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The Metabolically Healthy but Obese Individual Presents a Favorable Inflammation Profile

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Objective: The purpose of this study was to investigate the inflammatory state in obese women displaying the "metabolically healthy but obese" (MHO) phenotype.

Design: We examined the metabolic characteristics of 88 obese, sedentary postmenopausal women. Subjects were classified as MHO or as "at risk" based on the upper and lower quartiles of insulin sensitivity as measured by the hyperinsulinemic-euglycemic clamp technique. Thereafter, we determined 1) body composition, 2) body fat distribution, 3) plasma lipid and lipoprotein levels, 4) glucose homeostasis, 5) resting blood pressure, 6) peak oxygen consumption, and 7) inflammation markers as potential modulators of differences in the coronary risk profile.

Results: Twenty-two MHO women displayed high insulin sensitivity (15.35 ± 2.3 mg/min·kg fat-free mass), and 22 at risk subjects with low insulin sensitivity (7.98 ± 1.4 mg/min·kg fat-free mass) were identified. Despite comparable total body fatness between groups (47.7 ± 4.8 *vs.* 45.5 ± 4.4%; not significant), MHO individuals had significantly lower levels of visceral fat, fasting insulin, plasma triglycerides, high-sensitivity C-reactive protein (CRP), and α-1 antitrypsin levels and higher levels of high-density lipoprotein cholesterol than at risk individuals ($P < 0.05$). Stepwise regression analysis showed that CRP, fasting triglycerides, and the lean body mass index explained 19.5, 8.5, and 4.0%, respectively, of the variance observed in glucose disposal (total $r^2 = 0.320$; $P < 0.001$)

Conclusion: Results of the present study indicate that postmenopausal women displaying the MHO phenotype also have a favorable inflammation profile as shown by lower CRP and α-1 antitrypsin levels compared with insulin-resistant women. This suggests that a lower inflammation state, as attested by low CRP levels, could play a role in the protective profile of the MHO individual, and this may be associated metabolically to a lower risk for cardiovascular disease. **(*J Clin Endocrinol Metab* 90: 4145–4150, 2005)**

A UNIQUE SUBSET of obese individuals has been identified that appears to be protected against obesity-related metabolic disturbances (1–3). These individuals, now known as "metabolically healthy but obese" (MHO) individuals, despite having excessive body fatness, display a favorable metabolic profile characterized by high levels of insulin sensitivity, a favorable lipid profile, and no sign of hypertension. In fact, the metabolic profiles of MHO postmenopausal women are virtually indistinguishable from young lean women (4).

It appears that only one study has examined several metabolic characteristics associated with the protective profile of the MHO individual, including some potential causal factors (5). In that study, MHO women had higher levels of high-density lipoprotein (HDL)-cholesterol and lower levels of fasting triglycerides, fasting glucose, fasting insulin, as well as reduced glucose and insulin area under the curve during an oral glucose tolerance test. In multiple regression analysis, the authors identified two independent factors that distinguished MHO individuals from those "at risk." The two factors included an early age of obesity onset and low amounts of visceral adipose tissue, which together explained 35% of the variance in insulin sensitivity. Therefore, there remains a substantial unexplained variance (65%) in the metabolic profile of the MHO individual. Despite a general clinical awareness of the MHO individual, there is only a rudimentary understanding of factors and mechanisms underlying this phenotype.

Evidence suggests that MHO individuals may account for as much as 20–30% of the obese population (2, 3, 6). This is a striking finding and underscores the urgent need to identify and understand the other factors underlying the protective profile in MHO individuals. Recent studies have shown that elevated C-reactive protein (CRP) concentrations are associated with insulin resistance (7–9) and cardiovascular disease (10, 11). In addition, high levels of other inflammation-sensitive plasma proteins, such as haptoglobin, α-1 an-

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Abbreviations: ApoA1, Apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; FFM, fat-free mass; FMI, fat mass index; HDL, high-density lipoprotein; HE, hyperinsulinemic-euglycemic; HOMA, homeostasis model assessment; hsCRP, high-sensitivity CRP; HU, Hounsfield units; $IS_{(clamp)}$, insulin sensitivity; LBMI, lean body mass index; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); $M_{(clamp)}$, glucose disposal; MHO, metabolically healthy but obese; QUICKI, quantitative insulin sensitivity check index; SAT, sc adipose tissue; $VO_{2\ peak}$, peak oxygen uptake.

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titrypsin, and α-1 acid-glycoprotein or orosomucoid have also been shown to be associated with insulin resistance (12) and cardiovascular disease (13, 14).

These studies provide tantalizing evidence that several inflammation markers may be implicated in the protective metabolic profile of some obese individuals. Therefore, the purpose of this study was to investigate the inflammatory state of the MHO individual and potential modulators that could explain the protective profile of MHO postmenopausal women. We hypothesized that the MHO phenotype will be associated with a low inflammatory profile and that low CRP may account for a significant part in this protective profile of MHO postmenopausal women.

Subjects and Methods

Subjects

The present study was conducted in a newly characterize cohort of obese postmenopausal women. The study population consisted of 88 nondiabetic obese postmenopausal women aged between 44 and 73 yr old. Women were included in the study if they meet the following criteria: 1) body mass index (BMI) more than 27 kg/m^2, 2) cessation of menstruation for more than 1 yr and a follicle-stimulating hormone level of more than or equal to 30 U/liter, 3) sedentary (<2 h/wk of structured exercise), 4) nonsmokers, 5) low to moderate alcohol consumers (less than two drinks per day), 6) free of known inflammatory disease, and 7) no use of hormone replacement therapy. On physical examination or biological testing, all participants had no history or evidence of the following: 1) cardiovascular disease, peripheral vascular disease, or stroke, 2) diabetes (2 hr plasma glucose <11.0 mmol/liter after a 75 g oral glucose tolerance test), 3) orthopedic limitations, 4) body weight fluctuation ±2 kg in the last 6 months, 5) thyroid or pituitary disease, 6) infection by medical questionnaire examination and complete blood count, and 7) medication that could affect cardiovascular function and/or metabolism. The study was approved by the University of Montreal ethics committee.

Sequence of tests

After reading and signing the consent form, each participant was invited to the Metabolic Unit in the fasting state at 0730 h for a series of tests. After a 4-wk period of weight stabilization, patients underwent a 3 h hyperinsulinemic-euglycemic (HE) clamp. A blood draw was performed for the determination of a fasting lipid profile, analyses of insulin, as well as glucose and inflammation markers. Body composition measurements, assessed by dual-energy x-ray absorptiometry and the computed tomography (CT) technique, were performed a few days later after the HE clamp. Finally, a test for peak oxygen uptake ($VO_{2\ peak}$) was performed to assess fitness levels.

HE clamp

The study began at 0730 h after a 12-h overnight fast following the procedure described by DeFronzo *et al.* (15). An antecubital vein was cannulated for the infusion of 20% dextrose and insulin (Actrapid; Novo-Nordisk, Toronto, Canada). The other arm was cannulated for sampling of blood. Three basal samples of plasma glucose and insulin were taken over 40 min. Then, an insulin infusion was started at the rate of 75 mU/m^2·min for 180 min. Plasma glucose was measured each 10 min with a glucose analyzer (Beckman Coulter, Fullerton, CA) and maintained at fasting level with a variable infusion rate of 20% dextrose. Glucose disposal ($M_{(clamp)}$) was calculated as the mean rate of glucose infusion measured during the last 30 min of the clamp (steady-state) and is expressed as milligrams per minute per kilogram body weight or as milligrams per minute per kilogram fat-free mass (FFM). Insulin sensitivity ($IS_{(clamp)}$) was determined as follows: $IS_{(clamp)} = GIR_{ss}/G_{ss} \times \Delta I_{ss}$, where GIR_{ss} is the steady-state (milligrams per minute per kilogram), G_{ss} is the steady-state blood glucose concentration (milligrams per deciliter), and ΔI_{ss} is the difference between the steady-state and basal insulin concentration (microunits per milliliter) (16).

Identifying MHO and at risk subjects

In the study by Brochu *et al.* (5), MHO subjects were classified based on a "cut point" for insulin sensitivity using the HE clamp (>8.0 mg/min·kg of lean body mass) and at risk subjects with impaired insulin sensitivity (<8.0 mg/min·kg of lean body mass). It is well recognized that insulin resistance develops on a continuum, thus one can argue with the imperfect use of cut points to differentiate high *vs.* low insulin sensitivity phenotypes. Therefore, in the present study, using a more rigorous definition to define MHO subjects, we chose to identify MHO and at risk individuals by dividing the entire cohort into quartiles based on glucose disposal rates (M values/FFM). Women with M/FFM values in the upper quartile (M ≥ 12.62) (n = 22) were classified as having high insulin sensitivity and placed in the MHO group, whereas women with M/FFM values in the lower quartiles (M ≤ 9.29) (n = 22) were classified as low insulin sensitivity and categorized as at risk subjects. The at risk group is defined as a group that present metabolically abnormalities (*i.e.* insulin resistance and dyslipidemia), which may be associated with an increase risk of type 2 diabetes and/or cardiovascular disease.

Blood samples

After an overnight fast (12 h), venous blood samples were collected for the measurement of plasma concentrations of total cholesterol, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, glucose, and insulin. Plasma was analyzed on the day of collection. Analyses were done on the COBAS INTEGRA 400 (Roche Diagnostics, Montreal, Canada) analyzer for total cholesterol, HDL-cholesterol, triglycerides, and glucose. Total cholesterol, HDL-cholesterol, and triglycerides were used in the Friedewald formula (17) to calculate LDL-cholesterol concentration. Plasma nonesterified fatty acids were measured by commercial enzymatic colorimetric kits (Wako Chemicals, Richmond, VA). Insulin levels were determined by automated RIA (Medicorp, Montreal, Canada). Homeostasis model assessment (HOMA) was calculated according to the formula of Matthews *et al.* (18) and quantitative insulin sensitivity check index (QUICKI) was calculated as described previously (19) using the mean of three basal values of plasma glucose and insulin. Serum lipoprotein(a) [Lp(a)], apolipoproteins A1 and B (ApoA1 and ApoB), as well as high-sensitivity CRP (hsCRP), orosomucoid, haptoglobin, transferrin, albumin, α-1 antitrypsin, and ferritin were assessed by immunonephelometry on IMMAGE analyser (Beckman Coulter, Villepinte, France).

Blood pressure

Sitting blood pressure was determined as the average of the last four readings of five (at one per minute) in the left arm after subjects rested quietly for 10 min using a Dinamap automatic machine (Welch Allyn Inc., San Diego, CA).

Body composition

Body weight was measured using an electronic scale (Balance Industrielles, Montreal, Canada), and standing height was measured using a wall stadiometer (Perspective Enterprises, Portage, MI). Lean body mass and fat mass were evaluated by dual-energy x-ray absorptiometry (version 6.10.019; General Electric Lunar Corporation, Madison, WI). Waist circumference was measured with a flexible steel metric tape at the nearest 0.5 cm.

BMI [body weight (kilograms)/height (square meters)] was calculated. However, because the BMI is a nonspecific measure of fatness and leanness, we calculated the fat mass index (FMI) [fat mass/height (square meters)] and the lean body mass index (LBMI) [lean body mass/height (square meters)] (which taken together represent the BMI). One advantage of using the FMI and the LBMI, compared with the BMI alone, is that it amplifies the relative effect of aging and individual variations on body fat and lean body mass. Furthermore, interindividual variations in both variables in absolute value fail to allow an appropriate comparison among subjects of different sizes (20).

CT

A GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) was used to measure visceral and sc adipose

tissue (SAT) levels. The subjects were examined in the supine position with both arms stretched above their head. The position of the scan was established at the L4/L5 vertebral disc using a scout image of the body. Visceral adipose tissue area was quantified by delineating the intra-abdominal cavity at the internalmost aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The SAT area was quantified by highlighting fat located between the skin and the externalmost aspect of the abdominal muscle wall. Deep and superficial SAT areas were measured by delineating the sc fascia within the SAT and by computing areas of the layers of fat on each side of the fascia. The cross-sectional areas of fat were highlighted and computed using an attenuation range of −190 to −30 Hounsfield units (HU). Areas of skeletal muscle, fat, and muscle attenuation were calculated by delineating the regions of interest and then computing the surface areas using attenuation range of −190 to −30 HU for fat and 0 to 100 HU for skeletal muscle (21).

Aerobic capacity ($VO_{2\ peak}$)

Aerobic capacity was assessed on an ergocycle model 900 (Ergoline, Bitz, Germany), with an Ergocard (Medi Soft, Dinant, Belgium) cardiopulmonary exercise test station. Aerobic capacity was tested by a progressive test starting at 25 W with an augmentation of 25 W every 2 min. Subjects were asked to maintain a constant speed, and the level of resistance on the wheel was adjusted to preserve a constant power output. O_2 and CO_2 were measured by a direct system using a face mask. $VO_{2\ peak}$ was achieved when the power output could no longer be maintained. $VO_{2\ peak}$ was defined as the highest 30 sec average of oxygen consumption.

Statistical analysis

Statistical analyses were performed for the entire cohort for means differences between quartiles and for a stepwise multi-linear regression model. However, the groups of interest (MHO, top quartile of IS *vs.* at risk, lower quartile of IS) are only reported in the present study. The data are expressed as the mean ± SD. A one-way ANOVA was performed to analyze mean differences among the four groups. When significant differences were found, a Dunnett's *post hoc* test was performed to identify the magnitude of these differences. A Mann-Whitney rank sum test was used for nonparametric variables. Marginal estimates of CRP levels adjusted for visceral fat were calculated with an analysis of covariance (univariate general linear model). A stepwise multi-linear regression model determined which variables explained unique variance in glucose disposal values. Based on exploratory analyses and using biologically plausible hypotheses, independent variables considered in the final model for glucose disposal were LBMI, visceral fat, triglycerides, HDL-cholesterol, and CRP, in which all of these variables significantly correlated with glucose disposal. Significance was accepted at $P < 0.05$.

Results

Table 1 shows physical characteristics of MHO and at risk individuals. Both groups of women were comparable for age, height, body weight, BMI, fat mass, percentage body fat, FMI, bone mineral content, and waist circumference. Lean body mass, peripheral lean body mass, central lean body mass, and LBMI were significantly lower in MHO women compared with subjects in the at risk group ($P < 0.01$).

Metabolic variables are presented in Table 2. No differences between groups were noted for total cholesterol, LDL-cholesterol, free fatty acids, ApoA1, ApoB, Lp(a), resting systolic, as well as diastolic blood pressures and maximal oxygen uptake. MHO subjects had lower plasma triglyceride, total cholesterol/HDL-cholesterol, and triglycerides/HDL-cholesterol concentrations and higher plasma HDL-cholesterol levels ($P < 0.01$).

Table 3 shows fasting insulin as well as glucose and insulin sensitivity indexes. By design, both groups were significantly different for absolute and relative levels of glucose disposal rates as well as $IS_{(clamp)}$ ($P < 0.001$). In addition, MHO women showed higher QUICKI as well as lower fasting insulin and HOMA values than at risk women ($P < 0.001$). No statistically significant differences between groups were found for fasting glucose and $glycemia_{(steady\text{-}state)}$, but there was a trend for a lower $insulin_{(steady\text{-}state)}$ in MHO women ($P < 0.066$).

Table 4 shows body fat distribution measurements derived from CT. No differences were noted for superficial and deep SAT, as well as abdominal fat. However, MHO women had significantly less visceral adipose tissue than at risk subjects ($P < 0.05$). Leg muscle attenuation was not different between groups.

Table 5 shows inflammation markers. We found no differences between groups in orosomucoid, haptoglobin, transferrin, albumin, and ferritin. However, MHO subjects showed significantly lower levels of hsCRP and α-1 antitrypsin compared with at risk subjects ($P < 0.05$). hsCRP levels above 3 mg/liter has been shown to increase the risk of cardiovascular disease (22). Accordingly, in the MHO

TABLE 1. Physical characteristics of MHO and at risk individuals

Physical characteristics	MHO (n = 22)	At risk (n = 22)
Age (yr)	56.7 ± 6.7	59.2 ± 5.1
Height (m)	1.60 ± 0.05	1.62 ± 0.07
Weight (kg)	83.0 ± 10.8	91.7 ± 13.6
BMI (kg/m^2)	32.3 ± 4.1	34.8 ± 3.9
Fat mass (kg)	40.2 ± 8.8	41.8 ± 8.1
% Body fat	47.7 ± 4.8	45.5 ± 4.4
FMI (kg/m^2)	15.6 ± 3.3	15.9 ± 2.6
Lean body mass (kg)	40.4 ± 3.8[a]	47.4 ± 7.6
Peripheral lean body mass (kg)	18.7 ± 1.8[a]	21.4 ± 3.4
Central lean body mass (kg)	19.0 ± 2.4[a]	23.0 ± 4.5
LBMI (kg/m^2)	15.7 ± 1.7[a]	18.0 ± 2.2
Bone mineral content (kg)	2.4 ± 0.3	2.5 ± 0.3
Waist circumference (cm) (n = 21, 21)	96.3 ± 8.6	102.1 ± 9.2

Values are means ± SD.
[a] Significantly different from the at risk group ($P < 0.01$).

TABLE 2. Metabolic characteristics of MHO and at risk individuals

Metabolic characteristics	MHO (n = 22)	At risk (n = 22)
Total cholesterol (mmol/liter)	5.66 ± 0.78	5.46 ± 0.90
LDL-cholesterol (mmol/liter)	3.39 ± 0.63	3.13 ± 0.86
HDL-cholesterol (mmol/liter)	1.68 ± 0.35[a]	1.31 ± 0.22
Triglycerides (mmol/liter)	1.28 ± 0.46[a]	2.22 ± 0.96
Total cholesterol/HDL-cholesterol (mmol/liter)	3.46 ± 0.69[a]	4.26 ± 1.0
Triglycerides/HDL-cholesterol (mmol/liter)	0.819 ± 0.40[a]	1.81 ± 0.97
Free fatty acids (mmol/liter) (n = 20, 19)	0.623 ± 0.20	0.703 ± 0.18
ApoA1 (g/liter) (n = 22, 20)	1.43 ± 0.17	1.34 ± 0.18
ApoB (g/liter) (n = 22, 20)	1.01 ± 0.14	1.10 ± 0.17
Lp(a) (mg/liter) (n = 16, 21)	167.3 ± 162	409.5 ± 455
Systolic blood pressure (mm Hg)	123.3 ± 18.6	124.7 ± 14.0
Diastolic blood pressure (mm Hg)	75.0 ± 9.5	79.1 ± 7.7
$VO_{2\ peak}$ (ml/kg · min) (n = 21, 22)	18.0 ± 3.9	16.5 ± 2.9

Values are means ± SD.
[a] Significantly different from the at risk group ($P < 0.01$).

TABLE 3. Insulin sensitivity indexes of MHO and at risk individuals

Insulin sensitivity indexes	MHO (n = 22)	At risk (n = 22)
Fasting glucose (mmol/liter)	4.90 ± 0.48	5.13 ± 0.55
Fasting insulin (μU/ml) (n = 22, 21)	12.11 ± 4.5[a]	20.53 ± 8.4
HOMA (n = 22, 21)	2.70 ± 1.2[a]	4.68 ± 1.9
QUICKI (n = 22, 21)	0.335 ± 0.02[a]	0.309 ± 0.02
$IS_{(clamp)}$ (n = 22, 21)	309.7 ± 86.5[a]	163.2 ± 38.7
$M_{(clamp)}$ (mg/min · kg)	7.98 ± 1.4[a]	4.20 ± 0.76
$M/FFM_{(clamp)}$ (mg/min · kg FFM)	15.35 ± 2.3[a]	7.69 ± 1.3
$Glycemia_{(steady\text{-}state)}$ (mmol/liter)	4.86 ± 0.47	4.77 ± 0.38
$Insulin_{(steady\text{-}state)}$ (μU/ml) (n = 22, 21)	198.5 ± 21.9	219.6 ± 35.5

Values are means ± SD.
[a] Significantly different from the at risk group ($P < 0.05$).

group, only 35% of subjects had hsCRP levels more than 3 mg/liter *vs.* 80% in the at risk group (Fig. 1). When statistically controlling for visceral fat, significant differences in CRP levels between the groups were abolished (4.62 ± 3.1 *vs.* 3.07 ± 3.0 mg/liter; not significant).

We performed stepwise regression analysis to examine the independent predictors of glucose disposal. Table 6 illustrates the summary of the model. Our results shows that the variables of hsCRP, triglycerides, and the LBMI were independent predictors of glucose disposal, collectively explaining 32.0% of the variance ($P < 0.001$).

Discussion

The recognition of the MHO phenotype has been noted in the scientific literature, but little understanding has emerged to explain why MHO individuals do not present metabolic complications (23). These MHO individuals are insulin sensitive, normotensive, and have normal lipid profiles, despite having excessive fatness (2). It seems that only one study has investigated several metabolic variables that are associated with the protective profile of the MHO individual (5). In that study, MHO subjects were classified based on a cut point for insulin sensitivity using the HE clamp (> 8.0 mg/min·kg of lean body mass) and obese at risk subjects with impaired insulin sensitivity (<8.0 mg/min·kg of lean body mass). Results show that, despite similar levels of total body fatness in MHO and at risk obese postmenopausal women, MHO women showed 49% less visceral adipose tissue than at risk obese subjects. Consistent with the findings of higher insulin

TABLE 4. Body fat distribution of MHO and at risk individuals

Variables	MHO (n = 22)	At risk (n = 22)
SAT area (L4/L5, cm^2)	490.9 ± 128	512.9 ± 122
Superficial SAT area (cm^2)	250.1 ± 79.8	257.1 ± 68.0
Deep SAT area (cm^2) (n = 22, 21)	239.9 ± 56.8	257.4 ± 66.6
Abdominal fat (cm^2)	670.8 ± 149	740.0 ± 161
Visceral fat content (cm^2)	179.9 ± 53.9[a]	227.0 ± 64.6
Muscle attenuation	49.6 ± 3.7	54.7 ± 29.9

Values are means ± SD.
[a] Significantly different from the at risk group ($P < 0.05$).

TABLE 5. Inflammation markers of MHO and at risk individuals

Inflammation markers	MHO (n = 22)	At risk (n = 20)
hsCRP (mg/liter)	2.89 ± 2.8[a]	5.51 ± 3.7
Orosomucoid (g/liter)	0.822 ± 0.15	0.943 ± 0.21
Haptoglobin (g/liter)	1.17 ± 0.36	1.48 ± 0.59
Transferrin (g/liter)	2.44 ± 0.27	2.55 ± 0.38
Albumin (g/liter)	39.6 ± 3.4	40.4 ± 4.7
α-1 Anti-trypsin (g/liter)	1.19 ± 0.23[a]	1.38 ± 0.29
Ferritin (μg/liter)	50.4 ± 30	78.0 ± 66

Values are means ± SD.
[a] Significantly different from the at risk group ($P < 0.05$).

sensitivity in MHO women, they also showed a more favorable lipid profile, as evidenced by lower fasting triglycerides and higher HDL-cholesterol. In the present study, we confirm the results of Brochu *et al.* (5), which also show that MHO individuals has significantly lower visceral fat content and a more favorable lipid profile. Thus, identifying MHO individuals using either a glucose disposal rate cut point of 8.0 mg/min·kg of lean body mass or the upper quartile of glucose disposal rates produces comparable results.

To add to this body of literature, we attempted to provide new information on metabolic factors that characterize the profile of MHO postmenopausal women. For the first time, we found that a favorable inflammation profile was also a part of the protective profile of this unique subgroup of obese individuals. We hypothesized that inflammation markers were associated with and may play a protective role in MHO postmenopausal women. Results in the present study show that MHO women had 92.7% less CRP levels compared with the at risk subjects. This suggests that lower amounts of CRP levels, despite high levels of body fat, could contribute to the favorable metabolic profile observed in MHO individuals. In support of this idea, CRP concentrations explained 19.5% of the variation in glucose disposal in our cohort, which accounted for the greatest source of unique variance. This finding is in line with previous studies that suggest that CRP levels could be an important factor associated with variations in insulin sensitivity (7, 9, 24). It should be noted that, after controlling for visceral fat, the significant differences in CRP levels between the two groups were abolished. Therefore, this could suggest that lower CRP levels in MHO individuals appear to be a marker of lower visceral fat content. Although speculative, this could be due to lower levels of IL-6, which appears to be preferentially produced in visceral adipocytes and stimulates CRP production (25). In addition, despite a

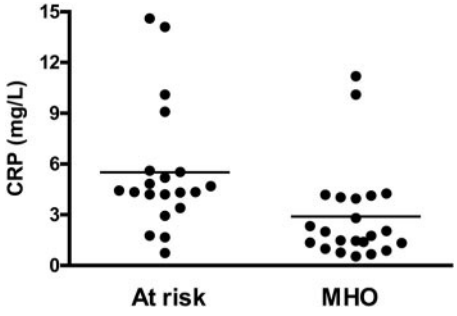

FIG. 1. Distribution and means of hsCRP levels in MHO and at risk subjects. Values are means ± SD.

TABLE 6. Stepwise regression analysis regarding independent predictors of glucose disposal in obese postmenopausal women

Dependent variable	Step	Independent variable	Relationship (+/−)	Partial r^2	Total r^2 cumulative	β coefficients	*P* value
Glucose disposal (mg/min · kg)	1	CRP	−	0.195	0.195	−0.295	0.006
	2	Triglycerides	−	0.085	0.280	−0.268	0.005
	3	LBMI	−	0.040	0.320	−0.231	0.032

significant mean difference, there is an overlap of CRP level between MHO and at risk subjects, underlying that, within each group, there is an important heterogeneity for the inflammatory profile (Fig. 1). Results observed with CRP are, however, strengthened by similar results obtained with another inflammatory protein. That is, α-1 antitrypsin levels were also significantly lower in MHO individuals compared with at risk subjects (1.19 ± 0.23 *vs.* 1.38 ± 0.29 g/liter, respectively). It has been shown that high levels of inflammation-sensitive plasma proteins such as α-1 antitrypsin are associated with insulin resistance (12). Moreover, higher levels of α-1 antitrypsin have been associated with an increased risk of myocardial infarction in men with low and high cardiovascular risk (26). Possible underlying mechanisms that have been associated with inflammation and insulin resistance have been reviewed previously (27). For example, it has been shown that insulin resistance could increase hepatic CRP production by attenuating the effect of insulin on the inhibition of acute-phase protein synthesis (28).

The second variable associated with a more favorable metabolic profile in MHO women was fasting triglycerides, explaining 8.5% of the variance of glucose disposal rates in our cohort. High levels of plasma triglycerides have been associated with an increase in insulin resistance (29), which has also been reported as a risk factor for cardiovascular disease (30). In the present study, we showed that fasting triglycerides were significantly lower in MHO subjects compared with at risk individuals (1.28 ± 0.46 *vs.* 2.22 ± 0.96 mmol/liter, respectively). Finally, the third variable associated with the protective profile in the MHO individual was the LBMI, explaining 4.0% of the variance in glucose disposal rates. The contribution of lean body mass to the pathogenesis and development of the metabolic syndrome has been reviewed previously (31). A general belief based on studies conducted over the past decades suggests that a high muscle mass is associated with higher insulin sensitivity. It is likely that this concept has been spread over the years because of the well-known role of muscle mass as an organ for glucose storage and utilization despite limited scientific data to support this notion. Interestingly, in a recent study, You *et al.* (32) reported that the metabolic syndrome was associated high lean body mass and high visceral fat content in older obese postmenopausal women. In the present study, lean body mass and visceral fat content in MHO subjects were significantly lower than at risk individuals (40.4 ± 3.8 *vs.* 47.4 ± 7.6 kg; 179.9 ± 53.9 *vs.* 227.0 ± 64.6 cm^2, respectively). Therefore, this could suggest, at least in part, that high lean body mass may be a potential modulator of insulin resistance in sedentary obese postmenopausal women.

The present study has several limitations. First, our cohort is only composed of nondiabetic sedentary obese postmenopausal women. Therefore, our findings are limited to this population. Second, we used a cross-sectional approach, which does not allow us to conclude to any causal associations between insulin sensitivity and inflammation markers as well as other metabolic risk factors in our cohort. Despite these limitations, our results are strengthened by using gold standard techniques as well as studying a well-characterized cohort with the measurement of various inflammation markers in a relatively large sample size.

In conclusion, results of the present study indicate that postmenopausal women displaying the MHO phenotype present a favorable inflammation profile as shown by lower CRP and α-1 antitrypsin levels than at risk subjects. This suggests that a low-grade inflammation state, in particular slight elevated circulating CRP levels, could play a role in the metabolic profile of obese women at risk and that lower CRP levels could be involved in the protective profile of the MHO individual, and this may be associated metabolically to a lower risk for cardiovascular disease.

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