Is There a Threshold of Visceral Fat Loss That Improves the Metabolic Profile in Obese Postmenopausal Women?

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It is presently unclear how much visceral adipose tissue (VAT) loss is needed to induce favorable metabolic changes. Cross-sectional studies have proposed that a threshold level of VAT exceeding 110 cm^2 in women induces deleterious changes in the metabolic profile. It is presently unclear, however, if significant decreases in VAT below this given threshold significantly improve the metabolic profile more as compared to decreases that remain below 110 cm^2. To examine whether achieving versus not achieving the proposed VAT threshold impacts differently on the metabolic profile in postmenopausal women, we examined the effects of a VAT loss below the 110-cm^2 threshold versus those individuals who remained higher than 110 cm^2 after a weight loss program. Twenty-five sedentary obese (baseline % body fat, 47.7% ± 4.1%; [mean ± SD]) postmenopausal women aged between 51 and 71 years (59.7 ± 5.6 years) and displaying high baseline levels of VAT accumulation (223 ± 45 cm^2) were submitted to a 1-year weight loss program with weight stabilization periods before and after weight reduction. Based on their loss of VAT after weight loss, subjects were characterized as "attainers" (post VAT levels < 110 cm^2; average, 96 ± 10 cm^2; n = 10) or "non-attainers" (post VAT levels > 110 cm^2; average, 171 ± 34 cm^2; n = 15). We compared changes in (1) plasma lipid-lipoprotein levels, (2) insulin sensitivity (euglycemic/hyperinsulinemic clamp), and (3) supine resting blood pressure between groups who achieved these 2 distinct levels of VAT. Attainers showed a 2-fold greater loss of VAT compared to non-attainers (−51.5% *v* −27.5%, *P* < .001). Attainers also showed a greater loss of body weight (−19.0% *v* −12.5%, *P* < .01) and fat mass (−34.8% *v* −18.4%, *P* < .001) after the program compared to non-attainers. Despite significant differences in the loss of total fat and VAT after the weight loss program, attainers and non-attainers showed comparable improvements for plasma high-density lipoprotein-cholesterol (HDL-chol) levels (+62.5% *v* +50.0%, *P* = not significant [NS]), cholesterol/HDL-chol ratio (−45.5% *v* −36.5%, *P* = NS), insulin sensitivity (+34.1% *v* +23.2%, *P* = NS), and resting systolic (−6.9% *v* −5.1%, *P* = NS) and diastolic (−11.3% *v* −11.1%, *P* = NS) blood pressure. These results do not favor the idea that attaining levels of VAT below a threshold of 110 cm^2 is necessary to favorably improve the metabolic profile in obese postmenopausal women. Achieving or not the proposed threshold of VAT, independently of baseline values, appears to yield similar metabolic improvements in obese postmenopausal women. More moderate losses of VAT appear to yield similar metabolic improvements as large losses.
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EXCESSIVE LEVELS of total body fat mass and particularly visceral adipose tissue (VAT) are associated with metabolic disturbances, such as dislipidemia, reduced glucose disposal, type 2 diabetes, and high blood pressure.[1-3] Williams et al[4] have proposed that obesity-related deteriorations in the metabolic profile are observed in women with VAT accumulations greater than 110 cm^2. Based on this proposal and the increased prevalence of generalized obesity in industrialized societies,[5,6] it is thus important to understand whether achieving a "critical level" of VAT is required to impact favorably on metabolic risk factors. That is, are there additional favorable changes on metabolic outcomes associated with losses under a critical level of VAT? One experimental strategy to address this question is to compare changes in metabolic outcomes in cohorts of individuals who achieve versus not achieve the proposed threshold of 110 cm^2 of VAT.[4]

The present study was conducted to examine this notion. Our hypothesis was that postmenopausal women who attained a level of VAT below 110 cm^2 would show greater improvements in their metabolic profile compared to those who remained above the threshold of 110 cm^2 after the weight loss program.

MATERIALS AND METHODS

Subjects

Twenty-five sedentary obese postmenopausal women aged between 51 and 71 years (59.7 ± 5.6 years [mean ± SD]) and displaying baseline levels of VAT ≥ 150 cm^2 (223 ± 45 cm^2) were studied. Women were included in the study if they had stopped menstruating for more than 1 year, and had a follicle-stimulating hormone level > 30 U/L. Participants were sedentary (<2 times a week of structured exercise), nonsmokers, and low to moderate alcohol consumers (≤2 drinks per day). All participants were apparently healthy and had no history or evidence on physical examination of (1) cardiovascular disease, peripheral vascular disease; or stroke; (2) diabetes; (3) moderate to severe hypertension (resting blood pressure >170/100 mm Hg); (4) orthopedic limitations; (5) body weight fluctuation > 5 kg in the previous 6 months; (6) thyroid or pituitary disease; and (7) medication that could affect cardiovascular function or metabolism. All participants signed an informed consent document. The University of Vermont Medical Sciences Committee on Human Research approved the study.

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Overview of Protocol

Women who were eligible for the study at screening were weight stabilized and were tested during 2 inpatient visits separated by 2 weeks at the General Clinical Research Center at the University of Vermont. Subjects were also weight-stable between the 2 visits. The first inpatient visit included measures of body composition, body fat distribution, and fasting blood draws for lipid and lipoprotein levels. The second inpatient visit included blood draws for lipid and lipoprotein levels, and a hyperinsulinemic/euglycemic clamp. An identical testing sequence was repeated after the weight loss program. This cohort was used in previous publications by our group.[1,7]

Weight Stabilization

Before and after the weight loss protocol, participating volunteers were submitted to a weight stabilization period (within 2 kg of body weight) that lasted on average 38 ± 22 days before pretesting and 84 ± 40 days before postintervention. The goal of this approach was to stabilize the various metabolic variables of interest that could have been altered by important body weight fluctuations (>2 kg) before and during the testing sequence. Macronutrient intake was also stabilized 3 days prior to testing with a standard diet provided by the metabolic kitchen of the General Clinical Research Center (GCRC) containing 55% carbohydrate, 30% fat, and 15% protein.

Weight Loss Protocol

Subjects entered into a medically supervised weight loss program, aimed at reducing body weight to approximately 120% of ideal body weight value if possible, as determined from the Metropolitan Life Insurance Tables.[8] The program consisted of a 1,200-kcal/d American Heart Association Step 2 Diet.[9] Food was self-selected with dietitian supervision on macronutrient selection, with or without the use of a modified fasting supplement (Medifast, Take Shape, Jason Pharmaceuticals, Baltimore, MD). During the weight loss program, participants were invited to participate in a weekly meeting/classroom to educate volunteers regarding the benefits of a low-fat diet as a component of their life. Subjects were in the weight loss protocol for an average duration of 13 ± 3 months, including weight stabilization prior to metabolic testing.

Peak Oxygen Consumption

Subjects performed a graded exercise test on treadmill to voluntary exhaustion to measure peak oxygen consumption (Vo_2) as previously described.[10] This test was done only at baseline. Standard 12-lead electrocardiograms were performed at the end of each 2-minute stage. Peak Vo_2 (L/min) was considered to be the highest value obtained during the test. Expired gas was analyzed during the exercise protocol using a Sensormedics Horizon metabolic cart (Yorba Linda, CA). Data collection included oxygen consumption (Vo_2) and respiratory exchange ratio (CO_2 production/O_2 consumption).

Body Composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance. Fat mass, lean body mass (LBM), and percentage of body fat were assessed using dual-energy X-ray absorptiometry (DEXA, model DPX-L; Lunar Radiation Corp, Madison, WI) as previously described.[11,12] During the scan procedure, subjects were asked to wear only a standard hospital gown and to maintain their supine position.

Computed Tomography

Visceral and subcutaneous adipose tissue were measured by computed tomography (CT) as previously described[13] using a GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI). 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 level using a scout image of the body. VAT area was quantified by delineating the intra-abdominal cavity at the internal most aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. Fat was highlighted and computed using an attenuation range of −190 to −30 Hounsfield Units (HU). The subcutaneous fat area was quantified by highlighting fat located between the skin and the external most aspect of the abdominal muscle wall.

CT was also used to measure mid-thigh cross-sectional skeletal muscle and fat areas, and muscle attenuation, the latter representing an estimate of muscle fat content.[14,15] Areas of skeletal muscle, fat, and muscle attenuation were calculated by delineating the regions of interest and then computing the surface areas using an attenuation range of −190 to −30 HU for fat, and 0 to 100 HU for skeletal muscle. Test-retest measures of the different body fat distribution indices on 10 CT scans yielded a mean absolute difference of ±1%.

Insulin Sensitivity Measurement During the Clamp

Basal and insulin-stimulated glucose kinetics were measured by the hyperinsulinemic-euglycemic clamp technique as described by DeFronzo et al[16] and implemented in our laboratory.[1,17] All subjects were tested after a 12-hour overnight fast at the GCRC and 3 days of standardized meals. An intravenous catheter was placed in an antecubital vein and a second one was placed retrograde in the contralateral hand for blood sampling. The hand was warmed in a box by a gentle stream of heated air (50 to 55°C) to produce arterialized venous blood. At 9 AM, the insulin infusion began and continued for an additional 2 hours. Insulin was infused at a rate of 240 pmol/m^2/min to attain postprandial peripheral insulin levels and suppress hepatic glucose output. Blood glucose was monitored every 5 minutes during the insulin infusion, and euglycemia was maintained throughout the clamp by infusing 20% dextrose at a variable rate. The rate of exogenous dextrose infusion reached a constant value by the second hour of the clamp. The mean rate of exogenous dextrose infusion during the last 30 minutes of the clamp was considered as the insulin sensitivity index or "M" value. Results from our laboratory for the entire cohort indicated coefficients of variation of 7% among subjects and 5% within subjects for the plasma glucose levels during the clamp, and concentrations of insulin achieved during the clamp at baseline were 716 ± 172 pmol/L (results not shown).

Biochemical Analyses

Plasma glucose concentrations were determined using a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin concentrations were estimated by modification of the radioimmunoassay technique of Starr et al.[18]

Plasma Lipid Profile Analysis

After a 12-hour fast, blood samples were obtained in the morning from an antecubital vein and stored into vacutainer tubes containing EDTA. Cholesterol and triglyceride concentrations in plasma and lipoprotein fractions were determined by enzymatic methods.[19,20] High-density lipoprotein-cholesterol (HDL-chol) fraction was measured in plasma supernatant after precipitation with dextran sulfate and magnesium sulfate.[21] The formula of Friedewald et al[22] was used to calculate plasma low-density lipoprotein-cholesterol (LDL-chol) concentrations.

Blood Pressure

As previously described,[23] systolic and diastolic sitting blood pressure were determined as the average of the last 4 readings of 5 (at 1/min) from a Dinamap (Johnson & Johnson, Tampa, FL) automatic

Table 1. Baseline Characteristics and Body Composition Before and After the Weight Loss Program

	Non-attainers (n = 15)			Attainers (n = 10)		
	Pre	Post	(% Change)	Pre	Post	(% Change)
Age (yr)	57.3 ± 4.7	—		59.3 ± 7.2	—	—
Peak $\dot{V}o_2$ (mL/kg/min)	18.8 ± 2.3	—		19.1 ± 3.0	—	—
Body weight (kg)	91.9 ± 13.7	80.4 ± 9.5‖	(−12.5)	85.4 ± 5.8	69.2 ± 6.5†¶	(−19.0)†
Body mass index (kg/m^2)	36.8 ± 5.6	31.8 ± 4.8‖	(−13.6)	33.1 ± 3.5	26.7 ± 3.5†¶	(−19.3)†
DEXA measures						
Percent body fat (%)	49.0 ± 4.0	46.0 ± 5.1¶	(−6.1)	45.6 ± 3.3*	37.3 ± 4.8‡¶	(−18.2)‡
Fat mass (kg)	43.5 ± 11.1	35.5 ± 10.6‖	(−18.4)	38.5 ± 4.7	25.1 ± 5.5†¶	(−34.8)‡
Lean body mass (kg)	45.7 ± 4.7	42.2 ± 3.2‖	(−7.7)	44.4 ± 4.4	41.6 ± 2.4§	(−6.3)
Bone mineral content (kg)	2.7 ± 0.3	2.7 ± 0.3	(0)	2.5 ± 0.2	2.5 ± 0.3	(0)

NOTE. Data are presented as means ± SD.
Mann-Whitney statistical analyses were used for comparisons between groups before and after treatment: *$P < .05$, †$P < .01$, ‡$P < .001$.
Wilcoxon signed rank tests were used to measure the effect of treatment within each group: §$P < .05$, ¶$P < .005$, ‖$P < .0005$.

machine. An appropriate cuff size was selected for each subject based on arm circumference. Measurements were performed in the Clinical Research Center more than 3 hours after the subject had checked in for an overnight stay and 4 hours after lunch. Conditions were carefully standardized: no talking, cuff on the right arm, and 10 minutes of rest.

Statistical Analyses

The post weight loss VAT area was compared to the threshold proposed by Williams et al[4] to characterize subjects as "attainers" (post VAT <110 cm^2; n = 10) or "non-attainers" (post VAT >110 cm^2; n = 15). Data are presented as means ± SD. Because of the number of subjects in each group, Mann-Whitney statistical analyses for nonparametric distribution were used to compare means. Wilcoxon signed rank test were used to determine the effect of treatment. Stepwise multiple linear regression analyses were used to determine which variables independently predicted changes in variables of interest. A level of significance of $P < .05$ was used for hypotheses testing. All statistical analyses were performed using Stat View 4.01 (Stat View 5.0.1; SAS Institute, Cary, NC) and Jump 3.1 (JUM 4.0.2; SAS Institute) statistical software programs.

RESULTS

Body Composition

Table 1 shows pre- and post-weight loss values for physical characteristics and body composition. Attainers and non-attainers, at baseline, were similar for age, Vo_2 max, body weight, body mass index, fat mass, lean body mass, and bone mineral content. However, the groups were different for baseline percent body fat ($P < .05$). Wilcoxon signed rank tests showed that both groups significantly lowered body weight, body mass index, percent body fat, fat mass, and lean body mass after the caloric restriction program (P values ranging from .05 to .0001). A group-by-time interaction term revealed that attainers showed significantly greater loss in percent body fat and fat mass after the weight loss program than non-attainers ($P < .005$, results not shown). After the weight loss program, attainers had a significantly lower body weight, body mass index, percent body fat, and total fat mass than non-attainers (P values ranging from .01 to .001). No effect of treatment was observed for bone mineral content.

Body Fat Distribution

Table 2 shows that both groups were similar for measures of body fat distribution at baseline. However, attainers showed significant lower leg muscle attenuation values than non-attainers at baseline ($P < .05$). Wilcoxon signed rank tests revealed that both groups significantly reduced subcutaneous and visceral adipose tissue at the L4-L5 level, as well as mid-thigh subcutaneous adipose tissue and muscle area (P values ranging from .05 to .0001). Both groups also significantly improved muscle attenuation after the caloric restriction program. Significant group-by-time interaction terms indicate that attainers showed greater reductions in their levels of abdominal subcutaneous fat ($P < .01$; results not shown). A trend was also

Table 2. Body Fat Distribution Measured by Computed Tomography Before and After the Weight Loss Program

	Non-attainers (n = 15)			Attainers (n = 10)		
	Pre	Post	(% Change)	Pre	Post	(% Change)
Abdominal level (L4-L5)						
Subcutaneous fat (cm^2)	514 ± 122	439 ± 146¶	(−14.6)	468 ± 94	291 ± 105†‖	(−37.8)‡
Visceral fat (cm^2)	236 ± 60	171 ± 34#	(−27.5)	198 ± 37	96 ± 10‡‖	(−51.5)‡
Mid-thigh level						
Subcutaneous fat (cm^2)	208 ± 63	183 ± 56§	(−12.0)	186 ± 42	147 ± 61§	(−21.0)
Muscle area (cm^2)	113 ± 13	104 ± 9‖	(−8.0)	108 ± 15	98 ± 11¶	(−9.3)
Leg muscle attenuation (HU)	45.0 ± 4.2	47.8 ± 5.6‖	(+5.5)	41.3 ± 3.4*	45.9 ± 5.7§	(+11.1)

NOTE. Data are presented as means ± SD.
Mann-Whitney statistical analyses were used for comparisons between groups before and after treatment: *$P < .05$, †$P < 0.01$, ‡$P < .001$.
Wilcoxon signed rank tests were used to measure the effect of treatment within each group: §$P < 0.05$, ¶$P < 0.01$, ‖$P < 0.005$, #$P < .001$.

Table 3. Metabolic Profile Before and After the Weight Loss Program

	Non-attainers (n = 15)			Attainers (n = 10)		
	Pre	Post	(% Change)	Pre	Post	(% Change)
Fasting plasma lipid profile						
Total cholesterol (mg/dL)	200 ± 42	216 ± 45‡	(+8.0)	184 ± 25	185 ± 21*	(+0.5)
Triglycerides (mg/dL)	192 ± 75	155 ± 43‡	(−19.3)	134 ± 58	113 ± 50*	(−15.7)
LDL-chol (mg/dL)	130 ± 44	137 ± 40	(+5.3)	125 ± 31	111 ± 17	(−11.2)
HDL-chol (mg/dL)	32 ± 7	48 ± 11§	(+50.0)	32 ± 5	52 ± 4§	(+62.5)
Chol/HDL-chol (mg/dL)	7.4 ± 2.2	4.7 ± 1.1§	(−36.5)	6.6 ± 1.4	3.6 ± 0.5†§	(−45.5)
Insulin sensitivity during the clamp						
M (mg/min)	314 ± 143	355 ± 170	(+13.1)	374 ± 167	480 ± 173‡	(+28.3)
M/LBM (mg/min/kg)	6.9 ± 2.9	8.5 ± 4.1	(+23.2)	8.5 ± 4.0	11.4 ± 3.9‡	(+34.1)
Resting blood pressure (mmHg)						
Systolic	136 ± 17	129 ± 13‡	(−5.1)	130 ± 16	121 ± 14‡	(−6.9)
Diastolic	72 ± 12	64 ± 11§	(−11.1)	71 ± 12	63 ± 12‡	(−11.3)

NOTE. Data are presented as means ± SD.

Mann-Whitney statistical analyses were used for comparisons between groups before and after treatment. *$P < .05$, †$P < .01$.

Wilcoxon signed rank tests were used to measure the effect of treatment within each group. ‡$P < 0.05$, §$P < .005$.

observed for a greater reduction in VAT for attainers ($P < .06$; results not shown). No significant group-by-time interaction term was observed for measures obtained at mid-thigh level. By design, attainers had significantly lower abdominal subcutaneous adipose tissue ($P < .01$) and VAT ($P < .001$) levels than non-attainers after the weight loss program.

Metabolic Profile

Table 3 shows that baseline values between groups were comparable for the lipid-lipoprotein profile, absolute and relative levels of insulin sensitivity, as well as resting systolic and diastolic blood pressure. Wilcoxon signed rank tests showed that the non-attainer group significantly increased total plasma cholesterol concentrations ($P < .005$) and decreased plasma triglyceride levels ($P < .005$) after the weight loss program. Interestingly, Wilcoxon signed rank analyses revealed similar and significant improvements for plasma HDL-chol levels and Chol/HDL-chol ratio after the weight loss program in both groups.

Results regarding the hemodynamic effects of the weight loss program indicated that both groups displayed similar changes for resting systolic (non-attainers: 136 ± 17 to 129 ± 13 mm Hg; attainers: 136 ± 17 to 129 ± 13 mm Hg; $P < .05$ in both cases) and diastolic blood pressure (non-attainers: 72 ± 12 to 64 ± 11 mm Hg; attainers: 71 ± 12 to 63 ± 12 mm Hg; $P < .01$ in both cases).

Finally, our results revealed that absolute and relative glucose disposal rates were improved but this only achieved statistical significance in the attainer group following the weight loss program (Table 3). Stepwise analyses indicated that improvements observed in glucose disposal were associated with baseline muscle attenuation and changes in muscle mass, explaining 23% ($P < .05$) and 20% ($P < .03$) of the variation observed, respectively (results not shown).

DISCUSSION

The accumulation of VAT above 110 cm^2 has been proposed as a potential threshold value associated with deteriorations in the metabolic profile.[4] Although intriguing, this threshold was initially proposed using cross-sectional data, and has not been tested using an intervention experimental design. To examine this concept, we studied 2 groups of obese postmenopausal women; the first group attained a VAT level below 110 cm^2 and the second group remained above the 110 cm^2 threshold level after the weight loss program.

Lipid Profile

The first finding is that despite a 2-fold greater loss in VAT between attainers (51.5%) versus non-attainers (27.5%), comparable improvements in the lipid profile were noted after the weight loss program. Previous studies have shown that minor decreases in total body weight (5% to 10%) favorably impact on metabolic risk factors associated with coronary artery disease.[24,25] This notion is consistent with the present study in which we noted that the non-attainers lost a 12.5% of their body weight, but significantly improved their lipid profile to the same extent than the attainers, with a 19.3% decrease in body weight. Although we acknowledge that biological thresholds are somewhat arbitrary, it does not appear that reaching a VAT value below 110 cm^2 (threshold proposed by Williams et al[4]) yields significantly greater improvements in the lipid profile than remaining over that level of VAT in postmenopausal women.

Glucose Disposal

The second major finding of the present study is that both groups increased the rate of glucose disposal, although this trend did not reach statistical significance in the non-attainer group. However, no difference was observed between groups for baseline values, post weight loss value, nor the delta change in glucose disposal. This may partly be due to the relatively small number of subjects in the study. The small subject size may also explain the fact that no correlation was observed between changes in VAT levels (absolute and relative) and variations in glucose disposal (results not shown). Further analyses using stepwise regression approaches revealed that baseline muscle attenuation (marker of muscle triglyceride content) and variations in lean body mass were the most important predictors of glucose disposal improvements in our

cohort of obese postmenopausal women after weight loss (result not shown). On the other hand, we found larger losses of VAT and a greater improvement in insulin sensitivity in the attainer group. These observations are in agreement with works from Kelley and Goodpaster showing that variations in insulin sensitivity are closely associated with muscle triglyceride content,[26] as well as recent data by the same group suggesting that the relationship between VAT loss and glucose disposal improvements is nonlinear.[27]

Resting Blood Pressure

Similarly to what we observed for the lipid profile, comparable improvements in resting systolic and diastolic blood pressure were reported after the weight loss program, despite large differences in total fat mass or VAT loss. Once again, achieving the proposed threshold of VAT did not contribute to further improve the hemodynamic profile of obese individuals.

In the present study, we have used a cut-off point of 110 cm^2, as this value as been reported to be associated with the presence of several metabolic alterations.[4] Additional studies have suggested different thresholds, that is, a value of 130 cm^2 has also been proposed.[28,29] We have performed other analyses using this threshold and, although the number of subjects in each group was different, results obtained were very similar to those obtained when the cut-off point of 110 cm^2 was used (results not shown).

Several limitations of our study should be noted. It is likely that the relatively normal metabolic profile in this sample of obese women at baseline may have led to the underestimation of metabolic improvements. For example, no changes were observed for LDL-chol levels. Incidentally, Nicklas et al[30] reported that postmenopausal women with the most abnormal baseline metabolic profile showed the greatest improvement in these measures after weight loss, which is in agreement with our observations. Moreover, because very few subjects in our study ($n = 5$) lost less than 20% of their baseline VAT value, it is unclear whether even smaller losses of VAT than those observed in our study improved the metabolic outcomes. Lastly, we suggest that larger samples of individuals be tested to more rigorously examine the relationship between loss of VAT and metabolic outcomes. Threshold changes among biologic variables are more rigorously addressed using larger sample sizes that attempt to examine a wider continuum of changes, instead of relying on a dichotomy approach (ie, above or below a given value).

Nonetheless, our observations do suggest obese postmenopausal women who achieve the proposed VAT threshold of 110 cm^2 yield comparable benefits in metabolic and hemodynamic variables as those who remained above the threshold after the weight loss program.

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