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Independent and opposite associations of hip and waist circumference with metabolic syndrome components and with inflammatory and atherothrombotic risk factors in overweight and obese women

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Abstract

Recent studies have shown independent and opposite associations of hip circumference (HC) and waist circumference (WC) with glucose intolerance, insulin resistance, and type 2 diabetes mellitus. However, no studies have simultaneously considered the independent contributions of both markers to metabolic proinflammatory and atherosclerotic risk factors. In this study, we examine the independent associations of WC and HC with metabolic syndrome and with proinflammatory and atherothrombotic features. Independent associations of thigh muscle and adipose tissue (AT) compartments with metabolic features were also studied. Abdominal and thigh muscle and AT distributions were assessed by computed tomography in 140 overweight and obese women (mean ± SD: age, 38.3 ± 0.5 years; body mass index, 30.4 ± 0.3 kg/m^2). Blood lipids and inflammatory and atherothrombotic markers were measured. For a given WC, a larger HC was inversely associated with fasting insulin (β = −0.288, P = .008), hemoglobin A_{1c} (β = −0.246, P = .041), and plasminogen activator inhibitor–1 concentrations (β = −0.241, P = .023). Contrarily, WC was related with an unfavorable metabolic profile. For a given WC, higher total thigh AT and total thigh subcutaneous AT masses were associated with lower hemoglobin A_{1c} (β = −0.244, P = .049; β = −0.233, P = .049) and low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (β = −0.252, P = .040; β = −0.245, P = .037). In addition, total thigh AT was related with leptin (β = 0.310, P = .012), whereas total thigh subcutaneous AT revealed opposite associations with fasting insulin concentrations (β = −0.239, P = .034). Total thigh muscular tissue mass was related with lower plasminogen activator inhibitor–1 (β = −0.164, P = .049) and fibrinogen concentrations (β = −0.222, P = .018). In conclusion, HC revealed independent and opposite associations with insulin resistance and atherothrombotic disturbances. Contrarily, a larger WC predicted an increased metabolic risk. These contrasting effects in diabetogenic and atherothrombotic disturbances were, respectively, mediated by gluteofemoral AT and thigh muscle tissue. Besides body mass index and WC screening relevance, HC can contribute to additionally predict health risk in overweight and obese women.

1. Introduction

Central and peripheral fat accumulation defines 2 different phenotypes of body composition. When trunk fatness is taken into account, fat accumulation within the hips and legs independently protects against impaired glucose metabolism [1-5] and development of both type 2 diabetes mellitus (DM) [1,6,7] and cardiovascular disease (CVD)–related mortality [7-9]. In addition, it was recently observed, both in cross-sectional and prospective follow-up studies developed in older women, that a greater fat deposition in the legs protects against insulin resistance (IR) and aortic calcification [10,11]. Most population studies use waist circumference (WC) to determine health risk because it is a well-established marker of several metabolic syndrome outcomes and CVD such as coronary artery disease [12,13].

On the other hand, for a given WC, age, and body mass index (BMI), a larger hip circumference (HC) is associated

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with enhanced glucose tolerance [2,4], better blood lipid profile, and lower incidence of some CVD end points [8,9] as well as type 2 DM risk [1,2]. These associations seem to be present not only in white individuals but also across different ethnic groups [14,15]. Regarding the independent and opposite associations and the potential protective role of a larger HC, when WC is taken into account, it has been suggested that both thigh adipose and muscle tissues seem to contribute to the decreased risk observed [1,14].

It has been proposed that both anthropometric markers may play different metabolic roles [4]. Previous studies that have investigated the independent associations of central and peripheral fat mass (PFM) or WC and HC with glucose intolerance [1-5], type 2 DM [1,2,14], CVD, and atherogenic risk profile [10-12] and mortality [9,11] have used measuring techniques that do not allow separate quantification of trunk visceral and subcutaneous fat as well as thigh subcutaneous and intermuscular adipose tissue (AT). Indeed, current knowledge regarding separate contributions of central and peripheral fatness to health-related effects are based in large measure on fat mass determination using dual-energy X-ray absorptiometry (DXA), which is unable to distinguish different abdominal and thigh AT and muscle compartments. However, evidence using advanced imagiologic methods, such as computed tomography (CT) and magnetic resonance imaging, has been suggesting that these body composition compartments are differentially related with major metabolic syndrome disturbances and thus with health risk [16].

In this context, we investigated the independent associations of WC and HC to metabolic syndrome features and to proinflammatory and atherothrombotic disturbances in a large sample of overweight and obese premenopausal women. Furthermore, we also examined the relevance of each thigh adipose and muscle tissue compartment to the selected metabolic syndrome risk factors.

2. Subjects and methods

2.1. Subjects

The participants in this investigation were recruited from the community for a 2-year weight loss program as previously described [17]. The study sample included 140 white sedentary women, all residents in the Lisbon area. Inclusion criteria required that the subjects were aged between 24 and 50 years, had a BMI between 24.9 and 40.0 kg/m^2, were premenopausal, were not currently pregnant, were not under medication that affected weight or body composition, had no history of cancer in the last 5 years, and had no clinical evidence of liver disease. Diabetes mellitus was also an exclusion criterion as well as hormonal dysfunction, Cushing syndrome, hypertension, CVD, stroke, coronary heart disease, and resting and exercise electrocardiograms abnormalities. Subjects taking oral medication to treat hyperglycemia, hypercholesterolemia, or hypertriacylglycerolemia were also excluded. All volunteers were informed about the research design and gave written consent to participate. The study protocol was designed in accordance with the Helsinki Declaration and was approved by the Human Subjects Institutional Review Board of the Faculty of Human Movement, Technical University of Lisbon.

2.2. Body composition assessments

2.2.1. Anthropometric variables

Body mass was measured to the nearest 0.01 kg on a calibrated scale after removing shoes and heavy clothing. Height was measured to the nearest 0.1 cm with a stadiometer (Seca, Hamburg, Germany). Waist circumference and HC were measured according to the procedures of Lohman et al [18]. Briefly, WC was measured with the subject standing, midway between the last rib and the upper edge of the iliac crest; and HC was measured at the greater gluteal curvature. Both measurements were taken with a stiff fiberglass tape to the closest 0.1 cm. All anthropometric measurements were taken by previously trained technicians and repeated 3 times, with the mean value being used. Body mass index was calculated as weight divided by height squared (kilograms per square meter).

2.2.2. Dual-energy X-ray absorptiometry

A pencil beam mode DXA (QDR-1500; Hologic, Waltham, MA) was used to measure total body fat mass (TBFM). All measurements were made with volunteers in the supine position with the arms separated from their trunk. The same technician performed the scans and completed the analysis according to the operator's manual. The intraobserver coefficient of variation (CV) for TBFM was 2.0%. The technical error of percentage of TBFM, as estimated in 2 repeated measures on 10 subjects, was 0.5%.

2.2.3. Measurement of thigh AT distribution

Cross-sectional CT (Somaton Plus; Siemens, Sorheim, Germany) thigh images were obtained using standard procedures described elsewhere [19]. All images were obtained using 120 kV, 480 mA, and 512 × 512 matrix with a 48-cm field of view. With the subjects supine and arms extended above their head, contiguous 7-mm–thick cross-sectional images of both legs were obtained between the inferior ischial tuberosity and the superior border of the patella. Several compartments of thigh AT (total, subcutaneous, and subfascia lata) and muscle tissue cross-sectional areas were measured. Each different type of thigh AT and muscle tissue compartment was simultaneously measured in both legs.

The tissue volume (cubic centimeters) identified in each image was calculated by multiplying the tissue area (square centimeters) by the image thickness (7 mm). Thigh AT volume (liters) was converted to mass units (kilograms) by multiplying the volume by the assumed constant fat density (0.92 kg/L) [20]. Total thigh muscle mass was also obtained multiplying volume (liters) by the constant density assumed for AT-free skeletal muscle (1.04 kg/L) [20].

A 7-mm cross-sectional image of both mid thighs, located at the midpoint distance between the anthropometric

markers previously described, was selected from the thigh scans performed.

2.2.4. Abdominal AT distribution

Abdominal AT was determined by acquisition of a single axial image at the L4-5 intervertebral space [19,21]. Total abdominal AT (TAAT), visceral AT (VAT), abdominal subcutaneous AT (Ab SAT), and superficial and deep SAT areas were measured. The boundary between VAT and SAT was defined using the abdominal and oblique wall muscles in continuity with the deep fascia of the paraspinal muscles and the anterior aspect of the vertebral body [22].

2.2.5. Measurement reliability

The reliability for both thigh and abdominal body composition compartments was calculated in 30 women, with intraobserver analyses performed on same images separated by 3 months. The same technician made all segmentation measurements; thus, only intraobserver error was calculated. Regarding mid thigh AT, subfascial AT (SFAT), and mid thigh muscular tissue, the intraobserver CVs were 0.4%, 2.5%, and 0.1%, respectively.

The intraobserver CVs were 0.7% for TAAT and 0.9% for VAT. For Ab SAT and superficial and deep Ab SAT, the intraobserver CVs were 0.8%, 3.1%, and 2.8%, respectively.

2.2.6. Image analysis

Once obtained, CT data were analyzed (Slice-O-matic, Version 4.2; Tomovision, Montreal, Quebec, Canada) based on image morphology. A combination of edge detection filters and watershed techniques was used [23]. Tissue segmentation was computed using standard Hounsfield units (HU) ranges: −190 to −30 HU for AT and 0 to +100 HU for skeletal muscle [23]. Thigh fascia lata was used to subdivide the SAT from SFAT as described elsewhere [19].

2.3. Blood analysis

Venous blood samples were collected at the antecubital vein after a 12-hour overnight fast. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and uric acid were measured by enzymatic colorimetric methods. Insulin was determined by electrochemiluminescence immunoassay; interleukin-6 (IL-6), by chemiluminescence immunoassay; and glycemia, by hexokinase method.

Plasma apolipoprotein A-1 (apo A-1), apolipoprotein B-100 (apo B-100), and C-reactive protein (CRP) concentrations were measured by a high-sensitivity particle-enhanced turbidimetric assay. Tumor necrosis factor–α (TNF-α) α was measured using a high-sensitivity enzyme-linked immunosorbent assay principle. Plasminogen activator inhibitor–1 (PAI-1) was measured in iced citrated plasma using the Coatest (Diagnostica Stago, Treveny, France) PAI method [24] (enzyme immunoassay), and fibrinogen was measured by clotting time. Hemoglobin A_{1c} (HbA_{1c}) was determined by high-pressure liquid chromatography. Adiponectin, leptin, and urinary cortisol were measured by radioimmunoassay.

2.4. Blood pressure

At the same day as body composition measurements, diastolic and systolic blood pressures were measured in the seated position after a minimum of 5-minute rest with a Dinamap semiautomatic oscillometric recorder (Dinamap; Critikon, Tampa, FL). A suitable cuff size was applied to the participants' upper arm, at the heart level. The mean of 3 consecutive measurements in each arm, separated by 1-minute time lapse, was calculated.

2.5. Premenopausal status

The premenopausal status of each participant was determined by the study physician based on her menstrual history; women were in the premenopausal stage if they reported regular menstrual cycles.

2.6. Statistical analyses

Data are presented as mean ± SD, unless otherwise indicated. Normality and homocedasticity of all variables were analyzed. Based on skewed distributions, log transformation was used to normalize distributions when necessary. Pearson correlation coefficients between both WC and HC and metabolic syndrome features studied were calculated. Multiple linear regressions, adjusted for age and BMI, were performed to study the independent associations of continuous HC and WC with major metabolic syndrome components and with proinflammatory and atherothrombotic metabolic disturbances (all entered as continuous variables). Independent contributions of WC and HC to abdominal and thigh body composition compartments, adjusted for age and BMI, were also studied. Further multiple linear regressions were developed to examine the associations of each thigh body composition compartment with metabolic syndrome features, independently of age, BMI, and WC.

Standardized β values are presented for direct comparisons of the multiple linear regression models results. Multicollinearity was studied by statistic tolerance, which determines how much the independent variables are linearly related to each another. The tolerance is calculated as $1 - R^2$ for an independent variable when it is predicted by the other independent variables already included in the model. If tolerance is inferior to 0.1, the stability of the regression model is disturbed by multicollinearity. Statistical significance was set as $P < .05$. All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL).

3. Results

The body composition and metabolic syndrome characteristics of the study population are presented in Tables 1 and 2. Despite some variation in the obesity degree ($25 < BMI \leq 45$ kg/m^2), most of the subjects were obese.

Subcutaneous AT was the major constituent of both abdominal and thigh AT area (75.1% and 93.9%, respectively),

Table 1
Characteristics of the study population (N = 140)

	Mean ± SD	Range
Anthropometric data		
Age (y)	38.3 ± 0.5	25.0-49.0
Weight (kg)	78.1 ± 1.0	59.1-107.8
BMI (kg/m^2)	30.4 ± 0.3	25.1-45.2
WC (cm)	87.2 ± 0.8	71.1-123.4
HC (cm)	111.4 ± 0.7	94.7-134.6
DXA		
Body fat (%)	46.5 ± 5.0	33.8-59.2
Abdominal AT		
TAAT (cm^2)	470.9 ± 12.1	211.9-910.8
VAT (cm^2)	111.3 ± 4.3	24.9-266.8
Ab SAT (cm^2)	353.6 ± 9.1	145.0-633.4
Thigh compartments		
Thigh AT (cm^2)	270.7 ± 6.9	132.9-509.1
Thigh SAT (cm^2)	261.6 ± 6.8	129.4-501.6
Thigh SFAT (cm^2)	3.5 ± 0.2	1.0-11.9
Muscle area (cm^2)	234.3 ± 2.6	176.3-324.7
TTAT mass (kg)	8.4 ± 2.1	4.0-14.8
TTSAT mass (kg)	7.9 ± 2.1	3.8-14.0
TTSFAT mass (kg)	0.6 ± 0.2	0.3-1.5
TTMT mass (kg)	6.1 ± 0.9	4.4-10.3

Values are means ± SD. Thigh AT indicates mid thigh adipose tissue; Thigh SAT, mid thigh subcutaneous adipose tissue; Thigh SFAT, mid thigh subfascial adipose tissue.

whereas VAT represented 23.6% of abdominal AT area. On the other hand, total thigh AT (TTAT) mass represented 57.9% of the total thigh mass. In our sample, 9.3% of the women met the

Table 2
Metabolic syndrome characteristics of the study population (N = 140)

	Mean ± SD	Range
TG (mg/dL)	101.48 ± 4.86	32.00-329.0
Fasting insulin (μIU/mL)	8.22 ± 0.32	2.40-17.9
Fasting glycemia (mg/dL)	89.48 ± 0.65	73.00-113.0
TC (mg/dL)	194.74 ± 3.86	101.00-307.0
HDL-C (mg/dL)	54.09 ± 1.05	29.00-91.0
LDL-C (mg/dL)	123.50 ± 3.54	45.00-255.0
TC/HDL-C ratio	3.74 ± 1.11	2.04-9.55
LDL-C/HDL-C ratio	2.38 ± 0.08	0.94-6.13
Apo A-1 (mg/dL)	139.05 ± 2.33	77.00-195.0
Apo B-100 (mg/dL)	86.68 ± 2.43	38.00-156.0
Apo A-1/apo B-100 ratio	1.74 ± 0.05	0.78-3.31
Systolic BP (mm Hg)	1 20.65 ± 1.43	90.00-175.0
Diastolic BP (mm Hg)	75.83 ± 0.93	50.00-101.0
CRP (mg/dL)	0.45 ± 0.03	0.03-1.14
IL-6 (pg/mL)	10.32 ± 0.56	0.80-31.5
TNF-α (pg/mL)	3.87 ± 0.23	0.90-14.1
PAI-1 (ng/mL)	21.18 ± 2.01	1.00-100.0
Fibrinogen (mg/dL)	369.38 ± 6.48	201.00-552.0
Adiponectin (ng/mL)	9.18 ± 6.44	2.93-41.0
HbA_{1c} (%)	4.87 ± 0.04	4.00-7.0
Cortisol (μg/d)	41.04 ± 1.69	6.00-105.0
Uric acid (mg/dL)	4.39 ± 0.97	2.40-8.5
Leptin (ng/mL)	32.92 ± 43.33	0.90-167.4

Values are means ± SD. BP indicates blood pressure.

Table 3
Independent contributions (standardized β coefficients) of waist and HC to metabolic syndrome components, adjusted for age and BMI

	WC	HC	Percentage of variance explained[a] (%)
TG (mg/dL)	0.337 *	−0.062	17.3 †
Fasting insulin (μIU/mL)	0.125	−0.288 **	24.5 †
Fasting glycemia (mg/dL)	0.490 ***	−0.067	16.3 †
TC (mg/dL)	0.015	−0.053	4.1
LDL-C (mg/dL)	0.036	−0.167	5.4
HDL-C (mg/dL)	−0.363 *	0.193	12.2 †
TC/HDL-C ratio	0.347 *	−0.149	19.0 †
LDL-C/HDL-C ratio	0.267	−0.215	15.4 †
Apo A-1 (mg/dL)	−0.329 *	0.056	5.4 †
Apo B-100 (mg/dL)	0.015	−0.163	7.3 †
Apo A-1/apo B-100 ratio	−0.137	0.197	7.8 †
Systolic BP (mm Hg)	0.170	0.227	8.6 †
CRP (mg/dL)	−0.063	0.030	9.7 †
IL-6 (pg/mL)	−0.396 *	−0.163	5.2
TNF-α (pg/mL)	0.123	−0.049	9.4 †
PAI-1 (ng/mL)	0.349 *	−0.241 *	26.7 †
Fibrinogen (mg/dL)	−0.037	−0.183	8.4 †
Adiponectin (ng/mL)	−0.186	−0.025	3.6
HbA_{1c} (%)	0.202	−0.246 *	13.0 †
Cortisol (μg/d)	0.272	0.004	3.8
Uric acid (mg/dL)	−0.273	−0.111	15.9 †
Leptin (ng/mL)	−0.327 *	−0.094	12.3 †

All variables were entered in the regression models as continuous variables. Age had only independent significant contribution in PAI-1 and uric acid.
[a] Variance explained by age, BMI, and WC and HC.
† Independent significant contribution of BMI, $P < .001$.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

Adult Treatment Panel III criteria for metabolic syndrome [25]. In bivariate models, both WC and HC were positively associated with inflammatory and atherogenic risk factors, as well as with glucose and lipid metabolism disturbances (data not shown).

The results of simultaneously adding WC and HC, adjusting for age and BMI, to predict metabolic syndrome components, and proinflammatory and atherothrombotic risk factors for CVD are shown in Table 3.

A large WC was associated with increased TG, fasting glycemia, apo A-1, and PAI-1 concentrations, as well as with a higher TC/HDL-C ratio. In addition, a larger WC was inversely related with lower concentrations of HDL-C, IL-6, and leptin. On the contrary, for a given WC, a large HC was inversely associated with fasting insulin, HbA_{1c}, and PAI-1 concentrations. The explained variance for each metabolic risk factor by HC and WC, independently of age and BMI, varied between 3.8% and 26.7%. In Fig. 1, partial correlation coefficients between both WC and HC and some of the metabolic syndrome features studied, after controlling for age, BMI, and each other, are presented.

The associations of each different thigh adipose and muscle tissue compartment with metabolic risk factors, independently of age, BMI, and WC, are presented in Table 4. For a given WC, higher TTAT and total thigh SAT

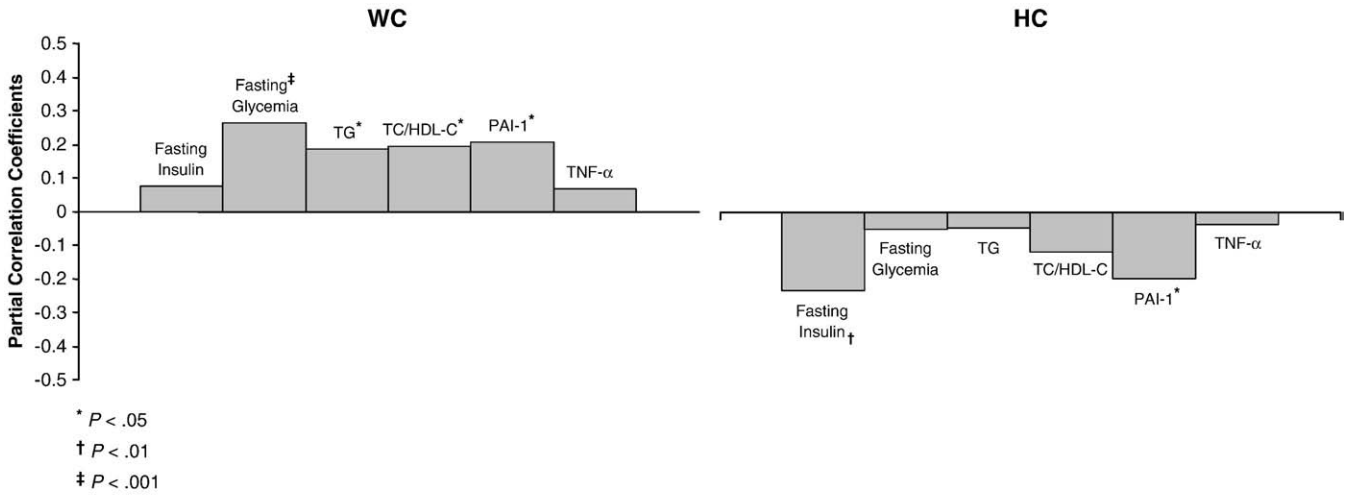

Fig. 1. Partial correlations between both WC and HC and the metabolic syndrome features studied after controlling for age, BMI, and each other.

(TTSAT) masses were both associated with lower HbA_{1c} concentrations, as well as with a lower LDL-C/HDL-C ratio. In addition, whereas TTAT mass was inversely related with leptin, TTSAT mass revealed independent and opposite associations with fasting insulin and HDL-C concentrations. On the contrary, total thigh SFAT (TTSFAT) did not reveal associations with any of the metabolic syndrome features studied. Furthermore, for a given WC, a higher total thigh muscular tissue (TTMT) mass was associated with lower PAI-1 and fibrinogen concentrations.

Table 4
Independent contributions (standardized β coefficients) of WC and thigh adipose and muscle tissue compartments to metabolic syndrome components, adjusted for age and BMI

	WC	TTAT	WC	TTSAT	WC	TTMT
TG (mg/dL)	0.297	−0.124	0.280	−0.142	0.321 *	0.029
Fasting insulin (μIU/mL)	0.172	−0.227	0.150	−0.239 *	0.255	−0.023
Fasting glycemia (mg/dL)	0.502 **	−0.100	0.503 **	−0.088	0.468 **	0.147
TC (mg/dL)	−0.036	−0.098	−0.031	−0.081	0.056	−0.114
LDL-C (mg/dL)	−0.057	−0.210	−0.063	−0.205	0.080	−0.128
HDL-C (mg/dL)	−0.266	0.232	−0.255	0.233	−0.324 *	−0.046
TC/HDL-C ratio	0.308 *	−0.188	0.308 *	−0.172	0.374 *	0.001
LDL-C/HDL-C ratio	0.228	−0.252 *	0.221	−0.245 *	0.334 *	−0.034
Apo A-1 (mg/dL)	−0.295	0.145	−0.298	0.121	−0.315	−0.062
Apo B-100 (mg/dL)	−0.049	−0.111	−0.064	−0.141	0.046	−0.113
Apo A-1/apo B-100 ratio	−0.133	0.218	−0.120	0.228	−0.234	0.050
Systolic BP (mm Hg)	0.169	0.104	0.156	0.066	0.069	0.126
CRP (mg/dL)	−0.015	0.233	−0.016	0.192	−0.058	−0.072
IL-6 (pg/mL)	−0.314	0.146	−0.318	0.122	−0.314	−0.122
TNF-α (pg/mL)	0.223	0.232	0.212	0.168	0.158	−0.028
PAI-1 (ng/mL)	0.362 *	−0.129	0.338 *	−0.157	0.478 ***	−0.164 *
Fibrinogen (mg/dL)	−0.018	−0.020	−0.029	−0.042	0.092	−0.222 *
Adiponectin (ng/mL)	−0.245	−0.085	−0.250	−0.084	−0.247	0.062
HbA_{1c} (%)	0.221	−0.244 *	0.210	−0.233 *	0.266	0.071
Cortisol (μg/d)	0.258	0.118	0.237	0.132	0.168	0.101
Uric acid (mg/dL)	−0.275	−0.028	−0.287	−0.051	−0.244	−0.048
Leptin (ng/mL)	−0.211	0.310 *	−0.225	0.225	−0.297	−0.035

All variables were entered in the regression models as continuous variables.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

4. Discussion

This study shows opposite associations between both WC and HC and atherogenic and prothrombotic features of metabolic syndrome and CVD, extending previous knowledge about the separate contributions of each anthropometric marker to health risk. In fact, independent and opposite effects of WC and HC were observed not only with major metabolic syndrome components but also with specific metabolic risk factors, which are relevant for diabetogenic and atherogenic risk assumption [2,3,8]. A unique feature of this study is that it addressed, for the first time, the contribution of each CT-measured abdominal and thigh adipose and muscle tissue compartment to the opposite associations verified between both WC and HC and health risk. It was already reported that, for a given WC, a larger HC is related with a lower risk for metabolic syndrome disturbances [1,2,14], type 2 DM [1,3,6,9], and CVD morbidity and mortality [6,9,26]. However, this independent and relative HC protective contribution to disease risk disappeared when WC was not taken into account. Indeed, in our study, bivariate models revealed that larger WC and HC were both associated with an unfavorable metabolic profile and a higher CVD risk factor.

On the other hand, consistently with previous observations [27], we observed that WC was related with increased VAT and Ab SAT areas, reflecting a morbidogenic body composition phenotype and metabolic profile, whereas a larger HC was inversely associated with both abdominal AT compartments (data not shown). After adjustment for age and BMI, multiple regression analyses between both anthropometric markers and the metabolic risk factors revealed positive associations between WC and glucose metabolism markers, hypercholesterolemia, hypertriacylglycerolemia, and PAI-1, a specific indicator of impaired fibrinolysis and atherothrombotic state [28], as well as inverse associations with leptin and apo A-1 concentrations (data not shown). A synergistic effect promoted by the simultaneous presence of hyperinsulinemia, hyperglycemia, and hypercholesterolemia in obese individuals that might enhance plasma PAI-1 concentrations was recently proposed, therefore explaining the associations observed in our study between WC and this particular thrombotic marker [29]. Despite previous evidence showing that hyperinsulinemia alone is also related with increased PAI-1 concentrations in obese and type 2 DM subjects, suggesting a direct link between IR and PAI-1 [28], it is still unclear whether insulin acts directly or via IR to enhance PAI-1 concentrations.

Plasminogen activator inhibitor–1 has also been associated with dyslipidemia, abdominal adiposity, and hypertension [29]. Moreover, it is known that AT is also an important source of angiotensin II, which might link the PAI-1 increase to renin-angiotensin system and, hence, to hypertension [30]. Despite the controversial opinions about regional AT differences in PAI-1 secretion, it was recently suggested that VAT, rather than Ab SAT, could be responsible for the raised PAI-1 values and IR observed in metabolic syndrome patients [31].

On the contrary, in our study, for a given WC, a large HC was associated with lower fasting insulin, HbA_{1c}, and PAI-1 concentrations. Despite the relative lower values observed in the variance that could be explained by HC, these results reinforce the protective effect of larger hips to glucose metabolism and IR markers, and further extend this notion to specific atherogenic and prothrombotic disturbances. Similarly, other studies have also reported that a larger HC (or a higher PFM) was independently associated with a more favorable plasma glucose and lipid profile [1,7,10], and a lower type 2 DM [3,4,14,32] and CVD risk [1,9,11]. These relative protective contributions of a larger HC to morbidity seem also to be present with risk of premature mortality, after adjustment for BMI [9,26].

A larger WC, reflecting central obesity, has been associated with a chronic inflammatory state, promoted by a low-grade plasma elevation of some adipokines and acute-phase reactants, such as TNF-α, IL-6, and CRP [33]. These inflammatory markers have been associated with type 2 DM [34], atherogenesis, and CVD [35]. Although not significant, WC and HC revealed an opposite association tendency not only with dyslipidemia markers, but also with some inflammatory risk factors, such as TNF-α, which seem to play an important mechanistic role in IR, down-regulating glucose transporter 4 and inhibiting insulin receptor activity [36]. Because TNF-α can induce IL-6 release, it has been suggested that TNF-α may be the "driver" behind metabolic syndrome [37]. In abdominally obese women, the concentrations of these adipokines are increased, whereas adiponectin, produced by both visceral and peripheral adipocytes, is commonly decreased [38]. Adiponectin presents antiatherogenic, anti-inflammatory, and insulin-sensitizing effects [39], which seem to be relevant to counteract the diabetogenic and atherogenic risk associated with obesity. In previous studies that have examined the contrasting contributions of both central fat mass and PFM to atherogenic glucose and lipid markers, as well to aortic calcification [7,10,11,14], the verified PFM protection against type 2 DM and atherosclerosis seemed to be mediated by insulin-sensitization effects associated with adiponectin physiological metabolism [40].

It is well recognized that HC variations can be explained by skeletal frame size, gluteofemoral muscle mass, or AT accumulation [3,4]. Moreover, it has been postulated that relatively narrow hips due to lack of thigh muscle mass are associated with a lower muscle insulin clearance [41] and an impaired muscle fatty acid oxidation capacity [6,8]. However, authors have been suggesting that HC seems to be more closely associated with leg fat mass in women [4]. In our study, contrarily to WC, a larger HC was not only independent and inversely related with both VAT and Ab SAT areas, but revealed also additional associations with

gluteofemoral AT and thigh muscle tissue compartments (data not shown).

Therefore, further analyses were developed to highlight the relevance of each thigh AT and muscle tissue compartment to the observed relative HC protective role to metabolic risk. For a given WC, higher TTAT and TTSAT masses were both associated with lower HbA_{1c} concentrations and a lower LDL-C/HDL-C ratio. A higher TTSAT mass was also inversely related with both fasting insulin and HDL-C concentrations, and a higher TTAT mass was associated with lower leptin concentrations. In contrast, TTSFAT did not reveal any association with the metabolic syndrome features studied. Furthermore, for a given WC, a higher TTMT mass was a significant predictor of lower PAI-1 and fibrinogen concentrations.

These observations suggest that, in overweight or obese women, the verified protective HC role in dyslipidemia and IR, when WC is taken into account, could be mediated by subcutaneous gluteofemoral AT. Indeed, it was already observed that, for a given amount of abdominal fat, low subcutaneous fat in the legs was associated with an unfavorable lipid profile [16]. In this context, it has been proposed that underlying hormonal factors, such as estrogen concentrations, may regulate preferential thigh AT accumulation [42]. In addition, gluteofemoral adipocytes are relatively less sensitive to catecholamine-stimulated lipolysis, being more sensitive to antilipolytic stimuli, when compared with VAT adipocytes [43]. These metabolic differences combined with a relatively higher activity of lipoprotein lipase in these thigh adipocytes promote the uptake of free fatty acids from circulation, providing a "buffer" that may carry out an antidiabetogenic and antiatherogenic effect, as well as a protection against liver, pancreas, and muscle ectopic fat storage [44].

Conversely, our results also suggest that thigh muscle tissue seems to be relevant for the observed protection against prothrombotic and atherosclerotic abnormalities. Although evidence has been highlighting the contributions of muscle tissue to a better metabolic profile [45] and lower insulin metabolism [41] and fatty acid oxidation capacity disturbances [6,8], these are novel observations that need further research. Furthermore, it is noteworthy that disturbances in glucocorticoid and growth hormone metabolism, age, sex, and behavioral factors, such as physical activity and diet, may underlie and confound these associations, needing therefore to be taken in consideration in future studies [46].

There are some limitations that should be mentioned. Despite the rigorous blood analysis protocol, we were not able to control for diet composition before blood sampling. Furthermore, all subjects were counseled to refrain from participating in any type of exercise at least 48 hours before blood sampling to avoid metabolic acute exercise interferences.

In summary, we found that, for a given WC, HC was inversely associated with IR markers and atherothrombotic disturbances. On the contrary, a larger WC was associated with a higher metabolic risk. The protective effect of relatively larger HC, when WC is taken into account, was extended to novel and specific metabolic syndrome features, with contrasting effects in diabetogenic markers mediated by gluteofemoral AT, whereas thigh muscle tissue seemed to mediate the protection against atherothrombotic risk factors. Therefore, in addition to BMI and WC screening relevance, HC can also contribute to CVD risk assumption in overweight and obese women.

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