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ORIGINAL ARTICLE

Regional fat mass by DXA: High leg fat mass attenuates the relative risk of insulin resistance and dyslipidaemia in obese but not in overweight postmenopausal women

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Objective. To investigate the influence of regional fat mass (FM) on insulin resistance and dyslipidaemia in obese postmenopausal women (BMI >30 kg/m^2) compared to overweight women (BMI <30 kg/m^2). Leg FM may attenuate the increased risk of cardiovascular disease and diabetes imposed by increased trunk FM in normal and overweight postmenopausal women. ***Material and methods***. Cross-sectional and consecutively referred patients comprising 63 obese and 36 overweight postmenopausal women. Body composition and regional FM by dual X-ray absorptiometry (DXA), fasting glucose, fasting insulin and C-peptide, insulin resistance by homeostasis model assessment (HOMA-IR), insulin sensitivity by quantitative insulin sensitivity check index (QUICKI) and metabolic clearance rate (MCRestOGTT), insulin secretion (HOMAsecr) and serum lipids were assessed. ***Results***. In obese subjects, leg FM was favourably associated with HOMA-IR ($p<0.05$), QUICKI ($p<0.05$), fasting glucose ($p<0.05$), fasting insulin ($p<0.05$), HOMAsecr ($p<0.05$) and total cholesterol/HDL ratio ($p<0.05$). Trunk FM was unfavourably associated with MCRestOGTT ($p<0.01$), QUICKI ($p<0.05$) and fasting insulin ($p<0.05$). Compared to leg FM, leg/trunk FM ratio was more strongly associated with fasting insulin ($p<0.001$), fasting C-peptide ($p<0.001$), HOMA-IR ($p<0.001$), MCRestOGTT ($p<0.001$), QUICKI ($p<0.001$), HOMAsecr ($p<0.001$), fasting glucose ($p<0.01$) and triglycerides ($p<0.01$). Stepwise multiple regression demonstrated that leg/trunk FM ratio was the most important variable with partial $R^2=0.26$ ($p<0.001$) for HOMA and $R^2=0.37$ ($p<0.001$) when QUICKI was used as the dependent variable. In overweight women, no associations between fat mass and parameters of insulin resistance or dyslipidaemia were found. ***Conclusions***. A high leg/trunk FM ratio as measured by DXA may give relative protection against diabetes and cardiovascular disease in obese postmenopausal women, but not in overweight women.

Keywords: DXA; dyslipidaemia; insulin resistance; leg fat mass; trunk fat mass

Introduction

Population-based and prospective cohort studies have demonstrated an increased risk of both cardiovascular disease and diabetes mellitus with increasing abdominal circumference in women [1–3]. Increases in hip circumference seem on the other hand to have a protective effect against these conditions [4–8]. Menopausal transition is associated with weight gain and a preferential increase in intra-abdominal fat [9]. Measurement of body composition by CT (computed tomography) [10] and DXA [11,12] has demonstrated that trunk fat mass (FM) is a strong independent predictor of insulin resistance and dyslipidaemia in postmenopausal women. Several studies have also suggested that peripheral adiposity may attenuate both insulin resistance and dyslipidaemia [10–15] or just lipid levels [16] in normal and overweight postmenopausal females. For the most part, these studies have been limited to females with average BMI of around 26 kg/m^2, but have also included obese subjects. The potential modifying effect on the metabolic syndrome of the peripheral FM in frankly obese postmenopausal females compared to overweight postmenopausal females has not been elucidated. Our aim was therefore to compare the influence of regional FM as determined by DXA on markers of insulin resistance and dyslipidaemia between a group of overweight and obese postmenopausal women.

Subjects and methods

Subjects

The study comprised 63 healthy, postmenopausal, Caucasian, Norwegian women aged between 46 and 75 years and consecutively referred for treatment of obesity (BMI >30 kg/m^2, range 30–44 kg/m^2). They were all >1 year past menopause. Subjects with a history of diabetes were excluded. Twenty-six women were current oestrogen users (2–26 years of duration). Fifteen women receiving thyroid medication were

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clinically and biochemically euthyroid. Nine women were receiving statins and 22 were being treated for hypertension. The overweight group comprised 36 healthy postmenopausal women aged between 55 and 64 years with BMI <30 kg/m^2 (range 25–30 kg/m^2) receiving no medication recruited from another clinical study [17]. An upper limit of weight of 125 kg was imposed, since this is close to the tolerance limit for the DXA table. Written informed consent was obtained from all participants, and because the study was conducted as part of our routine investigation of patients referred for treatment of obesity, no formal approval by the Regional Ethics Committee was required.

Methods

Height to the nearest 0.5 cm (Harpenden stadiometer) and weight to the nearest 0.5 kg (Seca scale, Sweden) were measured to calculate BMI as weight kg/m^2. Applying tight pressure, waist circumference was measured in the standing position at the mid-level between the iliac crest and the lower lateral costal margin, with the patient fully exhaled. Hip circumference was measured as the maximal distance around the hip, again applying tight pressure on the measuring tape. Total and regional FM and lean body mass (LBM) were measured by three different DXA (dual-energy X-ray absorptiometry) absorptiometers: Lunar Expert (version 1.92), Lunar Prodigy (version Encore/Lunar GE, Madison, Mich., USA) and Hologic Delphi W (version 11.1) (Hologic, Waltham, Mass., USA). The subjects were randomly assigned to an unoccupied machine and a conventional body composition of trunk and leg FM was measured. The trunk region includes the chest (separated from the head by the chin) and the abdominal/pelvic area. Separation of the legs from the pelvis: From a point at the extension of the horizontal line formed by the superior border of the iliac bone intercepted laterally by a line from both humeroscapular joints separating the arm, a line through the femoral neck is drawn that intercepts between the legs. Comparison of measurements of 21 subjects between our 3 absorptiometers over a broad range of BMI (21–39 kg/m^2) was highly correlated with Pearson's correlation coefficient ranging from 0.979 to 0.992 for FM ($p<0.0001$). All data were transformed to Prodigy values after statistical analysis had demonstrated that the introduction of correction factors for these calculations was appropriate ($R^2=0.99$–0.98). The correction factors were: FM Prodigy=1.079*Delphi or 0.954*Expert [18]. Overweight subjects were measured as previously described [17]. Long-term precision measured by weekly measurements of the Hologic whole body phantom revealed stable instrument function CV% less than 2, except for lean mass for Delphi (5.5 %) [18].

A 75 g oral glucose tolerance test (OGTT) was administered after an overnight fast in all obese subjects. Blood samples were obtained using a glucose dehydrogenase method before and 60 and 120 min after glucose ingestion for analysis of glucose in venous blood (HemoCue B-glucose analyser, Sweden), while insulin and C-peptide were determined in serum samples (Immulite 2000; DPC, Calif., USA). HOMA-IR was calculated (fasting plasma glucose (mmol/L)*fasting serum insulin (pmol/L)/135) as an estimate of insulin resistance [20,21] and HOMA secr (fasting insulin (pmol)*3.33/(fasting glucose (mmol/L)-3.5) as an estimate of beta cell function [19]. Quantitative insulin sensitivity check index (QUICKI) was calculated as 1/(log I0+log G0), where G0 and I0 are fasting glucose and insulin [21,22], and a modification of MCRestOGTT (18.8–0.271*BMI-0.00052*I120–0.27*G120), where G120 and I120 are the 2 h values of glucose and insulin, respectively, after an oral glucose load, was used as an estimate of insulin sensitivity [23]. HbA1c was measured by inhibition of latex agglutination (DCA 2000; Bayer, Germany). Serum levels of total cholesterol, HDL cholesterol and triglycerides were measured using a Beckman Synchron analyser (L.A. Calif., USA). LDL cholesterol was calculated [24]. In controls, only fasting blood samples were obtained.

Statistical analysis

All data were tested for normal distribution and are presented as continuously distributed variables with means and standard deviations (SD). Group comparisons were performed using Student's unpaired *t*-test or the Mann-Whitney rank sum test in the case of no normality, while Pearson's correlation coefficient or the Spearman rank order correlation was used to estimate correlations between variables. ANOVA one-way analysis was used when comparing tertial groups. Multiple stepwise regression analysis was performed to assess the relative importance of trunk FM and leg FM and leg/trunk FM ratio to the indices of insulin resistance and lipid metabolism. Generally, *p*-values <0.05 were considered significant in tests. All tests were performed two-sided. SigmaStat version 3.1 (Systat Software, Inc., Calif., USA) was used in analysis.

Results

Subject characteristics for anthropometry, body composition and metabolic variables are presented in Tables I and II. Overweight females were significantly less insulin-resistant than obese subjects

Table I. Characteristics and body composition of subjects.

	Obese	Overweight
	BMI >30 kg/m^2 (n=63)	BMI <30 kg/m^2 (n=36)
	Mean (SD)	Mean (SD)
Age (years)	58.3 (6.0)	57.9 (3.4)
Weight (kg)	96.4 (11.7)‡	75.5 (6.6)
BMI (kg/m^2)	35.1 (3.8)‡	27.6 (1.2)
DXA measurements		
Body fat %	48.8 (5.9)‡	40.8 (3.4)
Total fat mass (kg)	45.4 (11.3)‡	30.8 (3.9)
Trunk fat mass (kg)	23.5 (5.4)‡	14.9 (1.9)
Leg fat mass (kg)	13.6 (3.2)‡	10.1 (1.9)
Total lean mass (kg)	44.3 (10.9)‡	40.7 (8.2)

BMI=body mass index; body fat%=total fat mass/total body mass. Levels of significance: Unpaired t test. *$p<0.05$, †$p<0.01$, ‡$p<0.001$.

and had a more favourable lipid profile. To assess the potential influence of medications on insulin resistance and dyslipidaemia, the individuals were analysed by categories, i.e. whether receiving antihypertensives (alone or in combination) (n=22); thyroxin (n=15); oestrogens (n=26); statins (n=9) or subjects not taking any medication (n=15). There were no significant differences (ANOVA on ranks) in indices of body composition or any of the markers of insulin resistance (p=0.37 for HOMA-IR, p=0.27 for QUICKI, p=0.25 for HOMA secr, p=0.73 for MCRestOGTT) or for serum lipids (p=0.42 for total cholesterol, p=0.34 for HDL cholesterol, p=0.56 for triglycerides, p=0.30 for LDL cholesterol) between the different categories. All participants were therefore treated as one group.

Table II. Metabolic characteristics of subjects.

	Obese	Overweight
	BMI >30 kg/m^2	BMI <30 kg/m^2
	n=63	n=36
	Mean (SD)	Mean (SD)
Fasting glucose (mmol/L)	4.9 (1.4)	5.1 (1,04)
Fasting insulin (nmol/L)	146 (89)‡	70.6 (37.8)
Fasting C-peptide (nmol/L)	1436 (559)‡	814 (363)
HbA1C (%)	5.54 (0.56)	5.60 (0.36)
HOMA-IR	5.53 (4.19)‡	2.88 (1.34)
QUICKI	0.34 (0.09)‡	0.37 (0.12)
MCRest OGTT	4.0 (3.4)	–
HOMA secr	890 (875)†	407(224)
Total cholesterol (mmol/L)	6.08 (1.12)	6.16 (1.11)
HDL cholesterol (mmol/L)	1.35 (0.36)‡	1.61(0.36)
Total cholesterol/HDL cholesterol ratio	4.75 (1.27)†	4.00 (1.12)
LDL cholesterol (mmol/L)	3.95 (0.86)	3.86 (1.04)
Triglycerides (mmol/L)	1.69 (1.13)	1.43 (0.77)

HOMA-IR=insulin resistance by the homeostasis model assessment, QUICKI=quantitative insulin sensitivity check index, MCRestOGTT=metabolic clearance rate as an estimate of insulin sensitivity. HOMA secr=estimate of beta cell function. Levels of significance: Unpaired t-test. *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

In obese subjects (Table III), leg FM was favourably correlated with HOMA-IR, HOMAsecr, QUICKI, fasting glucose and fasting insulin (p=0.013, p=0.012, p=0.013, p=0.017 and p=0.035, respectively). In contrast, trunk FM was significantly and unfavourably correlated with MCRestOGTT (p=0.005), QUICKI (p=0.022) and fasting insulin (p=0.011). The relative importance of trunk and leg FM as predictors of insulin resistance is demonstrated in Figure 1 showing increasing HOMA-IR with increasing trunk FM and decreasing leg FM. Consequently, leg/trunk FM was more strongly associated than trunk FM and leg FM with HOMA-IR, QUICKI, HOMA secr, MCRestOGTT, fasting insulin and fasting C-peptide ($p<0.001$). Fasting glucose (p=0.002) was also favourably correlated to leg/trunk FM. There were negative correlations between body fat percent and QUICKI ($r=-0.26$, p=0.04) and positive correlations between body fat percent and HOMAsecr (r=0.29, p=0.02) as well as HOMA-IR (r=0.26, p=0.04). OGTT revealed that 12 obese subjects with normal fasting glucose had 2 h values of glucose in the range 10.1–15.6 mmol/L. When omitting these from analysis, the p-values remained <0.001 for correlations between leg/trunk FM ratio and insulin, HOMA-IR, QUICKI, HOMAsecr and C-peptide, while the correlation between leg/trunk FM ratio and MCRestOGTT was reduced (r=0.30, p=0.032). In the overweight group, only total FM and fasting insulin were significantly correlated (r=0.34, p=0.04).

In obese subjects (Table III), leg FM was favourably correlated to total cholesterol/HDL cholesterol ratio (p=0.012). Leg/trunk FM was favourably correlated with triglycerides (p=0.005) and total cholesterol/HDL cholesterol (p=0.048). Trunk FM was unfavourably correlated to triglycerides (p=0.018). None of the fat mass indices were correlated to serum lipids in the overweight group.

To further characterize the associations between leg and trunk fat and the metabolic variables, obese subjects were analysed by tertiles of leg FM (ANOVA) (data not shown). Women in the greatest leg FM tertile were less insulin-resistant than women in the lowest tertile (p=0.030 for HOMA-IR, p=0.048 for QUICKI, p=0.039 for HOMAsecr and p=0.04 for fasting insulin) in spite of greater weight, total FM and trunk FM ($p<0.001$). Women with higher leg FM had a more favourable total

Table III. Correlations (Pearson's or Spearman) between regional fat masses and parameters of insulin resistance and dyslipidaemia in 63 obese postmenopausal women and 36 overweight postmenopausal women.

	Obese			Overweight		
	BMI >30 kg/m^2			BMI <30 kg/m^2		
	$n=63$			$n=36$		
	Leg FM	Leg/trunk FM	Trunk FM	Leg FM	Leg/trunk FM	Trunk FM
Glucose (mmol/L)	−0.30*	−0.38†	0.00	−0.01	−0.11	0.14
Insulin (nmol/L)	−0.27*	−0.60‡	0.32*	0.08	− 0.09	0.29
HOMA-IR	−0.32*	−0.63‡	0.29*	0.08	−0.11	0.31
QUICKI	0.32*	0.63‡	−0.29*	−0.10	0.07	−0.30
MCRestOGTT	0.18	0.42‡	−0.35†			
HOMAsecr	−0.32†	−0.58‡	0.20	0.06	−0.12	0.30
C-peptide (nmol/L)	−0.22	−0.52‡	0.25	−0.10	−0.22	0.23
HbA1c%	−0.25*	−0.21	−0.05	−0.05	−0.13	0.11
Total cholesterol (mmol/L)	−0.13	−0.07	−0.04	0.18	0.21	−0.04
HDL cholesterol (mmol/L)	0.23	0.17	0.07	0.23	0.30	−0.14
Cholesterol/HDL ratio	−0.32*	−0.25*	−0.13	−0.18	−0.22	0.09
LDL cholesterol (mmol/L)	−0.13	0.05	−0.17	0.16	0.17	−0.00
Triglycerides (mmol/L)	−0.07	−0.35†	0.30*	0.05	−0.08	0.12

Levels of significance: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

cholesterol/HDL cholesterol ratio than women with the lowest tertile ($p=0.015$).

A stepwise multiple regression analysis using HOMA-IR as the dependent variable and age, use of medicaments, smoking, BMI, weight, height, total FM, LBM, trunk FM, leg FM, leg/trunk FM ratio, and percent body fat as independent variable candidates selected the leg/trunk FM ratio as the only contributor to the model with partial $R^2=0.26$ ($p<0.001$). When using QUICKI as dependent variable, again the leg/trunk FM ratio was selected as the only explanatory variable, $R^2=0.37$ ($p<0.001$). With MCRestOGTT as dependent variable, BMI: $R^2=0.24$ ($p=0.012$) and leg/trunk FM ratio: $R^2=0.14$ ($p=0.010$) were the only explanatory variables. When obese subjects with elevated 2 h glucose values during OGTT were omitted from analysis, leg/trunk FM remained the main contributor accounting for a partial $R^2=0.22$ ($p<0.001$) for HOMA; but age, too, was important with $R^2=0.29$ ($p=0.034$). With QUICKI as the dependent variable, leg/trunk FM ratio remained the only contributor ($R^2=0.31$ ($p<0.001$)), while MCRestOGTT only was explained by BMI ($R^2=0.16$ ($p=0.005$)). In the overweight group, multiple regression analysis revealed that only QUICKI as dependent and total FM as independent variables were accepted by the model ($R^2=0.12$, $p=0.038$). Furthermore, stepwise multiple regression analysis comprising the whole range of BMI (25–44 kg/m^2) revealed that leg/trunk FM ($R^2=0.24$ ($p<0.001$)) and belonging to the obese group ($R^2=0.29$, $p=0.024$) predicted HOMA-IR. These results remained when subjects with elevated 2 h values during OGTT were omitted from analysis (leg/trunk *FM* ratio $R^2=0.18$, $p<0.001$, belonging to the obese group $R^2=0.26$, $p=0.005$). Additionally, age contributed with $R^2=0.31$, $p=0.021$, but not in the subjects with normal 2 h values. Likewise, when QUICKI was used as the dependent variable, the model selected trunk FM ($R^2=0.24$, $p<0.001$), leg FM ($R^2=0.30$, $p=0.004$) and belonging to the obese group ($R^2=0.34$, $p=0.018$) as explanatory variables. However, when subjects with elevated 2 h values during OGTT were omitted from analysis, only trunk FM remained as an explanatory variable ($R^2=0.21$, $p<0.001$).

In obese individuals, linear regression analysis (Table IV) between leg/trunk FM and HOMA-IR demonstrated similar results in subjects with normal 2 h values and subjects including elevated 2 h values during OGGT ($R=0.47$ and $R=0.51$, respectively, $P<0.001$). Likewise, in these obese subjects, linear regression analysis between leg FM and HOMA-IR demonstrated similar results ($p=0.07$ for subjects with normal 2 h values and $p=0.02$ for subjects including elevated 2 h value). For QUICKI, similar results were obtained between subjects with normal 2 h values ($p=0.08$ for leg FM and $p<0.001$ for leg/trunk FM) and obese subjects including elevated 2 h values ($p=0.02$ for leg FM and $p<0.001$ for leg/trunk FM).

In contrast, overweight individuals demonstrated that linear regression analysis between HOMA-IR and leg/trunk FM ratio and HOMA-IR and leg FM were not significant ($p=0.60$ and 0.66). For QUICKI, the results were $p=0.77$ and $p=0.37$, respectively, suggesting the existence of a transition zone in regard to insulin resistance between overweight and obese

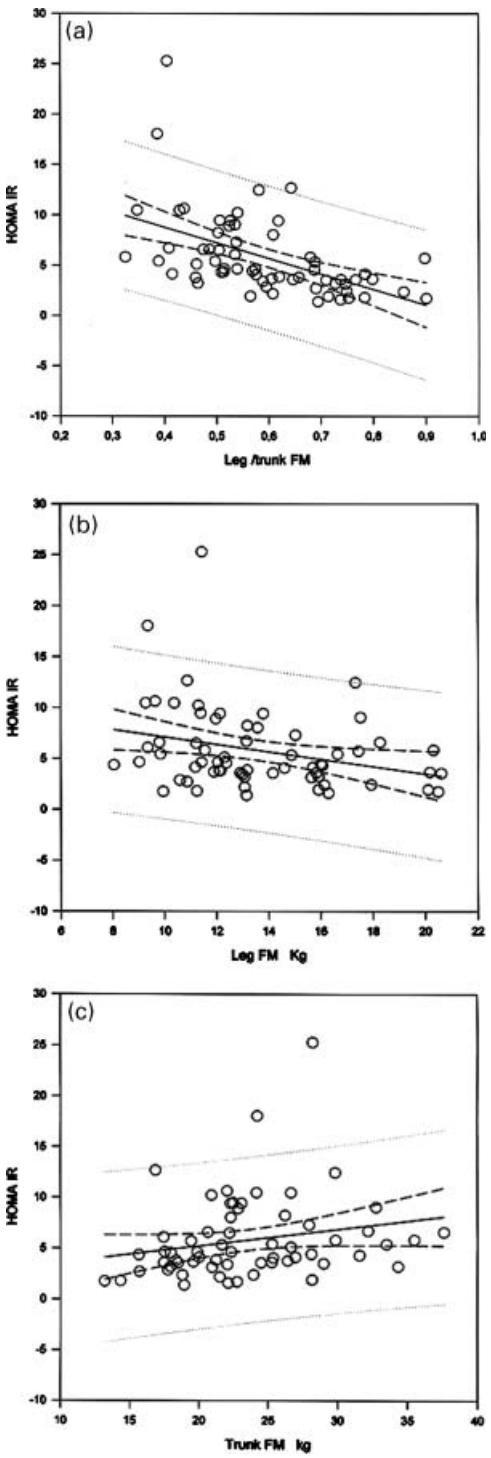

Figure 1. Regression analysis of leg/trunk FM, trunk fat mass and leg fat mass versus HOMA-IR in obese subjects. Lines of regression and their 95 % confidence intervals are depicted.

subjects. For all subjects, linear regression between BMI and HOMA and QUICKI was significant ($R=0.30$, $p<0.003$ and $R=0.39$, $p<0.001$, respectively). Regressions for BMI in overweight subjects ($R=0.31$, $p=0.07$ for QUICKI; $R=0.32$, $p=0$, 06 for HOMA) or obese subjects ($R=0.06$ for QUICKI; $R=0.00$, $p=0.995$ for HOMA) may indicate the existence of a transition zone also for BMI. Spearman rank order correlation between HOMA-IR and BMI displayed $r=0.43$ ($p=0.000$) for all subjects, $r=0.34$ ($p=0.045$) for overweight and $r=0.07$ ($p=0.59$) for obese subjects rendering support for existence of a transition zone.

Discussion

The main finding in our study is that a relatively high leg FM as measured by DXA may have an independent protective effect on insulin resistance and dyslipidaemia in obese postmenopausal women, but not in overweight postmenopausal women. In obese women, using the ratio leg/trunk FM demonstrates that for any given degree of trunk FM an increase in leg FM will attenuate the negative effect of trunk FM on indices of insulin resistance and dyslipidaemia. Consequently, increasing leg FM may confer an independent protective effect on cardiovascular risk factors related to insulin resistance. In addition, we have demonstrated that increasing leg/trunk FM has a favourable effect on insulin secretion as measured by HOMAsecr and MCRestOGTT. This may, however, be an epiphenomenon secondary to the relative reduction in insulin resistance seen with increasing leg/trunk FM ratio. Additionally, we found favourable effects of leg FM on cholesterol/HDL cholesterol and triglycerides in obese women but not in overweight women. Previous studies [10–15] comprising other methodologies demonstrating significant favourable associations between leg FM and markers of insulin resistance and dyslipidaemia in females, however, have encompassed subjects either younger [13] or older [11,14,15] than ours or have included female diabetics [13,14]. Although average BMI in these studies is lower than in our study, obese subjects were included and it is not known how much of these favourable effects of leg FM is attributable to obese subjects [10–15]. Our study is the first to suggest that the favourable effects of leg FM on insulin resistance and dyslipidaemia may be more pronounced in obese than in overweight subjects.

Our data in obese subjects on insulin resistance and lipid abnormalities correspond well with respective relations between these indices and trunk FM and leg FM reported in these previous studies using different methods for estimating FM and insulin resistance.

In overweight subjects, our findings point in the same direction, but not as pronounced as found by Munoz et al. [26], who, in normal/overweight subjects

Table IV. Linear regression analysis (y=a+bx) between HOMA-IR and fat masses in obese and overweight postmenopausal subjects.

	Obese (n=63)			Overweight (n=36)		
	Leg/trunk FM	Leg FM	Trunk FM	Leg/trunk FM	Leg FM	LTrunk FM
a	14.9	10.8	1.97	3.48	2.46	−0.11
b	−15.4	−0.00	0.16	−0.93	0.00	0.00
R	0.51	0.29	0.22	0.11	0.08	0.31
Rsqr	0.26	0.08	0.05	0.01	0.01	0.10
P-value	<0.001	0.02	0.09	0.54	0.66	0.06

(average BMI 25.8 kg/m^2 $\pm$ 4.3), found even negative correlations between insulin sensitivity (by frequently sampled intravenous glucose tolerance testing) and leg FM fat as well as trunk FM determined by DXA. Consequently, there seem to be indications that leg FM per se may be less protective or not protective at levels of BMI <30 kg/m^2. Indeed, this is also indicated in our multiple regression analysis, where belonging to the overweight or obese group is important in predicting HOMA-IR. Furthermore, in the overweight group, leg FM, trunk FM, leg/trunk FM ratio were not accepted by the multiple regression model or by the linear regression analysis between fat masses and HOMA-IR. This may indicate that a certain threshold of leg FM as measured by DXA is necessary if a protective effect on parameters of insulin resistance and dyslipidaemia is to be achieved.

The present study expands on the results from previous studies in normal and overweight postmenopausal females [11–15] demonstrating that trunk FM measured by DXA is strongly related to risk factors for diabetes and cardiovascular disease also in postmenopausal women with BMI >30 kg/m^2. Additionally, we extend previous data on the relationship between regional FM and insulin resistance by adding data on HOMA-IR, QUICKI and MCRest OGTT, which are considered more appropriate estimates of insulin resistance and sensitivity [19–23] than the indices used by van Pelt et al. [11,12].

Williams et al. [10] measured regional FM by CT in a large group of women, 17 to 77 years of age, with large variation in body fat (8.8 % to 48.1 %) and were the first to report that the amount of leg FM was favourably associated with cardiovascular risk factors (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides). Using similar methodology to estimate fat mass, Goodpaster et al. [25] found an unfavourable association between thigh adipose tissue as measured by CT and insulin resistance in a combined population of obese men and women. They found that while intramuscular and subfascial fat masses were related to insulin resistance (glucose clamp method), the subcutaneous thigh fat mass was not. While estimates of adipose tissue by CT is usually performed from a single or a few tissue slices, DXA allows estimates of total fat mass in defined regions, which may account for the demonstrated relationship between leg FM and markers of insulin resistance and dyslipidaemia.

The reasons for the opposite relations between trunk FM and leg FM to insulin resistance and dyslipidaemia in obese females remain obscure. Vascular, endocrine and other factors may be of importance. While venous blood from visceral tissues and parts of upper body tissues are drained to the liver by way of the portal vein and its collaterals, lower body venous drainage surpasses the liver by way of the inferior vena cava, leading to different metabolism of the two blood pools. Adipose tissue is recognized as being hormonally active and both leptin and adiponectin have been implicated in the relationship between subcutaneous FM and insulin resistance [27]. Of particular interest is the reverse association between adiponectin and obesity and insulin resistance. Previous studies [28] have shown that a positive relationship between adiponectin and insulin sensitivity uniformly exists in all subjects, lean or obese. However, a recent study [29] has demonstrated that this relationship is dependent on the degree of adiposity as well as insulin resistance or other risk factors related to the metabolic syndrome [30,31]. Two of the best predictors of adiponectin are HDL-cholesterol [30] and C-peptide [32]. Inverse associations between adiponectin to visceral adipose tissue as measured by computed tomography have recently been demonstrated, while subcutaneous adipose tissue correlated positively [33]. It is therefore possible that adiponectin may have an influence on the relationships between leg FM, leg/trunk FM as measured by DXA and indices of insulin resistance, but adiponectin was not measured in the present study.

Different responsiveness of regional fat masses to pituitary axis hormones have also been suggested in subjects with abdominal versus peripheral fatness

[34]. In an *in vitro* study a greater lipolytic activity was found in subcutaneous abdominal compared with subcutaneous femoral fat cells from obese females [35], which may have consequences for free fatty acid related insulin resistance. One mechanism has recently suggested that abdominal fat may be associated unfavourably and femoral fat with favourable lipoprotein lipase and hepatic lipase activities in plasma [36]. Another study has demonstrated variations in GLUT4 expression and insulin action in fat cells from different regions in obese females [37].

There are several limitations to the present study, the most important ones being that it is not population-based and has a relatively small sample size of overweight individuals. On the other hand, our population is most likely representative of females with an upper weight limit of 125 kg being referred for evaluation and treatment of obesity. Secondly, the measurements of body composition have been provided by three different fan beam densitometers. However, we have developed equations permitting calculation of FM between the three densitometers, thus rendering potential error negligible. Thirdly, the euglycaemic hyperinsulinaemic clamp method is considered the gold standard for assessing insulin resistance. The markers we used have been demonstrated to be closely related to results from euglycaemic hyperinsulinaemic clamp studies in a variety of conditions and are generally accepted markers of insulin resistance [40]. A further limitation may be the potential influence on risk factors and measurements of body composition of various medications such as oestrogens, antihypertensives, statins and thyroxine. Conflicting results exist regarding insulin sensitivity for postmenopausal oestrogen use [26,38,39], as well as differing effects of various antihypertensive medications, i.e. decrease by beta blockers and thiazides, neutral effect of calcium blockers, no effect or increase by ACE blockers, increase by angiotensin II blockers [41]. Significant improvement in insulin sensitivity has also been demonstrated by atorvastatin [42], while thyroxine supplementation to reach normal range TSH values seems to have little effect on insulin resistance. However, by way of multivariate analysis we were unable to find any difference in insulin sensitivity between subjects taking or not taking these medications, possibly suggesting that obesity, as such, overrides the more subtle effects of medications in our population.

In summary, we have demonstrated that in obese postmenopausal females a high leg/trunk FM ratio is associated with a favourable metabolic profile, suggesting a modifying effect of leg FM against diabetes and cardiovascular disease. However, this is not evident in overweight postmenopausal women. We also conclude that DXA is a suitable method for measuring regional FM in relation to assessment of insulin resistance and dyslipidaemia in clinical practice.

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