BMI >25 kg/m^2)	5 (22.7%)	6 (26.1%)	0.9	8 (28.57%)	3 (20%)	0.7
Smoker *	10 (45.4%)	6 (26.1%)	0.22	12 (42.85%)	4 (26.66%)	0.34
Fasting glucose (mg/dl)						
Mean ± SD	158.87 ± 38.52	178.13 ± 49.48	0.15	102.96 ± 13.59	105.86 ± 14.75	0.52
95% confidence interval	142.21–175.53	156.19–200.08		97.69–108.24	97.69-114.04	

*past or present

The study has been carried out in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki. All patients gave written informed consent, and the study protocol was approved by the ethics committee of the Cardio Med Medical Center, the center where the study was conducted.

STATISTICAL ANALYSIS

Statistical analyses were performed using InStat Graph Pad software. Fisher's exact test, and the Student's t-test for age, were used to compare the baseline characteristics of patients. The continuous values are expressed as the mean and standard deviation, and statistical significance was determined using the Mann-Whitney test. Linear regression was used to assess the correlation between the EF and the RI and the hs-CRP values. Logistic regression analysis was used to identify independent predictors of LV remodeling. The level of significance was set at $\alpha = 0.05$.

RESULTS

In Group 1, the hs-CRP values were 1.71 ± 0.78 mg/l, and in Group 2, 12.3 ± 11.1 mg/l (p = 0.0001).

Elevated levels of hs-CRP values recorded at 4 ± 2 days post-infarction were observed in only 34.88% of non-diabetic patients compared to 51.1% of diabetic patients. hsCRP values in the non-diabetic population were 1.78 ± 0.77 mg/l in the low-to-intermediate risk group and 5.34 ± 1.90 mg/l in the high-risk group.

The clinical baseline characteristics of the study population showed no significant differences between Group 1 and Group 2 in respect to age (p = 0.8 for the diabetic population, p = 0.4 for the non-diabetic population), gender (p = 0.3 for the diabetic population, p = 0.7 for the non-diabetic population), the presence of hypertension (p = 0.7 for the diabetic population, p = 0.16 for the non-diabetic population), dislipidemia (p = 1 for the diabetic population, p = 0.11 for the non-diabetic population) obesity (p = 0.9 for the diabetic population, p = 0.7 for the non-diabetic population), smoking status (p = 0.2 for the diabetic population, p = 0.34 for the non-diabetic population) and fasting glucose level (p = 0.1 for the diabetic population, p = 0.52 for the non-diabetic population) in the diabetic population (Table 1).

The echocardiographic and angiographic assessments at baseline showed no statistically significant differences between the hs-CRP groups in both diabetic and non-diabetic populations in regard to the ejection fraction, the LVED volume (Table 2) and the location of the infarction (40.9% vs. 16%, p = 0.13 for anterior infarctions, 40.9% vs. 26%, p = 0.5 for postero-inferior infarctions and 18.18% vs. 4.34%, p = 0.18 for lateral infarctions).

SIX-MONTH EVOLUTION OF THE EF, VENTRICULAR REMODELING AND hs-CRP AT BASELINE

In the diabetic population, the hs-CRP circulating levels at baseline correlated directly with the decrease in the EF from baseline to six months (r = 0.36, p = 0.01) (Figure 1A).

TABLE 2. Echocardiographic and angiographic data in patients with high versus low-to-intermediate risk

	Diabetic population			Non-diabetic population		
	Group 1 low–to-intermediate risk, hsCRP <3.0 mg/l n = 22	Group 2 high risk, hsCRP >3.0 mg/l n = 23	p value	Group 1 low–to-intermediate risk, hsCRP <3.0 mg/l n = 28	Group 2 high risk, hsCRP >3.0 mg/l n = 15	p value
hsCRP						
Mean ± SD	1.71 ± 0.78	12.3 ± 11.1	<0.0001	1.78 ± 0.77	5.34 ± 1.90	<0.0001
95% confidence interval	1.36–2.06	7.5–17.1		1.48–2.08	4.28–6.4	
Ejection fraction at baseline (%)			0.07			0.08
Mean ± SD	48.88 ± 4.64	46.26 ± 4.84		48.07 ± 5.07	45.4 ± 3.88	
95% confidence interval	44.19–48.36	38.62–43.08		46.11–50.03	43.24–47.55	
LVED diameter at baseline						
Mean ± SD	127.1 ± 16.5	134.4 ± 16.1	0.14	130.42 ± 15.7	122.8 ± 16.36	0.15
95% confidence interval	119.8 - 134.4	127.45–141.33		124.3-136.5	113.8–131.93	
Ejection fraction at 6 months (%)						
Mean ± SD	46.27 ± 4.7	40.85 ± 5.16	0.0006	44.46 ± 5.7	4.86 ± 4.89	0.05
95% confidence interval	44.19–48.36	38.62–43.08		42.22–46.7	38.15–43.57	
LVED diameter at 6 months						
Mean ± SD	142.5 ± 16.54	157.82 ± 15.3	<0.002	151 ± 17.61	146.6 ± 17.45	0.43
95% confidence interval	135.16–149.84	151.2–164.46		144.17–157.83	136.9–156.27	
Decrease in EF at 6 months (%)						
Mean ± SD	5.25 ± 4.68	11.3 ± 10.17	0.01	6.89 ± 9.06	9.4 ± 6.63	0.35
95% confidence interval	3.18–7.33	6.9–15.7		3.37–10.40	5.7–13.08	
Remodeling Index						
Mean ± SD	12.49 ± 6.76	17.85 ± 5.6	0.005	16 ± 13.6	19.06 ± 4.86	0.4
95% confidence interval	9.49–15.49	15.43–20.27		10.71–21.28	16.37–21.75	
Epicardial fat (mm)						
Mean ± SD	6.65 ± 2.17	8.02 ± 1.82	0.0002	6.48 ± 8.22	7.55 ± 9.28	0.0004
95% confidence interval	5.61–7.7	7.28–8.76		6.17–6.80	7.03–8.06	
No. of diseased coronary arteries						
Mean ± SD	1.86 ± 0.88	2.94 ± 0.64	0.04	2.03 ± 0.83	2.2 ± 0.77	0.53
95% confidence interval	1.46–2.25	2.07–2.6		1.17–2.36	1.77–2.63	

Levels of circulating hs-CRP at baseline significantly correlated with the RI at six months (r = 0.39, p <0.001) (Figure 1B). The enlargement of the left ventricle and remodeling index at six months after the infarction were significantly higher in Group 2, indicating a more pronounced remodeling of the left ventricle in the group with high hs-CRP levels and diabetes mellitus.

On the contrary, in the non-diabetic population, no statistically significant correlation was recorded between the hs-CRP levels at baseline and the decrease in EF at six months (r = 0.15, p = 0.33) (Figure 2A), or between the hs-CRP levels at baseline and the RI at six months (r = 0.19, p = 0.2034) (Figure 2B).

EPICARDIAL FAT THICKNESS, hs-CRP AND SIX-MONTH VENTRICULAR REMODELING

In the diabetic population, the epicardial fat thickness was significantly higher in patients who developed ventricular remodeling as compared with those who did not (8.02 ± 1.80 mm vs. 6.65 ± 2.17 mm, p = 0.02). Also, epicardial fat was significantly thicker in patients with higher levels of hs-CRP at 4 ± 2 days post-infarction as compared with the Group 1 hs-CRP levels (8.43 ± 1.83 mm vs. 6.41 ± 1.82 mm, p = 0.0006). The epicardial adipose tissue thickness was significantly correlated with the left ventricular remodeling in diabetic patients. Contrary to this, in the non-diabetic population, although patients with high levels of hsCRP demonstrated a significantly larger EFT (7.55 ± 9.28

TABLE 3. Multivariate predictors of 6-month remodeling in diabetic population

	Odds Ratio (95% CI)	p value
High hs-CRP value (>3 mg/dl)	4.1 (1.16–14.43)	0.03
Epicardial fat thickness	6.11 (1.51–24.66)	0.01
Anterior location of the infarction	4.8 (1.36–14.47)	0.01
High angiographic Syntax score	1.5 (0.45–4.9)	0.55
Troponin I	1.46 (0.48–1.56)	0.5
Peak CK-MB	0.74 (0.22–2.46)	0.7

vs. 6.48 ± 8.22; p = 0.0004), this was not accompanied by a significant remodeling of the left ventricle. The thickness of epicardial fat was not significantly higher in patients who developed ventricular remodeling compared to those who did not (71.38 ± 9.09 vs. 67.4 ± 10.17, p = 0.23) (Figure 4).

PREDICTORS FOR LV REMODELING AT 6 MONTHS POST-INFARCTION IN THE DIABETIC POPULATION

Multivariate analysis identified epicardial fat thickness (OR: 6.11, p = 0.01), the hs-CRP values (OR: 4.09, p = 0.03), and the anterior location of the infarction (OR: 4.8, p = 0.01) as the most significant independent predictors for left ventricular remodeling at six months post-infarction in the diabetic population (Table 3).

DISCUSSION

This study demonstrated that patients with type 2 DM and AMI, who express an increased inflammatory response at day 4 [± 2] following an infarction, as indicated by a significantly elevated concentration of hs-CRP and increased epicardial fat thickness, as shown by echocardiography, develop a detrimental LV remodeling to a significantly higher extent than those with low-level inflammation following the infarction. Patients with higher levels of hs-CRP also presented a significant increase in epicardial fat thickness, which was also correlated with the extent of the remodeling process following the infarction, indicative of the epicardial adipose tissue playing an important role in the alteration of the inflammatory reaction, following the infarction.

In a seven-year follow-up study on 1045 patients with type 2 diabetes, an elevated hs-CRP level was shown to be an independent risk factor for cardiovascular death.[12] However, the mortality risk increased only when the hs-CRP levels exceeded 3.0 mg/l. The patients with hs-CRP levels <3.0 mg/l presented a 1.6-fold lower cardiovascular mortality rate compared to those with hs-CRP >3.0 mg/l.[13] Therefore in the present study a hs-CRP reference value of 3.0 mg/l was selected as defining study groups at 4 [± 2] days post-infarction.

Release of hs-CRP into the circulation starts immediately after the infarction and reaches maximum levels in approximately 50 hours.[14] In the present study hs-CRP circulating levels were determined at 4 [± 2] days following the infarction in order to identify patients in whom the inflammatory response persisted beyond the normal period of augmentation of inflammatory markers.

This study indicates that the ventricular remodeling could be influenced by the increase in epicardial fat vol-

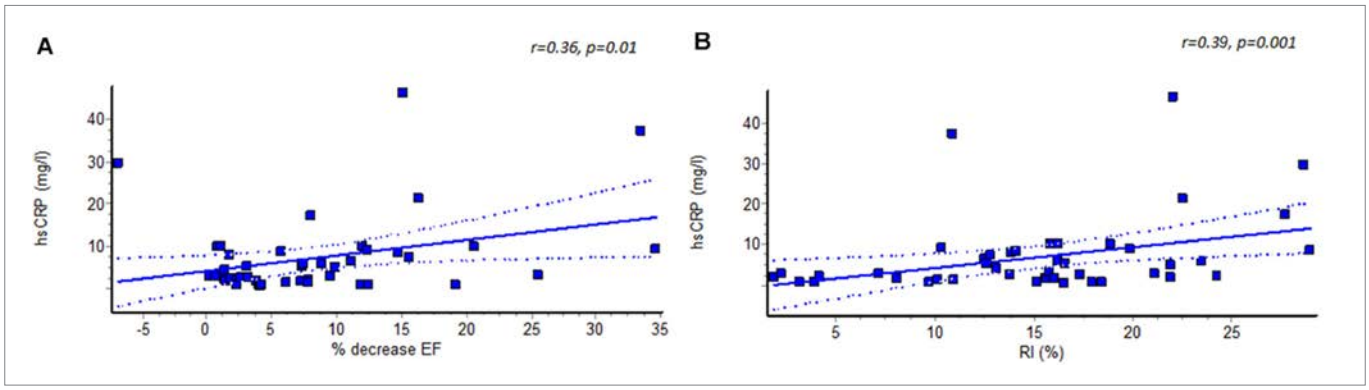

FIGURE 1. Six-month evolution of the EF, ventricular remodeling and hs-CRP at baseline in the diabetic population

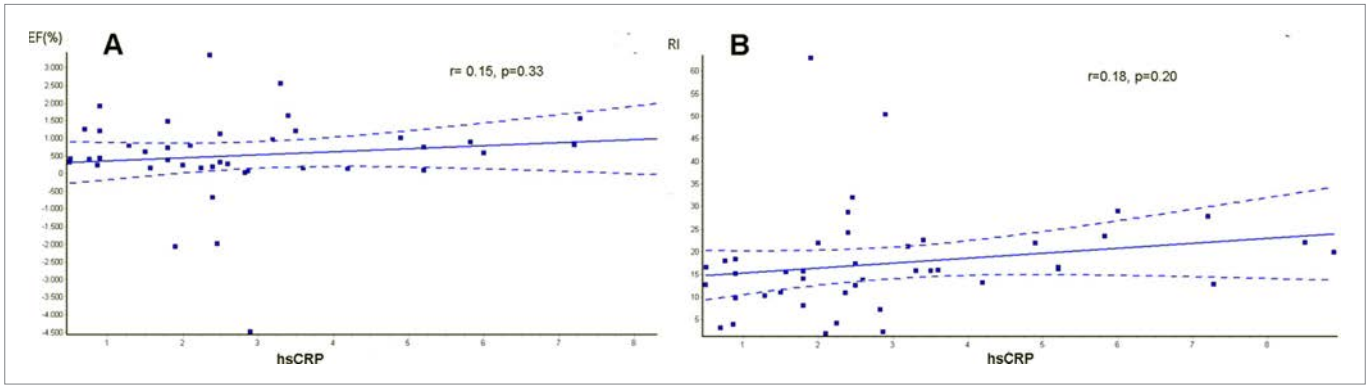

FIGURE 2. Six-month evolution of the EF, ventricular remodeling and hs-CRP at baseline in the non-diabetic population

ume, as a marker correlated with the degree of the inflammatory response in post-myocardial infarction diabetic patients.

It was found that diabetic patients with elevated circulating levels of hs-CRP at four days post-infarction exhibited larger amounts of epicardial adipose tissue, at the same time presenting a significantly lower EF (46.27% vs. 40.85%, p = 0.0006), more enlarged ventricles (142.5 ml vs. 157.82 ml, p = 0.002) and more expressed remodeling (12.49% vs. 17.86%, p = 0.002) at six months post-infarction than the diabetic patients without high levels of hs-CRP post-infarction. Thus, the results demonstrated that a persistence of an amplified inflammatory reaction in the first week post-infarction could significantly influence the development of deleterious ventricular remodeling and contribute to the alteration of ventricular function in post-infarction diabetic population, which could partially explain the poor prognosis associated with post-myocardial infarction ventricular remodeling and heart failure in this population.[15,16]

The Null hypothesis of this study was therefore rejected, as the study indicated significant differences between the groups with respect to persistence of elevated circulating levels of hs-CRP, as determined at 7 ± 2 days after an AMI, the epicardial fat thickness, as determined by 2D echocardiography and the evolution of the condition following an acute myocardial infarction, expressed by the evolution of ejection fraction and the amplitude of the LV remodeling at 6 months post-infarction.

Interestingly, the correlation between the increased inflammatory status and the evolution after an acute myocardial infarction was observed only in the diabetic

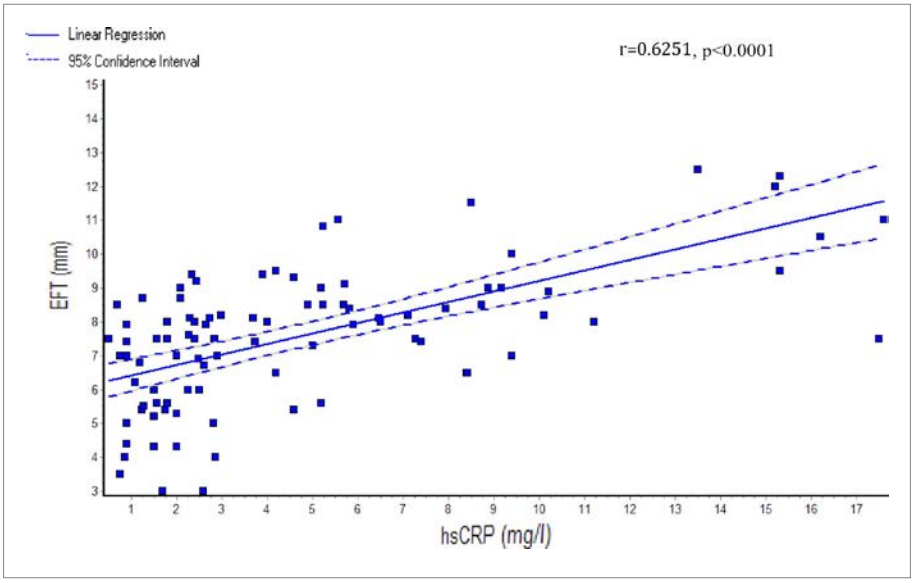

FIGURE 3. Correlation between the thickness of the epicardial adipose tissue and the circulating levels of hs-CRP

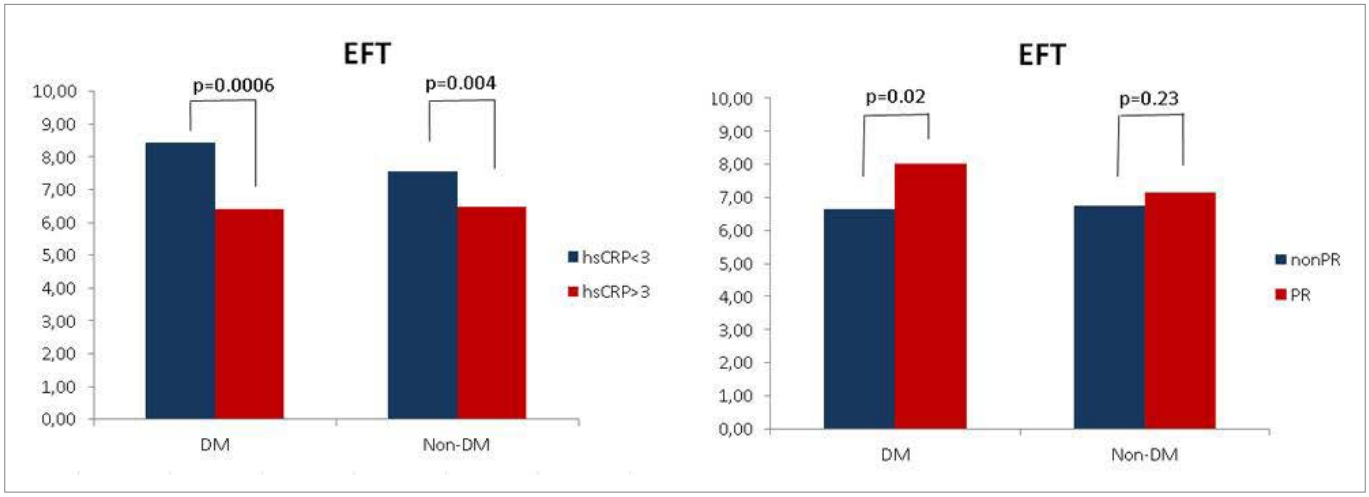

FIGURE 4. Epicardial fat thickness, hs-CRP and six-month ventricular remodeling

population, while for non-diabetic patients the increased inflammatory status, as expressed by an enlarged epicardial fat thickness and an increase in the hsCRP levels following the infarction were not mirrored by a significant increase of the remodeling process. This suggests that involvement of inflammation mediators, following an infarction, expressed to a greater extent, in the diabetic population.

A tentative conclusion is that in a diabetic population there may be many complex factors, in addition to ones already recognized in a non-diabetic population, which are involved in the complex process of remodeling development. Whether one or more of these factors represent an inflammatory biomarker or if this pronounced inflammation is merely a high risk marker reflecting other pathophysiological changes that lead to remodeling, remains to be established in further studies.

CONCLUSIONS

The present study indicates that in patients with type 2 DM and AMI, the epicardial adipose tissue thickness is correlated with a persistence of a marked inflammation at four days post-infarction and indicates a significant risk of a severe impairment of ventricular function in the post-infarction phase. Diabetic patients with increased epicardial fat levels presented a poorer outcome, as reflected by lower EF, marked enlargement of the ventricular cavities and the development of ventricular remodeling at six months, compared to those with lower values of EFT and to the non-diabetic patients. Therefore routine echocardiography assessment of epicardial fat thickness in the first days after an infarction may play a role assessing the risk of diabetic patients with AMI and aid defining subsets of diabetic patients at increased risk of ventricular remodeling and heart failure.

CONFLICT OF INTEREST

Nothing to declare.

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