Association of adiposity evaluated by anthropometric, BIA and DXA measures with cardiometabolic risk factors in non-obese postmenopausal women: the CoLaus/OsteoLaus cohort

Adiposity measurement tools and cadiometabolic risk factors in non-obese postmenopausal women

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Abstract

Background: After menopause, body composition changes with body fat accumulation, and an increase in cardiometabolic risk factors. Total fat mass, regional fat mass and visceral adipose tissue may be estimated with anthropometric measures, Bioelectrical Impedance Analysis (BIA) and Dual-energy X-ray Absorptiometry (DXA). The aim of our study was to assess which measurement correlated best with cardiometabolic risk factors in healthy non-obese postmenopausal women.

Methods: The CoLaus/OsteoLaus cohort included 1'500 postmenopausal women. We analyzed correlations between: 1) measurements of body composition assessed by anthropometric measures, Bioelectrical Impedance Analysis and Dual-energy X-ray and 2) these measurements and different cardiometabolic risk factors.

Results: In the 803 included participants (mean age 62.0 ± 7.1 year, mean body mass index 25.6 kg/m2± 4.4), correlations between total fat mass measured by BIA and total fat mass, android fat, gynoid fat or visceral adipose tissue measured by DXA are very close (from r=0.531, 99% CI 0.443-0.610 to r=0.704, 99% CI 0.640-0.758). Body mass index and waist circumference have a higher correlation with visceral adipose tissue (r=0.815, 99% CI 0.772-0.851 and r=0.823, 99% CI 0.782-0.858, respectively) than BIA (r=0.672, 99% CI 0.603-0.731). Among the anthropometric measurement and the measurements derived from DXA and BIA, visceral adipose tissue is the parameter most strongly associated with cardiometabolic risk factors. Visceral adipose tissue better explains the variation of most of the cardiometabolic risk factors than age.

Conclusion: BIA seems not to be a good tool to assess visceral adipose tissue. At the population level, waist circumference and body mass index seem to be good tools to estimate visceral adipose tissue. Visceral adipose tissue measured by DXA is the parameter most correlated with cardiometabolic risk factors, and could become a component of cardiometabolic marker on its own.

Key Words

Postmenopausal Women; Visceral Adipose Tissue; Cardiometabolic Risk Factors; Waist Circumference; Bioelectrical Impedance Analysis; Dual-Energy X-ray Absorptiometry

Introduction

Between 2000 and 2050, the proportion of the world's population over 60 years will double from about 11% to 22% according to the WHO[1]. Cardiovascular disease (CVD), diabetes and obesity are major public health conditions affecting this population, and the risk of cardiovascular events is at least double in postmenopausal women compared with premenopausal women [2]. The cardiometabolic risk factors (CMRF) associated with these conditions are easy to identify under certain conditions. However, it is difficult to identify them without a broad assessment in healthy, non-obese postmenopausal women. In such a population, it would be useful to screen individuals at risk of CVD with a simple anthropometric or body composition (BC) measurement.

With age and hormonal changes, total fat mass (TFM) tends to increase at the detriment of lean mass and accumulate preferentially in the abdomen [3]. TFM and more particularly the android fat (AF), is associated with type 2 diabetes and CVD [4]. AF has two components: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). VAT has the same characteristics as an endocrine organ by secreting leptin, adiponectin, and greater quantities of proinflammatory cytokines than does SAT. VAT is thus more strongly associated with CVD than SAT [5-9]. In postmenopausal women, FM has a higher proportion of VAT than SAT [3, 9, 10]. The association between AF or gynoid fat (GF) and CVD differs between genders [11].

Several measurement tools are available in clinical practice to estimate TFM and regional FM. Among anthropometric measurements (AM), body mass index (BMI) is used as an estimation of TFM, but this has been questioned [12]. Waist circumference (WC) or waist-to-hip ratio (WHR) are good predictors of CVD and are widely used [13], even though they are subject to considerable intra- and inter-observer variability [14, 15]. Recent data suggest that TFM evaluated by bioelectrical impedance analysis (BIA) is a better predictor of CVD risk than BMI or WC [16]. BIA is easy in use, non-invasive, inexpensive and reproducible, but the prediction equations are frequently unknown and manufacturer specific [3, 17, 18]. However, neither the AM, nor BIA allow to distinguish SAT from VAT. Higher cost, radiation exposure, and logistical complexity limit the use of Magnetic Resonance Imaging (MRI) or Computed Tomography (CT). In recent years, Dual-energy X-ray Absorptiometry (DXA) has become the reference tool for measuring BC, AF and GF distribution, and for splitting AF in VAT and SAT [19-23]. DXA is as accurate as MRI or CT to measure BC, and VAT assessed by multiple DXA devices has been validated against CT/MRI across a wide range of age and BMI values, including the elderly [14, 19, 23-27]. DXA is easy to use, requires no preparation, is fast with very good accuracy and reproducibility, and radiation exposure is low, but it is not transportable and requires a radiology technician [3, 19-23]. A direct comparison between AM and those derived from BIA and DXA is therefore necessary to determine which ones are more associated with CMRF.

The relationships between some CMRF and different BC measurements has been studied previously [28-32]. VAT has been proposed as a factor associated with some CMRF, particularly in obese women [30, 31, 33, 34]. The first aim of our study was to measure in a cohort of non-obese postmenopausal women (the CoLaus/OsteoLaus cohort) the correlations: 1) between AM, FM measurements from BIA and those derived

from DXA; and 2) between CMRF and anthropometric, BIA, or DXA measurements. For the second aim, we evaluated the variability of different CMRF explained by the measurement most correlated with CMRF.

Materials and methods

Participants

The OsteoLaus Study is a substudy of the CoLaus Study (www.colaus-psycolaus.ch), a prospective population-based cohort of women and men living in the city of Lausanne, Switzerland. The baseline and the follow-up methodologies of the CoLaus study have been reported previously [35]. The goal of OsteoLaus is to obtain more precise fracture risk models and to evaluate the link between CVD and osteoporosis. Detailed information on the OsteoLaus study have been reported previously [36].

At first CoLaus visit between September 2009 and September 2012, all participants benefited of venous blood samples, and anthropometric and BIA measures. During the first CoLaus visit, all women aged between 50 and 80 years participating in the CoLaus study were invited to participate in OsteoLaus. Of the initial 1704 women invited, 1500 (88%) accepted, and 1475 were included. At the inclusion of OsteoLaus, each participant had: 1) a questionnaire on clinical risk factors for fracture / osteoporosis; 2) a DXA to evaluate bone mineral density and bone texture. BC using DXA was introduced during the study, and included the last 1086 women (74%). The software for assessing VAT was acquired in summer 2016. The BC examinations carried out between 2010 and 2012 were re-analysed between July and September 2016. For technical reasons, 87 examinations could not be reanalyzed, rendering analysis of the aforementioned parameters impossible in these participants.

All participants with one interpretable BIA measurement and a complete BC measurement with DXA were included.

Anthropometric data and blood pressure

Anthropometric data were collected during the first follow-up of CoLaus and were described previously [37]. Briefly, body weight and height were measured with participants standing without shoes in light indoor clothing. Body weight was measured in kilograms to the nearest 0.1 kg using a Seca™ scale (Seca, Hamburg, Germany), which was calibrated regularly. Height was measured to the nearest 5 mm using a Seca™ height gauge (Seca, Hamburg, Germany). BMI was defined as weight (kg) divided by height (m) squared. WC was measured twice with a no stretchable tape over the unclothed abdomen at the midpoint between the lowest rib and the iliac crest. Hip circumference (HC) was measured twice at the greater trochanters. For waist and hip, the mean of the two measurements was used and WHR was calculated.

Blood pressure (BP) was measured thrice using an automated sphygmomanometer (Omron HEM907, Matsusaka, Japan) and the average of the last two measurements was used. Hypertension was defined as

a systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg during the visit and/or presence of anti-hypertensive drug treatment.

Biological data collection and medication

Venous blood samples were drawn after an overnight fast. All biological assays were performed at the clinical laboratory of the Lausanne University Hospital. All measurements were performed on plasma samples using enzymatic colorimetric assays (Roche Modular P chemistry analyzer, Roche Diagnostics, Basel, Switzerland). Glucose was assessed by glucose dehydrogenase with a maximum interassay coefficient of variation (CV) of 2.1% and a maximum intra-assay CV of 1.0%. Insulin was assessed by a solid-phase, 2-site chemiluminescent immunometric assay (Diagnostic Products Corporation) with a maximum intra-assay CV of 13.7%. The glucose to insulin ratio was used as a marker of insulin sensitivity.

HDL-C was assessed by cholesterol oxidase-phenol-aminophenazone + polyethylene glycol + cyclodextrin with a maximum interassay CV of 3.6% and a maximum intra-assay CV of 0.9%. TG were assessed by GPO-PAP with a maximum inter-assay CV of 2.9% and a maximum intra-assay CV of 1.5%. LDL-C was calculated using the Friedewald formula if TG < 4.6 mmol/l.

Adiponectin was assessed by ELISA (R&D Systems, Inc, Minneapolis, USA) with a maximum inter-assay CV of 8.3% and a maximum intra-assay CV of 8.3%. Leptin was assessed by ELISA (American Laboratory Products Company, Windham, USA) with a maximum inter-assay CV of 12.8% and a maximum intra-assay CV of 5.8%.

Diabetes mellitus was defined as fasting blood glucose ≥7.0 mmol/l and/or oral antidiabetic or insulin treatment. Medication (antihypertensive, lipid-lowering and antidiabetics drugs) was assessed by questionnaire and further confirmed during an interview where subjects were asked to provide the names of all (non)prescribed drugs. Each medication was coded according to the WHO-ATC drug classification.

Bioelectrical impedance analysis measurements

BIA analyses were performed as described by Bastardot et al.[37]. BIA was assessed using the Bodystat® 1500 body mass analyser, a single-frequency analyser, (Bodystat Ltd, Isle of Man, England) in the supine position after a 5-min rest. All metallic adornments were removed, and measurement was performed after a 5-min rest in the lying position. The electrodes were positioned on the right side of the body according to the manufacturer's instructions. Results were obtained as percentage of body fat (%BF); body FM was calculated as weight × %BF and expressed in kilogram.

DXA measurements

All participants underwent a BC measurement by DXA scan on a Discovery DXA System (Hologic, Inc., Marlborough, MA, USA). All BC measurements were performed in accordance with the guidelines of the International Society for Clinical Densitometry [38]. Details of the procedure have been reported previously

[39]. Briefly, participants were placed in a supine position and the regions of interest (ROIs) were defined by the analytical program and included total body, trunk, head, pelvis, upper limbs, lower limbs, and android and gynoid regions. The lower boundary of the android region was defined at the pelvis cut line and the upper boundary above the pelvis cutline by 20% of the distance between the pelvis and chin. The upper boundary of the gynoid ROI was defined below the pelvis cut line by 1.5 times the height of the android space, and gynoid ROI height was equal to 2 times the android ROI height. For each region, DXA scanned weight of total mass, FM, and lean mass. VAT was measured as the fat tissue located deep in the abdomen around the internal organs and expressed in grams. AF and GF, expressed in % of total mass and VAT were analysed in a second step from the initial BC images. TFM was expressed in grams and % of total mass.

Contribution of VAT in the variability of CMRF

We calculated first the variability of the different CMRF explain by age and treatments (antihypertensive, antidiabetic and lipid-lowering drugs). We then added into the model, among the AM and the measurements derived from BIA and DXA, the measurement most strongly associated with CMRF. As VAT was the most strongly associated with CMRF, VAT was added in the model.

Ethical statement

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03). The approval was renewed for the first (reference 33/09) follow-up. The CoLaus and OsteoLaus (reference 215/09) studies were performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

Statistical analysis

Statistical analysis were conducted using Stata version 15.1 (Stata Corp, College Station, TX, USA). Due to their skewed distribution, triglycerides, leptin and adiponectin were log-transformed prior to analysis. Descriptive results were presented as number of participants (percentage) for categorical variables and as average±standard deviation for continuous variables. Comparison between excluded and included participants was performed using chi-square for categorical variables and student's t-test for continuous variables.

Associations between anthropometric, BIA and DXA measurements and between CMRF were assessed using Spearman's nonparametric correlations. Results were expressed as coefficients and their 99.9% confidence intervals (CI). Selection of the obesity marker most related with CMRF was based on the 99.9% CI of the Spearman correlation coefficient and on the results of a stepwise forward regression analysis

including all obesity markers standardized to have a mean of zero and a standard deviation of 1, with a p-value for entry of 0.05.

Multivariable associations were assessed using linear regression adjusting for age and antihypertensive, lipid-lowering or antidiabetic therapy if needed; results were expressed as beta coefficients. Beta coefficients are the regression coefficients obtained by standardizing all variables to have an average of 0 and a standard deviation of 1, and can be interpreted as multivariable-adjusted correlation coefficients. The variability of the CMRF explained by VAT was assessed by estimating the increment in the R-square value of a linear regression model using the CMRF as a continuous dependent variable and age (continuous), antihypertensive (dichotomous, 0=no, 1=yes), lipid-lowering (dichotomous, 0=no, 1=yes) or antidiabetic therapy (dichotomous, 0=no, 1=yes) (if needed) and VAT (continuous) as independent variables, relative to the same model omitting VAT. Adequacy of the linear regression was assessed by computing and plotting the residuals of the model including the confounders and the VAT. All distributions were considered as Gaussian.

~~Due to the number of tests performed, statistical significance was considered for a two-sided test with p<0.001.~~ For each CMRF, there were 10 obesity markers tested; hence, according to Bonferroni correction, a threshold of 0.05/10=0.005 for a two-sided test should be considered for statistical significance. This threshold was further reduced to <0.001 to decrease the type 1 error in our analyses.

Results

Characteristics of participants

Of the initial 1475 women, 672 (45.6%) were excluded. The reasons for exclusion are provided in Figure 1 and the characteristics of the included and excluded participants are provided in Table 1. Excluded participants were older, had higher BMI, presented more frequently with hypertension and diabetes, and took antihypertensive and lipid-lowering drugs more frequently than included participants.

Figure 1: Flow chart of the study

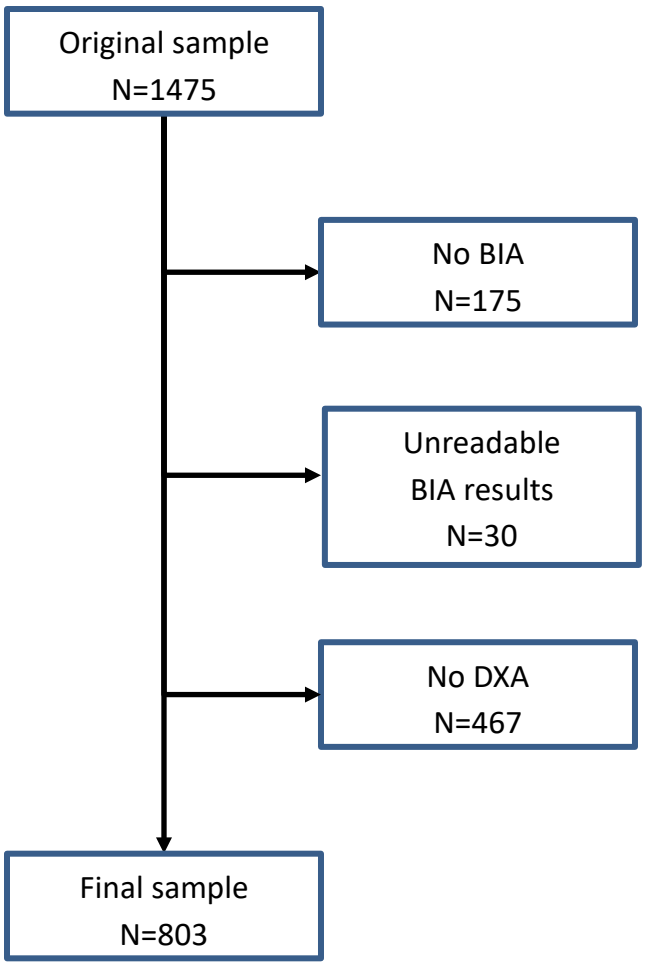

Table 1: comparison between included and excluded participants

	Included	Excluded	p-value
N	803	672	
Age (years)	62.0 ± 7.1	67.5 ± 6.9	<0.001
BMI (kg/m^2)	25.6 ± 4.4	26.3 ± 4.7	0.002
Hypertension (%)	292 (36.4)	341 (51.4)	<0.001
Antihypertensive drugs (%)	204 (25.4)	235 (35.4)	<0.001
Diabetes (%)	48 (6.0)	61 (9.2)	0.019
Antidiabetic drugs (%)	23 (2.9)	27 (4.1)	0.207
Hypolipidemic drugs (%)	137 (17.1)	155 (23.3)	0.003

BMI: body mass index. Results are expressed as number of participants (column percentage) or as average ± standard deviation. Between-group comparisons are done using chi-square for categorical variables and student's t-test for continuous variables.

Correlation between BIA and DXA

The correlations between TFM measured by BIA and total and regional FM measured by DXA range from r=0.531 for GF to r=0.704 for TFM estimated in % (Table 2). The correlations between DXA TFM in % and in grams, and regional FM measures were always higher (from r=0.767 for VAT to r=0.881 for AF and TFM in %) than those obtained with TFM measured by BIA. GF has the highest correlation with TFM estimated in % by DXA (r=0.843, 99% CI 0.806-0.874). The lower limit of the confidence interval is higher than the upper limit of the confidence interval of the other correlations. VAT has the highest correlation with AF (r=0.892, 99% CI 0.866-0.914). The lower limit of the confidence interval is higher than the upper limit of the confidence interval of the other correlations.

Table 2: Correlations between anthropometric measurements, total fat measured by BIA and DXA and regional fat measurements measured by DXA

	BMI	Waist (cm)	Hip (cm)	Waist/hip ratio	Total FM BIA (kg)	Total FM DXA (%)	Total FM DXA (gr)	Android fat (%)	Gynoid fat (%)
Waist (cm)	0.809 (0.764; 0.845)								
Hip (cm)	0.835 (0.796; 0.867)	0.860 (0.826; 0.887)							
Waist/hip ratio	0.353 (0.247; 0.451)	0.671 (0.602; 0.730)	0.240 (0.128; 0.346)						
Total FM BIA (kg)	0.709 (0.647; 0.763)	0.645 (0.572; 0.708)	0.646 (0.573; 0.709)	0.305 (0.196; 0.406)					
Total FM DXA (%)	0.816 (0.773; 0.851)	0.699 (0.635; 0.754)	0.738 (0.680; 0.786)	0.287 (0.177; 0.390)	0.704 (0.640; 0.758)				
Total FM DXA (gr)	0.913 (0.891; 0.930)	0.817 (0.774; 0.852)	0.860 (0.826; 0.887)	0.340 (0.233; 0.439)	0.664 (0.594; 0.725)	0.913 (0.891; 0.930)			
Android fat (%)	0.804 (0.759; 0.841)	0.752 (0.696; 0.798)	0.737 (0.679; 0.786)	0.381 (0.277; 0.476)	0.676 (0.608; 0.734)	0.881 (0.852; 0.905)	0.858 (0.824; 0.886)		
Gynoid fat (%)	0.588 (0.507; 0.659)	0.434 (0.335; 0.524)	0.527 (0.438; 0.606)	0.083* (-0.033;0.197)	0.531 (0.443; 0.610)	0.843 (0.806; 0.874)	0.709 (0.646; 0.762)	0.633 (0.558; 0.697)	
VAT (gr)	0.815 (0.772; 0.851)	0.823 (0.782; 0.858)	0.772 (0.721; 0.815)	0.467 (0.371; 0.553)	0.672 (0.603; 0.731)	0.767 (0.714; 0.810)	0.827 (0.786; 0.860)	0.892 (0.866; 0.914)	0.471 (0.376; 0.556)

BIA: bioelectrical impedance analysis; BMI: body mass index; cm: centimetre; DXA: dual-energy X-ray absorptiometry FM: fat mass; gr: gram; kg: kilogram; VAT: visceral adipose tissue.

Results are expressed as Spearman rank correlation coefficient and their 99% confidence intervals.

P-value was <0.001 for all results, excepted * not significant

Correlation between anthropometric measurements and those from BIA or DXA

The correlations between AM and TFM evaluated by BIA or DXA, and regional FM measurements are summarized in Table 2. They are all significant (p<0.001), except the one between WHR and GF. BMI is positively correlated with all TFM measures, with highest correlation with DXA values in grams (r=0.913, 99% CI 0.891-0.930). The lower limit of the confidence interval is higher than the upper limit of the confidence interval of the other correlations. WC has the best correlation with TFM estimated in grams by DXA and with VAT (r>0.800). The lower limit of the confidence interval is higher than the upper limit of the

confidence interval of the correlations with BIA. VAT is positively correlated with BMI and WC (r>0.800). The lower limit of the confidence interval is always higher than the upper limit of the confidence interval of the correlations with BIA.

Correlation between cardiometabolic risk factors and anthropometric, BIA, or DXA measurements

Systolic and diastolic BP are positively correlated with all anthropometric, BIA, and DXA measurements, with the exception of systolic BP and GF (Table 3). There is no correlation between total cholesterol and the different measurements. HDL-C is inversely correlated with all measurements, and TG positively correlated with all measures except GF. LDL is either not or poorly correlated (maximal r=0.166) with any measure of body composition. Considering the different lipid markers, the highest correlation is obtained with VAT and the lowest with GF. Glucose and insulin are positively correlated with all anthropometric, BIA, and DXA measurements, the highest correlation with VAT and the lowest with GF. Adiponectin is inversely correlated with most of the measurements, but has no correlation with BIA, TFM estimated in % by DXA, and GF. Leptin is significantly correlated with all measurements; with highest correlations obtained with TFM estimated by DXA in grams or %.

Among AM, correlations with CMRF were higher and very close for BMI, WC or HC than for WHR. Among AM and FM measurements by BIA or DXA, VAT has the highest correlations with CMRF for most, excepted systolic blood pressure and leptin. The results of the stepwise analyses are summarized in **supplementary table 1**. In 9 of the 12 analyses, VAT was selected first.

Table 3: Correlations between cardiometabolic risk factors and anthropometric, BIA and DXA measurements.

	BMI	Waist (cm)	Hip (cm)	Waist/hip ratio	Total FM (BIA)
Blood pressure					
Systolic (mmHg)	0.230 (0.118; 0.337)	0.230 (0.117; 0.337)	0.220 (0.107; 0.328)	0.142 (0.026; 0.254)	0.315 (0.206; 0.416)
Diastolic (mmHg)	0.298 (0.189; 0.400)	0.266 (0.155; 0.370)	0.269 (0.158; 0.373)	0.136 (0.020; 0.248)	0.264 (0.153; 0.369)
Lipid markers					
Total cholesterol (mmol/L)	-0.014* (-0.130; 0.102)	0.036* (-0.080; 0.151)	0.023* (-0.093; 0.138)	0.030* (-0.087; 0.145)	0.080* (-0.036; 0.194)
HDL cholesterol (mmol/L)	-0.410 (-0.502; -0.309)	-0.384 (-0.478; -0.280)	-0.370 (-0.466; -0.266)	-0.204 (-0.312; -0.090)	-0.299 (-0.401; -0.190)
LDL cholesterol (mmol/L)	0.085* (-0.032; 0.199)	0.116 (0.000; 0.229)	0.107* (-0.010; 0.220)	0.064* (-0.053; 0.179)	0.139 (0.023; 0.251)
Total /HDL cholesterol ratio	0.356 (0.251; 0.454)	0.364 (0.259; 0.461)	0.348 (0.242; 0.446)	0.193 (0.079; 0.303)	0.305 (0.196; 0.407)
Triglycerides (mmol/L)	0.344 (0.238; 0.443)	0.389 (0.286; 0.483)	0.360 (0.255; 0.457)	0.220 (0.107; 0.328)	0.326 (0.218; 0.425)
Metabolic markers					
Glucose (mmol/L)	0.348 (0.242; 0.446)	0.368 (0.263; 0.464)	0.304 (0.195; 0.406)	0.293 (0.184; 0.396)	0.359 (0.254; 0.456)
Insulin (mIU/L)	0.559 (0.474; 0.634)	0.565 (0.481; 0.640)	0.529 (0.439; 0.607)	0.330 (0.222; 0.429)	0.511 (0.420; 0.592)
Adiponectin (microgr/L)	-0.191 (-0.305; -0.073)	-0.199 (-0.312; -0.081)	-0.163 (-0.278; -0.043)	-0.132 (-0.248; -0.011)	-0.106 (-0.223; 0.015)
Leptin (microgr/L)	0.688 (0.619; 0.746)	0.652 (0.577; 0.716)	0.672 (0.600; 0.733)	0.296 (0.182; 0.402)	0.569 (0.482; 0.646)

Table 3 (continued): Correlations between cardiometabolic risk factors and anthropometric, BIA and DXA measurements.

	Total FM DXA (%)	Total FM DXA (gr)	Android fat (%)	Gynoid fat (%)	VAT (gr)
Blood pressure					
Systolic (mmHg)	0.206 (0.092; 0.314)	0.204 (0.090; 0.312)	0.219 (0.106; 0.326)	0.110* (-0.006; 0.223)	0.290 (0.180; 0.393)
Diastolic (mmHg)	0.277 (0.167; 0.381)	0.298 (0.189; 0.400)	0.292 (0.182; 0.394)	0.182 (0.068; 0.292)	0.315 (0.207; 0.416)
Lipid markers					
Total cholesterol (mmol/L)	0.050* (-0.066; 0.165)	0.020* (-0.096; 0.136)	0.076* (-0.041; 0.190)	0.050* (-0.066; 0.165)	0.061* (-0.055; 0.176)
HDL cholesterol (mmol/L)	-0.309 (-0.410; -0.200)	-0.366 (-0.463; -0.261)	-0.363 (-0.460; -0.258)	-0.123 (-0.236; -0.008)	-0.465 (-0.552; -0.369)
LDL cholesterol (mmol/L)	0.134 (0.018; 0.247)	0.116 (0.000; 0.229)	0.166 (0.051; 0.277)	0.099* (-0.017; 0.213)	0.166 (0.050; 0.276)
Total /HDL cholesterol ratio	0.312 (0.203; 0.413)	0.344 (0.238; 0.443)	0.380 (0.276; 0.475)	0.141 (0.025; 0.252)	0.459 (0.362; 0.546)
Triglycerides (mmol/L)	0.295 (0.186; 0.398)	0.328 (0.221; 0.428)	0.368 (0.263; 0.464)	0.110* (-0.006; 0.223)	0.453 (0.356; 0.541)
Metabolic markers					
Glucose (mmol/L)	0.288 (0.178; 0.391)	0.325 (0.217; 0.425)	0.341 (0.234; 0.440)	0.130 (0.015; 0.243)	0.397 (0.295; 0.491)
Insulin (mIU/L)	0.509 (0.417; 0.590)	0.536 (0.447; 0.614)	0.565 (0.481; 0.639)	0.295 (0.186; 0.398)	0.601 (0.522; 0.671)
Adiponectin (microgr/L)	-0.109* (-0.226; 0.012)	-0.166 (-0.281; -0.046)	-0.185 (-0.299; -0.066)	0.046* (-0.075; 0.166)	-0.229 (-0.341; -0.112)
Leptin (microgr/L)	0.733 (0.672; 0.785)	0.743 (0.684; 0.793)	0.702 (0.635; 0.758)	0.576 (0.490; 0.652)	0.681 (0.610; 0.740)

BIA: bioelectrical impedance analysis; BMI: body mass index; cm: centimetre; DXA: dual-energy X-ray absorptiometry; FM: fat mass; gr: gram; VAT: visceral adipose tissue.

Results are expressed as Spearman rank correlation coefficient and their 99% confidence intervals.

P value was <0.001 for all results, except those marked with * (not significant).

Variability of blood pressure and blood tests explained by visceral adipose tissue

We first assessed the variability of BP and blood tests explained by age and treatment (for BP, diabetes and lipids), and then their variability by adding VAT (Table 4). Age and treatments explain a large variation of systolic BP, total cholesterol, LDL-C and glucose (7.0 to 25.2%). VAT explains 5% of the variability of the diastolic BP. Among lipid markers, VAT explains nearly 15% of the variability of HDL-C and TG. Among metabolic markers, VAT explains 25.3% of the variability of insulin and 37.5% of the variability of leptin. For all these, VAT explains most of the variability as compared to age and treatment (more than double).

Table 4: Percentage of variability of blood pressure and blood tests explained by visceral adipose tissue

	P-value	Beta coefficient for VAT	R^2 without VAT	R^2 with VAT	% explained
Blood pressure					
Systolic (mm Hg)	<0.001	0.158	17.3	19.4	2.0
Diastolic (mm Hg)	<0.001	0.247	4.9	9.9	5.1
Lipid markers					
Total cholesterol (mmol/L)	0.026	0.079	8.8	9.2	0.4
HDL cholesterol (mmol/L)	<0.001	-0.427	3.8	20.3	16.5
LDL cholesterol (mmol/L)	<0.001	0.193	7.0	10.2	3.3
Total /HDL cholesterol ratio	<0.001	0.426	1.2	17.6	16.4
Triglycerides (mmol/L)	<0.001	0.402	6.5	21.1	14.6
Metabolic markers					
Glucose (mmol/L)	<0.001	0.280	25.2	32.3	7.2
Insulin (mg/L)	<0.001	0.524	8.1	33.3	25.3
Adiponectin (microgr/L)	<0.001	-0.243	0.1	5.6	5.5
Leptin (microgr/L)	<0.001	0.626	1.1	38.7	37.5

R^2 :The variability of the CMRF was assessed by estimating the increment in the R-square value of a linear regression model using the CMRF as dependent variable and age, antihypertensive, lipid-lowering or antidiabetic therapy (if needed) and VAT as independent variables, relative to the same model omitting VAT. VAT: visceral adipose tissue.

Discussion

Our results indicate that in healthy non-obese postmenopausal women, the correlations between TFM measured by BIA and TFM, AF, GF or VAT measured by DXA are very close, and that BMI and WC are better correlated with VAT than with BIA. Among the AM and the measurements derived from the DXA and BIA, VAT is the parameter most strongly associated with CMRF.

Correlation between BIA and DXA

We found positive significant relationships between %TFM measured by single frequency-BIA and Hologic DXA. Several studies compared BIA with DXA measurements in different populations, but our study is one of the few comparing DXA and BIA in postmenopausal women. There are many BIA devices on the market (single-frequency and multi-frequency devices, hand-to-hand portable devices, hand-to-foot devices) that each have their own equations to estimate BC [22]. The same is true for the DXA measurement, with different manufacturers (Hologic, Lunar, Norland, Osteosys, DMS) each with their own formulas and equations [40]. It is therefore not possible to compare our results with those of other studies. Furthermore, only few studies compared BC estimate with DXA and BIA in elderly and particularly in healthy non-obese postmenopausal women [41-43]. This studies found good correlation for TFM between BIA and DXA. In our study, the degrees

of correlation between TFM measured by BIA and TFM, AF, GF or VAT measured by DXA were very close. It is therefore not possible to conclude which part of the regional fat influences more the TFM measured by BIA. These results suggest that BIA seems not to be a good tool to assess VAT in postmenopausal women but remains good to assess TFM.

Correlation between anthropometric measurements and those from BIA or DXA

Among AM, BMI has the highest correlation with TFM estimated in grams, and WC with TFM estimated in grams and with VAT, all measured by DXA. WHR has always a lower correlation with TFM and VAT than BMI and WC. BMI is used to assess overall obesity, but it is not clear if BMI alone is a good reflect of CVD. WC seems to be a better indicator than BMI for CMRF related to CVD in postmenopausal women [29]. WC has been approved for assessing central obesity but cannot differentiate SAT from VAT. It is not established if WC can be used in postmenopausal women [4, 27].

Our results, that among AM, WC and BMI have higher correlations with TFM and VAT and with CMRF, are consistent with those observed in other studies. In a cohort of 146 elderly white women (age 74±4 years), BMI was strongly related to TFM and only moderately related to VAT (measured by CT) [44]. In a 150 non-obese healthy Caucasian postmenopausal cohort (age 54±7 years), BMI was highly correlated with TFM estimated in % by DXA, whereas all DXA-derived indices of central fat distribution (chest, abdomen, pelvis) were strongly correlated with WC [14]. Another study showed that WC had a higher correlation with trunk FM, followed by BMI in 80 Brazilian postmenopausal women (age 55.6±7.5 years). WHR was moderately correlated with trunk FM [45]. In a population of younger US women (age 47.3±10.4 years) including 1'667 adults, both WC and BMI had a higher correlation with FM and SAT than with VAT [30]. This result in a younger population than ours can be explained by the FM changes occurring after the menopause with more abdominal (particularly visceral) fat [3, 10]. In a cohort of mixed-ancestry South African elderly population (mean age 55 years, 207 women and 46 men), postmenopausal women had higher %FM, greater WC, more VAT, and less GF than premenopausal women, even with the same BMI [46]. The authors found that VAT accounted for the greater variance with CMRF. Changes in VAT occurring in aging women are better predicted by changes in WC than by changes in WHR [47]. In a large meta-analysis including 16'129 participants of different kind of populations, correlation between VAT and WC was higher than that of VAT and BMI [48]. In summary, our results and those of other studies suggest that, at a population level, WC and BMI appear to be good proxy measures of VAT in non-obese postmenopausal women. However, at the individual level, for a same BMI, GF and AF may differ, and for a same WC, SAT and VAT may differ.

Correlation between cardiometabolic risk factor and anthropometric, BIA, or DXA measurements

The correlations between CMRF and AM are higher with BMI or WC than with WHR or HC. When AM and FM measures are compared, VAT shows the strongest correlation for most CMRF. In our study, correlation of CMRF with VAT is always higher than with WC and BMI (except for leptin), although correlation coefficients are close except for lipid parameters and diastolic blood pressure.

Several studies have shown a better correlation between CMRF and VAT than other fat compartments in postmenopausal women [2, 28-31]. DXA BC parameters are correlated with CMRF (positive correlation for TG, fasting plasma glucose (FPG), systolic and diastolic BP, and negative correlation for HDL-C), and VAT shows the strongest correlation [14, 28, 49, 50]. In 423 Caucasian postmenopausal women (age 58.1±6.3 years), VAT measured by DXA and WC were better correlated with CMRF than other fat compartments and BMI [29]. VAT was significantly correlated with LDL-C, total cholesterol and inversely correlated with HDL-C. In a population of 74 centrally obese hypertensive women (age 49.8±7.5 years), VAT accumulation, more often after menopause, was associated with higher levels of BP and insulin resistance [34]. In a recent study comparing 150 pre- and 150 postmenopausal Indian women, VAT was positively associated with FPG, TG, systolic and diastolic BP and negatively correlated with HDL-C in postmenopausal women but not in premenopausal women [28]. Another recent study including 97 women with a follow-up of 5.1 years at the menopausal transition showed a positive association between total and regional FM and BP and robust negative association with HDL-C in both pre- and postmenopausal state [2]. They found that the absolute change in systolic BP did not correlate significantly with change in TFM, regional FM and lean mass but the rise in diastolic BP was significantly associated with the absolute increments in AF and VAT. In a community-based Korean cohort of 565 people aged > 65 years (including 278 female, 76.0±8.8 years) VAT and AF amount were strongly correlated with most CMRF compared to SAT or GF [51]. They also found that both VAT and AF were negatively correlated with adiponectin. We found that adiponectin is inversely correlated with most of the anthropometric and DXA measurements, but has no correlation with BIA, TFM measured in % by DXA, and GF. Another study found a strong correlation between VAT and decreasing adiponectin levels in Japanese men and women (6,221 men and 775 women, 25 to 75 years) [52]. As VAT is the parameter the most strongly associated with the different CMRF, and is easily measurable, it could become a component of cardiometabolic marker on its own. Its estimation could be proposed during a DXA check-up for osteoporosis in countries where it is practiced.

Variability of blood pressure and blood tests explained by visceral adipose tissue

VAT has a good correlation with CMRF due to the fact that it is an endocrine organ with secretion of various hormones and inflammatory molecules [5-8]. In patients with central obesity, increased VAT is generally associated with insulin resistance, high risk of type 2 diabetes, dyslipidemia, and high mortality [8]. VAT adipocytes differ from SAT adipocytes in terms of greater metabolic activity, greater sensitivity to lipolysis and greater insulin resistance. In addition, VAT produces free fatty acids, consumes glucose and is more sensitive to adrenergic stimulation than SAT [8]. In our study, of all anthropometric and fat segment measurements, VAT was the most strongly correlated with CMRF. We therefore tried to quantify the variability of these CMRF explained by VAT. We found that VAT explains 5% of the variability of the diastolic BP, nearly 15% of the variability of HDL-C and TG, 25.3% of the variability of insulin, and 37.5% of the variability of leptin. Interestingly, VAT better explains the variation of most of the CMRF than age. In a cohort of 5427 non-obese Chinese adults (35 to 74 years, women 59.6%), those with at least two CMRF were

compared with those without risk factors [53]. Regardless of age, VAT was always higher in women with CMRF than in those without risk factors. These results may suggest an increased occurrence of cardiovascular events as shown by the Women's Health Initiative study, which followed 2683 postmenopausal women with normal BMI and no CVD for 17.9 years [54]. Higher percent AF, but neither TFM nor fat percentage, was associated with increased risk of cardiovascular events. Lifestyle changes, including increased physical activity and healthier eating habits, are the cornerstone of treatment for patients with abdominal obesity and excess VAT. It would be useful to know whether such interventions reduce VAT in non-obese women, and thus the risk of CVD events. Such data are still rare, and the results are controversial. A recent meta-analysis showed that high-intensity interval training (HIIT) programs significantly decrease weight, total and abdominal FM in women. However, HIIT was only effective in decreasing AF in women with excess adiposity and before menopause [55]. Another study, including 49 postmenopausal (age 57±6 years) South Asian women who participated in two 12-week aerobic exercise programs, found significant associations between changes in fasting insulin, glucose and homeostatic model assessment of insulin resistance with change in VAT. The association between change in VAT and CMRF was independent of change in other BC variables [56]. In obese patients, the changes in VAT and abdominal SAT areas seem to differ according to the type of intervention: exercise or calorie restriction diet. The change in VAT area was similar to the change in abdominal SAT area in the exercise groups compared to placebo, whereas in the calorie restriction diets groups (with or without exercise), the decrease in VAT area was half that of SAT [57]. Further studies are needed to define specific interventions to decrease VAT in non-obese postmenopausal women, and to determine the VAT threshold below which women are protected from CVD.

Strengths and limitations

To our knowledge, this study is the first comparing different fat segments measured by DXA (and not CT or MRI) and anthropometric measures with CMRF in a population of healthy non obese postmenopausal women. The strength of our study is the size of the sample, and the characteristics of the population included, namely healthy non obese postmenopausal women, some of whom have different CMRF. The data collected are of very good quality due to strict protocols and rigorous formation of trained personnel. Our study has a number of limitations, the first being the cross-sectional design. Second, our results are not generalizable to premenopausal women, men and non-Caucasian postmenopausal women. Third, we considered the risk factors globally and not individually. Estimation of each individual risk factor would be of interest to better compare the relationships with VAT. Finally, we did not take into account physical activity, caloric intake and hormonal treatment that can play a role in the amount and type of fat. Fourth, the SAT has not been evaluated. Therefore, it is not possible to know what association exists between the various CMRF and SAT. However, it was demonstrated that in obese women, all measures of body fat distribution except SAT were associated with CMRF, of which VAT was the most strongly associated [33].

Conclusion

In our cohort of non-obese postmenopausal women, the correlations between TFM measured by BIA and total or regional fat measured by DXA were very close, suggesting that BIA seems not to be a good tool to assess VAT. BMI and WC have a higher correlation than BIA with VAT; they may be surrogate measures for estimating VAT at the population level, but not at the individual level.

As VAT is the measurement most strongly associated with the different CMRF, it could become a composite cardiometabolic marker on its own. Its estimation could be proposed during a DXA check-up for osteoporosis in countries where it is practiced. Further studies are needed to confirm these results, and to evaluate its relationship to hard end-points as cardiovascular diseases to validate its role as an independent marker. Specific interventions to reduce VAT in non-obese postmenopausal women and a VAT threshold should then be defined.

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Conflict of interest

Elisabeth Stamm, Pedro Marques-Vidal, Elena Gonzalez Rodriguez, Peter Vollenweider, Didier Hans and Olivier Lamy declare that they have no conflict of interest

Author Contributions

ES wrote most of the article; PMV collected data, made part of the statistical analysis and wrote part of the article; OL revised the article for important intellectual content and wrote part of the article. PMV had full access to the data. OL is the guarantor of the study. PV, EGR and DH participated in the development of the study and revised the article.

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