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Pericardial and visceral, but not total body fat, are related to global coronary and extra-coronary atherosclerotic plaque burden

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ABSTRACT

Background: To explore the relationship between coronary and extra-coronary atherosclerotic plaque burden with total and regional fat depots among patients undergoing ECG-gated aortic computed tomography angiography (CTA).

Methods: The subjects of this study comprised a cohort of consecutive patients who underwent ECG-gated thoracoabdominal CTA. We assessed the number of coronary segments with plaques (segment-involvement score, SIS); and the extra-coronary atherosclerotic plaque burden, comprising the aorta and supra-aortic trunks, iliofemoral arteries, and visceral arteries (extra-coronary SS). Total and regional fat volume (FV) were calculated.

Results: A total of 2700 vascular segments were evaluated in 90 patients. Obese patients ($n = 31$, 34%) showed similar coronary SIS ($p = 0.41$) and extra-coronary SS ($p = 0.22$) than non-obese patients. General body fat measurements were not related to atherosclerotic plaque burden scores, without associations between coronary or extra-coronary plaque burden and BMI ($p = 0.68$, and $p = 0.91$), abdominal circumference ($p = 0.13$, $p = 0.89$), total body FV ($p = 0.50$, $p = 0.98$), or abdominal FV ($p = 0.51$, $p = 0.99$). Pericardial FV was related to coronary SIS ($p < 0.0001$) and extra-coronary SS ($p = 0.008$), and visceral FV was related to the coronary SIS ($p = 0.006$) and extra-coronary SS ($p = 0.056$). Abdominal subcutaneous fat was inversely related to coronary SIS ($p = 0.038$) and extra-coronary SS ($p = 0.010$). Pericardial FV was identified as the only independent predictor of extensive coronary [OR 1.020 (95% CI 1.001–1.039), $p = 0.036$] and extra-coronary [OR 1.018 (95% CI 1.001–1.036), $p = 0.035$] plaque burden.

Conclusions: In the present study, pericardial and visceral fat were associated with an increased atherosclerotic burden, whereas we identified an inverse relationship between subcutaneous abdominal fat and plaque burden.

1. Introduction

The increased cardiovascular morbidity and mortality among obese patients is generally attributed to the association between obesity and several cardiovascular risk factors, as well as to the promotion of insulin-resistance and a pro-inflammatory state [1,2]. Notwithstanding, several studies including a meta-analysis of individual-level data have reported conflicting evidence comprising a negative correlation between coronary disease burden and the body mass index (BMI), as well as a decline in the association of obesity to years of life lost [3–5]. Moreover, among older adults, there is no clear relationship between obesity and mortality [6]. Such controversial or paradoxical behavior might be at least in part related to the rough definition of obesity based on the BMI, a poor index of adiposity [7–9]. Likewise, abdominal circumference is a good estimate of abdominal fat although it fails to distinguish between subcutaneous and visceral fat. On the contrary, regional adipose tissue (AT) deposits are related to divergent cardiometabolic profiles and prognosis, and can be measured accurately using computed tomography (CT). Overall, both visceral and pericardial fat have been associated with a worse prognosis, while subcutaneous abdominal fat may play, paradoxically, a beneficial role [10–12].

All these findings have been evaluated in individual reports exploring the relationship between specific regional fat depots and coronary or extra-coronary atherosclerosis [13]. Nevertheless, the association between global (coronary and extra-coronary) plaque burden and regional fat has not been elucidated. In our institution, CT angiograms (CTA) of the aorta involving the thoracic portion are performed using ECG-gating with dose modulation. This allows motion-free images of the thoracic aorta, enabling a higher diagnostic confidence compared to non-gated aortic CTA, as well as an accurate assessment of the coronary tree [14,15]. Accordingly, the purpose of this study was to explore the relationship between coronary and extra-coronary atherosclerotic plaque burden with total and regional AT depots among patients undergoing ECG-gated thoracoabdominal aortic CTA.

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2. Methods

2.1. Study design and patient enrollment

This investigator-driven observational study comprised a cohort of consecutive patients aged between 33 and 87 years who underwent ECG-gated thoracoabdominal CTA in our institution between January 2016 and September 2017. Patients who refused to provide *Habeas data* were excluded. Among patients with repeated (follow-up) scans, only the first scan was included. Patients with previous endovascular aortic repair (EVAR), aortic bifemoral bypass, valve surgery, or coronary artery bypass graft (CABG) surgery were excluded. Patients were referred to our institution to undergo thoracoabdominal CTA for various indications including aortic dilatation, guidance of trancatheter aortic valve replacement, and atherosclerotic disease or suspicion of acute aortic syndrome (Appendix). A radiologist blinded to the CTA collected data regarding demographical characteristics and cardiovascular risk factors. The protocol was approved by the institutional ethics committee and all studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

2.2. Image acquisition

In our institution, CTA scans involving the thoracic aorta are acquired using ECG-gating techniques in order to avoid motion artifacts and to enable more accurate measurements [16]. Scans were acquired in three centers of the same institution using 64 (n = 24), 128 (n = 15), 256 (n = 37) slice CT scanners (Brilliance CT family; Philips Healthcare, Cleveland, USA) and a high definition CT (n = 14) scanner (Discovery HD 750, GE Medical Systems, Milwaukee, USA) with a single breath-hold from the supra-aortic trunks to the pubic symphysis. Among patients acquired using the high-definition scanner, the thoracic aorta CTA was acquired using ECG-gating, whereas abdominal non-gated CTA was performed immediately after the gated thoracic acquisition. Acquisition parameters were: 100–120 kV (according to the body mass index); 150–300 mAs (z-axis modulation was used on 64-, 128-, and 256-slice CT scanners); variable pitch; 0.5–0.75 rotation time; DFOV adjusted to the patient size; reconstructions using 1–1.5 mm slice thickness and 0.5 mm interval. Particular care was taken to acquire images with a sufficiently wide field of view in order to avoid missing (subcutaneous fat) data. CTA were acquired after intravenous administration of 80–100 mL of iodinated contrast (iobitridol, Xenetix 350TM, Guerbet, France) according to the BMI and body habitus. Angiograms were performed using a dual phase protocol, with the total undiluted contrast medium injected at a rate of 4–4.5 mL/s, followed by a 30 mL chasing bolus of normal saline at 3–4 mL/s.

2.3. Image analysis

Images were transferred to a dedicated workstation (Brilliance Workspace, Philips Healthcare, Cleveland, Ohio, USA), and analyses were performed by an experienced observer blinded to the clinical data. Two phases of the cardiac cycle were stored and available for the analysis, one systolic (37.5–40% of the R-R interval) and one mid-diastolic (75–78% of the R-R interval), and images were analyzed in the phase with the least motion artifacts. Axial planes, average multiplanar, and maximum intensity projection reconstructions (1–5 mm thickness) were used to assess the presence and extent of coronary and extra-coronary atherosclerotic plaque burden. The number of coronary segments with mixed or calcified plaques (segment-involvement score, coronary SIS) was calculated as previously described [17,18]. Methodological details regarding the assessment of coronary and extra-coronary plaque burden can be found in the appendix section. In brief, the extra-coronary atherosclerotic plaque burden comprised the presence and extent of disease in the thoracoabdominal aorta (including supra-aortic trunks), iliofemoral arteries, and visceral arteries. Thereafter, two scores were developed; one involving the number of regions involved (extra-coronary SIS), and other score (extra-coronary SS) involving both the extra-coronary SIS and a number of correction factors of orthogonal extension and severity (longitudinal and axial extension, degree of stenosis, and high-risk characteristics).

2.4. Anthropometric and regional fat measurements

Fat tissue was calculated using a semiautomated volumetric module dedicated software (Brilliance Workspace, Philips Healthcare, Cleveland, Ohio, USA), as previously defined, as tissue between −190 and −30 Hounsfield units [19]. Total body fat volume (FV) was assessed from the thoracic inlet to the cranial aspect of the femoral heads using a volume rendering technique, and all FV measurements were indexed to the body surface (cm^3/m^2). For FV measurements all automatically detected tissue were verified for accuracy and adjustments were made manually, and sequentially, in sagittal, coronal, axial views, and using the three dimensional rendered fat shell (Figs. 1–2). Visceral FV was defined as the fat enclosed by the visceral cavity, whereas subcutaneous abdominal FV was defined as the difference between abdominal FV and visceral FV. Pericardial FV measurements comprised slices between 15 mm above the cranial border of the left main coronary artery and the diaphragm. The anterior edge was defined by the chest wall and the posterior edge by the aorta and the bronchus (the posterior mediastinum was excluded). In order to avoid intricate visualization of the pericardium particularly among lean patients, pericardial FV involved both epicardial and paracardial fat. In this regard, the MESA study has shown a very high correlation between pericardial and epicardial fat [20]. Finally, subcutaneous abdominal AT thickness (anterior plus posterolateral thickness) was measured at the level of the abdominal circumference measurement (coincident with cranial border of the iliac crest).

2.5. Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± SD, or median (interquartile range), as indicated. Comparisons between continuous variables were performed using independent samples *t*-test, one-way analysis of variance, and Bonferroni (post-hoc comparisons) tests, as indicated. Comparisons between categorical variables were performed using chi-square tests. Correlations between continuous variables were assessed using Pearson correlation coefficients. On the basis of an interim analysis showing that the mean coronary SIS was 2.5 and 5.0 at the lowest and highest pericardial FV tertiles, we calculated a sample size of 29 subjects per tertile (n = 87 overall) in order to achieve a power of 80% to detect a true difference in population means, considering a type I error of 0.05 (two-sided), a SD of 2.5 in the lowest tertile and of 4.0 in the highest tertile. Logistic regression analysis was performed to identify potential predictors of extensive coronary plaque burden (coronary SIS >5), and of an extra-coronary SS >12.85 (upper tertile) including the following variables in the model (enter method): sex, age, hypercholesterolemia, hypertension, diabetes, smoking, total body FV (cm^3/m^2), pericardial FV (cm^3/m^2), visceral FV (cm^3/m^2), and subcutaneous abdominal fat thickness (mm). In order to assess the interobserver agreement for the assessment of regional FV, coronary, and extra-coronary plaque burden, 20 cases were randomly selected and re-analyzed independently by two observers. These data were analyzed using intraclass correlation coefficients (ICC; two-way random effect model, absolute agreement, and average measurement) with 95% confidence intervals. A two-sided p value of <0.05 indicated statistical significance. Statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY) and MedCalc Software (Ostend, Belgium).

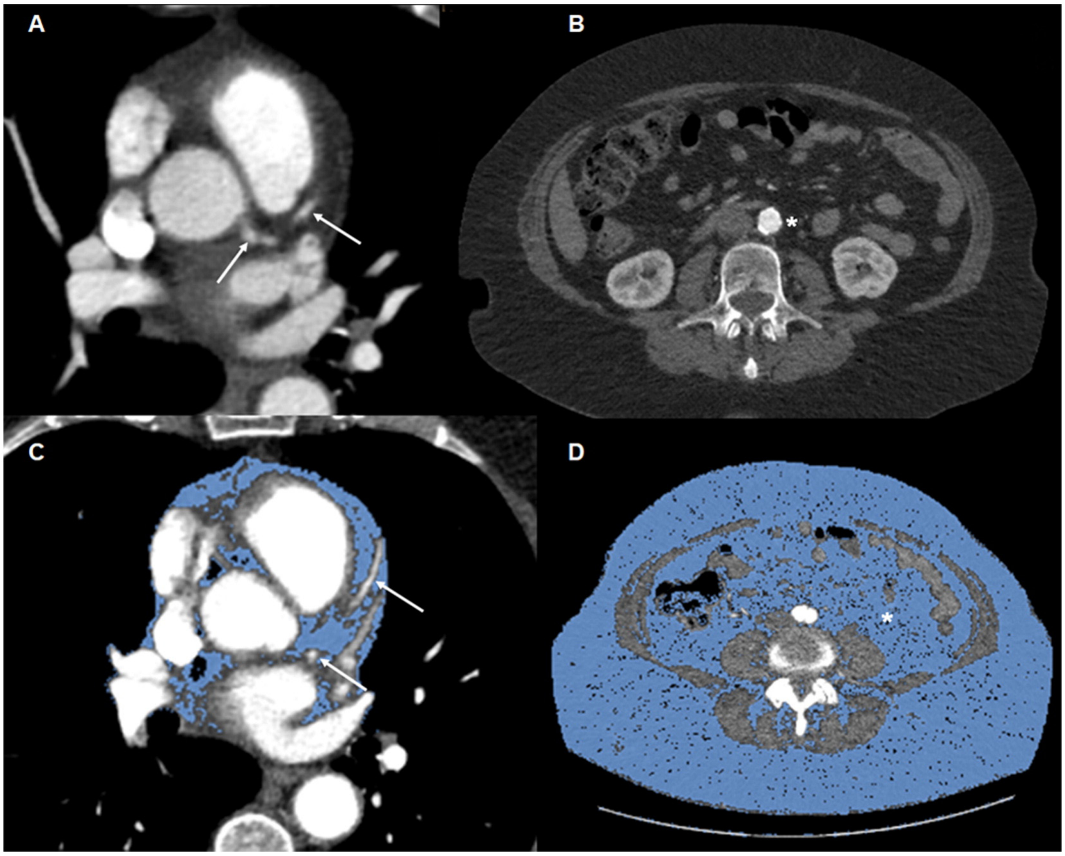

Fig. 1. Obese female, with large subcutaneous fat accumulation and no evidence of coronary disease. Seventy year-old female, CTA indicated due to ascending aorta dilatation. She has multiple coronary risk factors (hypertension, hypercholesterolemia, smoking) and a BMI of 31.2 kg/m^2. No evidence of coronary atherosclerosis is detected (SIS 0, arrows in panels A and C). Extra-coronary SS was 11.0 (* in panel B). Total body FV was 12,390 cm^3/m^2 (above the 75% percentile). Pericardial FV was 84 cm^3/m^2 (below median) and abdominal FV (blue, in panel D) was 8518 cm^3/m^2 (above the 75% percentile), of which only 32% was visceral fat (*, in panel D).

3. Results

3.1. Study population

Between January 2016 and September 2017, a total of 114 patients underwent ECG-gated thoracoabdominal CTA in our institution. Four patients were excluded since they did not provide *Habeas data*, and one patient due to a repeated scan. Nineteen patients were further excluded since they had previous EVAR, aortic bifemoral bypass, valve surgery, or CABG. Accordingly, the study population was comprised by 90 patients. The mean age was 66.4 ± 12.5 years, 61 (68%) were male and 15 (17%) had diabetes. Most scans were indicated in patients with suspicion or documentation of aortic dilatation, of which 32 (36%) were subsequently confirmed. Detailed demographical characteristics are depicted in the appendix.

We identified a good interobserver agreement regarding regional FV measurements [ICC 0.99 (95% CI 0.98; 0.99)], coronary SIS [ICC 0.97 (95% CI 0.93; 0.99)], and extra-coronary SS [ICC 0.96 (95% CI 0.89; 0.98)].

3.2. Atherosclerotic plaque burden: sex-related differences and influence of obesity

A total of 2700 vascular segments (appendix) were evaluated in 90 patients. Sixty-seven (74%) patients had evidence of coronary atherosclerosis (coronary SIS>0), with a median coronary SIS of 3.0 (interquartile range 0.0; 7.0). Males showed a significantly higher coronary SIS than females (4.8 ± 4.0 vs. 2.7 ± 2.9, $p = 0.006$). We did not identify sex-related differences regarding extra-coronary SS (males 10.2 ± 5.8, females 9.5 ± 5.8, $p = 0.58$). Obese patients ($n = 31$, 34%) showed similar coronary SIS (4.6 ± 4.4 vs. 3.9 ± 3.5, $p = 0.41$) and extra-coronary SS (10.2 ± 5.9 vs. 9.8 ± 5.7, $p = 0.22$) than non-obese patients.

3.3. General and specific body fat measures

General body fat measurements did not show sex-related differences, with similar BMI (males 28.8 ± 4.5 kg/m^2, females 29.2 ± 7.4 kg/m^2, $p = 0.75$), abdominal circumference (males 103.4 ± 10.9 cm, females 99.4 ± 11.3 cm, $p = 0.11$), and total body FV (males 7883.7 ± 2700.9 cm^3/m^2, females 8462.5 ± 2696.9 cm^3/m^2, $p = 0.34$). Significant sex-related differences were observed concerning regional fat depots, with males showing a significantly larger extent of pericardial FV (120.3 ± 61.5 cm^3/m^2, vs. 79.9 ± 32.8 cm^3/m^2, $p = 0.001$). Total abdominal FV was similar between genders (males 5679.0 ± 2027.0 cm^3/m^2, females 5905.7 ± 1796.4 cm^3/m^2, $p = 0.61$). However, males showed higher visceral FV (2800.8 ± 1248.4 cm^3/m^2, vs. 1965.1 ± 865.1 cm^3/m^2, $p = 0.002$), whereas females showed significantly higher abdominal subcutaneous AT both measured in thickness (males 82.1 ± 25.7 mm, females 94.7 ± 23.5 mm, $p = 0.03$) and volume (males 2880.4 ± 1097.7 cm^3/m^2, females 3940.6 ± 1306.9 cm^3/m^2, $p < 0.0001$). Regarding the relative discriminatory abdominal fat, males had a significantly higher percent of visceral fat compared to females (48.1 ± 12.3% vs. 32.7 ± 10.3%, $p < 0.0001$).

3.4. Relationship between global and regional fat and atherosclerotic plaque burden

General body fat measurements were not related to coronary SIS (Fig. 2). This was consistent for BMI ($r = 0.08$, $p = 0.46$), abdominal

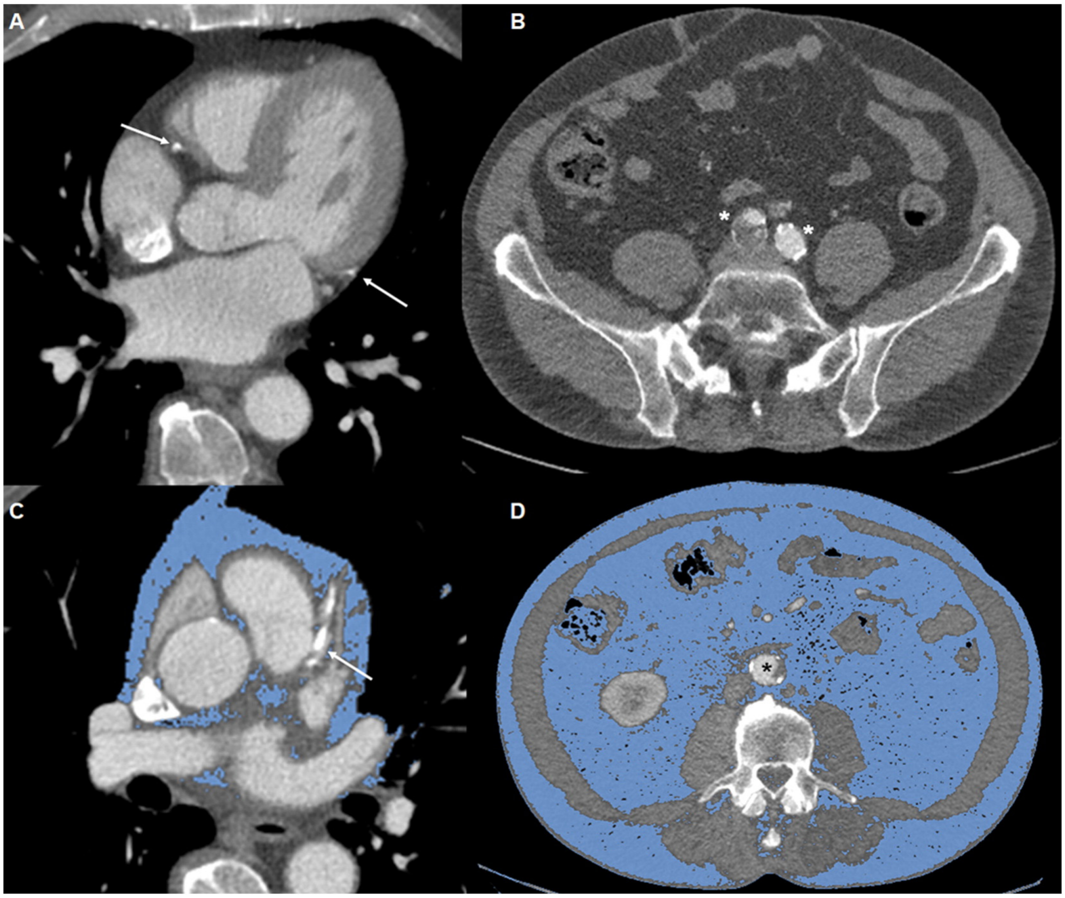

Fig. 2. Male with normal BMI, large visceral fat and extensive plaque burden. Sixty-four year-old male with CTA indicated for a dilated aorta, and diabetes and hypertension as risk factors. His BMI is 22.4 kg/m^2 (1.89 m, 80 kg). However, he has very extensive coronary (coronary SIS 13, arrows in panels A and C) and extra-coronary (extra-coronary SS 15.7, * in panels B and D) plaque burden. Total body FV was 8333 cm^3/m^2, pericardial FV 99 cm^3/m^2, and abdominal FV 6088 cm^3/m^2, of which 75% was visceral.

circumference ($r = 0.15$, $p = 0.16$), total body FV ($r = 0.09$, $p = 0.41$) and abdominal FV ($r = 0.11$, $p = 0.29$). Albeit relatively weak, significant relationships were identified between regional fat depots and coronary SIS, and this was consistent along pericardial FV ($r = 0.50$, $p < 0.0001$), visceral FV ($r = 0.32$, $p = 0.002$), subcutaneous abdominal AT thickness ($r = -0.30$, $p = 0.004$). Furthermore, significant relationships were also identified between extra-coronary SS and regional fat depots including pericardial FV ($r = 0.37$, $p < 0.0001$) and abdominal subcutaneous AT thickness ($r = -0.38$, $p < 0.0001$).

After discrimination in BMI tertiles, we did not identify relationships between BMI and any coronary or extra-coronary atherosclerotic plaque burden scores. Similarly, no relationships were found between abdominal circumference, total body FV, or abdominal FV tertiles and any atherosclerotic plaque burden score. These results are portrayed in Tables 1 and 2, and in the appendix.

Patients at the highest pericardial FV tertiles showed higher coronary SIS (lower tertile 2.23 ± 2.6, mid tertile 4.00 ± 3.6, upper tertile 6.03 ± 4.2, $p < 0.0001$) and extra-coronary SS (lower tertile 6.43 ±

Table 1
Coronary and extra-coronary atherosclerotic burden according to general fat measurement tertiles.

	Lower tertile	Mid tertile	Upper tertile	p value	T1 vs. T3[a]
Body mass index (kg/m^2) tertiles:					
Coronary SIS (mean ± SD)	3.70 ± 3.81	4.00 ± 3.24	4.55 ± 4.36	0.68	NS
Coronary SIS >5 (n, %)	10 (33%)	10 (33%)	11 (36%)	0.98[b]	
Extra-coronary SIS (mean ± SD)	8.13 ± 4.33	8.14 ± 4.24	8.35 ± 4.38	0.97	NS
Extra-coronary SS (mean ± SD)	10.07 ± 6.02	9.56 ± 5.48	10.17 ± 5.90	0.91	NS
Abdominal circumference (cm) tertiles:					
Coronary SIS (mean ± SD)	3.00 ± 3.11	4.33 ± 3.99	4.93 ± 4.14	0.13	NS
Coronary SIS >5 (n, %)	8 (27%)	11 (37%)	12 (40%)	0.53[b]	
Extra-coronary SIS (mean ± SD)	7.70 ± 4.47	8.43 ± 4.49	8.50 ± 3.93	0.73	NS
Extra-coronary SS (mean ± SD)	9.56 ± 6.05	10.01 ± 5.91	10.26 ± 5.44	0.89	NS
Total fat volume (cm^3/m^2) tertiles:					
Coronary SIS (mean ± SD)	3.43 ± 3.05	4.57 ± 4.13	4.27 ± 4.19	0.50	NS
Coronary SIS >5 (n, %)	8 (27%)	12 (40%)	11 (37%)	0.52[b]	
Extra-coronary SIS (mean ± SD)	7.97 ± 4.69	8.50 ± 3.68	8.17 ± 4.50	0.89	NS
Extra-coronary SS (mean ± SD)	9.89 ± 6.30	10.10 ± 5.18	9.83 ± 5.91	0.98	NS

T1, lower tertile; T3, upper tertile. SIS refers to segment-involvement score and SS to severity score.

[a] Bonferroni.

[b] Chi-square tests.

Table 2
Coronary and extra-coronary atherosclerotic burden according to regional fat depots.

	Lower tertile	Mid tertile	Upper tertile	p value	T1 vs. T3[a]
Pericardial fat volume (cm^3/m^2) tertiles:					
Coronary SIS (mean ± SD)	2.23 ± 2.56	4.00 ± 3.59	6.03 ± 4.21	<0.0001	<0.05
Coronary SIS >5 (n, %)	5 (17%)	10 (33%)	16 (53%)	0.011[b]	
Extra-coronary SIS (mean ± SD)	6.43 ± 4.67	8.43 ± 3.99	9.77 ± 3.52	0.008	<0.05
Extra-coronary SS (mean ± SD)	7.71 ± 5.95	9.99 ± 5.31	12.12 ± 5.27	0.011	<0.05
Abdominal fat volume (cm^3/m^2) tertiles:					
Coronary SIS (mean ± SD)	3.43 ± 3.00	4.33 ± 3.99	4.50 ± 4.37	0.51	NS
Coronary SIS >5 (n, %)	7 (23%)	12 (40%)	12(40%)	0.29[b]	
Extra-coronary SIS (mean ± SD)	8.03 ± 4.58	8.37 ± 4.07	8.23 ± 4.28	0.96	NS
Extra-coronary SS (mean ± SD)	9.92 ± 6.19	10.02 ± 5.53	9.88 ± 5.71	0.99	NS
Visceral fat volume (cm^3/m^2) tertiles:					
Coronary SIS (mean ± SD)	3.10 ± 2.83	3.30 ± 3.11	5.87 ± 4.70	0.006	<0.05
Coronary SIS >5 (n, %)	7 (23%)	9 (30%)	15 (50%)	0.077[b]	
Extra-coronary SIS (mean ± SD)	7.10 ± 4.85	7.87 ± 4.31	9.67 ± 3.21	0.056	NS
Extra-coronary SS (mean ± SD)	8.73 ± 6.25	9.53 ± 5.97	11.57 ± 4.73	0.14	NS
Abdominal subcutaneous fat volume (cm^3/m^2) tertiles:					
Coronary SIS (mean ± SD)	4.03 ± 3.54	4.50 ± 4.34	3.73 ± 3.61	0.74	NS
Coronary SIS >5 (n, %)	10 (33%)	10 (33%)	11 (37%)	0.95[b]	
Extra-coronary SIS (mean ± SD)	8.70 ± 4.31	8.27 ± 3.94	7.67 ± 4.62	0.65	NS
Extra-coronary SS (mean ± SD)	10.95 ± 6.21	9.63 ± 5.02	9.24 ± 6.01	0.49	NS
Abdominal subcutaneous fat thickness (mm) tertiles:					
Coronary SIS (mean ± SD)	5.20 ± 3.90	4.33 ± 3.95	2.73 ± 3.26	0.038	<0.05
Coronary SIS >5 (n, %)	13 (43%)	11 (37%)	7 (23%)	0.25[b]	
Extra-coronary SIS (mean ± SD)	9.60 ± 3.80	8.63 ± 4.00	6.40 ± 4.47	0.010	<0.05
Extra-coronary SS (mean ± SD)	11.89 ± 5.47	10.40 ± 5.65	7.54 ± 5.43	0.010	<0.05

T1, lower tertile; T3, upper tertile. SIS refers to segment-involvement score and SS to severity score.

[a] Bonferroni.

[b] Chi-square tests.

4.7, mid tertile 8.43 ± 4.0, upper tertile 9.77 ± 3.5, p = 0.008). Visceral AT was also related to the coronary SIS (lower tertile 3.10 ± 2.8, mid tertile 3.30 ± 3.1, upper tertile 5.87 ± 4.7, p = 0.006) and extra-coronary SS (lower tertile 7.10 ± 4.9, mid tertile 7.87 ± 4.3, upper tertile 9.67 ± 3.2, p = 0.056).

Conversely, patients at the lowest abdominal subcutaneous AT thickness tertile showed the highest coronary SIS (lower tertile 5.20 ± 3.9, mid tertile 4.33 ± 4.0, upper tertile 2.73 ± 3.4, p = 0.038) and extra-coronary SS (lower tertile 9.60 ± 3.8, mid tertile 8.63 ± 4.0, upper tertile 6.40 ± 4.5, p = 0.010). Table 2 and the appendix show these results in detail.

Finally, after logistic regression analysis, pericardial FV was identified as the only independent predictor of a coronary SIS >5 [OR 1.020 (95% CI 1.001–1.039, p = 0.036)]. Furthermore, pericardial FV was also identified as the only independent predictor of the highest extra-coronary SS tertile [OR 1.018 (95% CI 1.001–1.036, p = 0.035)].

4. Discussion

Albeit not devoid from controversy, vast amount of prognostic information has been assembled about the clinical consequences of obesity. Nevertheless, the distinctive impact of global and regional fat deposits on coronary and extra-coronary atherosclerosis remains elusive.

ECG-gated CTA of the aorta offers the unique possibility to assess the global burden of atherosclerotic plaque involving the coronary tree, aorta and supra-aortic trunks, and both iliofemoral and visceral arteries. In the past decade, numerous studies have reported that the burden of atherosclerotic disease has great clinical relevance regardless of the degree of luminal encroachment. This has been more clearly revealed in the coronary tree, with a similar outcome among patients with non-obstructive but extensive (SIS>5) disease compared to those with obstructive but non-extensive disease [21,22]. Indeed, the ease and predictive value of a coronary SIS>5 has been also been demonstrated among patients undergoing conventional chest CT scans [23].

The main finding of the present study was that regional fat, but not general body fat measurements, were significantly related to coronary and extra-coronary atherosclerotic plaque burden. In particular, pericardial and visceral fat were associated with an increased atherosclerotic burden, whereas we identified an inverse relationship between subcutaneous abdominal AT and plaque burden.

It is noteworthy that general body fat measurements including BMI, abdominal circumference, total body FV, and even abdominal FV were similar between genders and not related to coronary or extra-coronary plaque burden. In opposition, regional fat depots were significantly related to sex as well as to coronary and extra-coronary atherosclerotic plaque burden. Overall, these findings might shed some light towards the understanding of the aforementioned conflicting evidence and/or paradoxical clinical outcomes reported using the BMI as a marker of adiposity [9].

In the past decade, numerous studies have indicated that pericardial fat might have an important role in the pathophysiology of endothelial dysfunction and coronary atherosclerosis by means of multiple local and systemic mechanisms including release of pro-atherogenic cytokines, promotion of a state of hypercoagulability, and increased intramyocardial lipid [24]. Indeed, a number of investigations have found an association between pericardial FV and high-risk plaque features [25,26]. Relevantly, pericardial FV is more closely related to coronary atherosclerosis extension than to stenosis severity, and such role seems to be independent of the BMI [12,20,27]. In the present study, pericardial FV was identified as the only independent predictor of extensive coronary and extra-coronary plaque burden. In line with these findings, we found that visceral FV, of recognized similar embryologic origin than pericardial fat, was similarly related to plaque burden [19,28].

It is noteworthy that subcutaneous AT was inversely related with both coronary and extra-coronary plaque burden. These findings are in keeping with recent studies showing that the presence of large subcutaneous fat accumulation might entail protection against carotid and coronary atherosclerosis, and to lower rates of cardiac events and mortality [10,29]. In this regard, we identified a significant negative relationship between subcutaneous AT thickness, a very simple and straightforward measurement, and both coronary and extra-coronary plaque burden.

To the best of our knowledge, our study is the first to explore within a single scan the relationship between thoracoabdominal (coronary and extra-coronary) plaque burden and both general and regional fat depots. Previous studies have explored associations between pericardial fat and different site-specific extra-coronary atherosclerosis burden, although none has reported the interplay between regional fat and atherosclerosis along such a wide and comprehensive topographic range [13].

Our findings add to the increasing evidence exposing the shortcomings of general body fat measurements as predictive markers of atherosclerosis compared to regional fat measurements, and might partially explain the inconclusive and controversial link to the so-called obesity paradox [9]. Furthermore, our findings underscore the emerging clinical relevance of pericardial fat and visceral fat as markers of not only coronary, but also extra-coronary atherosclerotic plaque burden. Besides, based on previous studies reporting neutral or even protective cardiometabolic effects of subcutaneous fat and to the substantial gender differences found in our study regarding both regional pericardial and abdominal (visceral/subcutaneous) fat content, such dissimilar ectopic fat distribution between genders might potentially contribute to the understanding of the sex-related differences in plaque burden [30].

5. Study limitations

Although powered to detect differences between groups, the relatively small population included might lead to selection bias. Likewise, patients underwent aortic CTA for various clinical indications, potentially affecting vessels and adiposity differently. Moreover, data regarding baseline medication that might impact both atherosclerotic burden and body fat were not available. In this regard, traditional risk factors have been included in the regression models as dummy variables that do not take into consideration the type, extent, and length of treatment. However, aside from very few exceptions, this is how traditional risk factors have been included in most published regression models. Furthermore, data regarding other potentially relevant risk factors such as insulin-resistance, creatinine clearance, and serum uric acid were not available.

The degree of coronary stenosis has not been fully validated among aortic CTA studies, therefore within the coronary territory only the extension of disease (SIS) was assessed, that has been established as an independent predictor of major adverse events [22,23,31]. Likewise, in order to avoid potential misclassification and in line previous studies showing limited prognostic value of non-calcified plaques, we only computed calcified and mixed coronary lesions [18]. In addition, given the anatomic characteristics derived from CT images, readers were not blinded to the patient's body habitus. It is noteworthy that abdominal circumference measurements cannot be directly extrapolated to the conventional anthropometric measurement, since the later is performed at end expiration and with the subject standing. The prognostic value of coronary and extra-coronary plaque burden as well as of regional fat depots remains outside the scope of our investigation and warrants further studies. Finally, we cannot rule out the possibility that inflation of type I error due to multiple comparisons may have confounded our results.

6. Conclusions

In the present study including a comprehensive vascular assessment from the supra-aortic trunks up to the common femoral arteries, regional adipose tissue depots but not general body fat measurements were significantly related to coronary and extra-coronary atherosclerotic plaque burden. Particularly, pericardial and visceral fat were associated with increased plaque burden, whereas subcutaneous abdominal adipose tissue might stand as a neutral or even protective fat depot.

Conflict of interest

We declare that Patricia Carrascosa is Consultant of GE Healthcare. None of the other authors have conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.01.106.

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