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CARDIOVASCULAR IMAGING

ORIGINAL ARTICLE

Quantification of epicardial fat with cardiac CT angiography and association with cardiovascular risk factors in symptomatic patients: from the ALTER-BIO (Alternative Cardiovascular Bio-Imaging markers) registry

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PURPOSE
We aimed to assess the association between features of epicardial adipose tissue and demographic, morphometric and clinical data, in a large population of symptomatic patients with clinical indication to cardiac computed tomography (CT) angiography.

METHODS
Epicardial fat volume (EFV) and adipose CT density of 1379 patients undergoing cardiac CT angiography (918 men, 66.6%; age range, 18–93 years; median age, 64 years) were semi-automatically quantified. Clinical variables were compared between diabetic and nondiabetic patients to assess potential differences in EFV and adipose CT density. Multiple regression models were calculated to find the clinical variables with a significant association with EFV and adipose CT density.

RESULTS
The median EFV in diabetic patients (112.87 mL) was higher compared with nondiabetic patients (82.62 mL; $P < 0.001$). The explanatory model of the multivariable analysis showed the strongest associations between EFV and BMI (β=0.442) and age (β=0.365). Significant yet minor association was found with sex (β=0.203), arterial hypertension (β=0.072), active smoking (β=0.068), diabetes (β=0.068), hypercholesterolemia (β=0.046) and cardiac height (β=0.118). The mean density of epicardial adipose tissue was associated with BMI (β=0.384), age (β=0.105), smoking (β=0.088), and diabetes (β=0.085).

CONCLUSION
In a large population of symptomatic patients, EFV is higher in diabetic patients compared with nondiabetic patients. Clinical variables are associated with quantitative features of epicardial fat.

Epicardial adipose tissue (EAT) is a fat storage tissue located beneath the pericardium (Fig. 1), representing approximately 15% of the cardiac weight (1, 2).

The physiologic distribution of EAT is characterized by major representation in the atrioventricular septa and interventricular sulcus, where it surrounds coronary arteries (3). EAT is a visceral fat that secretes inflammatory mediators, and it acts as paracrine promotor of atherosclerosis by means of adipokines and proinflammatory cytokines (e.g., monocyte chemotactic protein 1, interleukin 6, and tumor necrosis factor α) (4). Such local modulators drive the chemotaxis of inflammatory cells into the arterial wall leading to chronic vascular remodelling, notably in coronary arteries (1, 5, 6). Several studies showed the association between epicardial fat volume (EFV) and atherosclerotic plaques associated with higher risk of cardiovascular events (1, 7–11).

Epicardial adipose tissue can be measured with different imaging techniques: ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) (12, 13). Cardiac CT angiography (CCTA) with volumetric acquisition shows the highest spatial resolution and reproducibility for quantitative analysis of EFV, including the assessment of the CT attenuation coefficient (14–16). A number of studies described EFV features mainly in asymptomatic subjects, with a minor proportion of symptomatic subjects. Such heterogeneity is not ideal for the stratification of cardiovascular risk, which accounts also for symp-

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toms, beyond physiologic and diagnostic parameters (5, 9).

Among traditional cardiovascular risk factors, diabetes mellitus (DM) is associated with mortality from systemic atherosclerosis (17). Noteworthy, diabetic patients were shown to carry an increased amount of EAT (18, 19). However, this association was not confirmed in every study evaluating EFV and clinical characteristics (20, 21). A retrospective study showed a 7.4% prevalence of DM in Parma residents which is higher than the age-standardized prevalence for individuals living in the neighbouring areas of Northern Italy (i.e., 4%) (22). The Alternative Cardiovascular Bio-Imaging markers (ALTER-BIO) registry comprises symptomatic individuals referred at the University Hospital of Parma because of cardiovascular symptoms. This large registry could provide information about the distribution of EFV in symptomatic individuals and, in particular, between diabetic and nondiabetic individuals.

The purpose of this study was to compare EFV and clinical characteristics between diabetic and nondiabetic subjects, in a large population of patients with clinical indication to CCTA and a relatively high prevalence of DM. Furthermore, we aimed to test the association between the characteristics of EAT and the demographic, morphometric and clinical data of a homogeneous population of symptomatic individuals.

Methods

Patients selection

The patients who underwent CCTA between October 2006 and November 2010 at the University Hospital of Parma (Parma, Italy) were retrospectively retrieved from the picture archiving and communication system (PACS). The study has been approved by the Institutional Review Board of the University Hospital of Parma and written informed consent was waived. Selection criteria were as follows: A) suspicion for obstructive coronary artery disease (CAD) based on clinical and instrumental data (symptoms included typical or atypical chest pain, asthenia, dyspnoea, palpitations, arrhythmias, syncope and neurological manifestations, i.e., headache, transient ischemic attack) (23); B) availability of volumetric CCTA dataset for quantitative measurements; C) availability of demographic and biometric parameters, including sex, age, smoking habit, and body mass index (BMI), patients with BMI ≥30 kg/m^2 considered obese (24); D) availability of the following clinical parameters: a) DM defined by fasting hyperglycemia, HbA1c ≥6.5% (25), or glucose lowering therapy; b) arterial hypertension defined by systolic arterial pressure ≥140 mmHg or diastolic arterial pressure ≥90 mmHg, or antihypertensive therapy (26); c) cardiovascular medical history as follows: previous cardiac disease, broadly defined acute coronary syndrome (ACS), broadly defined known vascular disease (e.g., aortic dissection, abdominal aortic aneurysm, subarachnoid hemorrhage), and family history of CAD – including acute myocardial infarction or sudden cardiac death – reported in a 1st degree relative; d) blood analysis including serum creatinine, lipid profile (HDL-cholesterol, LDL-cholesterol, and triglycerides), and glycemia. Presence of hypercholesterolemia, hypertriglyceridemia, and hypolipemic therapy was retrieved from the medical charts.

Exclusion criteria was the presence of previous coronary revascularization (percutaneous or surgical).

CCTA procedure

CCTAs with electrocardiographic gating were acquired with two multidetector scanners: a 64-slice Somatom Sensation Cardiac scanner (Siemens Medical Solutions) and a 128-slice Somatom Definition Flash scanner (Siemens Medical Solutions). Before the scan, a sublingual tab of nitroglycerine (0.3 mg) was administered to provide transient coronary dilation. Patients presenting with heart rate >60 beats per minute were administered 5 mg of intravenous atenolol under electrocardiographic and pressure monitoring, provided the absence of contraindication to the administration of β-blocker (e.g., asthma, bronchospasm, or systolic arterial pressure values <100 mmHg). Images were acquired before and after the intravenous injection of iodinated contrast agent (Iomeron 400, Bracco; 80–120 mL apportioned to the body weight, injection rate 3.5–5 mL/s) through the antecubital vein followed by a saline chaser (50 mL), using a double syringe injector. The acquisition of the angiographic phase was automatically triggered by opacification of the ascending aorta ≥100 HU.

CCTA quantitative analysis

EFV was independently measured by two operators with a quantitative semi-automated procedure using a postprocessing workstation (MMWP, Siemens Medical Solutions) and its segmentation software (Volume) (14, 27). The operator manually traced 8 to 10 regions of interest (ROI) along the margins of the fibrous pericardium at different levels on cardiac axial slices, from the pulmonary valve to the lowest slice with a detectable pericardium. The ROIs were interpolated by a segmentation algorithm based on densitometric threshold (density range between -190 HU and -30 HU). Then, the selected volume was visually reviewed with multiplanar reconstructions and manual editing, until the definition of the optimal outline of EFV (expressed in mL) (28) (Figs. 2 and 3). The upper normal limit for

Main points

- Cardiac CT angiography can quantitatively assess epicardial fat volume (EFV) and CT density.
- EFV is higher in diabetic patients compared with nondiabetic patients.
- Epicardial fat density is lower in diabetic patients compared with nondiabetic patients.

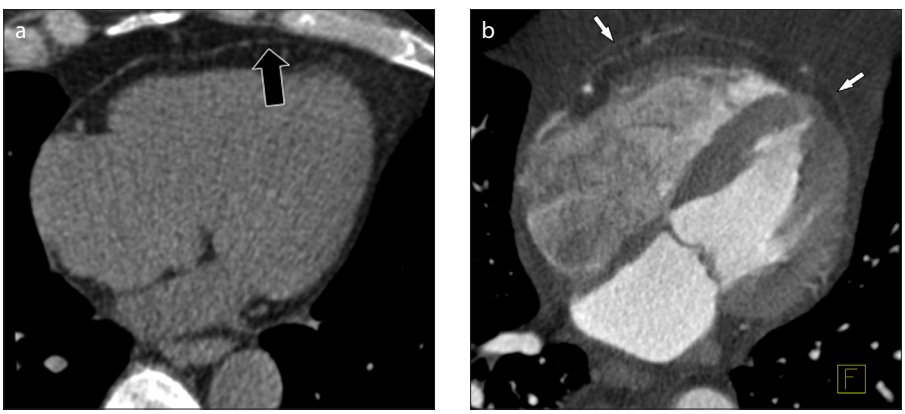

Figure 1. a, b. Native **(a)** and contrast-enhanced **(b)** multiplanar reformatted (MPR) CT images of the heart showing epicardial fat *(black arrow)* and pericardium *(white arrows)*.

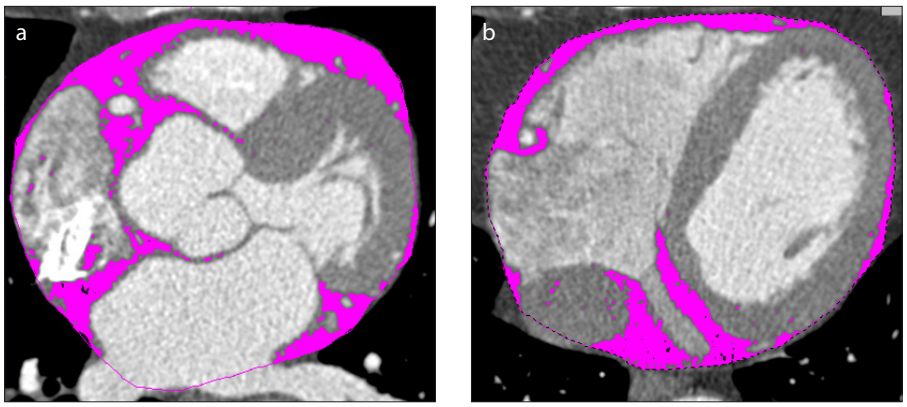

Figure 2. a, b. Magnifications of a cardiac CT angiography image in the axial view (at two different anatomical levels) show the segmentation process of epicardial fat *(pink areas)* performed by the quantification software. The *pink dotted* line represents the region of interest.

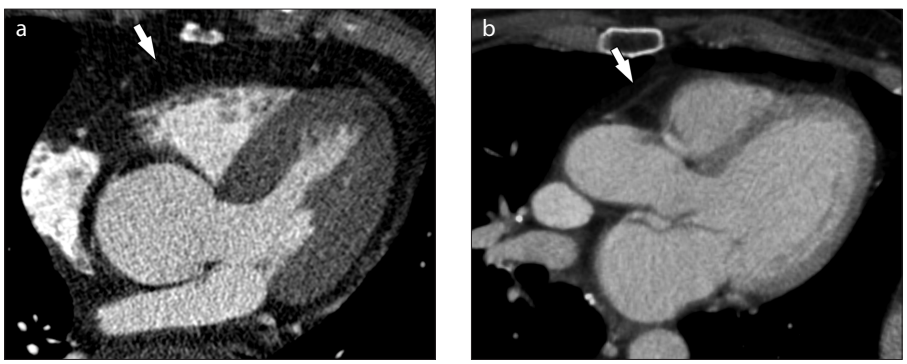

Figure 3. a, b. Multiplanar reformatted (MPR) CT images of two different patients **(a, b)**. The pericardium is highlighted by the *white arrows*. The two patients display different values of EFV, with higher amount in image **(a)**.

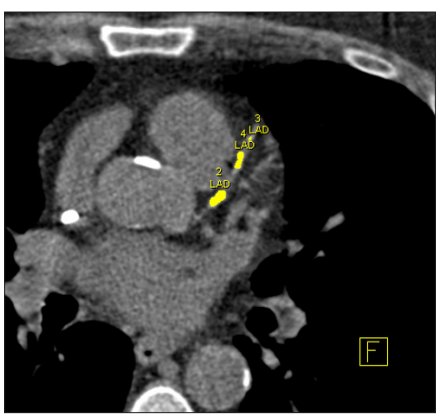

Figure 4. Quantification of coronary artery calcifications. The left anterior descending coronary artery is highlighted in *yellow* and the total amount of calcium is assessed by a dedicated software as the sum of pixel with density above 130 HU.

EFV was set at 100 mL, as previously proposed by Sarin et al. (14).

The software calculated also the mean density of the EAT (expressed in HU) and its standard deviation (SD), and cardiac height (namely, the distance between the upper and lower slice within the segmented volume, expressed in cm).

Coronary artery calcifications (CAC) were quantified by a dedicated semi-automated software (CaScore, Siemens Medical Solutions) for segmentation of dense areas in the coronary artery (density threshold > 130 HU) (Fig. 4). The overall CAC score for each patient was calculated using the Agatston score algorithm (29). CAC scores were stratified into 4 groups (group 0: 0; group 1: 1–100; group 2: 101–300; group 3: >400).

Statistical analysis

The coefficient of variation was calculated to assess interobserver reproducibility between the operators involved in measuring EFV (27). The interobserver variability was assessed by the intraclass correlation coefficient (ICC) for continuous variables. Furthermore, Lin's concordance correlation coefficient (CCC) acted as index of reproducibility between the operators' measurements and the mean of each paired measurement (30). According to McBride et al. (31), we considered almost perfect agreement at CCC >0.990 (31). Normality of data distribution was assessed by Shapiro-Wilk test. Normally distributed variables were reported as mean and SD, non-normally distributed variables were reported as median and interquartile range (IQR). Appropriate comparison tests were used for parametric variables and for nonparametric variables. Chi-square test was used to compare categorical variables. All variables were compared between diabetic and nondiabetic patients to assess differences in conventional clinical data and potential difference in EFV. Given the absence of outliers with an excessive influence on models, Pearson's univariate correlation coefficient was used. Finally, multiple regression model was used, including all the clinically relevant variables that showed significance at the univariate analysis. Only variables with a variance inflation factor <2 were included to test the multicollinearity. The EFV was evaluated as logarithmic value (logVol) to normalize the residuals and to keep the whole population sample. For such models, standardized coefficients were reported instead of the significance. A P value ≤ 0.05 was deemed statistically significant. The statistical analysis was performed by statistical software IBM SPSS Statistics, 23 (IBM Corp.).

Table 1. Demographic and clinical features of patients

Clinical feature	
Male gender, n (%)	918 (66.6)
Age (years), median (IQR)	64 (18)
Smoking history, n (%)	
Never smoker	797 (57.8)
Former smoker	279 (20.2)
Current smoker	303 (22)
BMI (kg/m^2), median (IQR)	26.7 (5.33)
Obesity, n (%)	297 (21.5)
DM, n (%)	338 (24.5)
Hypertension, n (%)	953 (69.1)
Previous ACS, n (%)	250 (18.1)
Hypercholesterolemia, n (%)	777 (56.3)
Hypertriglyceridemia, n (%)	145 (10.5)

IQR, interquartile range; BMI, body mass index; DM, diabetes mellitus; ACS, acute coronary syndrome.

Results

The coefficient of variation for measurements of EFV performed in 250 patients was 9%. ICC was excellent (0.980, 95%CI 0.963–0.988). Lin's CCC was 0.995, namely above the threshold of excellent agreement, for both operators. Therefore, the remaining CCTAs were independently read by either operator.

EFV was measured for 1379 patients with clinical indication to CCTA. Demographic and clinical information are listed in Table 1. Three clinical parameters were available for only a portion of the dataset, as follows: lipid-lowering therapy (available for 1307/1379 patients, 95%), triglycerides levels (available for 539/1379 patients, 39%), and HDL-cholesterol levels (available for 403/1379 patients, 29%). Lipid-lowering therapy by statins was administered to 40.2% of patients (525/1307), of whom 92% (483/525) had hypercholesterolemia, and 13.9% (73/525) had hypertriglyceridemia. CAC were quantified on 1.351 patients (median CAC score 58, IQR, 452), the distribution was as follows: 388 (28.7%) in group 0, 344 (25.5%) in group 1, 253 (18.7%) in group 2, and 366 (27.1%) in group 3.

The comparison of the clinical characteristics between diabetic and nondiabetic patients is summarized in Table 2, reporting the results of chi-square tests. EFV >100 mL was recorded in 63.6% (215/338) of diabetic and 36.6% (381/1041) of nondiabetic patients ($P < 0.001$) (14). Diabetic patients were older ($P < 0.001$), had higher BMI ($P < 0.001$), and were more frequently obese ($P < 0.001$); furthermore, they suffered from arterial hypertension ($P < 0.001$), hypercholesterolemia ($P = 0.050$), and showed more frequently a medical history of ACS ($P = 0.042$).

Looking at the comparisons involving quantitative variables, EFV was significantly higher in diabetic patients (range, 21.37–442.21; median, 112.87; IQR, 68.07) compared with nondiabetic patients (range, 11.27–317.99; median, 82.62; IQR, 62.17) (Mann Whitney U test, $P < 0.001$). Furthermore, the mean density of EAT was lower in diabetic patients (-80.78±6.06 HU) as compared to nondiabetic patients (-78.19±5.27 HU; independent-samples t-test, $P < 0.001$). Higher CAC scores were seen in diabetic individuals ($P < 0.001$) and EFV was higher in diabetic patients with greater CAC scores ($P = 0.001$).

Considering the overall sample, there was a positive correlation between EFV and CAC scores ($\rho=0.343$, $P < 0.001$). Finally, there was a negative correlation between densitometric value and both EFV ($\rho= -0.634$, $P < 0.001$) and BMI ($\rho= -0.438$, $P < 0.001$). In particular, between EAT density and EFV there was a similar negative correlation for both diabetic and nondiabetic patients ($\rho= -0.615$, $P < 0.001$ and $\rho= -0.613$, $P < 0.001$, respectively).

Table 2. Clinical features of the patients according to the diabetic status

Clinical features	Diabetic patients	Nondiabetic patients	*P*
Epicardial fat volume (median, 91.46 mL)			
Below median	99 (29.3)	451 (43.3)	< 0.001
Above median	239 (70.7)	590 (56.7)	
Gender			
Male	226 (66.9)	692 (66.5)	0.947
Female	112 (33.1)	349 (33.5)	
Age (median, 64 years)			
Below median	137 (40.5)	591 (56.8)	< 0.001
Above median	201 (59.5)	450 (43.2)	
Body mass index (median, 26.27 kg/m^2)			
Below median	91 (26.9)	543 (52.2)	< 0.001
Above median	247 (73.1)	498 (47.8)	
Arterial hypertension			
Yes	274 (81.1)	679 (65.2)	< 0.001
No	64 (18.9)	362 (34.8)	
Patients with previous acute coronary syndrome			
Yes	74 (21.9)	176 (16.9)	0.042
No	264 (78.1)	865 (83.1)	
Vasculopatic patients			
Yes	65 (19.2)	225 (21.6)	0.398
No	273 (80.8)	816 (78.4)	
Hypercholesterolemia			
Yes	206 (60.9)	571 (54.9)	0.050
No	132 (39.1)	470 (45.1)	
Hypertriglyceridemia			
Yes	37 (10.9)	108 (10.4)	0.766
No	301 (89.1)	933 (89.6)	
Smoking history			
Nonsmoker	202 (59.8)	595 (57.2)	0.411
Former/current smoker	136 (40.2)	446 (42.8)	

The multivariable analysis developed explanatory models for EFV (adjusted $R^2=0.475$, $P < 0.001$) and EAT mean density (adjusted $R^2=0.241$, $P < 0.001$). For EFV, the strongest associations were found with BMI ($\beta=0.442$) and age ($\beta=0.365$). Other significant associations were found with sex ($\beta=0.203$), arterial hypertension ($\beta=0.072$),

Table 3. Association between clinical variables and epicardial fat volume and CT-based epicardial adipose tissue mean density

	Epicardial fat volume[a] (mL)		Epicardial adipose tissue[b] (mean HU)	
Coefficients	β	*P*	β	*P*
Constant		< 0.001		< 0.001
Diabetes mellitus	0.068	0.001	-0.085	0.001
Cardiac height	0.118	< 0.001	0.162	< 0.001
Age	0.365	< 0.001	-0.105	< 0.001
Gender	0.203	< 0.001	-0.031	0.203
Body mass index (BMI)	0.442	0.001	-0.384	< 0.001
Smoking history	0.068	0.001	-0.088	< 0.001
Hypertension	0.072	0.001	-0.040	0.125
Hypercholesterolemia	0.046	0.026	-0.033	0.181
Hypertriglyceridemia	-0.016	0.433	0.024	0.325
Vasculopathy	0.016	0.421	0.005	0.846
Previous acute coronary syndrome	0.015	0.448	0.011	0.655

[a]Epicardial fat volume is expressed as logarithmic value.
[b]Epicardial adipose tissue mean density is expressed as Hounsfield Unit.

active smoking (β=0.068), DM (β=0.068), hypercholesterolemia (β=0.046), and cardiac height (β=0.118) (Table 3).

Similarly, the mean density of EAT was associated with BMI (β=0.384) and age (β=0.105). Significant, yet minor, association was found with smoking (β=0.088), DM (β=0.085), and cardiac height (β=0.162) (Table 3).

Discussion

In a population of patients with clinical indication to CCTA, an excess of EAT was seen in diabetic patients, independently from other morphometric and clinical cardiovascular risk factors. These results set the role of DM in the balance of visceral fat deposit and supports the role of EAT as a metabolically active tissue with quantitative modifications due to dysmetabolic conditions, namely DM.

In keeping with prior studies, we have shown that the quantification of EFV by CT is reproducible (27). The independent quantification was particularly beneficial because it allowed a reduction of the overall time required for the read-out of the large study population. The same observation can be translated to implementation of this measurement to clinical practice. Of note, quantitative measurements of EAT did not require additional radiation exposure, as they were obtained from datasets acquired for clinical practice.

Compared with the resident population of Parma, our study sample included a greater prevalence of DM (24.5% vs. 7.4%) (22). This high prevalence allowed us to expand upon the relationship between EAT and DM by focusing on patients with cardiovascular symptoms referred to CT evaluation of a suspected obstructive CAD. Mahabadi et al. (9) showed that EFV was associated with DM in 4093 individuals, with a prevalence of 12.4% diabetics. Furthermore, they reported that EFV was directly associated with the presence of cardiovascular risk factors, in individuals without medical history of CAD, acute myocardial infarction, and cardiac surgery (9). Konishi et al. (32) showed positive correlation between pericardial fat volume and markers of DM in patients with suspected CAD, and a prevalence of 33% diabetics over 171 subjects. Wang et al. (33) reported that EFV was higher in 49 diabetic patients compared with 78 nondiabetic controls. In a population of 402 patients, EFV was higher in men with arterial hypertension, hypercholesterolemia, and smokers, but not in patients with DM (20). Similarly, Bos et al. (21) reported in a large population of patients that DM was not related with EFV in the multivariate analysis, whereas there was a significant relation in the univariate analysis. Our multivariable analysis showed a significant association between DM and EFV, notably in a large population with a remarkable component of diabetic patients. Further parameters associated with increased EFV were age, sex, BMI, smoking, arterial hypertension, and hypercholesterolemia. We postulate that the association between EFV and age may partially include the effect of DM toward an increase of EFV, as older individuals show the highest prevalence of DM (34). Indeed, clinical characteristics of the metabolic syndrome (e.g., obesity, dyslipidemia, and hypertension) were significantly associated with EFV, probably acting as confounders for EFV (35). Iacobellis et al. (36) showed association between EAT and impaired insulin sensitivity as well as fasting glucose, and Gorter et al. (27) reported a significant association between EFV and metabolic syndrome, underlining a tight correlation between the systemic disease and the conspicuity of visceral fat and its metabolic activity. Yorgun et al. (37) showed that the strongest independent variables related with EAT thickness were metabolic syndrome, BMI, and age. Furthermore, they reported that serum triglyceride levels were not correlated with an increased EAT thickness. Previous studies demonstrated the presence of a correlation between EFV and triglycerides (32, 38). However, the degree of correlation was wide. Dong et al. (39) found a very weak correlation between the two variables. Furthermore, Mookadam et al. (40) did not find association between triglycerides an EAT thickness on echocardiography, and Hell et al. (41) reported that hypertension was the only significant cardiovascular risk factor for EFV and EAT density. In our study, we hypothesize that the lack of correlation in the multivariable analysis between EFV and hypertriglyceridemia could be related to the administration of lipid-lowering therapy in 452 patients with normal levels of circulating triglycerides (452/525, 86.1%) at the moment of the scan; therefore, statins might have biased triglyceride levels causing the lack of correlation between EFV and triglycerides (42).

Currently, there is not consensus for the normal range of EFV (14, 28). It was report-

ed that EFV was positively associated with multiple cardiovascular risk factors, with a significant association with metabolic syndrome in patients with EFV >100 mL (14, 38, 43, 44). In patients with clinical indication to CCTA, we report median EFV of 82.62 mm^3 in nondiabetics and of 112.87 mm^3 in diabetics. Diabetic patients were significantly more represented above the 100 mL threshold of EFV, conversely the nondiabetic patients were mostly below.

In our study population, diabetic individuals had higher CAC scores than nondiabetic individuals. This observation is in keeping with previous studies reporting a higher frequency of CAC, a complication of atherosclerotic lesions, in diabetic individuals (45). Diabetic individuals are at risk for accelerated atherosclerosis and Wang et al. (33) suggested that the association between EAT, metabolic syndrome, and atherosclerosis could be related by a common pathway for obesity, adiposity, metabolic syndrome, and inflammation. We found that individuals with higher EFV had higher CAC scores, this was in keeping with previous reports from asymptomatic populations (21, 46, 47). The association between EFV and CAC is a subject of current debate as either direct or indirect mechanism. Mahabadi et al. (48) postulated that shared risk factors could explain the increasing amount of CAC in patients with higher EFV. Nevertheless, a systematic review from Spearman et al. (10) proposed that EAT surrounding coronary arteries may be a determinant of atherosclerosis, arterial stiffness and CAC, but the mechanism is not fully understood yet.

Several studies showed that EAT density values on CT may vary according to histologic features. In particular, adipose tissue with higher HU shows a lower amount of intracellular lipids and a richer vascularization (49). The adipocytes' hypertrophy was associated with increased pro-inflammatory macrophages (50). An increased attenuation value was related to the fibrosis of the adipose tissue's extracellular matrix (51). In our study, EAT density and EFV were negatively correlated for both diabetic and nondiabetic patients. This correlation is consistent with the results of Mahabadi et al. (52), who reported a modest, yet significant, inverse correlation between these two morphometric parameters. We showed that diabetic patients had lower EAT density and higher EFV. We hypothesize that the adipose tissue in diabetic individuals could be more frequently characterized by hypertrophic adipocytes (with lower EAT density) and, potentially, associated high level of proinflammatory macrophages. Such a pattern might be a contributor to the increased cardiovascular risk of diabetic patients, notably via the paracrine effect of visceral fat reservoir in tight proximity to coronary arteries.

Our study presents some limitations. First, as a cross-sectional study we could evaluate only associations and not causality. Second, it was not possible to obtain full clinical information for a minority of the study patients owing to the retrospective study fashion. Anamnestic and demographic information were retrieved from radiology reports and from the review of medical charts; however, for three clinical parameters, data were available for only a portion of the study population.

In conclusion, our results show that EFV is increased in diabetic patients compared with nondiabetic, in the subset of symptomatic patients. In particular, higher EFV in diabetics might add to systemic mediators of endothelial stress and enhance coronary vasculopathy by means of increased paracrine metabolic activity of EAT. On this basis, further analyses are fostered on the possible association between the CT characteristics of EAT and CT markers of coronary disease, in both diabetics and nondiabetics.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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