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Epicardial fat thickness is increased in menopausal patients in comparison with premenopausal patients with similar excess weight: a cross-sectional study

Elena Gangitano[1,2], Giuseppe Barbaro[1], Lucio Gnessi[1], Gianluca Iacobellis[3] and Carla Lubrano[1*]

Abstract

Background The prevalence of excess weight and ageing is notably high in contemporary Western societies. The effectiveness of body mass index (BMI) and waist circumference as tools for identifying excess weight and ectopic fat deposition, both associated with an increased cardiovascular risk, is questionable.

Methods Our objective is to compare women affected by overweight and obesity during fertile years and menopausal time and identify easily accessible clinical parameters associated with ectopic fat deposition, providing valuable insights into cardiovascular risk. Over 1300 female patients with excess weight referred to the CASCO Centre (High Specialization Centre for the Care of Obesity) at Umberto I Polyclinic in Rome, Italy, were included. Each participant underwent a DXA scan and a cardiac ultrasound, and blood tests to verify menopausal status and evaluate metabolic profile and hepatic steatosis through indirect measurements.

Results 775 patients were in the pre-menopausal phase and 617 in the post-menopausal phase. The two cohorts did not differ in BMI, total body fat and lean mass, or waist circumference. However, the post-menopausal group showed an increased visceral fat deposition, evaluated by waist-to-hip ratio and epicardial fat thickness (EFT), and a worse metabolic profile.

Conclusion Menopause is associated with a worsening of the metabolic features observed in obesity, with an increase in visceral fat deposition. Of note, these alterations are more pronounced despite similar BMI and waist circumference.

Keywords Obesity, Excess weight, Menopause, Epicardial fat, Epicardial adipose tissue, Ectopic fat

Introduction

The prevalence of excess weight is worryingly increasing worldwide, in parallel with progressive ageing in industrialized countries. Ageing favours the onset of the components of the metabolic syndrome, such as hypertension, impaired glucose tolerance and dyslipidaemia, with an overall increased cardiovascular risk. Menopause is a physiological event in a woman's life, during which the change in hormonal secretion determines a modification in fat amount and distribution [1–3], and an increase

*Correspondence:
Carla Lubrano
carla.lubrano@uniroma1.it
[1] Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
[2] Unicamillus- Saint Camillus International University of Health Sciences, Rome, Italy
[3] Division of Endocrinology, Diabetes and Metabolism, University of Miami, Miami, FL, USA

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in cardiometabolic risk factors [4, 5]. These factors may be exacerbated when excess weight is already present. Obesity may be associated with a variety of hormonal and metabolic alterations, that are extremely wide, and comprehend type 2 diabetes, insulin resistance, hepatic steatosis, dyslipidaemia, empty sell, altered bone structure and altered immune response [6–13]. This complex picture is often associated with metabolic syndrome, which configures a higher cardiovascular risk [14]. The epicardial adipose tissue (EAT) is directly in contact with the myocardium and is located within the pericardium. It can be measured through echocardiography, after being identified as the echo-free space set between the outer surface of the myocardium and the visceral layer of the pericardium, as already described by Iacobellis et al. [15, 16]. The thickness of EAT is an indicator of visceral fat deposition and can be considered a novel cardiovascular risk factor [17–19]. Anyway, EAT is a fat deposit with unique characteristics: thanks to its position, it can mechanically protect the myocardium; it stores free fatty acids, that will be directly used by the myocardium; it is able to synthesize cytokines which act on the myocardium; as a brown fat depot, can provide direct heating to the myocardium [20]. Moreover, it has been recently proposed as a marker for or coronary microvascular dysfunction [21]. Therefore, we wanted to compare women affected by overweight and obesity in the fertile age and women in their menopause, focusing on body composition, epicardial fat thickness, metabolic profile and bone indices, and identify some parameters easy to assess in the routine clinical practice, which may be good predictors of visceral fat deposition, independently from the use of BMI and waist circumference.

Materials and methods

Subjects

Female patients admitted to the CASCO Centre (High Specialization Centre for the Care of Obesity), Polyclinic Umberto I, Sapienza University of Rome, from 2014 to 2021, were screened during their first admission. Medical history, physical exam and laboratory assays were performed for all patients, as part of routine diagnostic workup. The complete assessment, including biochemical parameters, epicardial fat thickness, and DXA-scan were performed within a time frame of 2 months.

Menopause was assessed biochemically with the assay of FSH (follicle-stimulating hormone) LH (luteinizing hormone) and oestradiol, and according to clinical findings and the hormonal results patients were divided into 2 groups: menopausal patients and non-menopausal patients.

A written informed consent was obtained from all participants. The patients who did not give their informed consent were excluded. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was reviewed and approved by the Ethics Committee of Sapienza University of Rome (protocol code CE5475, approved the 24th October 2019, and amendment protocol n. 0513/2024, approved the 6th June 2024).

Anthropometric measurements

Anthropometric parameters were obtained at 9 a.m., in fasting conditions, with subjects wearing light clothing and no shoes. Body weight and height were obtained using the same stadiometer and calibrated scale for all patients. Body Mass Index (BMI) was obtained by dividing weight by squared height (kg/m^2). Waist circumference was measured at the iliac crest, and hip circumference was measured around the pelvis at the widest point. The tape was parallel to the floor and did not compress the skin. The waist-to-hip ratio (WHP) was obtained by dividing waist circumference by hip circumference.

Laboratory assays

Blood samples were collected from fasting patients by venipuncture between 8 and 9 a.m. Samples were then transferred to the local laboratory and handled according to the local standards of practice. A complete metabolic assessment was performed, with the measurement of fasting glucose and insulin, cholesterol and triglycerides. Insulin resistance was assessed with the HOMA-IR, calculated as fasting insulin (UI/L) x fasting glucose (mg/dL)/405 and patients were defined as insulin resistant when the value exceeds 2.5.

Evaluation of hepatic steatosis

Evaluation of hepatic steatosis was obtained with non-invasive methods, based on laboratory and anthropometric measurements, including AST, ALT, insulin and BMI. The formulas used were: hepatic steatosis index (HIS), NAFLD liver fat score (NAFLD -LFS) and Fatty Liver Index (FLI).

The HSI was calculated with the formula HSI = 8 × ALT/AST ratio + BMI (+2, in case of diabetic patient; +2, because of female sex female). The diagnosis of diabetes mellitus was based on a fasting glucose of ≥ 126 mg/dL, HbA1c ≥ 6,5% or therapy with anti-diabetic medication. The cut-off value used to discriminate NAFLD was 35.

FLI was calculated with the formula FLI = ($e^{0.953}$ x loge (triglycerides) + 0.139 x BMI + 0.718 x loge (GGT) + 0.053 x waist

circumference − 15.745)/ $(1+e^{0.953 \times \log e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745})\times 100$. The cut-off value used to discriminate NAFLD was 60.

NAFLD-LFS was calculated with the formula.

$$LFS = -2.89 + 1.18\left[\underset{MetabolicSyndr.}{(Yes=1, No=0)}\right] + 0.45\left[\underset{TypeIIDM}{(Yes=2, No=0)}\right] + 0.15(insulin[mU/L]) + 0.04(AST[U/L]) - 0.94\left[\frac{AST}{ALT}\right]$$

A NAFD-LFS value ≥ 1.257 indicated the presence of steatosis.

Dual energy X-ray absorptiometry

All patients underwent DXA (Hologic-Discovery A, software version 12.5.3:2) to evaluate the mineral bone density of the hip and lumbar spine from L2 to L4, and total body composition. DXA was performed with subjects wearing light clothing and no shoes. Bone values that we evaluated included lumbar spine and hip T-score, lumbar spine and hip bone mineral density (BMD), expressed in g/cm2. Osteoporosis was diagnosed when the T-score was equal to or below -2,5. Trabecular Bone Score (TBS) was calculated with the software TBS iNsight. Bone microarchitecture was considered normal when TBS ≥ 1.35, partially degraded when 1.2 < TBS < 1.35 and degraded when TBS ≤ 1.2 [22].

For the total body composition, we considered the values of Body Fat or Fat Mass (FM), Trunk Fat, and Fat-Free Mass or Lean Mass (FFM), expressed in absolute value in Kg and percentage.

Epicardial adipose tissue (EAT)

All patients underwent an ultrasound evaluation of the epicardial fat thickness, identified at the interface of the external myocardium wall and visceral pericardium, expressed in mm. The evaluation was carried out by the same expert cardiologist, to minimize interobserver variability. Intima media thickness (IMT) was also evaluated.

Statistical analysis

The statistical analysis was performed using the software Statistica, version 14 StatSoft Inc. and MedCalc® Statistical Software version 20.111 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2022). Descriptive statistics (n, mean, SD) were calculated for continuous variables. The distribution of continuous variables was tested with the Shapiro–Wilk test and variables were expressed as mean ± standard deviation (SD). Independent samples Student's t-test was used to assess differences between groups, that were considered statistically significant when $p < 0.05$.

Results

1392 female patients affected by overweight or obesity were enrolled. 775 were in the pre-menopausal time, and 617 in the post-menopausal time. Demographics, anthropometric measurements and body composition findings by DXA are displayed in Table 1. Our two cohorts did not differ in BMI, total body fat and lean mass, or waist circumference. Anyway, a worse hip-to-waist ratio was noted in the post-menopausal group, and it was confirmed by increased trunk fat percentage at DXA scan results, sign of increased visceral fat deposition.

BMD was reduced in the post-menopausal group, as expected at an older age.

Regarding the metabolic profile, impaired fasting glucose (IFG) was observed in the menopausal group, which was not present in the younger age group. On the other hand, a fasting lower insulin was noted, maybe indicating a progression towards the development of type 2 diabetes. Anyway, the Homa index was higher in the post-menopausal group. Blood pressure was higher in the post-menopausal group, with the

Table 1 Anthropometric measurements, body composition and bone data by DXA scan

	Pre-menopause *n* = 775	Post-menopause *n* = 617	*p*
Age (years)	38.6 ± 9.8	57.8 ± 9.1	< 0.01
Weight (kg)	94.8 ± 25	90.5 ± 20.7	< 0.01
Height (cm)	1.62 ± 0.1	1.59 ± 0.1	< 0.01
BMI (Kg/m^2)	35.9 ± 9.5	35.8 ± 8	ns
Waist (cm)	113 ± 18	114 ± 16	ns
WHR	0.96 ± 0.1	0.98 ± 0.1	< 0.01
Body fat (%)	41 ± 7.6	41 ± 6.2	ns
Fat free Mass (%)	59 ± 7.6	58.4 ± 6.2	ns
Fat mass (kg)	37 ± 13	37 ± 11	ns
Fat free mass (kg)	51 ± 10	51 ± 11	ns
Trunk fat (%)	38.2 ± 9	39.4 ± 6	< 0.01
TB BMD (g/cm^2)	1.14 ± 0.1	1.07 ± 0.1	< 0.01
L2-L4 BMD (g/cm^2)	1.08 ± 0.1	0.97 ± 0.1	< 0.01
Hip BMD (g/cm^2)	1.01 ± 0.1	0.93 ± 0.1	< 0.01
TBS	1.31 ± 0.1	1.19 ± 0.1	< 0,01

Data are expressed as mean ± SD. *BMI* body mass index, *WHR* waist-to-hip ratio

Table 2 Biochemical parameters and vital signs

	Pre-menopause *n = 775*	Post-menopause *n = 617*	*p*
Fasting glucose (mg/dl)	93 ± 22	104 ± 31	< 0.01
Fasting insulin (mIU/l)	19 ± 16	17 ± 15	< 0.01
HOMA-IR	4.7 ± 5	4.8 ± 5	< 0.05
Cholesterol LDL (mg/dl)	117 ± 36	127 ± 37	< 0.01
Cholesterol HDL (mg/dl)	51 ± 12	53 ± 13	< 0.05
Triglycerides (mg/dl)	120 ± 87	132 ± 76	< 0.01
Systolic Blood Pressure (mmHg)	121 ± 17	132 ± 16	< 0.01
Diastolic Blood Pressure (mmHg)	77 ± 11	81 ± 10	< 0.01
Heart Rate (bpm)	71 ± 10	69 ± 11	< 0.01

Data are expressed as mean ± SD

Table 3 Indices of ectopic fat deposition

	Pre-menopause *n = 775*	Post-menopause *n = 617*	*p*
EAT (mm)	7.4 ± 0.9	8.0 ± 0.8	< 0.01
NAFD-LFS	3.1 ± 2.7	2.8 + 3.4	< 0.01
HSI	45 ± 9	45 ± 7	ns
FLI	74 ± 29	78 ± 25	< 0.01
IMT right	0.67	0.82	< 0.01
IMT left	0.68	0.82	< 0.01

Data are expressed as mean ± SD. *EAT* epicardial adipose tissue, *NAFLD-LFS* Non-alcoholic fatty liver disease liver fat score, *HIS* hepatic steatosis index, *FLI* Fatty Liver Index FLI, *IMT* intima media thickness

systolic pressure tendentially elevated (132 mmHg). LDL and HDL cholesterol and triglycerides were increased in the post-menopausal group (Table 2).

Indices of ectopic fat deposition are shown in Table 3. Epicardial fat thickness was increased in the post-menopausal group. The fatty liver index indicated a higher hepatic fat deposition in the post-menopausal group, conversely to NAFLD-LFS, which was reduced, and HIS, which did not differ among groups. Anyway, all the 3 indexes indicated the presence of hepatic steatosis in both groups.

FSH and LH, after adjustment by age, positively correlated with EFT, while on the contrary estradiol negatively correlated with EFT (Fig. 1).

The percentage of trunk fat, the waist-to-hip ratio and EAT are predictive of hepatic steatosis defined with the FLI (Table 4). Moreover, EAT also correlates with bone mineral density and trabecular bone score (Table 4).

Discussion

Our findings suggest that menopause plays an important role in the worsening of the metabolic profile of female patients with excess weight. The menopausal time is associated with an overall worsening of lipid profile and an increased prevalence of metabolic syndrome, which in the complex configures a higher cardiovascular risk [4, 23]. Nevertheless, menopause and ageing determine a variation in body composition, with an increase in total body and abdominal fat [24]. In line with these findings, our cohort of menopausal women face increased visceral fat and ectopic fat deposition, as pointed out by the increase in the waist-to-hip ratio, the trunk fat and the epicardial fat thickness. Epicardial fat is strictly associated with metabolic syndrome [25, 26] and can be considered a cardiovascular risk factor [17]. Epicardial adipose tissue and peri-coronary epicardial adipose tissue are associated with coronary artery calcification, in both premenopausal and post-menopausal women [27, 28]. Epicardial fat thickness presents important sex-specific characteristics. Some authors report it is similar in men and women younger than 60 years old [29] and others that is thicker in women regardless of age [25], but it is anyway peculiarly increased in post-menopausal and older women in comparison with men and pre-menopausal women [25, 29]. As a confirmation of the role of oestrogens, whose levels influence EFT [27, 30], interventional studies in which oral-conjugated equine oestrogens were administered to menopausal women, reduced risk of increase in epicardial adipose tissue and atherosclerosis progression was observed [31, 32]. Anyway, also other hormones are implicated in EFT, such as growth hormone [33]. Higher epicardial adipose tissue volume has also been associated with increased left ventricular mass, cardiac remodelling and diastolic dysfunction in both sexes, or only in women, and in postmenopausal women independently from body mass index [25, 29, 34]. Moreover, differences among races were reported, as black women had lower EAT compared to white women even after correction for BMI, which was higher, probably because of a bigger subcutaneous fat [35]. In our cohort the epicardial adipose tissue is thicker in menopausal women compared to the women in the pre-menopausal stage. These findings are in line with previous studies, in which bigger epicardial and paracardial adipose tissues and total heart adipose tissue were observed in late peri and post-menopausal women [25, 30] independently from age and obesity assessed with BMI [30]. The EAT in our post-menopausal cohort is beyond 7.5 mm, which has been identified as the threshold for high-risk EAT [36]. The novelty of our findings is that EFT is thicker in menopausal women independently not only from BMI, but also from waist circumference, which did not differ

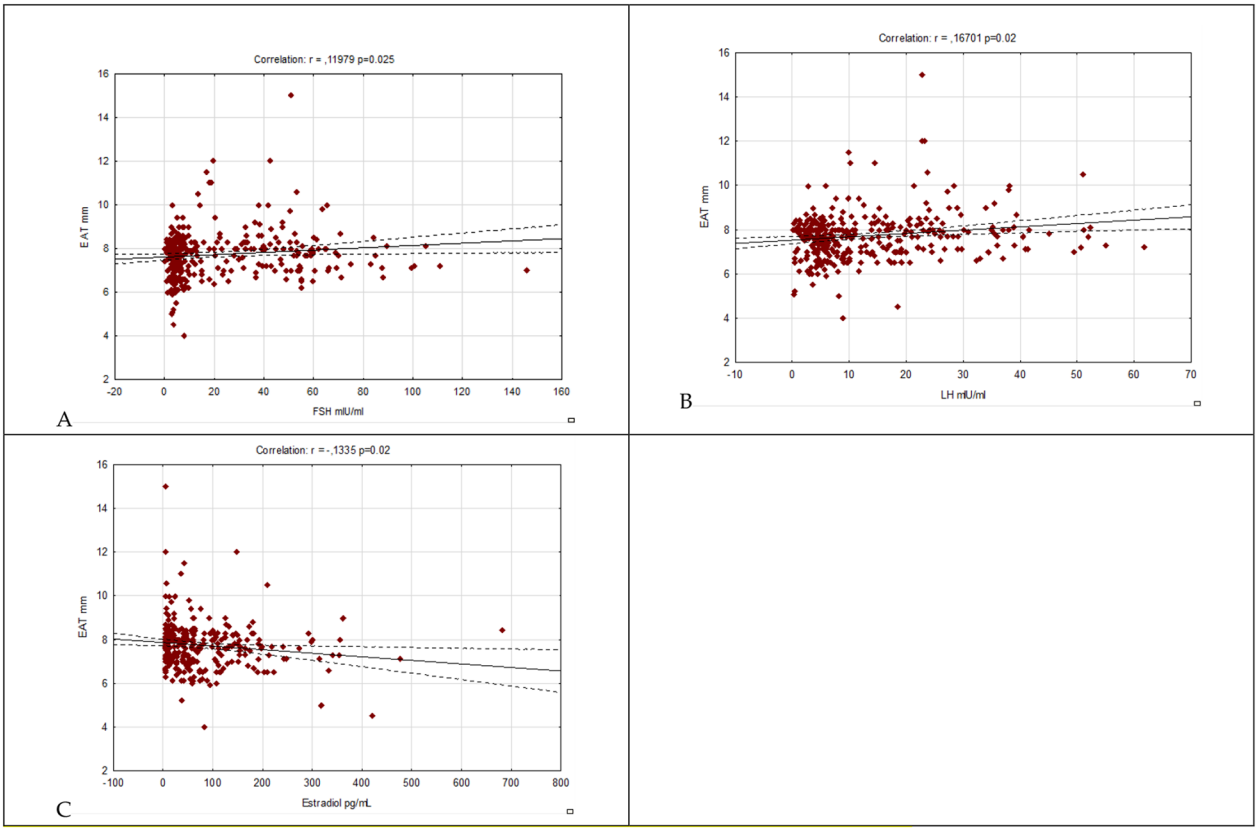

Fig. 1 Correlation between FSH (**A**), LH (**B**), estradiol (**C**) and EAT adjusted by age. *FSH* Follicle-stimulating hormone, *LH* Luteinizing Hormone, *EAT* epicardial adipose tissue

among groups. This aspect is particularly interesting, since it points out that not only BMI, whose power has been recently questioned, but also waist circumference, which is at the moment proposed as a better marker of visceral obesity, are not ideal for identifying menopausal patients with higher visceral fat deposition, and therefore is not ideal to predict their cardiovascular risk. Further confirmation is given by DXA scans, which show an increased percentage of trunk fat in menopausal women, suggesting a reshaping of the fat distribution, probably related to a greater fat deposition in truncal ectopic sites, such as the epicardial site. Conversely, indirect indices of hepatic steatosis did not provide noteworthy differences between the two groups, that were both affected. All the indices of adiposity (EAT, WHR and trunk fat percentage) do correlate with hepatic steatosis measured with FLI. Moreover, regression analysis shows that EAT predicts also bone mineral density. In menopausal patients, the effect of weight excess and ageing may be additive. To strengthen this hypothesis, we should remember that epicardial fat tissue is subject to ageing, as any tissue, and this determines a change in its secretory functions of adipokines, in its transcriptome and its brown fat properties [37]. The identification of a reliable clinical parameter to identify ectopic fat deposition is important, to treat the affected patients promptly and properly. In fact, many of these metabolic alterations and ectopic fat depots- epicardial adipose tissue included- are modifiable cardiovascular risk factors. The alterations associated with weight excess may be at least partially reversed by weight loss, dietary habits and physical activity [38]. Diet, in fact, plays a role not only in the metabolic health of the individual, but also influences many other physiological functions, such as respiratory function, response to infectious diseases, fertility and sleep [39–45]. Since menopausal age is particularly at risk for developing metabolic, sleep and cardiovascular issues, easy measurement of ectopic fat deposition in the clinical setting may be particularly useful for identifying and treating menopausal women with weight excess and ectopic fat deposition, who are already at a higher risk for cardiovascular complications for the coexistence of both excess weight and ageing. To the best of our knowledge, this is the first study comparing the two populations of women in their pre and postmenopausal status, with a similar weight excess according to the gold standard measures, to further assess their

Table 4 Multiple Regression analysis for FLI (A), BMD (B) and TBS (C) as dependent variables

(A)	**R = 0.731 R^2 = 0.534 Adjusted R^2 = 0.530 F(4.476) = 136.50 p**					
	b*	**Std.Err. of b***	**B**	**Std.Err. of b**	**t(476)**	***p***
Intercept			−106.603	9.320	−11.437	< 0.01
Age (years)	−0.027	0.032	−0.055	0.066	−0.823	ns
Trunk fat (%)	0.495	0.032	1.810	0.117	15.451	< 0.01
WHR	0.151	0.034	41.136	9.264	4.440	< 0.01
EAT (mm)	0.469	0.034	9.911	0.727	13.618	< 0.01
(B)	**R = 0.124 R^2 = 0.015 Adjusted R^2 = 0.008 F(4.74) = 2.258 p**					
	b*	**Std.Err. of b***	**B**	**Std.Err. of b**	**t(574)**	***p***
Intercept			−33.104	23.438	−1.412	ns
Age (years)	0.034	0.043	0.137	0.178	0.774	ns
Trunk fat (%)	0.035	0.043	0.245	0.299	0.819	ns
WHR	−0.035	0.045	−18.010	22.887	−0.786	ns
EAT (mm)	0.113	0.045	4.868	1.943	2.504	< 0.05
(C)	**R = 0.552 R^2 = 0.304 Adjusted R^2 = 0.291 F(4.208) = 22.789 p**					
	b*	**Std.Err. of b***	**B**	**Std.Err. of b**	**t(208)**	***p***
Intercept			1.969	0.084	23.382	< 0.01
Age (years)	−0.282	0.060	−0.002	0.001	−4.682	< 0.01
Trunk fat (%)	−0.177	0.062	−0.004	0.001	−2.866	< 0.05
WHR	−0.167	0.065	−0.218	0.085	−2.550	< 0.05
EAT (mm)	−0.201	0.064	−0.027	0.009	−3.138	< 0.01

FLI Fatty Liver Index, *BMD* Bone Mineral Density (g/cm^2), *TBS* Trabecular Bone Score, *WHR* waist-to-hip ratio, *EAT* epicardial adipose tissue, *b** unstandardized beta

metabolic profile, beyond BMI and waist circumference. Among the limitations of our study, we may include the cross-sectional design of the study, as a longitudinal design would have permitted us to revaluate the patients in their menopausal status. As future directions, new studies on menopausal patients should be performed, in order to better focus on the study and the prevention of the cardiovascular events and metabolic comorbidities in this sex and age-specific period of life, which has its own peculiar cardiometabolic profile and risks, Moreover, the identification of other even more accurate and specific tools to identify markers of metabolic derangements in the clinical practice is warranted for the next future.

Conclusions

The results obtained are of interest because highlight the worsening of the metabolic profile and the increased ectopic fat deposition, especially at the epicardium level, in the post-menopausal group, and these features are strictly related to a higher cardiovascular risk. Moreover, not only BMI, but also waist circumference, which is increasingly proposed to identify metabolic disruption and obesity, are not accurate tools to assess visceral fat deposition. In fact, post-menopausal patients had increased epicardial fat and a worse metabolic profile respect to the pre-menopausal patients, despite similar BMI and waist circumference. In clinical practice, the routine use of DXA, CT scans and MRI is not feasible. The epicardial adipose tissue thickness, conversely, represents a raffinate and useful parameter of ectopic fat deposition, and its measurement through ultrasound makes it feasible and repeatable over time. Therefore, it can be easily used in clinical practice, to identify the patients in whom excess weight is also accompanied by increased ectopic fat deposition. In the future, additional studies aimed at identifying reliable cut-offs for increased cardiovascular risk within this specific population who is already at a higher cardiovascular risk should be run.

Abbreviations

BMI	Body mass index
EFT	Epicardial fat thickness
EAT	Epicardial adipose tissue
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
WHP	Waist-to-hip ratio
HIS	Hepatic steatosis index
NAFLD –LFS	NAFLD liver fat score
FLI	Fatty Liver Index
BMD	Bone mineral density
TBS	Trabecular Bone Score
FM	Fat Mass
FFM	Fat-Free Mass
IMT	Intima media thickness

SD	Standard deviation
IFG	Impaired fasting glucose

Supplementary Information

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Supplementary material 1.

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Author contributions
Conceptualization, E.G., G.I. and C.L.; data collection, G.B., C.L.; statistical analysis, data curation, formal analysis, methodology and validation, C.L.; writing—original draft preparation, E.G.; writing—review and editing, L.G., G.I., C.L. All authors have read and agreed to the published version of the manuscript. C.L. had access to all data and statistical analysis and guarantees for their integrity and accuracy.

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Availability of data and materials
Data are available from the corresponding author upon a reasonable request.

Declarations

Ethics approval and consent to participate
Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Polyclinic Umberto 1—Rome (protocol code CE5475, date of approval 24th October 2019, and protocol n. 0513/2024, date of approval 6th June 2024).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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