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Effects of Visceral Adipose Tissue Reduction on CVD Risk Factors Independent of Weight Loss: the Look AHEAD Study

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Abstract

Objectives—To determine if the reduction of visceral adipose tissue (VAT) volume by lifestyle intervention improved risk factors for cardiovascular disease (CVD) independently of weight loss amount.

Design—Ancillary study of randomized-controlled trial

Setting—Data analysis using multivariable regression models

Participants—Participants of the Look AHEAD (Action for HEalth in Diabetes) Fatty Liver Ancillary Study.

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Declaration

Competing interests: The authors declare that there is no conflict of interest

Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Guarantor: Jeanne Clark

Contributorship: A.S. analyzed and interpreted data, performed statistical analysis, wrote the manuscript, and reviewed/edited the manuscript. M.L. and S.U. analyzed and interpreted data and reviewed/edited the manuscript. F.L.B., S.B., H.P., and A.B. reviewed/edited the manuscript. J.M.C. provided the study concept and design, interpreted data, and reviewed/edited the manuscript.

Conflict of Interest

None.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

Main outcome measures—Correlations between changes in VAT and in CVD risk factors, while adjusting for weight loss and treatment (intensive lifestyle intervention [ILI] vs. diabetes support and education [DSE]).

Results—Of 100 participants analyzed, 52% were women, and 36% were black, with a mean age of 61.1 years. In the DSE group, mean weight and VAT changed by 0.1 % ($p=0.90$) and 4.3% ($p=0.39$), respectively. In the ILI group, mean weight and VAT decreased by 8.0% ($p<0.001$) and 7.7% ($p=0.01$), respectively. Across both groups, mean weight decreased by 3.6% ($p<0.001$), and mean VAT decreased by 1.2% ($p=0.22$); the decrease in VAT was correlated with the increase in HDL-cholesterol (HDL-C; $R=-0.37$; $p=0.03$). There were no correlations between changes in VAT and blood pressure, triglycerides, LDL-C, glucose, or HbA1c. After adjusting for age, race, gender, baseline metabolic values, fitness, and treatment group, changes in HDL-C were not associated with changes in VAT, while weight changes were independently associated with decrease in glucose, HbA1c, and increase in HDL-C.

Conclusions—VAT reduction was not correlated with improvements of CVD risk factors in a sample of overweight and obese adults with type 2 diabetes after adjusting for weight loss.

Keywords

Visceral adipose tissue; VAT; cardiovascular disease; weight loss

Introduction

Visceral adipose tissue (VAT) accumulation is associated with multiple cardiovascular disease (CVD) risk factors, including hypertension, impaired fasting glucose, type 2 diabetes, and metabolic syndrome [1]. Increased VAT volume increases free fatty acid secretion and the plasma levels of several proinflammatory cytokines such as C-reactive protein, tumor necrosis factor- α and interleukin-6 [2], which may contribute to CVD and its risk factors. Reduction of VAT could play a role in reducing dyslipidemia, improving insulin sensitivity, and lowering blood pressure [3].

Many short-term clinical trials have shown that weight loss, as a consequence of lifestyle intervention, reduces CVD risk factors [4–6]. One hypothesis is that this effect stems from reduced visceral adiposity. A weight reduction study in premenopausal female obese patients found that improved plasma glucose was more strongly correlated with decreased visceral fat volume than with decreased body weight [7]. A three-year lifestyle modification program showed that VAT change correlated with changes in triglycerides (TG), 120-min oral glucose tolerance test results, and fasting insulin levels after adjusting for changes in subcutaneous adipose tissue (SAT) [8].

Several studies have shown that exercise can improve CVD risk factors even in the absence of significant weight loss or after controlling for weight change [9, 10]. Gibbs et al. [9] reported that increased fitness caused small improvements in several CVD risk factors beyond weight loss. Additionally, other studies [10] found that blood pressure, HDL-cholesterol, TG, and insulin sensitivity improve with exercise even with minimal or no weight loss.

Moreover, Ross et al. [11] found that exercise without weight loss was associated with significant reductions in VAT. While exercise reduces VAT, it is unknown whether changes in VAT achieved through a comprehensive lifestyle intervention correlate with improvement in CVD risk factors after accounting for weight change. Furthermore, most studies have been performed in younger subjects without type 2 diabetes.

However, some scientists have proposed that both VAT and SAT have pathogenic potential [12]. They found that deep SAT has a higher proportion of saturated fatty acids, and most of the systemic circulating free fatty acid originates from SAT [13]. Thus, SAT is also strongly related to insulin resistance and cardiovascular risk [14].

Our study was aimed to examine the pathogenicity of VAT to cardiovascular disease. We hypothesized that VAT volume reduction would improve CVD risk factors independent of weight loss. To test this hypothesis, we investigated whether VAT reduction was associated with improved CVD risk factors, independent of the amount of weight loss, after 12 months using data from the Fatty Liver Ancillary Study of the Look AHEAD (Action for Health in Diabetes) trial.

Research Design and Methods

Study design, participants, and clinical characterization

The Look AHEAD study was a multicenter randomized trial designed to test the effects of an intensive lifestyle intervention (ILI) intended to produce weight loss in overweight or obese adults with type 2 diabetes. Participants were eligible if they had type 2 diabetes, were 45–76 years of age, and had a BMI of at least 25 kg/m². Participants had to pass a maximal graded exercise test (GXT) by achieving 4 metabolic equivalents (METs) and reaching 85% of age-predicted maximal heart rate (220 – age) or a score of 18 on the Borg rating of perceived exertion scale for participants taking a β -blocker [15]. Exclusion criteria included hemoglobin A1c (HbA1c) >11%, TG 600 mg/dL, or blood pressure 160/100 mm Hg. More detailed information about the study methods including the protocol, 1- and 4-year results, and results at the end of the trial have been published [4,16–18].

Eligible participants were randomized to one of two groups, either an ILI or a Diabetes Support and Education (DSE) group. Both interventions have been described in detail [16,17]. Participants in the ILI group were encouraged to lose at least 10% of their initial weight at 12 months through a combination of moderate caloric restriction (1,200–1,500 kcal/day for those individuals weighing <114 kg and 1,500–1,800 kcal/day for those weighing >114 kg, with <30% calories from fat and <10% from saturated fat) and increased physical activity with a goal of 175 minutes of moderate intensity physical activity per week. The DSE group was offered 3 educational sessions per year, addressing general topics of diet, exercise, and social support. Participants were not given counseling in behavioral strategies for changing diet and physical activity or individual goals, and were not weighed during the sessions.

In total, 244 participants at one Look AHEAD site, who were part of the Fatty Liver Ancillary Study, were eligible for the current analysis. Of these, 151 underwent proton

magnetic resonance spectroscopy (^1H MRS) at baseline, and 102 underwent a ^1H MRS at 12 months [19]. We used ^1H MRS to determine hepatic fat. We excluded 2 participants because of missing data on the main CVD risk factors (weight, blood pressure, fasting glucose, lipid profiles, insulin resistance), which resulted in the 100 participants that were included in these analyses.

Measurements

Participants underwent extensive data collection at baseline and at 12 months of the study. Data on age, sex, race/ethnicity, and medication use were obtained using a questionnaire. Height was measured at baseline using a standard stadiometer. Weight and waist circumference were measured on all participants at baseline and at 12 months by study staff who were masked to participants' treatment status. Blood samples for measurement of glucose, insulin, HbA1c, and lipids were obtained by venipuncture the morning after an overnight fast.

Cardiorespiratory fitness was measured at baseline by a maximal graded exercise test (GXT) and at 1 year by a submaximal GXT using the walking speed from the baseline test. Change in fitness was computed as the difference in estimated METS calculated based on the specific workload [20] between points during the baseline test, when >80% of maximal heart rate was attained, and termination of the 1-year test [4,21]. Rating of perceived exertion (RPE) was assessed using the Borg 15-category scale (range is on a scale from 6–20) during the last 15 seconds of each stage and at the point of test termination. If the participant was taking a beta-blocking medication, the baseline test was considered valid if RPE was ≤ 18 at the point of termination. For participants taking β -blockers at either time point, the submaximal test was terminated at the point when the participant first reported achieving or exceeding a rating of 16 on the RPE scale. Axial magnetic resonance T1-weighted images (8 slices, 10-mm thickness, 1-mm interslice distance) were acquired at vertebral bodies L2–L3. A breath-hold technique was applied to avoid breathing-induced artifacts. We used “NIH Image” software to estimate intra-abdominal fat volume, which comprises total adipose tissue (TAT), VAT, and SAT. These measurements were highly reliable, with intraclass correlation coefficients of 0.96–0.99 [22]. Hepatic steatosis was defined as $\geq 5\%$ hepatic fat by ^1H MRS.

Statistical analysis

Demographic characteristics, anthropometric measurement, laboratory results, and body composition data are described as proportion or mean and standard deviation as appropriate. Variables with significant deviation from normal distribution were transformed logarithmically before being analyzed. Insulin and Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) was analyzed after excluding 14 participants who were taking insulin. HOMA-IR was calculated according to the homeostatic model as $\text{Insulin (uIU/ml)} \times \text{Glucose (mmol/L)} / 22.5$. ANOVA, paired *t*-test, or Pearson's chi-square tests were used to compare continuous and categorical data across tertiles of VAT percentage reduction. We analyzed changes in body composition (TAT, SAT, and VAT) using absolute difference and relative change (percent change).

To examine the correlation between changes in weight, waist circumference, and adipose tissue composition with 1-year changes in cardiovascular and metabolic parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP], TG, HDL-C, LDL-cholesterol [LDL-C], fasting glucose, HbA1c, and HOMA-IR), we used Pearson's correlation coefficient. We tested for factors that significantly impact the cardiovascular and metabolic parameters (p value<0.05) in the univariate model. Additionally, we included those factors and used multiple linear regression models to investigate the independent association between VAT changes and changes in CVD risk factors, with and without adjustment for change in weight by reporting beta-coefficient, 95% confidence interval, and the explained variance (R^2) from 4 sequential models: 1) a baseline model with age, race, gender, baseline metabolic values, cardiovascular fitness, and treatment group (ILI or DSE); 2) a model that included all variables in model 1 plus change in weight only; 3) a model that included all variables in model 1 plus VAT change only; and 4) a model with all the variables in model 1 and both change in weight and change in VAT. For the analyses of lipid profile outcomes, we adjusted for lipid-lowering medications. Similarly, in the analyses of glycemic outcomes, we adjusted for antidiabetic medications; in the analyses of blood pressure outcomes, we adjusted for antihypertensive use.

We conducted sensitivity analysis of the multiple linear regression analysis using just the participants in the ILI group, because they were actively losing weight through the study intervention. We also conducted analysis using percent change in TAT instead of percent weight change. All statistical tests were two-sided, and p values <0.05 were considered significant. We used STATA version 12.0 (Stata Corporation, College Station, TX) to conduct all analysis.

Results

Population characteristics

We evaluated 100 participants: 46 in the ILI and 54 in DSE treatment arms, which included 52 women and 36 black participants, with a mean age of 61.1 (6.5) years and baseline weight of 100.5 (17.1) kilograms. There were no differences in gender, race, age, weight, cardiovascular fitness, and VAT at baseline between the two treatment arms. Table 1 shows baseline values, changes in weight at 12 months, waist circumference, CVD risk factors, fitness, and adipose tissue composition stratified by tertile of VAT reduction at 12 months. Participants in the highest tertile of VAT reduction (>9.4% loss) had significantly lower baseline HDL-C ($p=0.03$). After 12 months, weight decreased by 3.8 (8.3) kg ($p<0.001$) or 3.6 (7.4) % across both study arms, and mean VAT reduction was 6.0 cm³ ($p=0.22$) or 1.2%. Among the 100 participants, 69 and 50 participants lost VAT and weight, respectively. Only LDL-C ($p=0.04$), HbA1c ($p=0.02$), and hepatic fat ($p=0.03$) significantly decreased after twelve months. In DSE, mean weight and VAT increased by 0.1% ($p=0.90$; 95% CI: -1.6 to 1.4) kg and 4.3% ($p=0.39$; 95% CI: -18.6 to 7.3) cm³, respectively. In ILI, mean weight and VAT decreased by 8.0% ($p<0.001$; 95% CI: 5.7 to 10.9) kg and 7.7% ($p<0.01$; 95% CI: 5.4 to 34.0) cm³, respectively (Supplemental Table 1). No significant differences were found across tertiles of VAT change and changes in TAT, SAT, SBP, DBP, TG, glucose, HbA1c,

HOMA-IR, hepatic fat, or fitness. Distribution of VAT change in ILI and DSE were shown in Fig.1.

Correlations with CVD risk factors

Correlations of percent changes in weight, waist circumference, and adipose tissue composition (TAT, SAT, and VAT) with changes in CVD risk factors are shown in Table 2. Changes in weight and waist circumference were strongly correlated with changes in TAT, SAT, and VAT. Weight loss was correlated with an increase in HDL-C ($r=-0.30$) and correlated with a decrease in HbA1c ($r=0.27$). VAT reduction, however, was only correlated with an increase in HDL-C (correlation coefficient $=-0.37$, $p=0.03$) (Table 2).

Determinants of 1-year changes in CVD risk factors

Results of multivariable adjusted linear regression analyses for percent changes of weight and VAT and individual CVD risk factors are shown in Table 3. In model 1, the explained variance for changes in these risk factors ranged from 9.7 to 39.3%. In model 2, every percent reduction in weight was associated with a decrease in TG (beta coefficient =3.3, 95% CI 0.2–6.3; $p<0.05$) and fasting glucose (beta coefficient =1.9, 95% CI 0.5–3.4; $p<0.01$), and associated with an increase in HDL-C (beta coefficient $=-0.4$, 95% CI -0.7 to -0.2 ; $p<0.01$). These effects of weight loss were attributable for the additional 4.6% of explained variance for changes in TG, 11.9% in HDL-C, and 6.4% in glucose (Table 3). In model 3, every percent reduction in VAT was significantly associated only with an increase in HDL-C (beta coefficient $=-0.1$, 95% CI -0.2 to -0.03 ; $p<0.01$) and were attributable for the additional 7.9% of explained variance.

Finally, in model 4, we added both percent reduction in weight and VAT to model 1. In this model, every percent reduction in VAT was not significantly associated with any improvement in CVD risk factors. In contrast, every percent reduction in weight was associated with a decrease in glucose (beta coefficient = 2.7, 95% CI 1.0–4.3; $p<0.01$) and HbA1c (beta coefficient =0.04, 95% CI 0.004–0.08; $p<0.05$), and increased in HDL-C (beta coefficient = -0.3 , 95% CI -0.6 to -0.04 ; $p<0.05$). Percent changes in weight and VAT, in addition to the baseline model 1, accounted for 0.2–13.4% of the explained variance for changes in CVD risk factors.

Sensitivity analysis

A multiple regression analysis using only participants from the ILI group who were actively losing weight was performed (Table 4). In model 1, the explained variance for changes in these risk factors ranged from 5.3 to 61.9%. In model 2, every percent reduction in weight was associated with a decrease in TG (beta coefficient =2.6, 95% CI 1.1–4.8; $p<0.01$) and associated with an increase in HDL-C (beta coefficient $=-0.5$, 95% CI -0.9 to -0.2 ; $p<0.01$). These effects of weight loss were attributable for the additional 12.7% of explained variance for changes in TG and 3.7% in HDL-C. In model 3, every percent reduction in VAT was significantly associated only with a decrease in LDL-C (beta coefficient =0.4, 95% CI 0.03–0.7; $p<0.05$) and TG (beta coefficient =0.5, 95% CI 0.02–1.0; $p<0.05$), and an increase in HDL-C (beta coefficient $=-0.1$, 95% CI -0.2 to -0.01 ; $p<0.05$). In model 4, every percent reduction in weight was associated with a decrease in TG (beta coefficient =2.3, 95% CI

0.6–4.0; $p < 0.05$), and increased in HDL-C (beta coefficient = -0.5 , 95% CI -0.9 to -0.06 ; $p < 0.05$).

A multiple regression analysis that replaced percent reduction in weight with percent reduction in TAT was performed (Supplemental Table 2). In model 1, the explained variance for changes in these risk factors ranged from 9.7 to 39.3%. In model 2, every percent reduction in TAT was associated with an increase in HDL-C (beta coefficient = -0.1 , 95% CI -0.2 to -0.1 ; $p < 0.05$). In model 4, neither change in TAT nor VAT was associated with change in cardiovascular risk factors.

Discussion

In this cohort of overweight and obese participants with type 2 diabetes, we found that study participants had a significant decrease in LDL-C, HbA1c, and hepatic fat. Decrease in VAT was significantly associated with an increase in HDL-C before adjusting for weight change. But change in VAT was not independently associated with improvement in any other cardiovascular risk factors in this cohort.

Our study showed an improvement in HDL-C with reduction in VAT before adjustment for weight change. This is consistent with findings from a previous weight loss intervention study, which showed that HDL-C improvement was accompanied by weight and VAT loss [23]. It has been postulated that regular aerobic activity, at moderate or high intensity, is associated with increased concentrations of HDL-C [24] and visceral fat loss [11].

In other reports, weight loss and visceral adiposity reduction induced by either diet, exercise, or both, were shown to improve CVD risk factors including blood pressure, plasma TG [8], and insulin sensitivity [5]. However, we observed no independent statistical association existed between VAT reduction and improvements in CVD risk factors. One explanation was that weight loss in our samples was relatively low compared to others [5,8], which might result in not being able to observe a relationship between CVD risk factors and weight or VAT reduction. Another explanation for the difference is that our study only included participants with diabetes, while the aforementioned studies did not. It also has been reported that improvements in insulin sensitivity are associated with improvements in aerobic fitness and skeletal muscle mass [25]. Submaximal cardiorespiratory fitness in this cohort was not significantly improved with VAT loss compared with that in other cohorts [11], which could be one explanation for the lack of improvement in insulin sensitivity.

Another explanation is that a reduction of total body fat (including SAT and VAT) has the greatest potential to improve cardiometabolic parameters. This is based on evidence that adipose tissue deposits are interdependent and often function as a single organ, with increased VAT being reflective of the pathogenesis of both SAT and VAT [12]. Thus, while total weight reduction clearly correlates with improvement in CVD risk factors in overweight and obese patients, given the understanding of the interplay of VAT and SAT, it is unclear that VAT should have an independent association with improvement in CVD risk factors. Our study supports the recommendation of the adult overweight and obesity

guideline that a modest weight loss of 5 – 10% of baseline weight in six months can result in substantial improvement in metabolic disease [26].

The finding in the study is important as it provides information on the significance of weight loss that predicts reduction in CVD risk factors. Our finding supports the main results of the Look AHEAD trial [18] that found a greater improvement of CVD risk factors in the ILI group, which had higher loss of weight compared to the DSE group. In the main results of Look AHEAD, there was no difference of primary outcome (composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina) between ILI and DSE groups. One of these explanations of non-difference in cardiovascular risk was the small difference in weight loss between the two groups (averaged 4% over the course of the study, but only 2.5% at the end). Our study shows that more than reduction in VAT, reduction in weight itself is important in reducing cardiovascular risk in diabetes.

Our study has a number of limitations. First, the study sample was relatively small, limiting our power to detect differences. Only 66% of individuals who underwent a baseline MRS study had a 12-month study as well. However, compared with those without MRS at follow-up, those with MRS at follow-up were similar with respect to age, gender, BMI, SBP, DBP, HDL-C, LDL-C, fasting glucose, HbA1c, HOMA-IR, hepatic fat, fitness level (p-value >0.05 for all). Second, mean percent changes in VAT in our study were relatively small compared with results in a systematic review of weight loss studies [27]. It is possible that the difference in types of intervention [28] and in the characteristics of the study population (type 2 diabetes, older adults, high proportion of black participants) may explain the different results [29]. The change in weight and VAT in our study reflects what the participants in this study group achieved, and may be reflective of what older adults with diabetes achieve with this type of intervention. Further study would be needed to determine whether greater reductions in VAT could be achieved in this population with a different intervention, and would rather have association with change in CVD risk factors. Participants in this study remained under the care of their usual physicians and may have had changes made to their medications, including dose changes by these physicians, or for safety reasons by the study physicians. We were not fully able to account for all of these medication changes. In addition, we do not have physical activity data (maximal oxygen consumption or VO_2 max), which is expected to reduce VAT and modulate CVD risk factors (HDL-C) without any significant effect of body weight. Also, we do not have habitual diet data and don't know the effects of fat intake on lipid levels. Finally, the subjects in this study were all recruited at one site included in the multicenter randomized trial; thus, the findings may not be generalizable to the general population.

In conclusion, we did not find that VAT reduction, independent of weight loss, was associated with improved CVD risk factors in overweight or obese adults with diabetes. These findings imply that total weight loss seems to correlate just as well with metabolic abnormalities as VAT loss. Studies with a larger sample size and well-characterized physical activity measurements are needed to better address these questions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig.1.
Distribution of change in VAT (%) by intervention group

Table 1

Baseline, 1-year, and absolute changes in weight, cardiovascular risk factors, fitness, and body composition according to tertile of VAT reduction in a subset of patients of the Look AHEAD study

Characteristics/risk factors	Tertile of VAT reduction			
	Overall	1	2	3
VAT (cm ³)				
Baseline (log)	5.4 (0.4)	5.2 (0.4)	5.4 (0.4)	5.4 (0.4)
1-year (log)	5.3 (0.5)	5.4 (0.4)	5.4 (0.4)	5.1 (0.5)
Absolute change	−6.0 (49.3)	42.9 (26.0)	−1.6 (15.8)	−56.5 (33.6)
Weight (kg)				
Baseline	100.5 (17.1)	100 (14.3)	101.7 (20.7)	99.9 (16.1)
1-year	96.8 (17.7)	99.5 (15.3)	98.8 (21.5)	92.0 (14.8)
Absolute change	−3.8 (8.3)	−0.5 (5.6)	−2.9 (6.8)	−7.9 (10.0) *
TAT (cm ³)				
Baseline (log)	6.2 (0.3)	6.2 (0.3)	6.2 (0.3)	6.3 (0.3)
1-year (log)	6.2 (0.3)	6.3 (0.3)	6.2 (0.3)	6.0 (0.3)
Absolute change	−23.6 (97.6)	50.3 (57.8)	−8.8 (41.7)	−112.9 (101.1)
SAT (cm ³)				
Baseline (log)	5.6 (0.4)	5.7 (0.3)	5.5 (0.5)	5.6 (0.4)
1-year (log)	5.5 (0.4)	5.7 (0.3)	5.5 (0.5)	5.4 (0.4)
Absolute change	−17.7 (59.5)	3.2 (43.2)	−5.8 (37.4)	−50.9 (76.8)
SBP (mmHg)				
Baseline	131.5 (16.2)	130.0 (15.6)	129.6 (16.9)	135.0 (16.0)
1-year	127.6 (15.8)	127.7 (14.8)	128.4 (17.0)	126.6 (16.0)
Absolute change	−3.9 (18.0)	−2.2 (15.7)	−1.2 (18.9)	−8.3 (19.0)
DBP (mmHg)				
Baseline	73.7 (9.1)	71.8 (8.6)	74.1 (8.2)	75.3 (10.3)
1-year	72.4 (10.1)	71.9 (11.6)	73.8 (9.9)	71.5 (8.6)
Absolute change	−1.3 (10.6)	0.1 (12.7)	−0.3 (9.2)	−3.8 (9.6)
TG (mg/dL)				
Baseline (log)	4.8 (0.5)	4.8 (0.5)	4.8 (0.5)	4.8 (0.5)
1-year (log)	4.7 (0.5)	4.8 (0.5)	4.7 (0.6)	4.7 (0.6)
Absolute change	−5.7 (57.2)	−1.8 (57.3)	0.1 (121.3)	−19.1 (63.5)
HDL-C (mg/dL)				
Baseline	46.6 (13.2)	51.6 (15.9)	44.8 (11.5)	43.1 (10.2) †
1-year	49.2 (13.7)	50.8 (14.2)	48.9 (14.3)	48.0 (12.9)
Absolute change	2.7 (7.6)	−0.5 (7.6)	4.3 (5.9)	4.3 (7.5) †
LDL-C (mg/dL)				
Baseline	113.5 (31.9)	105.8 (33.0)	123.5 (29.3)	110.5 (31.5)
1-year	104.3 (30.6)	102.8 (30.3)	103.6 (30.3)	102.9 (26.4)
Absolute change	−9.2 (24.5) †	−3.1 (17.7)	−19.9 (23.0)	−7.6 (29.2) †

Characteristics/risk factors	Tertile of VAT reduction			
	Overall	1	2	3
Fasting glucose (mg/dL)				
Baseline	139.1 (41.2)	135.9 (36.6)	134.1 (41.8)	149.5 (43.2)
1-year	137.1 (43.1)	143.9 (54.9)	129.5 (23.1)	139.8 (23.1)
Absolute change	−2.0 (47.2)	8.0 (56.7)	−4.6 (43.3)	−9.7 (42.2)
HbA1c (%)				
Baseline (%)	7.2 (1.1)	7.3 (1.0)	7.1 (1.1)	7.3 (1.1)
1-year (%)	6.8 (1.2)	7.0 (0.9)	6.6 (0.8)	7.0 (1.6)
Change (%)	−0.4 (1.0) [†]	−0.3 (0.7)	−0.5 (0.8)	−0.3 (1.4)
HOMA-IR				
Baseline	19.2 (21.2)	18.5 (10.0)	16.9 (8.1)	24.1 (37.7)
1-year	18.4 (16.5)	17.0 (12.0)	16.8 (12.1)	22.6 (26.0)
Absolute change	−0.8 (27.4)	−1.5 (12.1)	−0.1 (11.0)	−1.5 (46.6)
Hepatic fat (%)				
Baseline	7.7 (7.4)	8.0 (6.5)	7.7 (7.5)	7.3 (8.4)
1-year	5.6 (6.5)	7.2 (8.5)	5.8 (4.9)	4.1 (5.5)
Absolute change	−2.1 (6.7) [†]	−0.8 (6.9)	−1.9 (7.7)	−3.2 (5.3)
Fitness (METS)				
Baseline	5.0 (1.4)	5.2 (1.6)	5.4 (1.4)	4.9 (1.5)
1-year	5.1 (1.5)	5.1 (1.7)	5.6 (1.7)	5.0 (1.5)
Absolute change	−0.1 (0.4)	−0.1 (0.2)	−0.2 (0.8)	−0.1 (0.3)

Data are means (SD). Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HOMA-IR, Insulin and Homeostasis Model of Assessment-Insulin Resistance

*
p<0.01,

[†]
p<0.05 by t-test (Baseline vs. 1-year) or ANOVA (across tertile of VAT reduction).

Table 2

Correlations between changes in weight, waist circumference, TAT, SAT, VAT, insulin resistance, and 1-year changes in CVD risk factors

	Weight (%)	WC (cm)	TAT (%)	SAT (%)	VAT (%)
TAT (%)	0.69*	0.48*	—	—	—
SAT (%)	0.64*	0.42*	0.84*	—	—
VAT (%)	0.52*	0.39*	0.84*	0.47*	—
SBP (mmHg)	0.14	0.18	0.12	0.06	0.11
DBP (mmHg)	0.02	0.08	0.0	−0.11	0.07
TG (mg/dL)	0.09	0.05	0.14	0.04	0.15
HDL-C (mg/dL)	−0.30*	0.20	−0.3*	−0.19	−0.37*
LDL-C (mg/dL)	−0.05	0.11	0.04	0.0	0.08
Fasting glucose (mg/dL)	0.18	0.21	−0.05	0.02	−0.11
HbA1c (%)	0.27*	0.33*	0.10	0.10	0.10
HOMA-IR	0.05	−0.14	0.03	0.09	−0.02

Abbreviations: WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HOMA-IR, Insulin and Homeostasis Model of Assessment-Insulin Resistance.

* $p < 0.05$ by Pearson's correlation coefficient.

Table 3

Association of 1-year changes in CVD risk factors and Percent Changes in VAT and Weight

Cardiovascular risk factors	Model 1	Model 2	Model 3	Model 4
SBP (mmHg) (N=98) [‡]				
Weight (%)	–	0.3 (–0.3–0.7)	–	0.2 (–0.5–0.8)
VAT (%)	–	–	0.03 (–0.1–0.2)	0.003 (–0.2–0.2)
R ²	39.3%	39.9%	39.4%	40.0%
DBP (mmHg) (N=98) [‡]				
Weight (%)	–	–0.1 (–0.4–0.3)	–	–0.1 (–0.5–0.3)
VAT (%)	–	–	0.01 (–0.1–0.1)	0.02 (–0.1–0.1)
R ²	34.6%	34.7%	34.6%	34.8%
LDL (mg/dL) (N=93) [§]				
Weight (%)	–	0.5 (–0.3–1.3)	–	0.3 (–0.7–1.2)
VAT (%)	–	–	0.2 (–0.1–0.4)	0.1 (–0.2–0.4)
R ²	34.0%	35.3%	35.8%	36.1%
TG (mg/dL) (N=98) [§]				
Weight (%)	–	3.3 (0.2–6.3) [*]	–	2.7 (–0.7–6.2)
VAT (%)	–	–	0.7 (–0.2–1.7)	0.4 (–0.7–1.4)
R ²	16.9%	21.5%	19.4%	21.9%
HDL-C (mg/dL) (N=93) [§]				
Weight (%)	–	–0.4 (–0.7– –0.2) [‡]	–	–0.3 (–0.6–0.04) [*]
VAT (%)	–	–	–0.1 (–0.2– –0.03) [‡]	–0.05 (–0.1–0.03)
R ²	9.7%	21.6%	17.6%	23.1%
Fasting glucose (mg/dL) (N=90) [¶]				
Weight (%)	–	1.9 (0.5–3.4) [‡]	–	2.7 (1.0–4.3) [‡]
VAT (%)	–	–	0.03 (–0.5–0.5)	–0.5 (–1.0–0.1)
R ²	30.4%	36.8%	30.4%	39.0%
HbA1c (%) (N=98) [¶]				
Weight (%)	–	0.03 (–0.002–0.06)	–	0.04 (0.004–0.08) [*]
VAT (%)	–	–	–0.0005 (–0.01–0.01)	–0.007 (–0.02–0.005)
R ²	19.2%	22.5%	19.2%	23.8%
HOMA-IR (N=69) [¶]				
Weight (%)	–	0.8 (–0.5–2.1)	–	1.0 (–0.5–2.5)
VAT (%)	–	–	0.02 (–0.4–0.4)	–0.1 (–0.6–0.3)
R ²	9.9%	12.4%	10.0%	12.9%
Hepatic fat (%) (N=96)				
Weight (%)	–	0.2 (0.05–0.4)	–	0.2 (–0.02–0.4)
VAT (%)	–	–	0.06 (–0.005–0.11)	0.03 (–0.04–0.09)
R ²	35.3%	39.7%	38.0%	40.2%

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HOMA-IR, Insulin and Homeostasis Model of Assessment-Insulin Resistance; R^2 : variability

Data are presented as beta coefficients (95% CI) associated with percent changes in weight or VAT. Model 1 was adjusted for age, race, gender, baseline metabolic values, cardiovascular fitness, and treatment group assignment. Model 2: Model 1 + weight change, Model 3: Model 1+ VAT change, Model 4: Model 1 + weight change + VAT change.

*
p<0.05,

†
p<0.01.

‡
Analysis for SBP and DBP were adjusted for use of antihypertensive medications.

¶
Analysis for glucose, HbA1c, and HOMA-IR were adjusted for use of any diabetes medications.

§
Analysis for TG, HDL-C, and LDL were adjusted for use of lipid lowering medications

Table 4

Association of 1-year changes in CVD risk factors and Percent Changes in VAT and Weight in ILI group

Cardiovascular risk factors	Model 1	Model 2	Model 3	Model 4
SBP (mmHg) (N=42)				
Weight (%)	–	–0.1 (–0.7–0.6)	–	0.1 (–0.6–0.9)
VAT (%)	–	–	–0.1 (–0.3–0.1)	–0.1 (–0.3–0.1)
R ²	61.9%	62.0%	57.5%	57.7%
DBP (mmHg) (N=42)				
Weight (%)	–	0.1 (–0.4–0.5)	–	0.1 (–0.4–0.6)
VAT (%)	–	–	–0.01 (–0.1–0.1)	–0.02 (–0.2–0.1)
R ²	39.0%	39.2%	39.0%	39.4%
LDL (mg/dl) (N=40)				
Weight (%)	–	0.2 (–1.0–1.4)	–	–0.6 (–1.9–0.7)
VAT (%)	–	–	0.4 (0.03–0.7) *	0.5 (–0.1–0.9)
R ²	30.8%	31.1%	40.4%	42.0%
TG (mg/dl) (N=42)				
Weight (%)	–	2.6 (1.1–4.8) †	–	2.3 (0.6–4.0) *
VAT (%)	–	–	0.5 (0.02–1.0) *	0.2 (–0.4–0.7)
R ²	54.2%	66.9%	59.7%	67.4%
HDL-C (mg/dl) (N=40)				
Weight (%)	–	–0.5 (–0.9–0.2) †	–	–0.5 (–0.9–0.06) *
VAT (%)	–	–	–0.1 (–0.2–0.01) *	–0.03 (–0.2–0.1)
R ²	20.4%	24.1%	27.9%	38.8%
Glucose (mg/dl) (N=37) ¶				
Weight (%)	–	1.4 (–1.1–4.0)	–	2.9 (–0.06–5.9)
VAT (%)	–	–	–0.3 (–1.3–0.6)	–1.0 (–2.1–0.1)
R ²	29.4%	32.6%	30.8%	40.0%
HbA1c (%) (N=42) ¶				
Weight (%)	–	0.03 (–0.03–0.08)	–	0.04 (–0.02–0.1)
VAT (%)	–	–	–0.004 (–0.02–0.01)	–0.01 (–0.03–0.01)
R ²	26.6%	28.7%	27.0%	31.4%
HOMA-IR (N=25) ¶				
Weight (%)	–	0.6 (–0.9–2.1)	–	1.16 (–0.5–2.8)
VAT (%)	–	–	–0.2 (–0.7–0.3)	–0.4 (–1.0–0.2)
R ²	5.3%	9.2%	8.5%	19.9%
Hepatic fat (%) (N=44)				
Weight (%)		0.2 (0.03–0.4)		0.3 (0.06–0.4)
VAT (%)			0.002 (–0.06–0.06)	–0.04 (–0.1–0.03)
R ²	52.5%	58.6%	52.5%	60.2%

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HOMA-IR, Insulin and Homeostasis Model of Assessment-Insulin Resistance; R^2 : variability

Data are presented as beta coefficients (95% CI) associated with percent changes in weight or VAT. Model 1 was adjusted for age, race, gender, baseline metabolic values, cardiovascular fitness, and treatment group assignment. Model 2: Model 1 + weight change, Model 3: Model 1+ VAT change, Model 4: Model 1 + weight change + VAT change.

*
p<0.05,

†
p<0.01.

‡
Analysis for SBP and DBP were adjusted for use of antihypertensive medications.

¶
Analysis for glucose, HbA1c, and HOMA-IR were adjusted for use of any diabetes medications.

§
Analysis for TG, HDL-C, and LDL were adjusted for use of lipid lowering medications