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Regional Differences in Adipose Tissue Hormone/Cytokine Production Before and After Weight Loss in Abdominally Obese Women

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Abstract

Objective—To compare the regional differences in subcutaneous adipose tissue hormone/cytokine production in abdominally obese women during weight loss.

Design and Methods—Forty-two abdominally obese, older women underwent a 20-week weight loss intervention composed of hypocaloric diet with or without aerobic exercise (total energy expenditure: ~2800 kcal/week). Subcutaneous (gluteal and abdominal) adipose tissue biopsies were conducted before and after the intervention.

Results—Adipose tissue gene expression and release of leptin, adiponectin, and interleukin 6 (IL-6) were determined. The intervention resulted in significant weight loss (-10.1 ± 0.7 kg, $P < 0.001$). At baseline, gene expression of adiponectin were higher ($P < 0.01$), and gene expression and release of IL-6 were lower (both $P < 0.05$) in abdominal than in gluteal adipose tissue. After intervention, leptin gene expression and release were lower in both gluteal and abdominal adipose tissue compared to baseline ($P < 0.05$ to $P < 0.01$). Abdominal, but not gluteal, adipose tissue adiponectin gene expression and release increased after intervention (both $P < 0.05$).

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Conflict of Interest Statement

The authors declared no conflict of interest.

Conclusion—A 20-week weight loss program decreased leptin production in both gluteal and abdominal adipose tissue, but only increased adiponectin production from abdominal adipose tissue in obese women. This depot-specific effect may be of importance for the treatment of health complications associated with abdominal adiposity.

Keywords

Adipose Tissue; Hormones; Cytokines; Weight Loss; Abdominal Obesity

Introduction

Adipose tissue expresses and releases a number of hormones and cytokines, such as leptin, adiponectin, and interleukin 6 (IL-6), which are important factors in the regulation of energy intake and inflammatory responses (1). Leptin is an adipose-derived hormone that regulates energy intake and expenditure by inhibiting appetite and altering energy metabolism (2). Adiponectin is an adipose-derived protein that acts as an anti-inflammatory agent and an insulin sensitizer (2, 3). IL-6 is released mostly by non-fat cells within adipose tissue (4) and plays an important role in promoting local and systemic inflammatory reactions (5).

Obesity is a major risk factor for cardiovascular disease and diabetes (6, 7). Circulating levels of leptin and IL-6 levels are elevated, and levels of adiponectin are lower, in obese, compared to non-obese, individuals (8). Abdominal obesity is an independent metabolic risk factor (9). In our previous study, insulin resistance and glucose intolerance were related to abdominal, adipose tissue IL-6 and adiponectin gene expression in abdominally obese, older women (10). These findings indicate that regional adipose tissue hormone/cytokine production may play an important role in mechanisms of metabolic complications associated with abdominal obesity.

Recent studies indicate that genes involved in inflammatory responses and metabolism are differently expressed in abdominal and lower-body adipose tissue (11), and developmentally programmed differences may contribute to the distinct phenotypic characteristics of peripheral fat in women (12). In abdominally obese women, abdominal adipose tissue, compared to lower body adipose tissue (i.e. gluteal adipose tissue), may have more active metabolic properties (13) and may respond differently to weight loss. However, the depot differences in adipose tissue hormone/cytokine production in response to weight loss are still not known in this specific population that has elevated metabolic risk.

Therefore, the purpose of this study was to investigate: 1) whether there were differences between abdominal and gluteal subcutaneous adipose tissue leptin, adiponectin, and IL-6 production in abdominally obese older women; and 2) whether there were depot differences in the response of subcutaneous adipose tissue leptin, adiponectin, and IL-6 production to weight loss by diet and exercise.

Methods

Subjects

Participants (n=42) in this study were from a subset of 112 women who were recruited for a larger trial, and main study results were previously published (14). Primary inclusion/exclusion criteria were: 1) overweight or obese (BMI = 25–40 kg/m²) and abdominally obese (waist girth > 88 cm), 2) middle-aged or older (age = 50–70 years) and postmenopausal (at least one year without menses), 3) non-smoking, 4) not on hormone replacement therapy, 5) sedentary (< 15 min of exercise, 2 times/week) in the past 6 months, and 6) weight-stable (< 5% weight change) for at least 6 months.

The initial screening included a medical history review, physical examination, fasting blood profile (lipoprotein lipids and glucose) and 12-lead resting electrocardiogram. Women were also excluded if they had: 1) untreated hypertension (blood pressure > 160/90 mmHg), 2) hypertriglyceridemia (triglycerides > 400 mg/dl), 3) insulin-dependent diabetes, 4) active cancer, or 5) liver, renal or hematological disease. All women also underwent a graded exercise test to exclude those with an abnormal cardiovascular response to exercise.

The study was approved by the Wake Forest University Institutional Review Board for Human Research. All women signed informed consent to participate in the study.

Weight Loss Intervention

All women underwent 20 weeks of intervention composed of hypocaloric diet with or without aerobic exercise. The diet intervention was comprised of providing the participants with lunch and supper meals prepared by the Wake Forest University General Clinical Research Center (GCRC) metabolic kitchen staff. The women purchased and prepared their breakfast meal, in consultation with a registered dietitian. Women were allowed to consume non-caloric, non-caffeinated beverages and were provided with a daily calcium supplement (1000 mg/day). A subset of the women (n=28) also walked on a treadmill at moderate to vigorous intensity, for 30–55 min each day, 3 days/week. The total calorie/energy deficit was adjusted to be ~2800 kcal/week, and the average daily calorie intake recorded by all women was 99% of the provided calorie level. All measures were collected before and after the 20-week intervention.

Body Composition

Height and weight were measured to calculate BMI (kg/m²). Waist and hip circumferences were measured by a tape measure. Fat mass and percent body fat were measured by dual energy X-ray absorptiometry (Hologic Delphi QDR, Bedford, MA). Visceral and subcutaneous adipose tissue volumes around the abdomen were measured by a four-slice multidetector computed tomography system (GE Medical Systems, Milwaukee, WI).

Blood Measures

Blood samples were collected in EDTA-treated vacutainers via venipuncture in the early morning after an overnight fast. The samples were centrifuged at 4°C for 20 min, and plasma was separated and stored at –70°C until analysis. Plasma triglycerides (TG), total

cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by standardized hospital laboratory procedures. Plasma concentrations of leptin, adiponectin and IL-6 were measured by enzyme-linked immunosorbent assay (ELISA) using Quantikine kits (R&D Systems, Minneapolis, MN).

Oral Glucose Tolerance Test

After an overnight fast, a 20-gauge polyethylene catheter was placed in an antecubital vein for blood sampling. Blood samples were drawn at different time points before (10 and 0 min) and after (30, 60, 90, and 120 min) a 75-g glucose ingestion for the determination of plasma glucose and insulin. Plasma glucose was measured with the glucose hexokinase method (Bayer Diagnostics, Tarrytown, NY). Plasma insulin was determined by a chemiluminescent immunoassay (Siemens, Malvern, PA). The estimate of insulin sensitivity by homeostasis model assessment (HOMA) score was calculated with the following formula: fasting plasma insulin (U/ml) \times glucose (mmol/l) / 22.5, which is equal to fasting insulin (pmol/l) \times glucose (mg/dl) 2,815 after unit conversions (15). Glucose and insulin areas during OGTT were determined with Tai's model: $1/2 \times 30 \times (y_{0\text{min}} + 2y_{30\text{min}} + 2y_{60\text{min}} + 2y_{90\text{min}} + y_{120\text{min}})$, where y represents insulin or glucose concentrations at the different time points (16).

Adipose Tissue Leptin, Adiponectin and IL-6 Production

Subcutaneous (abdominal and gluteal) adipose tissue biopsies were conducted under local anesthesia (1% lidocaine) after an overnight fast. Adipocyte size was determined as previously described (17). Adipose tissue mRNA was extracted, and reverse transcription (RT) was performed by using the Advantage RT-for-PCR Kit (Clontech, Palo Alto, CA); real-time quantification of target gene (leptin, adiponectin, and IL-6) to β -actin mRNA was performed, using ABI Taqman gene expression assay kits on an ABI PRISM 7900 Sequence Detection System (Applied Biosystems, Foster City, CA) (10). Adipose tissue *in vitro* hormone/cytokine release was processed in a subset of these 42 subjects as previously described (4), and levels of leptin, adiponectin, and IL-6 in the release media were determined by using the Milliplex immunoassay (Millipore, St. Charles, MO).

Statistical Analyses

Data analyses were performed using IBM SPSS Statistics 20 (Armonk, NY). For variables that were not normally distributed, the logarithm of each was used for parametric statistical analyses. Changes in variables were calculated by using post-intervention minus pre-intervention values. We did not see an exercise effect on changes in metabolic and hormone/cytokine variables; therefore, the following analyses were performed in the whole cohort. Paired t-tests were used to compare pre- and post-intervention values on all variables, and depot differences (abdominal vs. gluteal) on adipose tissue variables. Pearson's correlation was used for analysis of relationships between changes in variables. All data are presented as mean \pm standard error, and the level of significance was set at $P < 0.05$ for all analyses.

Results

Participant Characteristics, Body Composition and Metabolic Variables

For all 42 participants, mean age was 58 ± 1 years and mean postmenopausal time was 13 ± 2 years; 45% of the women were African American.

Body composition variables before and after the intervention are shown in Table 1. At baseline, adipocyte size was significantly larger in gluteal than in abdominal adipose tissue ($P < 0.01$). The 20-week intervention resulted in significant weight loss (-10.1 ± 0.7 kg, -1.2 to -20.3 kg; -11.5 ± 0.8 %, -1.4% to -22.9%), and decreased fat mass, percent body fat, waist circumference, hip circumference, waist-to-hip ratio, abdominal and gluteal subcutaneous adipocyte size, and abdominal subcutaneous and visceral fat volumes ($P < 0.01$ to $P < 0.001$).

Metabolic variables before and after the intervention are shown in Table 2. The intervention reduced plasma triglyceride levels ($P < 0.05$), but did not change levels of total cholesterol, HDL cholesterol, and LDL cholesterol. The intervention significantly reduced fasting glucose, glucose area, fasting insulin, insulin area, and HOMA index ($P < 0.05$ to $P < 0.001$), and tended to lower 2-hour glucose and 2-hour insulin during the OGTT test ($P = 0.07$ and $P = 0.16$, respectively).

Circulating Levels of Leptin, Adiponectin, and IL-6

Circulating levels of leptin, adiponectin and IL-6 before and after the intervention are shown in Table 3. The intervention reduced circulating levels of leptin ($P < 0.001$), and IL-6 ($P < 0.05$), and increased circulating adiponectin levels ($P < 0.05$).

Abdominal and Gluteal Subcutaneous Adipose Tissue Leptin, Adiponectin and IL-6 Production

Gluteal and abdominal adipose tissue gene expression and release levels of leptin, adiponectin and IL-6 before the intervention are shown in Table 4. At baseline, gene expression of adiponectin was higher ($P < 0.01$), and gene expression and release of IL-6 were lower (both $P < 0.05$) in abdominal than in gluteal adipose tissue. There were no depot differences in gene expression and release of leptin and release of adiponectin at baseline.

As shown in Figure 1, the weight loss intervention decreased leptin gene expression and release levels in both gluteal and abdominal adipose tissue ($P < 0.05$ to $P < 0.01$). As shown in Figure 2, the intervention increased abdominal adipose tissue adiponectin gene expression and release (both $P < 0.05$), but did not change gluteal adiponectin production. The intervention did not alter gluteal and abdominal adipose tissue IL-6 production as indicated in Figure 3.

Relationship Between Changes in Adipose Tissue Production of Leptin, Adiponectin and IL-6 and Changes in Body Composition and Metabolic Variables

Over the 20-week weight loss intervention, there were no significant correlations between changes in adipose tissue gene expression or release levels of leptin, adiponectin and IL-6

and changes in their respective circulating levels. However, changes in abdominal leptin gene expression were positively related to changes in subcutaneous abdominal adipose tissue volume ($r=0.48$, $P<0.01$). Additionally, changes in gluteal leptin gene expression were positively related to plasma LDL cholesterol levels ($r=0.43$, $P<0.05$), and were negatively related to HDL cholesterol levels ($r=-0.43$, $P<0.05$). Changes in abdominal adiponectin gene expression were negatively related to changes in 2-hour glucose levels during OGTT ($r=-0.40$, $P<0.05$). In both gluteal and abdominal adipose tissue, changes in IL-6 gene expression were positively related to changes in glucose area during OGTT ($r=0.67$, $P<0.01$ and $r=0.46$, $P<0.05$, respectively).

Discussion

This study compared the regional differences in subcutaneous adipose tissue leptin, adiponectin and IL-6 production in abdominally obese women before and after weight loss. Our findings surprisingly support that adiponectin gene expression was higher, and IL-6 gene expression and release were lower, in abdominal than in gluteal adipose tissue. Additionally, weight loss reduced both abdominal and gluteal adipose tissue leptin gene expression and release, but preferentially increased abdominal adipose tissue adiponectin gene expression and release in these women.

Similar to our findings, in a recent study, contrary to the authors' original hypothesis, gluteal subcutaneous adipose tissue had a greater inflammatory gene expression profile than abdominal subcutaneous adipose tissue (18). The authors questioned about the protective nature of gluteo-femoral fat. In our current study, we did see a significant larger fat cell size in the gluteal than abdominal adipose tissue, and this could be the reason why abdominal adipose tissue has higher adiponectin expression and lower IL-6 production. Based on our previous report, circulating metabolic risk factors are related to abdominal adipose tissue cytokines (10); therefore, the location of adipose tissue, but not the absolute expression or release levels of hormones and cytokines from local adipose tissue, may play a more important role in the regulating mechanism of metabolic syndrome.

Our findings that weight loss reduced adipose tissue leptin gene expression and release are supported by previous weight loss intervention studies (19, 20). However, none of these studies measured leptin production in different fat depots. Our study is the first one to report that weight loss reduced leptin expression and release levels in both abdominal and gluteal adipose tissue in obese individuals. Interestingly, we observed that weight loss only altered abdominal, but not gluteal, adipose tissue adiponectin gene expression and release levels in these abdominally obese women. Several previous studies reported that hypocaloric diet did not alter abdominal subcutaneous adipose tissue adiponectin gene expression in obese subjects (21–23), and one study reported that adiponectin gene expression in subcutaneous adipose tissue of obese women responds rapidly to short-term very low calorie diet (24). Our findings that weight loss increased abdominal adipose tissue adiponectin production are similar to those in previous weight loss studies involving both diet and exercise interventions. For example, weight loss by diet and exercise reduced adipose tissue inflammation, determined from an increased mRNA expression of adiponectin and a decreased expression of pro-inflammatory cytokines (25, 26). Another interesting finding of

our study is that change in a metabolic variable (glucose intolerance) was related to change in abdominal, but not gluteal adipose tissue adiponectin gene expression. These differences could be due to more active metabolic properties (e.g. higher blood flow rate and temperature) of the abdominal adipose tissue compared to the gluteal adipose tissue in abdominally obese women (13).

We did not see a significant reduction in IL-6 production from abdominal and gluteal adipose tissue in older women following weight loss. Similarly, short-term to medium-term weight loss by hypocaloric diet with or without exercise did not alter IL-6 gene expression in abdominal adipose tissue in obese individuals (26, 23). However, very low calorie diet for 3 to 10 weeks reduced IL-6 levels in adipose tissue of obese women (21, 19). Moreover, excessive weight loss by laparoscopic adjustable gastric banding significantly reduced subcutaneous adipose tissue IL-6 gene expression in severely obese patients (27). Interestingly, a recent study reported that a dietary weight loss program composed of 1 month of very low calorie diet, 2 months of low calorie diet and 3 months of weight maintenance, lowered IL-6 gene expression in abdominal, but not gluteal adipose tissue in obese postmenopausal women (28). It is possible that the approach and magnitude of weight loss are important factors for these significant findings.

In the current study, we did not see any significant correlations between changes in adipose tissue hormone/cytokine production and changes in their circulating levels over the 20-week intervention. Adipose tissue is an endocrine organ with regional variations in metabolic properties (29). Since we only collected subcutaneous adipose tissue, it is possible that weight loss affected hormone/cytokine production in other adipose tissue regions (e.g. visceral fat and intra-muscular fat) more than subcutaneous fat. Additionally, although adipose tissue is a major organ to release these hormones/cytokines into the circulation, there are other tissues and cells (e.g. endothelial cells and innate immune cells) that also contribute to the altered circulating levels in obesity and in response to weight loss (30).

The mechanisms through which weight loss altered adiponectin production in abdominal adipose tissue are still unclear. A recent study reported that diet and exercise shifted the adiponectin multimer distribution towards a lower molecular weight and increased the number of anti-inflammatory macrophages, and tended to decrease the number of pro-inflammatory macrophages in subcutaneous abdominal adipose tissue (31). Additionally, only whole adipose tissue samples were processed and analyzed for cytokine/hormone production in the current study. It would be helpful to understand the mechanisms of adipose tissue metabolism if cytokine/hormone production could be measured in isolated adipocytes and stromal vascular cells within adipose tissue (4).

In conclusion, weight loss by hypocaloric diet and aerobic exercise reduces leptin gene expression and release in both gluteal and abdominal adipose tissue, but only increases adiponectin gene expression and release from abdominal adipose tissue in abdominally obese women. Considering the role of abdominal adipose tissue adiponectin in regulating metabolic function, this depot-specific effect may be of importance for the treatment of health complications associated with abdominal adiposity. Further studies will need to focus on the mechanisms through which weight loss alters regional adipose tissue hormones/

cytokines and the related changes in metabolic function in obese individuals. Moreover, similar studies are also needed to be completed in other subgroups, such as individuals with gluteofemoral obesity.

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TY, XW, KMM, MFL, JLD and BJN supervised the study. TY, XW, KMM, and RY acquired the data; TY, XW, KMM, RY analyzed and interpreted data; TY performed data analysis and drafted the manuscript; DWG and BJN were responsible for study concept and design; BJN obtained research funding. We thank the study coordinators, nurses, lab technicians, and exercise physiologists for their assistance, and thank all the subjects for their participation in the study. This study was supported by NIH grants R01-AG/DK20583, P30-AG21332, P30-DK072488, and M01-RR07122.

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What is already known about this subject?

- Circulating levels of leptin and interleukin 6 levels are elevated, and levels of adiponectin are lower, in obese, compared to non-obese, individuals
- There is regional variation in hormone/cytokine production by adipose tissue.
- Insulin sensitivity is related to abdominal, but not gluteal hormone/cytokine gene expression in abdominally obese women.

What does this study add?

- This study presents several significant strengths, in particular the use of 4 adipose biopsies per person (2 depots at 2 time points), intervention, measuring both expression and secretion, and a significant sample size of abdominally obese older women.
- Our findings surprisingly support that adiponectin gene expression was higher, and IL-6 gene expression and release were lower, in abdominal than in gluteal subcutaneous adipose tissue.
- Interestingly, weight loss only increased adiponectin gene expression and release from abdominal, but not gluteal adipose tissue in abdominally obese women. This depot-specific effect may be of importance for the treatment of health complications associated with abdominal adiposity.

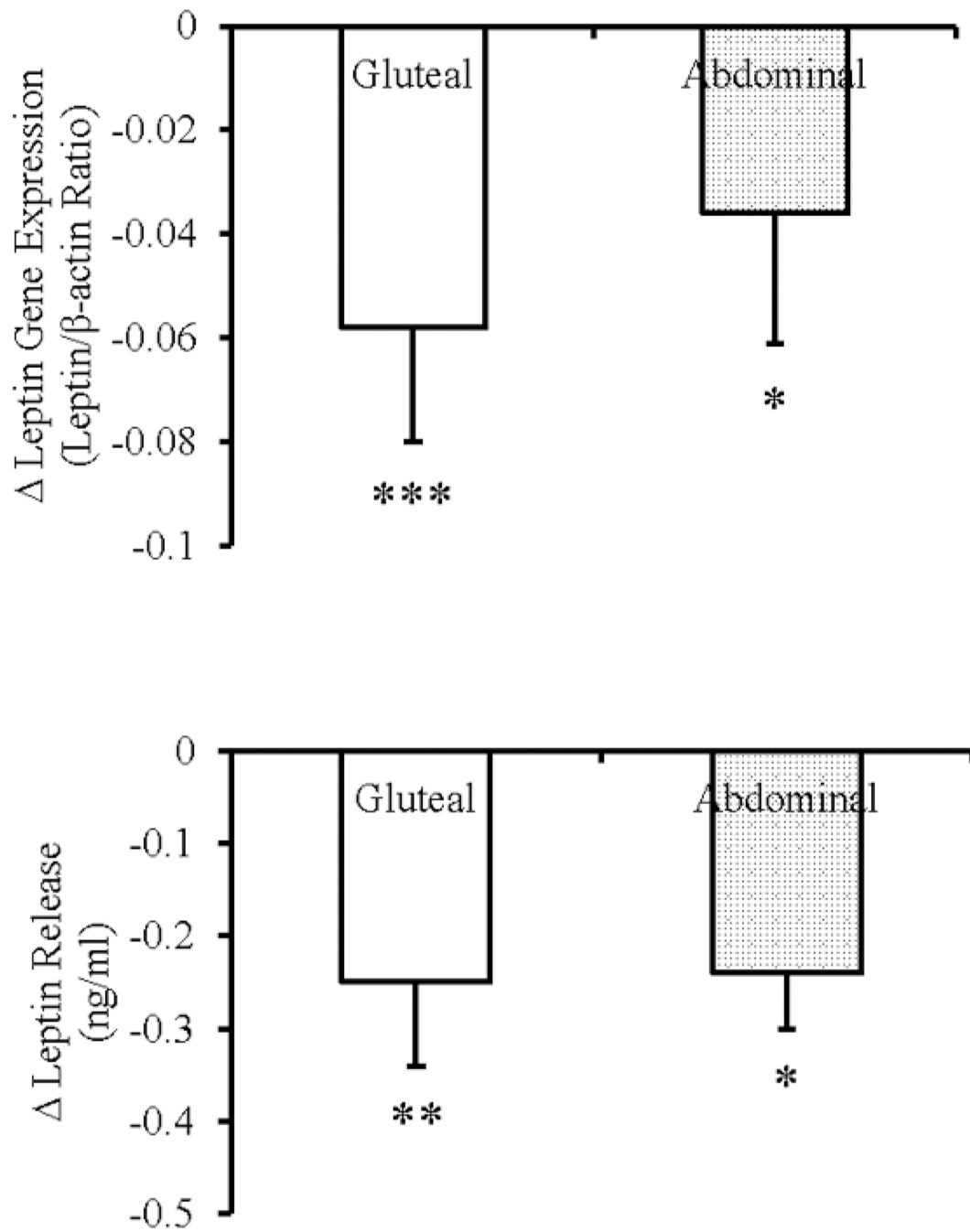


Figure 1. Changes in gluteal and abdominal adipose tissue leptin after the 20-week diet and exercise intervention. Values are in mean \pm SE. N=27-42. * P<0.05, ** P<0.01 *** P<0.001 post- vs. pre-intervention values.

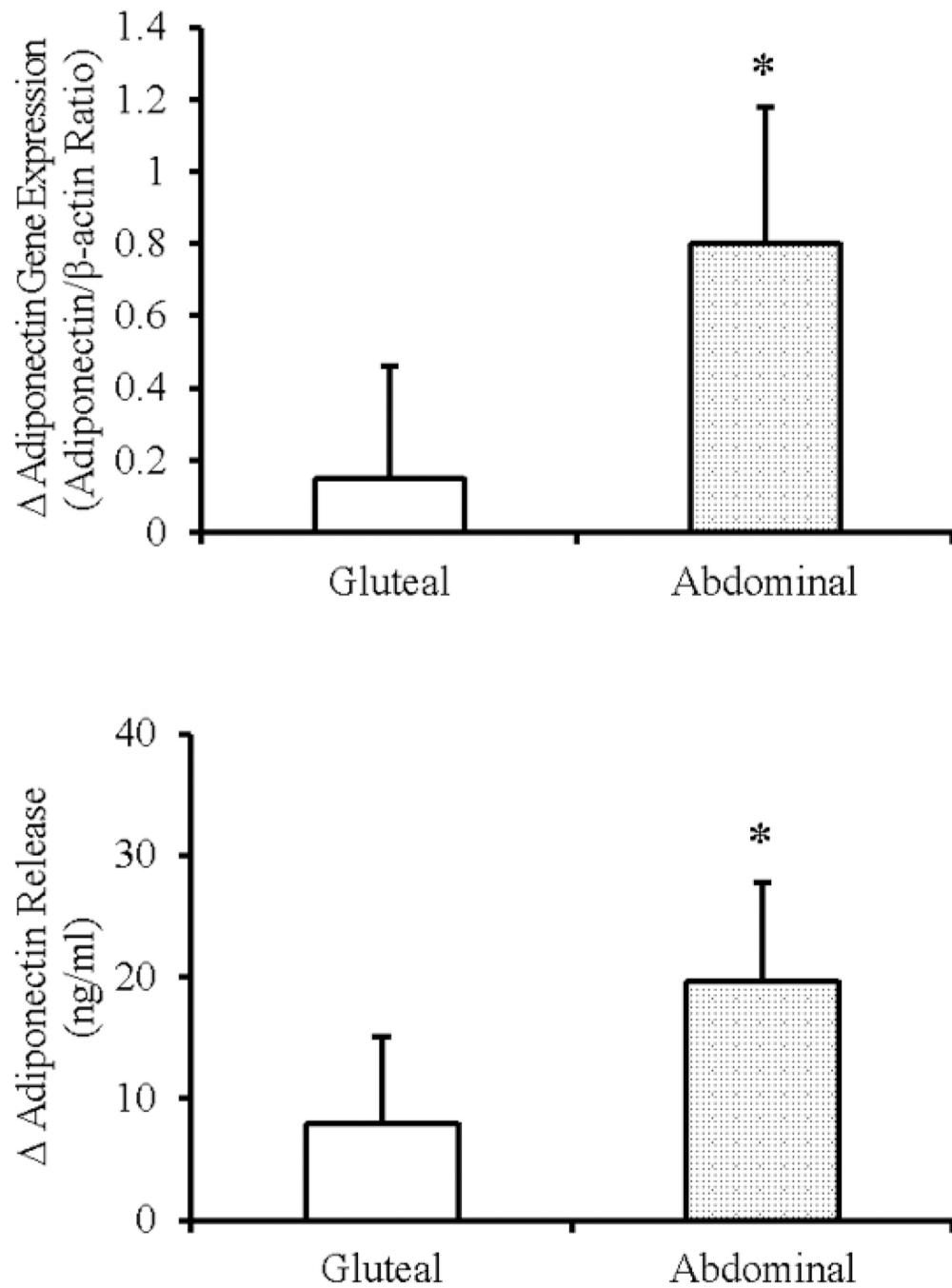


Figure 2. Changes in gluteal and abdominal adipose tissue adiponectin after the 20-week diet and exercise intervention. Values are in mean \pm SE. N=27–42. * P<0.05 post- vs. pre-intervention values.

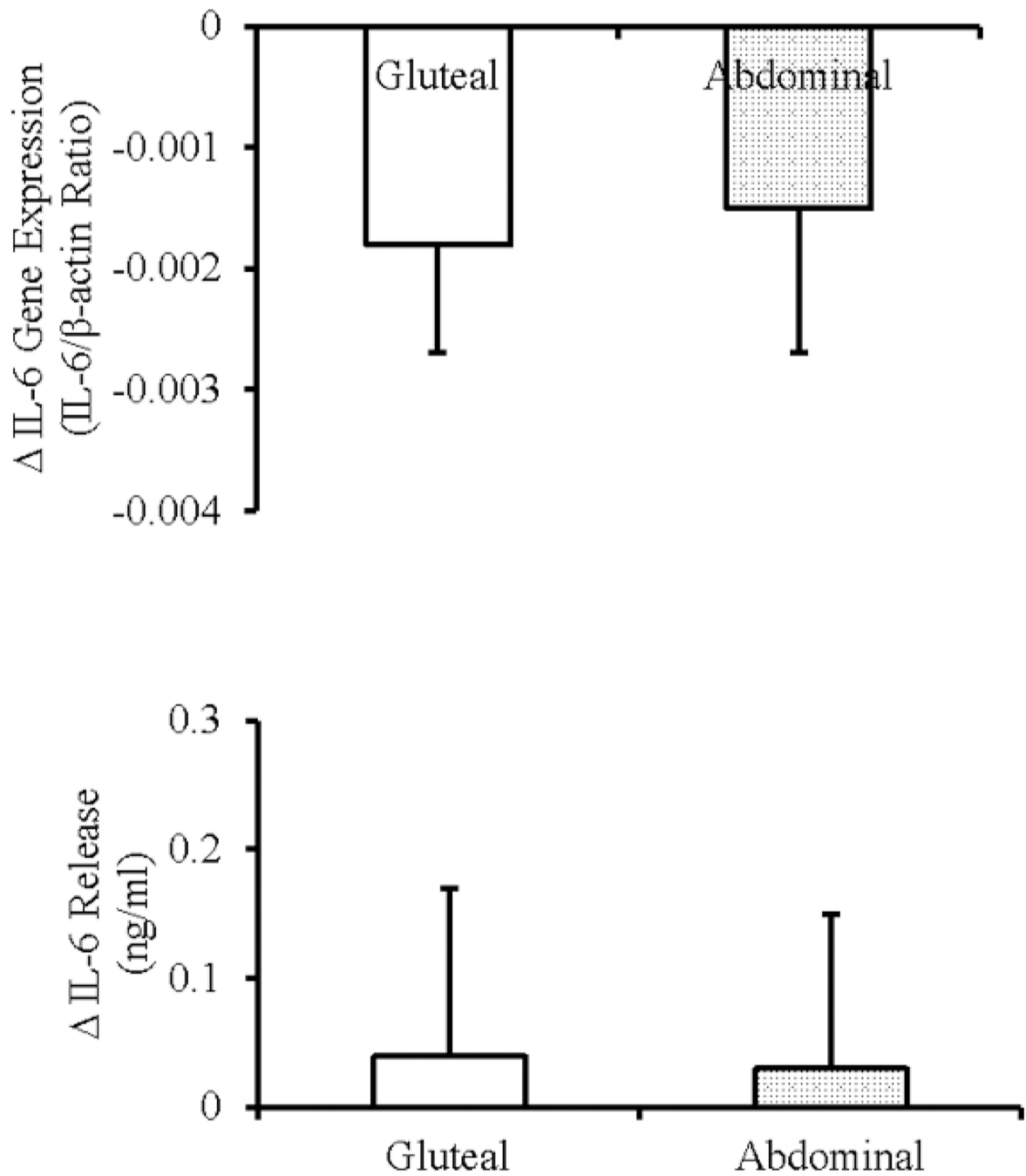


Figure 3. Changes in gluteal and abdominal adipose tissue IL-6 after the 20-week diet and exercise intervention. Values are in mean \pm SE. N=27-42.

Table 1

Body composition before and after the 20-week weight loss intervention.

	Pre-intervention	Post-intervention
Weight (kg)	87.9±1.7	77.8±1.7 ***
Body mass index (kg/m ²)	33.0±0.6	29.1±0.6 ***
Fat mass (kg)	38.7±1.1	31.3±1.1 ***
Percent fat (%)	42.5±0.5	38.9±0.7 ***
Waist (cm)	98.9±1.4	89.3±1.5 ***
Hip (cm)	117.4±1.4	109.0±1.5 ***
Waist-to-hip ratio	0.84±0.01	0.82±0.01 **
Abdominal fat cell size (µg)	0.83±0.02	0.73±0.02 ***
Gluteal fat cell size (µg)	0.95±0.03	0.76±0.02 ***
Abdominal Subcutaneous fat (cm ³)	5805±236	4840±256 ***
Abdominal Visceral fat (cm ³)	2254±134	1744±116 ***

All data are means±SE. N=42.

** P<0.01,

*** P<0.001 compared with baseline (pre-intervention).

Table 2

Circulating metabolic risk factors before and after the 20-week diet and exercise intervention

	Pre-intervention	Post-intervention
Triglycerides (mg/dl)	125.5±8.7	108.6±6.5 *
Total cholesterol (mg/dl)	193.1±4.8	186.8±4.4
HDL cholesterol (mg/dl)	49.5±1.8	50.4±1.6
LDL cholesterol (mg/dl)	118.5±4.5	115.3±4.1
Fasting glucose (mg/dl)	96.7±1.7	92.5±1.6 *
2-hour glucose (mg/dl)	137.4±7.9	122.7±5.1
Glucose area (mg/dl·2h)	17483±633	15644±479 ***
Fasting insulin (pmol/l)	64.1±5.0	46.8±5.4 **
2-hour insulin (pmol/l)	516.2±64.5	440.5±53.5
Insulin area (pmol/l·2h)	52864±4590	42277±3638 *
HOMA index	2.25±0.20	1.57±0.20 **

All data are means±SE. N=42.

* P<0.05,

** P<0.01,

*** P<0.001 compared with baseline.

Table 3

Circulating hormones and cytokines before and after the 20-week weight loss intervention.

	Pre-intervention	Post-intervention
Leptin (ng/ml)	38.0±2.9	21.0±2.2 ***
Adiponectin (µg/ml)	7.93±0.62	9.34±0.79 *
IL-6 (pg/ml)	2.93±0.31	2.39±0.27 *

All data are means±SE. N=42.

* P<0.05,

*** P<0.001 compared with baseline.

Table 4

Gluteal and abdominal adipose tissue hormones and cytokines before the 20-week weight loss intervention.

	Gluteal	Abdominal
Leptin gene expression (leptin/ β -actin)	0.19 \pm 0.02	0.20 \pm 0.03
Leptin release (ng/ml)	0.81 \pm 0.08	0.68 \pm 0.06
Adiponectin gene expression (adiponectin/ β -actin)	2.79 \pm 0.22	3.55 \pm 0.21**
Adiponectin release (ng/ml)	76.2 \pm 3.7	69.5 \pm 5.1
IL-6 gene expression (IL-6/ β -actin)	0.0033 \pm 0.0008	0.0020 \pm 0.0005*
IL-6 release (ng/ml)	0.70 \pm 0.10	0.48 \pm 0.07*

All data are means \pm SE. N=42 for hormone/cytokine gene expression and N=27 for hormone/cytokine release.

* P<0.05,

** P<0.001 compared with gluteal fat depot.