

The impact of abdominal fat on abdominal aorta calcification measured on non-enhanced CT

Limor Goldenberg, MD^a, Walid Saliba, MD^b, Hashem Hayeq, MD^c, Rabea Hasadia, MD^c, Abdel-Rauf Zeina, MD^{d,*}

Abstract

Cardiovascular (CV) morbidity, atherosclerosis, and obesity are all targets of clinical concern and vast research, as is the association between them. Aim of this study is to assess the impact of adipose tissue (including visceral and subcutaneous fat) on abdominal aorta calcification measured on non-enhanced computed tomography (CT). We retrospectively included 492 patients who underwent non-enhanced CT scans during workup for clinically suspected renal colic. All scans were reviewed for abdominal aorta calcification, liver attenuation, and thickness of visceral and subcutaneous fat. Multivariate general linear regression models were used to assess the association between abdominal aorta calcium score and adiposity measures. In the model that included only adiposity measures; visceral fat thickness had statistically significant direct association with abdominal aorta calcium score ($B=67.1$, $P<.001$), whereas subcutaneous pelvic fat thickness had a significant inverse association with abdominal aorta calcium score ($B=-22.34$, $P<.001$). Only the association of subcutaneous pelvic fat thickness with abdominal aorta calcium score remained statistically significant when controlling for age, sex, smoking, hypertension, diabetes mellitus, and hyperlipidemia ($B=-21.23$, $P<.001$). In this model, the association of visceral fat remained statistically significant in females ($B=84.28$, $P=.001$) but not in males ($B=0.47$, $P=.973$). Visceral fat thickness and subcutaneous pelvic fat thickness were found to have opposing associations with abdominal aorta calcium score. This suggests that while visceral fat may have a lipotoxic effect on aortic atherosclerotic processes, subcutaneous pelvic fat may have a protective role in these processes.

Abbreviations: CT = computed tomography, CV = cardiovascular, CVD = cardiovascular disease, HU = Hounsfield units.

Keywords: abdominal visceral fat, aortic calcification, atherosclerosis, calcium score, non-enhanced CT

1. Introduction

The burden of atherosclerotic disease is unbearably heavy as it remains a major cause of death and morbidity in industrialized societies, involved in the pathogenesis of cardiovascular (CV) events and peripheral vascular disease. Vascular calcification is a complicating factor observed in advanced atherosclerosis. The mechanism of the vascular calcification process is multifactorial and incompletely understood combining elements of inflammation, dysregulated metabolism, and osteogenesis.^[1] The presence and extent of vascular calcification can be considered merely a marker

for atherosclerotic load, or it may serve on its own as an agent of disease. There is vast scientific interest in the matter of vascular calcification in terms of both risk factors for its occurrence, and possible outcomes of its presence.

Scanning and scoring of coronary artery calcium (CAC) has been established as an imaging biomarker of atherosclerosis, with strong prognostic correlation.^[2,3] However, research of atherosclerosis and vascular calcification includes not only the coronary arteries but also vessels such the carotids, renal arteries, and unsurprisingly—the aorta. The sclerotic process in the aorta is considered to begin with fatty streaks that are present as early as childhood, progressing to atherosclerotic lesions which appear in many young adults, and may advance further to calcified lesions and plaques.^[4]

Aortic calcification is a valuable marker, as its presence and degree have been associated with the extent and severity of coronary artery calcification and disease^[5,6] (absence of abdominal aortic calcification has a high negative predictive value to rule out coronary artery disease),^[7] CV events,^[8–10] peripheral artery disease in patients with type 2 diabetes mellitus,^[6] stroke,^[11] risk of fractures,^[12] and all-cause mortality.

Aortic calcification can be evaluated by either plain X-Ray (chest,^[9] abdomen, and lateral lumbar radiograms);^[8,13] vertebral Dual-energy X-ray absorptiometry (DXA);^[14] computed tomography (CT); electron beam CT (EBCT); CT angiography (CTA); ¹⁸F-NaF-PET/CT;^[15] Near-infrared fluorescent imaging (tested in murine models)^[16] or autopsy studies. There are several different scoring methods of calcification, of which the most vastly used is the Agatston score, combining calcified plaque area and density as derived from CT scans.^[2]

Risk factors for the progression of calcified atherosclerosis in general, and specifically for aortic calcification, include age,^[6,17–19] hypertension,^[6] smoking,^[6,20] dyslipidemia,^[6] exercise level (negatively related),^[17] chronic kidney disease,^[21] and ethnicity.^[22] Few

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The Institutional Review Board at Hillel Yaffe Medical Center approved this retrospective study.

The authors have no conflicts of interest to disclose.

^a Department of Internal Medicine B, Hillel Yaffe Medical Center, Hadera, Affiliated with the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology,

^b Department of Community Medicine and Epidemiology, Carmel Medical Center, Affiliated with the Faculty of Medicine, Technion- Israel Institute of Technology,

^c Division of General Surgery, Hillel Yaffe Medical Center, Hadera, Affiliated with the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa,

^d Department of Radiology, Hillel Yaffe Medical Center, Hadera, Affiliated with the Faculty of Medicine, Technion- Israel Institute of Technology, Haifa, Israel.

* Correspondence: Abdel-Rauf Zeina, Department of Radiology, Hillel Yaffe Medical Center, P.O.B. 169, Hadera 38100, Israel (e-mail: raufzeina@gmail.com).

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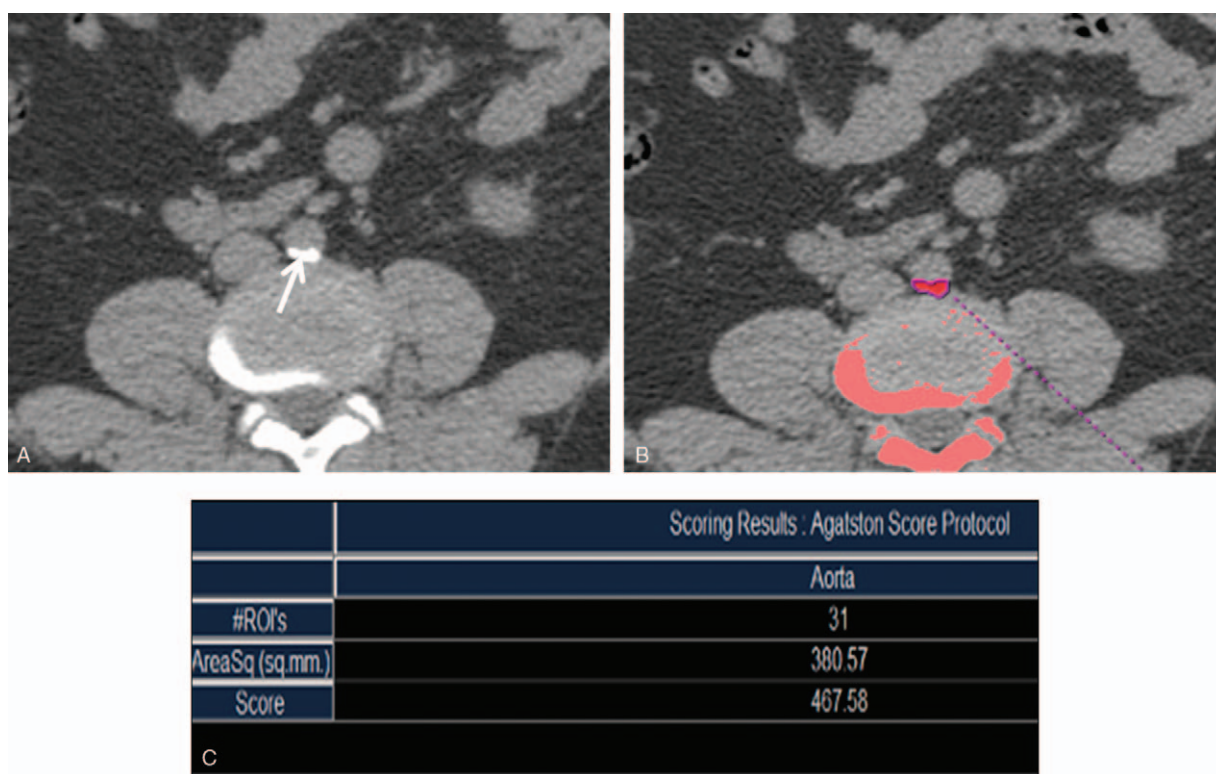


Figure 1. Representative abdominal aorta calcium measurement using postprocessing software and calcium analysis tool (Philips Brilliance Workspace Portal, Version 6.02, by Philips Medical Systems Netherlands B.V). Axial non-enhanced CT image shows a calcified plaque (arrow) in the infrarenal abdominal aorta (A). The postprocessing software automatically highlighted the aortic calcification (color red) and a ROI was manually drawn around the aortic wall on each axial non-enhanced CT image containing visible calcifications (B), defined as CT density greater than or equal to 130 HU. The postprocessing software then summed the individual calcification areas and densities, calculating total calcification area and Agatston score (C).CT=computed tomography, HU=Hounsfield units, ROI=region of interest.

studies examined the relation between aortic calcification and body composition: abdominal lean muscle area and visceral fat area were not generally found to be significantly associated with aortic atherosclerosis,^[22–24] while gender subdivision found an association between visceral fat and abdominal aorta calcification in women only.^[25] Subcutaneous fat was unexpectedly found to be inversely associated with atherosclerosis.^[22,24] Therefore, the aim of this study was to examine the correlation of abdominal aortic calcium (AAC) with abdominal adipose tissue (including visceral and subcutaneous fat) and hepatosteatosis, measured on non-enhanced CT, in a large patient population.

2. Materials and methods

2.1. Study population

The study sample included 492 adult patients (age ≥ 18 years), who underwent non-enhanced abdominal CT scans, due to clinically suspected renal colic, in our Imaging Institute throughout the years 2013 to 2014. The only exclusion criterion was age younger than 18 years. In all CT scans reviewed, image quality was high enough to allow adequate analysis, thus there was no exclusion due to low image quality. Demographic and clinical data including the patients' age, gender, smoking status and comorbidities, such as diabetes mellitus, hypertension, and hyperlipidemia, were collected from the medical files. Our institutional review board approved this retrospective study and waived the requirement for informed consent.

2.2. CT protocols

A 64-detector row CT scanner (Brilliance-64, Philips Healthcare, Cleveland, Ohio, USA) was used to perform the abdomen-pelvis CT scan. All patients were in the supine position and were scanned from the lung base to the pubic symphysis. We performed a non-contrast scan. The scanning parameters were as follows: tube voltage, 120 kVp; collimation, 64×0.6 mm; rotation speed, 0.75 s; pitch, 0.8; reconstruction thickness, 3 mm. Sagittal and coronal reformatted images were generated with a thickness of 3 mm. Each CT examination was retrospectively reviewed by 2 board-certified radiologists. Image review was performed (in consensus) on a PACS workstation.

2.3. Abdominal aortic calcification scoring

Abdominal Aorta Calcium Score was obtained using Philips Brilliance Workspace Portal, Version 6.02, by Philips Medical Systems Netherlands BV. Circular regions-of-interest (ROI) were manually drawn around the aortic wall on each axial unenhanced image containing visible calcifications, defined as CT density greater than or equal to 130 Hounsfield units (HU), from the level of the celiac axis to aortic bifurcation, taking care not to include any vertebral bone area. The 130 HU threshold is recommended by the software vendor and is commonly used for CT assessment of arterial calcification.^[25–27] The postprocessing software then summed the individual calcification areas and densities, calculating total calcification area and Agatston score (Fig. 1).

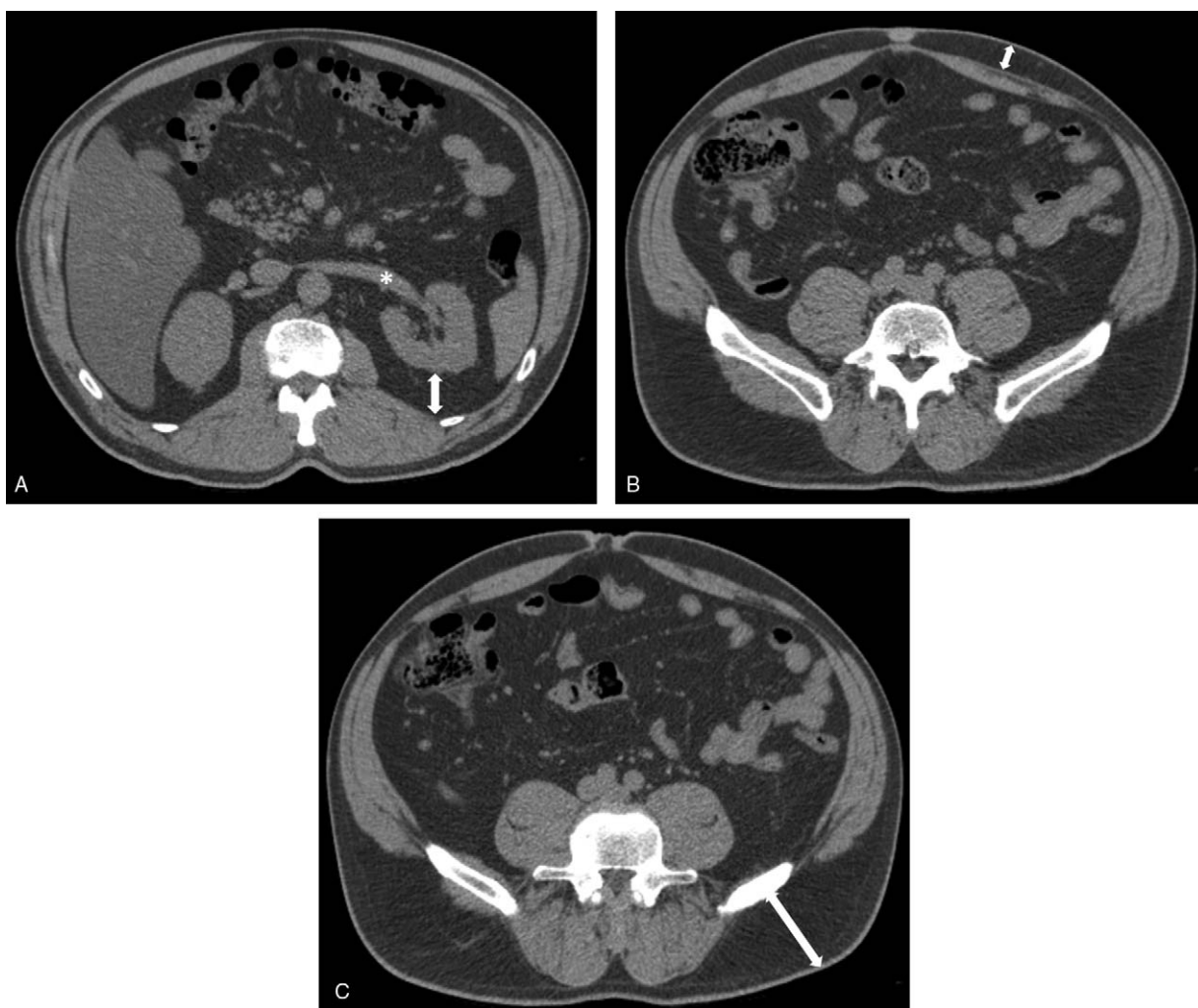


Figure 2. Measurements of fat thickness on CT slices. Location of measurement is marked by double-headed arrow. (A) Retro-renal visceral fat: measured using the vertical distance between the left posterior renal capsule and the junction of the abdominal wall and paraspinal musculature at the level of the left renal vein (asterisk). (B) Abdominal subcutaneous fat: measured at the umbilical level, as the distance between the rectus abdominis to the skin over the anterior abdomen. (C) Pelvic subcutaneous fat: measured at the iliac crest level, as the distance between the iliac crest and the posterior skin. CT=computed tomography.

2.4. Measurement and criteria setting

2.4.1. Fat thickness measurements. Visceral fat: For the evaluation of visceral fat level, we measured the thickness (mm) of retro-renal fat. This measurement is performed at the level of the left renal vein and includes the pre-renal and para-renal fat from the surface of the kidney to the inner abdominal wall (Fig. 2A).

Subcutaneous abdominal fat: The thickness of subcutaneous abdominal fat was measured at the umbilical level, as the distance between the rectus abdominis to the skin over the anterior abdomen (Fig. 2B).

Subcutaneous pelvic fat: The thickness of the subcutaneous pelvic fat was measured at the iliac crest level, as the distance between the iliac crest and the posterior skin (Fig. 2C).

2.4.2. Liver density measurements. The difference between liver and spleen densities (CT_{L-S}) was chosen as the defining criterion for hepatosteatosis in this study. Normally, liver density is higher by about 10 HU from that of the spleen. Livers were defined as fatty when the hepatic density, averaged over the 3-segment measurements, was at least 9 HU lower than that of the

spleen. The specifics of liver and spleen density measurements have been described in our previous study.^[28]

2.5. Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics 22.0 program. All tests are 2-tailed, with statistical significance set as $P < .05$. Continuous variables are reported as means and standard deviations along with medians and interquartile ranges. Categorical variables are reported as absolute values and proportion. Multiple Linear regression analysis was used to examine the univariate and multivariate relation between abdominal aorta calcium score (the dependent variable) and adiposity measures (independent variables). The unstandardized regression coefficient (B) is reported. For continuous variables, it reflects the effect on the dependent variable for each increment of 1 unit in the independent variable.

3. Results

A total of 492 patients were included in the study. The mean age was 47.27 years (SD 14.04), and 74.8% of the participants were

Table 1
Study population characteristics (n=492).

Baseline Characteristics	
Age	
Mean ± SD	47.27 ± 14.04
Median (IQR) [†]	46.50 (37.00–58.00)
Gender	
Male*	368 (74.8%)
Female*	124 (25.2%)
Medical History	
Smoking*	110 (22.4%)
Hypertension*	113 (23%)
Diabetes Mellitus*	77 (15.7%)
Hyperlipidemia*	111 (22.6%)
Radiographic Measurements	
Visceral fat (mm)	
Mean ± SD	9.24 ± 8.18
Median (IQR) [†]	6.60 (2.80–14.30)
Subcutaneous Abdominal fat (mm)	
Mean ± SD	27.02 ± 14.01
Median (IQR) [†]	24.90 (19.30–32.60)
Subcutaneous Pelvic fat (mm)	
Mean ± SD	63.48 ± 16.94
Median (IQR) [†]	62.30 (52.52–74.52)
Fatty Liver*	79 (16.1%)
Abdominal Aorta Calcium Score	
Mean ± SD	748.18 ± 1937.49
Median (IQR) [†]	12.86 (0.00–452.18)

* Presented as absolute value (proportion).

[†] IQR=Interquartile Range, SD=standard deviation.

male. Table 1 portrays the demographic, clinical and radiological characteristics of the study population.

Age, hypertension, diabetes mellitus, hyperlipidemia, and thickness of visceral fat were directly and significantly associated with abdominal aorta calcium score in univariate linear regression analysis, whereas a significant inverse association was found with subcutaneous pelvic fat thickness (B=−14.3, P=.006) (Table 2).

Three different multivariate linear regression analyses were performed. The first model included only the four CT adiposity measures. In this model, a significant association with abdominal aorta calcium score was detected for visceral abdominal fat and

Table 2
Univariate linear regression analysis for the association with abdominal aorta calcium score.

	B Coefficient	P value
Demographic Factors		
Age*	68.70	<.001
Gender: Female vs Male	120.19	.55
Comorbidities		
Smoking	−30.66	.88
Hypertension	1010.40	<.001
Diabetes Mellitus	946.95	<.001
Hyperlipidemia	1280.75	<.001
Radiographic Findings		
Visceral fat, mm [*]	46.62	<.001
Subcutaneous Abdominal fat, mm [*]	−12.35	.48
Subcutaneous Pelvic fat, mm [*]	−14.13	.006
Fatty Liver	−96.34	.69

* The B coefficient for continuous variables reflects the effect on abdominal aorta calcium score for each increment of 1 unit in the value of that variable.

subcutaneous pelvic fat, (B=67.1, P<.001) and (B=−22.34, P<.001), respectively.

After further adjustment for demographic variables and comorbidities, the association with subcutaneous pelvic fat remained statistically significant (Table 3).

The positive association of abdominal aorta calcium score with visceral fat width remained significant in the fully adjusted model when limited to female gender only (B=84.28, P=.001). The association with fatty liver and umbilical subcutaneous fat, however, did not reach statistical significance regardless of gender selection. A comparison between males and females in the magnitude and the direction of the association of the different adiposity measures with abdominal aorta calcium score is depicted in Figure 3.

4. Discussion

In the present study abdominal aorta calcium score was significantly associated with CV risk factors (hypertension, diabetes mellitus, hyperlipidemia) correlating to a recent meta-analysis that determine abdominal aorta calcification was an independent predictor of CV disease (CVD) events.^[10] Moreover, a statistically significant positive association of visceral abdominal adipose tissue with abdominal aorta calcium score was found in both univariate and multivariate analysis. Indeed, visceral adipose tissue has been repeatedly uncovered as an important risk factor for metabolic and CV disease, including coronary atherosclerosis^[29,30] and cerebrovascular lesions.^[31] Lipotoxicity is a relevant term in this matter, used to describe the deleterious effect of tissue fat accumulation, initially regarding glucose metabolism, but increasingly associated with other processes, including atherosclerosis, through the possible mechanism of fat-induced chronic inflammation.^[32] Positive associations between total periaortic adipose tissue volume and CV disease have been established based on data from the Framingham Heart Study and others.^[33,34] Using CT for quantification of aortic adiposity and aortic dimensions, Thanassoulis et al^[33] demonstrated that periaortic adipose tissue volume was associated with thoracic and abdominal aortic dimensions. This association persisted after adjustment for CVD risk factors and visceral adipose tissue volume.^[33] In accordance with our results, the impact of visceral abdominal adipose tissue on abdominal aorta calcification has also been demonstrated. Studies have shown that periaortic adipose tissue volume is correlated with the quantity of visceral abdominal adipose tissue. Lehman et al^[34] demonstrated that thoracic aortic adipose tissue was associated with thoracic calcification in models containing visceral abdominal tissue. Moreover, thoracic peri-aortic adipose tissue was associated with abdominal aortic calcification in models containing visceral abdominal adipose tissue and CVD risk factors.^[34]

Jensky et al demonstrated a significant positive association of CT-quantified visceral fat with aortic calcification.^[35] However, the current study results show in the multivariate analysis the association of visceral adipose tissue with abdominal aorta calcium score did not withhold the addition of traditional CV risk factors to the model unless the model was limited to female gender only. This gender-related observation has been noted in previous research.^[25] Thus, suggesting necessity to reexamine the lipotoxic role of visceral fat in the process of abdominal aorta calcification, which specifically in women, is independent of other examined factors. Hormonal pathways and tissue-factors have been studied to explain the gender-related difference in atherosclerosis, but further research is still required.^[36]

Table 3
Multivariate linear regression analysis for the association with abdominal aorta calcium score.

	Model I*		Model II† partially adjusted		Model III‡ fully adjusted	
	B Coefficient	P value	B Coefficient	P value	B Coefficient	P value
Visceral fat, mm	67.10	<.001	17.51	.14	19.71	.10
Subcutaneous Abdominal fat, mm	-4.50	.52	0.11	.99	0.34	.96
Subcutaneous Pelvic fat, mm	-22.34	<.001	-20.12	.01	-21.23	<.001
Fatty Liver	-235.30	.33	-164.56	.45	-153.39	.48
Age, years	—	—	66.89	<.001	62.96	<.001
Female Gender, %	—	—	-27.99	.89	11.86	.95
Smoking, %	—	—	—	—	25.85	.89
Hypertension, %	—	—	—	—	-213.28	.38
Diabetes Mellitus, %	—	—	—	—	-63.85	.80
Hyperlipidemia, %	—	—	—	—	519.35	.03

* Model I—adjusted only for adiposity measures (visceral and subcutaneous fat, fatty liver).

† Model II—adjusted for adiposity measures + Age + Gender.

‡ Model III—adjusted for adiposity measures + Age + Gender + Comorbidities (smoking, diabetes Mellitus, hypertension, hyperlipidemia).

In the present study among the examined measures of adiposity, only pelvic subcutaneous fat was found to have a solid statistically significant association with abdominal aorta calcium score. This association withstood the addition to the model of possible confounders having previously proven effects on the atherosclerotic process: age, smoking status, hypertension, hyperlipidemia, and diabetes mellitus. This association is a negative one—suggesting a protective role of subcutaneous fat on abdominal aorta calcification, as was implied in previous research.^[24] Our results, however, relate to pelvic subcutaneous fat, and not abdominal subcutaneous fat as previously presented. In fact, in this

study, the association of abdominal subcutaneous fat and abdominal aorta calcium score was statistically non-significant in all the univariate and multivariate analysis models, unlike the results presented by Jensky et al.^[35] This may infer a variance in the calcific effect by different body fat distributions (as expressed in the traditional concept of “apple” versus “pear” body shape, and the much-studied waist-to-hip ratio).^[37] Karastergiou et al review discussing “the biology of pear shape” summarizes several examples and possible mechanisms for the lower cardiometabolic risk associated with pear-shaped body fat distribution, related to gender, genetics, and microenvironment factors.^[38]



Figure 3. Multivariate B coefficient showing the magnitude and the direction of the association of the different adiposity measures with abdominal aorta calcium score among males and females.

Although research has tied non-alcoholic fatty liver and atherosclerosis, through possible mechanisms involving inflammatory mediators, insulin resistance, oxidative stress and endothelial damage, the specific link between fatty liver and aortic atherosclerosis has only been weakly and partially established. In this study, no significant association was found between fatty liver and abdominal aorta calcium score. Unlike previous studies, this was still the case when the model was limited to female gender only^[39] and even in a univariate analysis before adjustment to other factors such as visceral fat thickness.^[40] Further research will be required to determine the association and paths between these 2 conceptually related disorders.

A limitation of this study is the composition of the study population. Subjects underwent CT scanning for specific medical indications and thus limiting generalization of the findings to the general population. However, performing non-contrast CT as a means of screening and diagnosis is not rational both financially and in terms of exposure to radiation. Nonetheless, the associations derived from the study population are internally valid as measurements were standardized and consistent with accepted methods.

In conclusion: our study found a negative association between pelvic subcutaneous fat thickness and abdominal aorta calcification, and a positive association between visceral fat thickness and abdominal aorta calcification, the latter association particularly robust in women. The association between body compositions and adiposity measures with aortic calcification has not been widely investigated. Further knowledge of these associations could aid in risk stratification and identification of subsets of the population who may benefit from aortic calcification assessment and primary or secondary prevention of CV disease. These associations could also be used to identify pathogenesis mechanisms and treatment targets in atherosclerotic disease.

Author contributions

Conceptualization: Limor Goldenberg, Abdel-Rauf Zeina.

Data curation: Limor Goldenberg, Walid Saliba, Abdel-Rauf Zeina.

Formal analysis: Limor Goldenberg, Walid Saliba, Rabea Hasadia, Abdel-Rauf Zeina.

Investigation: Hashem Hayeq, Rabea Hasadia, Abdel-Rauf Zeina.

Methodology: Walid Saliba, Rabea Hasadia.

Resources: Hashem Hayeq.

Software: Walid Saliba, Hashem Hayeq, Rabea Hasadia.

Supervision: Walid Saliba.

Validation: Abdel-Rauf Zeina.

Visualization: Hashem Hayeq, Rabea Hasadia.

Writing – original draft: Limor Goldenberg, Abdel-Rauf Zeina.

Writing – review & editing: Abdel-Rauf Zeina.

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