Computed Tomography Study of the Effect of Orlistat on Visceral Adipose Tissue Volume in Obese Subjects

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ABSTRACT: **Background:** Obesity has become a major public heath problem worldwide.

Objectives: To examine the effect of orlistat in promoting weight loss and its specific effect on visceral adipose tissue and subcutaneous adipose tissue as evaluated by computed tomography.

Methods: A prospective case series study of 10 obese subjects was conducted. The 6 women and 4 men, age 50–67 years (mean 59 ± 8 years), had a mean body mass index of 34.1 ± 3.2 kg/m^2. All subjects were prescribed a mildly hypocaloric diet (600 kcal/day deficit). In addition, all subjects were treated with orlistat 120 mg 3 times a day for 20.1 ± 7 weeks.

Results: The subjects had lost approximately 8.2 kg each, or 8.4% of their initial body weight. Mean body weight decreased from 98 ± 13 to 89.8 ± 13.6 kg at the last follow-up visit ($P = 0.0001$); mean BMI decreased from 34.1 ± 3.2 to 30.3 ± 3.9 kg/m^2 ($P = 0.0001$), and mean waist circumference from 113.8 ± 11.4 to 107.6 ± 10 cm ($P = 0.0006$). Mean total abdominal adipose tissue volume, evaluated by computed tomography, decreased from 426 ± 104.3 to 369.8 ± 99.6 mm^3 ($P = 0.0001$). Mean abdominal SAT volume decreased from 251.1 ± 78.8 to 224 ± 81.1 mm^3 ($P = 0.006$), and mean abdominal VAT volume decreased from 176 ± 76.7 to 141.6 ± 67 mm^3 ($P = 0.0001$). Thus, the total abdominal adipose tissue volume for the whole group decreased by 15.4%, and most of this decrease was attributable to the reduction in VAT (24.8%) as opposed to SAT (only 12% reduction) ($P = 0.03$). The weight reduction that occurred during the study was accompanied by a statistically significant reduction in levels of total cholesterol, low density lipoprotein-cholesterol, triglycerides, and fasting blood glucose.

Conclusions: Our results demonstrate the effect of orlistat in reducing human visceral adipose tissue as evaluated by CT. The benefit of the treatment is further supported by the statistically significant reduction in cardiovascular risk factors.

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KEY WORDS: obesity, computed tomography, adipose tissue, cardiovascular risk, orlistat

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Obesity is becoming increasingly common and has been recognized as a major public health problem worldwide [1-3]. Obesity induces multiple metabolic abnormalities that contribute to the pathogenesis of diabetes mellitus and cardiovascular disease [4-6]. It is associated with an increased morbidity and mortality risk, causing an estimated 280,000 to 325,000 deaths annually in the United States [1-3].

There is growing evidence that obesity-related risks are associated with the regional distribution of body fat rather than the quantity of body fat [7-13]. Furthermore, it is important to distinguish between subcutaneous adipose tissue that contains small insulin-sensitive adipocytes and the deeper visceral adipose tissue which is metabolically more active. These findings highlight the clinical relevance of evaluating regional body fat distribution in the fight against obesity. The diagnostic gold standard method at present is computed tomography, which has been found to differentiate VAT from SAT [14-18].

Pharmacologic therapy has been proposed as an adjunct to diet, exercise and lifestyle changes to improve long-term weight loss. Studies have shown that orlistat (Xenical®, Hoffmann La Roche, Nutley, NJ, USA), a hydrogenated derivative of a bacterial lipase inhibitor, promotes weight loss by blocking the action of gastrointestinal and pancreatic lipases. A dose of 120 mg three times daily reduces dietary fat absorption by approximately 30% [7-9].

The aim of the present study was to examine the effect of orlistat in promoting weight loss and its specific effect on the VAT and SAT as evaluated by CT. To the best of our knowledge, this is the first report in the English-language medical literature on the influence of orlistat on body fat distribution using CT.

SUBJECTS AND METHODS

A prospective case series design was used. The study group consisted of 10 obese subjects (6 women, 4 men) aged 50 to 67 years (mean 59 ± 8 years). Mean body mass index was 34.1 ± 3.2 kg/m^2, and mean height was 169 ± 6 cm. All subjects volunteered to participate in the study and provided written informed consent. Subjects with uncontrolled hypertension,

BMI = body mass index
SAT = subcutaneous adipose tissue
VAT = visceral adipose tissue

pharmacologically treated diabetes, or significant cardiac, renal, hepatic, gastrointestinal, psychiatric or endocrine disorders were excluded. Other exclusion criteria were weight loss of more than 4 kg in the 3 months preceding the study, surgery for weight reduction, bulimia or laxative abuse, use of any drug that might have influenced body weight or plasma lipids in the month before the study, and drug or alcohol abuse. The study protocol was approved by the institutional ethics committee.

At the start of the study, the subjects were prescribed a mildly hypocaloric diet (< 600 kcal/day deficit of which fat accounted for approximately 30% of the energy supply). In addition, all subjects were treated with orlistat (Xenical®), 120 mg 3 times a day, for 20 ± 7 weeks

ANTHROPOMETRY MEASUREMENTS

The subjects were weighed on a scale barefoot and in light clothing. Weight was measured within 0.2 kg; height was measured to within 0.5 cm. Waist circumference was measured using a spring scale at the level midway between the lower rib margin and the iliac crest, at the end of gentle expiration, with the subject standing and wearing only underwear. BMI was calculated by computer as weight in kilograms divided by height in meters squared (kg/m^2).

COMPUTED TOMOGRAPHY

CT examinations were performed with the Helicat II CT scanner (Picker, Haifa, Israel). Patients were examined in the supine position, with both arms stretched above the head. Four contiguous overlapping scans were performed at the level of the L4-L5 disk space, starting at the inferior endplate of the L4 vertebra. Scan parameters were as follows: thickness 6.5 mm, scan interval 3 mm, tube voltage 140 kV, and tube current 250 mAs.

Using the 3D volume definition program to define density areas, we measured the total abdominal adipose tissue within the scanned volume, the VAT (i.e., intraabdominal fat), and the SAT. The TAT area was calculated by delineating the abdomen with a graph pen and then computing subcutaneous fat using an attenuation range of -190 to -30 Hounsfield units [10-13,15]. Within the muscle wall around the abdominal cavity, a line was drawn to measure the abdominal VAT area. The SAT area was obtained by subtracting the abdominal VAT area from the TAT area.

ASSESSMENT

A detailed medical history, physical examination, and measures of body weight, height, and waist circumference were recorded at the first visit and were remeasured at every visit. The last body weight measurement was recorded after 27 weeks. Plasma concentrations of cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, triglycerides, and glucose were measured at the beginning and end of the study. Blood pressure and heart rate were measured at each visit. Blood pressure was measured on the right arm with the patient in a sitting position after at least 5 minutes of rest, using an aneroid sphygmomanometer.

TAT = total abdominal adipose tissue

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation and categorical variables as number of patients (n) and frequency of patients (%). To test associations between variables, simple and partial correlation analyses were performed. Differences between observations for the same variable over time were evaluated by paired *t*-test.

All analyses were performed with SPSS for Windows (version 11, Chicago, IL). A two-tailed *P* value of < 0.05 was considered significant.

RESULTS

Subjects were followed for a mean duration of 20 ± 7 weeks. By the end of follow-up, the subjects had lost approximately 8.2 ± 4 kg each, or 8.4% of their initial body weight. Mean body weight decreased from 98 ± 13 at the start of the study to 89.8 ± 13.6 kg at the last follow-up visit ($P = 0.0001$); mean BMI decreased from 34.1 ± 3.2 to 30.3 ± 3.9 kg/m^2 ($P = 0.0001$); and mean waist circumference from 113.8 ± 11.4 to 107.6 ± 10 cm ($P = 0.0006$) [Table 1].

Table 1. Characteristics of study sample before treatment and after 20 weeks

	Pre-treatment	Post-treatment	*P*
Body weight (kg)	98 ± 13	89.8 ± 13.6	0.0001
Height (cm)	169 ± 5.6	169 ± 5.6	NS
BMI (kg/m^2)	34.1 ± 3.2	30 ± 3.9	0.0001
Systolic BP (mmHg)	138.3 ± 13.6	134.5 ± 15.6	NS
Diastolic BP (mmHg)	76 ± 11.5	69 ± 12.7	NS
Heart rate (bpm)	74.5 ± 12.5	71.5 ± 3.9	NS
Waist circumference (cm)	113.8 ± 11.4	107.6 ± 10	0.0006
Cholesterol (mg/dl)	203 ± 28.8	188.8 ± 31.5	NS
Triglycerides (mg/dl)	172 ± 54	123.5 ± 45.5	0.002
HDL (mg/dl)	45.6 ± 6.1	52.8 ± 16.3	NS
Triglycerides / HDL	3.9 ± 1.6	2.4 ± 0.9	0.005
LDL (mg/dl)	114.2 ± 33	116.2 ± 21.2	NS
Glucose (mg/dl)	115.5 ± 47.7	100.2 ± 14.2	NS
TAT (mm^3)	426 ± 104.3	369.8 ± 99.6	0.0001
SAT (mm^3)	251.1 ± 78.8	224 ± 81.1	0.006
VAT (mm^3)	176 ± 76.7	141.6 ± 67	0.002

Values are mean ± S.D

BMI = body mass index, BP = blood pressure, LDL = high density lipoprotein, LDL = low density lipoprotein, TAT = total adipose tissue, SAT = subcutaneous adipose tissue, VAT = visceral adipose tissue.

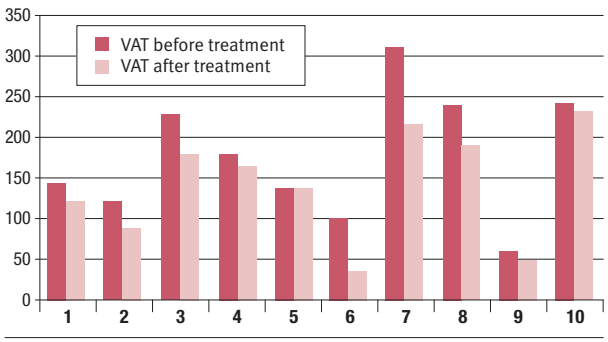
Mean abdominal TAT volume, evaluated by 3D volume definition CT, decreased from 426 ± 104.3 to 369.8 ± 99.6 mm³ (P = 0.0001). Mean abdominal SAT volume decreased from 251.1 ± 78.8 to 224 ± 81.1 mm³ (P = 0.006), and mean abdominal VAT volume decreased from 176 ± 76.7 to 141.6 ± 67 mm³ (P = 0.0001) [Tables 1 and 2 and Figure 1]. Thus, the TAT volume for the whole group decreased by 15.4%, and most of this decrease was attributable to the reduction in VAT (24.8%) as opposed to SAT (only 12% reduction) (P = 0.03) [Table 2]. Individually, on CT evaluation, the main reduction occurred in the intraabdominal fat in seven subjects and in the subcutaneous fat in three.

The weight reduction that occurred during the study was accompanied by a statistically significant reduction in levels of total cholesterol, LDL-cholesterol, triglycerides, and fasting blood glucose [Table 1]. We also observed a reduction in mean diastolic blood pressure, from 76 ± 11 to 69 ± 13 mmHg, and in mean systolic blood pressure from 138 ± 1 to 134 ± 16 mmHg, but the difference did not reach statistical significance [Table 1].

Table 2. CT measurements (mm³) of abdominal adipose tissue before and after treatment

	Pre-treatment			Post-treatment			
Patient no.	TAT	SAT	VAT	TAT	SAT	VAT	VAT reduction (%)
1	391.1	244.9	146.2	336.1	214.6	121.6	24.6 (16.8)
2	432.5	311.8	120.8	390.1	298.9	91	29.8 (24.6)
3	428	198.7	229.3	346.3	170.4	176	53.3 (23.2)
4	313.6	125.3	188.3	284.4	111.1	173.3	15 (8)
5	509.8	373.5	135.9	502.6	366	136.6	-0.7 (0)
6	346.3	248.9	97.4	230.9	155	34.2	63.2 (64.9)
7	588.4	285.4	307.4	470	251.1	218.9	88.5 (28.8)
8	392.4	155.8	236.6	323.2	140	183.2	53.4 (22.5)
9	285.2	227	60.2	288.7	237.6	51.1	9.1 (15.1)
10	578.7	340	238.7	525.6	295.3	230.3	8.4 (3.5)

Figure 1. CT measurements of ventral abdominal adipose tissue before and after treatment



DISCUSSION

The present prospective study in 10 obese subjects revealed that treatment with the gastrointestinal lipase inhibitor orlistat resulted in a weight loss of approximately 8.2 kg or 8.4% of initial body weight. This rate of weight loss, achieved within a mean of 20.7 ± 7 weeks, is close to the 9–10% weight loss reported in patients treated with orlistat for one year, compared to 4–6% in the placebo-treated group, in two controlled clinical trials of 2 years duration [7,8].

In daily practice, obesity is traditionally determined indirectly by the BMI or by waist circumference, a measure of abdominal obesity. However, neither of these measures quantifies the type and distribution of adipose tissue. Using CT for this purpose, we found that most of the reduction in TAT volume was accounted for by a decrease in VAT rather than SAT. In 7 of the 10 treated subjects, the main fat loss involved the VAT, and in only 3, the SAT. Overall, there was a 24.8% reduction in VAT and 12% in SAT. To the best of our knowledge, this is the first report in the English-language medical literature in which CT was used to confirm the effect of orlistat on body fat distribution. Although the recognized gold standard method to evaluate intraabdominal fat distribution (VAT, TAT, and SAT volumes) is multislice CT [14-17,19-22], we used single-slice CT at the L4-L5 level in order to minimize unnecessary exposure of our patients to X-rays. Several studies have reported a very high correlation between the VAT area on single-slice CT at L4-L5 and the VAT volume measured by multislice CT [19-22].

Similar findings to ours were reported by a group from Japan [25] at the 43rd Annual Meeting of the European Association for the Study of Diabetes (EASD) in 2007. Using a multicenter, controlled, double-blind design with CT evaluation, these authors demonstrated that rimonabant (Acomplia®, Sanofi Avantis, Paris, France) effectively reduced visceral fat in 526 obese subjects. The VAT area was reduced to a significantly greater extent in the group receiving rimonabant 20 mg (-40.6 cm²) than in the placebo group (-20.3 cm²) (P < 0.0001).

Adipose tissue, once considered a passive depot for energy stores, is now recognized as a potent and metabolically active endocrine organ. The human body contains two types of adipose tissue with different anatomic and metabolic characteristics: SAT is located directly under the skin and contains small insulin-sensitive adipocytes; VAT is wrapped around the organs in the abdomen and contains large insulin-resistant adipocytes. The VAT is metabolically more active. The visceral adipocytes secrete a variety of cytokines, including leptin, adiponectin, resistin, tumor necrosis factor-alpha, and interleukin-6. Tumor necrosis factor and IL-6 inhibit insulin receptor signaling and block insulin action. Thus, excess visceral fat, which is present in patients with abdominal obesity, leads to metabolic imbalances, such as lipid disorders, insulin resistance and type 2

LDL = low density lipoprotein

IL = interleukin

diabetes – all risk factors for cardiometabolic disease [23-25]; its reduction improves insulin sensitivity, lipid profile, and serum adipocytokine level [9]. Accordingly, we have demonstrated that even a modest weight loss and reduction in VAT were associated with a significant reduction in levels of total cholesterol, LDL-cholesterol, triglycerides and fasting blood glucose. We also observed a decrease, although not statistically significant, in diastolic and systolic blood pressure. These findings support CT measurement of VAT as better predictors of obesity-related risks than the BMI.

Our findings are in agreement with other controlled studies [7,8,] where the weight reduction in the patients treated with orlistat was accompanied by a greater decrease in plasma total cholesterol and LDL-cholesterol concentration than would have been expected from weight loss alone. This independent cholesterol-lowering effect is a consequence of the drug's ability to reduce energy uptake from fat and constitutes an important advantage of pharmacologic treatment of obesity.

In another study, Fox et al. [10] evaluated the abdominal CT findings of 3001 participants in the Framingham Heart Study and observed that VAT was more strongly associated with metabolic risk factors than SAT. In addition, in a study of 169 asymptomatic subjects, Arsenault and co-workers [13] reported more VAT accumulation in men with low, as opposed to high, cardiorespiratory fitness. The study stressed the importance of VAT as a predictor of coronary artery disease.

The present study has several limitations: First, the study was performed prospectively in a single center, so the sample size was small. Nevertheless, the association of a modest reduction in body weight, waist circumference and BMI with the reduction in VAT compared to SAT was statistically significant, as was the accompanying reduction in laboratory risk factors. Second, as mentioned, we used the 3D volume definition program to measure the TAT, VAT and SAT within the scanned area. However, several previous studies found this technique to be highly accurate [14-17,20,25]. Third, the high exposure to radiation with the use of CT remains a matter of concern. In order to minimize unnecessary X-ray exposure, we used single-slice CT at the level of L4-5. This decision was prompted by recent studies reporting a very high correlation between the VAT area measured on single-slice CT and VAT volume measured on multislice CT [19-22].

In summary, the present study provides the first direct evidence on the effects of orlistat in reducing human visceral adipose tissue. The benefit of this treatment was further supported by the statistically significant reduction in cardiovascular risk factors. More studies are needed to confirm the effect of orlistat on intraabdominal adipose tissue.

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