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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1096 – 1101
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Degree of weight loss required to improve adipokine concentrations and decrease fat cell size in severely obese women

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Received 13 February 2009; accepted 8 April 2009

Abstract

Adipose tissue physiology plays an important role in mediating disease risk. Weight loss in obese individuals improves indicators of adipocyte physiology. However, the *minimum* degree of weight loss required to elicit improvements remains unknown. The objective of the present study was to determine the minimum weight loss required to improve adipokine profile and decrease fat cell size in severely obese women. Thirteen severely obese women (body mass index, 50 ± 3 kg/m^2; age, 35 ± 1 years) consumed a low-calorie diet for 3 weeks with the goal of losing 5% of their initial weight. Subjects were divided into 2 weight loss groups posttreatment: less than 5% weight loss and 5% to 10% weight loss. Body weight was reduced ($P < .05$) in both groups (−1.4 ± 1.0 and −6.8 ± 0.6 kg, respectively). Adiponectin concentrations increased ($P < .05$) by 20% in the 5% to 10% weight loss group only. Likewise, leptin and resistin decreased ($P < .05$) by 37% and 27%, respectively, in the group that lost more weight. Visceral and subcutaneous fat cell size was 41% and 37% smaller ($P < .01$), respectively, in the 5% to 10% weight loss group. Smaller visceral adipocyte size was related to lower insulin ($r = 0.82$, $P = .01$) and glucose ($r = 0.58$, $P = .04$) concentrations posttreatment. These findings suggest that a minimum weight loss of 5% is required to improve adipokine profile and decrease fat cell size in severely obese women. These changes in adipocyte physiology may be linked to reductions in metabolic disease risk in this population.

1. Introduction

Excess fat content in adipose tissue is strongly associated with the development of several obesity disorders including coronary heart disease (CHD) and type 2 diabetes mellitus [1]. Although the mechanisms underlying these obesity-related disorders remain unclear, recent evidence suggests that adipose tissue physiology (ie, fat cell–derived hormones and fat cell size) may provide a link between obesity and disease risk [1,2]. To date, more than 25 fat cell–derived hormones (ie, adipokines) have been discovered. Of these, adiponectin, leptin, and resistin have received considerable attention. Adiponectin exerts both insulin-sensitizing and antiatherogenic effects, and circulating levels of this beneficial adipokine increase with weight loss [3]. Leptin, in contrast, exhibits proatherogenic and proinflammatory properties; and concentrations of this hormone decrease as body weight declines [4]. Resistin, like leptin, has been implicated in the pathogenesis of insulin resistance and atherosclerosis, and is reduced when body mass decreases [5]. Circulating levels of these hormones are, in part, dictated by fat cell size. Obese individuals have larger visceral and subcutaneous fat cells when compared with their normal-weight counterparts [2]. Larger adipocytes release higher amounts of the proinflammatory mediators leptin and resistin, and lower amounts of the anti-inflammatory adipokine adiponectin [2]. As an individual loses weight, concomitant decreases in fat cell size are often observed [2].

Findings from the 2007 Behavioral Risk Factor Surveillance System survey estimate that 3 of every 100 women in the 20- to 39-year–old age group are severely obese (body mass index [BMI] >35 kg/m^2) [6]. Carrying extra weight puts these women at increased risk for both CHD and type 2 diabetes mellitus. Losing weight, even a relatively small amount of weight, has been shown to improve metabolic disease risk indicators, such as insulin, glucose, and C-reactive protein (CRP) concentrations [7]. Small decreases in body weight also reduce fat cell size [8] and improve

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0026-0495/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.04.010

circulating adipokine profile [9,10]. However, the precise *minimum* degree of weight loss required to improve these parameters of adipose tissue physiology in the severely obese has yet to be elucidated. Moreover, whether significant improvements in adipose tissue physiology, induced by this minimal degree of weight loss, are related to beneficial modulations in metabolic disease indicators also remains unknown.

Accordingly, the objective of this study was to determine the *minimum* degree of weight loss required to improve adipokine concentrations and decrease fat cell size in severely obese women. Whether improvements in these adipocyte parameters are associated with favorable alterations in metabolic risk was also evaluated.

2. Methods

2.1. Subjects

Severely obese women scheduled for gastric banding surgery for weight reduction were recruited from the University of Illinois Medical Center in Chicago. Key inclusion criteria were as follows: female; BMI greater than 35 kg/m^2; premenopausal; nonpregnant; free of cardiovascular disease; free of cancer; free of gastrointestinal, renal, pulmonary, hepatic, or biliary disease; no history of thyroid dysfunction; and not taking medications that would interfere with study outcomes. Only women were included in the sample to avoid a possible confounding effect of sex on study outcomes. The protocol was approved by the Office for the Protection of Research Subjects at the University of Illinois at Chicago. Before the commencement of the study, all volunteers gave their written informed consent to participate in the trial.

2.2. Low-calorie liquid diet protocol

A 5% weight loss protocol is generally initiated before laparoscopic gastric banding to reduce the enlarged fatty liver that accompanies morbid obesity. This protocol requires patients to consume a low-calorie liquid diet (~40% energy restriction daily) for 3 weeks before surgery. To decrease energy intake by approximately 40%, each subject attended individual dietary counseling sessions with a Registered Dietician. During these sessions, volunteers were taught how to attain daily caloric goals by consuming 3 servings per day of low-fat dairy products (ie, low-fat milk, low-fat yogurt, or cottage cheese), 2 servings per day of protein drinks (ie, Slim-Fast Optima [Slim-Fast, Englewood, NJ]), and 2 servings per day of juice-based items (ie, apple juice or fruit popsicles). Subjects were permitted to consume unlimited amounts of noncalorie beverages including coffee, tea, and sugar-free sodas. This liquid diet provided approximately 50% of energy as carbohydrates, 25% of energy as protein, and 25% of energy as fat. Teaching aids, which outlined the caloric contents of commonly ingested liquid food items, and sample menus were distributed to the volunteers. Compliance with the liquid diet was determined by way of weigh-ins that took place 3 weeks before surgery and on the day of surgery. Subjects were instructed not to change their habitual physical activity during the course of the study.

2.3. Body weight, blood collection, and adipose tissue sampling protocol

Body weight was assessed in the fasted state without shoes at baseline and at the end of the 3-week diet period. Twelve-hour fasting blood samples were collected at baseline and posttreatment. Blood was centrifuged for 15 minutes at 520*g* and 4°C to separate plasma from red blood cells and was stored at −80°C until analyzed. Adipose tissue samples were collected from anterior abdominal depots. Visceral samples were obtained from the intraabdominal cavity (omental fat), and subcutaneous samples were obtained from below the skin at the site of the incision on the day of surgery.

2.4. Plasma adipokines

Circulating concentrations of adiponectin, leptin, and resistin were measured by enzyme-linked immunosorbent assay (Linco Research, St Charles, MO) according to the manufacturer's instructions.

2.5. Fat cell size

Adipose tissue samples were rinsed in 0.85% NaCl solution and then placed into a solution of 10% phosphate-buffered formalin. The samples were then sectioned and stained with hematoxylin and eosin, and embedded in paraffin. Sections were sliced at a thickness of 4 μm at 3 different depths (at least 200 μm apart) within the same tissue sample and fixed to slides. Samples were then observed under a microscope, and cell size was determined using an AxioImager M1 epifluorescence microscope (Zeiss, Germany) and Image J software (version 1.37 for Mac OSX; National Institutes of Health, Bethesda, MD). In each preparation, 400 cells from various parts of the tissue slice were sized for calculation of mean cell size.

2.6. Metabolic and inflammatory parameters

Fasting insulin was measured at baseline and posttreatment with a chemiluminescence immunoassay using an Advia Centaur reagent set and Advia Centaur Immulite 2500 instrument (Siemens Diagnostics, Tarrytown, NY). Fasting blood glucose was assessed with a hexokinase assay using the Roche Modular Analyzer (Roche Diagnostics, Indianapolis, IN). C-reactive protein was quantified using Roche immunoturbidity latex-enhanced high-sensitivity CRP assay on the Roche Modular Analyzer system (Roche Diagnostics).

2.7. Statistical analysis

Results are presented as means ± standard error of the mean (SEM). At the conclusion of the study, subjects were divided into 2 weight loss groups (ie, < 5% weight loss group

Table 1
Body weight and BMI of subjects grouped according to percentage of weight loss

	Weight loss group	Baseline[a]		Posttreatment		Change (%/kg/m^2)		P value[b]
		Mean	SEM	Mean	SEM	Mean	SEM	
Body weight (kg)	<5% Weight loss	137	±18	135	±18	−1.4	±1.0	.04
	5%-10% Weight loss	130	±13	121	±11	−6.8	±0.6	.01
BMI (kg/m^2)	<5% Weight loss	52	±4	51	±4	−0.8	±0.5	.04
	5%-10% Weight loss	49	±4	44	±4	−5.0	±0.4	.01

[a] Baseline values were not significantly different between weight loss groups for body weight or BMI: independent-samples t test.
[b] Within-group differences comparing baseline to posttreatment: paired-samples t test.

and 5% to 10% weight loss group). All data were tested for normal distribution with the Shapiro-Wilk test for normality. Independent-samples t tests were used to determine differences between weight loss groups at baseline for body weight, BMI, adipokine concentrations, fat cell size, and metabolic parameters. Paired-samples t tests were used to determine whether statistically significant within-group differences existed for body weight, BMI, adipokine concentrations, fat cell size, and metabolic parameters after weight loss. Pearson correlations were used to evaluate how adipokine concentrations relate to body weight, fat cell size, and metabolic parameters. A level of statistical significance at P less than .05 was used in all analyses. Data were analyzed using SPSS software (version 17.0; SPSS, Chicago, IL).

3. Results

3.1. Baseline characteristics of all subjects combined

Thirteen severely obese women (BMI, 38-69 kg/m^2) were recruited to participate in the study. The mean BMI of all the subjects combined was 50 ± 3 kg/m^2 (classified as grade III obesity). At baseline, glucose levels (98 ± 8 mg/dL) were in the reference range, whereas insulin (27 ± 4 μU/mL) and CRP levels (17 ± 5 mg/L) were elevated. Mean age of the women was 35 ± 1 years.

3.2. Body weight changes by liquid diet

At the end of the study, subjects were divided into 2 weight loss groups: (1) less than 5% weight loss (n = 6) and (2) 5% to 10% weight loss (n = 7). There were no differences between groups at baseline for body weight or BMI (Table 1). Mean age of the subjects in the less than 5% weight loss group (35 ± 2 years) was similar to that of the 5% to 10% weight loss group (34 ± 2 years). Significant reductions ($P < .05$) in body weight and BMI from baseline were noted in both groups (Table 1).

3.3. Degree of weight loss required to improve adipokine concentrations

Changes in adipokine concentrations over the course of the trial in both weight loss groups are displayed in Table 2. Adiponectin concentrations increased ($P < .05$) by 20% in subjects who lost 5% to 10% of their initial body weight, but was unaltered in the group who lost less than 5% of body weight. Similarly, leptin and resistin concentrations were reduced ($P < .05$) by 37% and 27%, respectively, in the 5% to 10% weight loss group, but were not changed in the less than 5% weight loss group. Thus, it appears that a minimum weight loss of 5% from baseline is required to favorably modulate concentrations of these key adipokines.

3.4. Degree of weight loss required to decrease fat cell size

Subcutaneous and visceral fat cell size after 3 weeks of diet is displayed in Fig. 1. Subcutaneous adipocyte size was approximately 37% smaller ($P < .05$) in the subjects who lost 5% to 10% of their initial body weight relative to those who lost less than 5% of their initial body weight. Likewise, visceral adipocyte size was approximately 41% smaller ($P < .05$) in the 5% to 10% weight loss group when compared with the less than 5% weight loss group (Fig. 2). Visceral adipocytes in both groups were 20% smaller ($P < .05$) than subcutaneous adipocytes. These findings suggest that losing

Table 2
Adipokine concentrations of subjects grouped according to percentage of weight loss

	Weight loss group	Baseline[a]		Posttreatment		Change (%)		P value[b]
		Mean	SEM	Mean	SEM	Mean	SEM	
Adiponectin (ng/mL)	<5% Weight loss	8826	±583	9234	±1394	8.2	±18.0	.12
	5%-10% Weight loss	7747	±956	9365	±1334	19.7	±6.5	.02
Leptin (ng/mL)	<5% Weight loss	99	±13	94	±15	−8.5	±6.7	.24
	5%-10% Weight loss	86	±12	57	±10	−36.8	±5.7	.01
Resistin (ng/mL)	<5% Weight loss	46	±11	26	±11	−11.6	±15.8	.81
	5%-10% Weight loss	37	±9	28	±8	−27.4	± 7.5	.02

[a] Baseline values were not significantly different between weight loss groups for adiponectin, leptin, or resistin: independent-samples t test.
[b] Within-group differences comparing baseline to posttreatment: paired-samples t test.

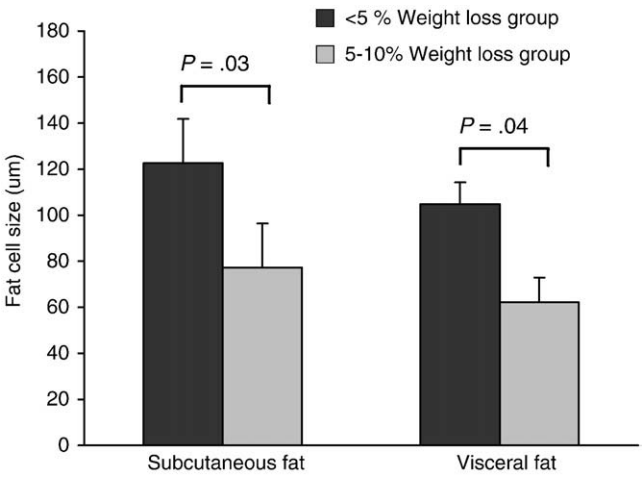

Fig. 1. Subcutaneous and visceral fat cell size after 3 weeks of diet grouped according to percentage of weight loss. Mean ± SEM. Subcutaneous and visceral adipocytes were smaller ($P < .05$) in the subjects who lost 5% to 10% of their initial body weight compared with those who lost less than 5% of their initial body weight (independent-samples t test).

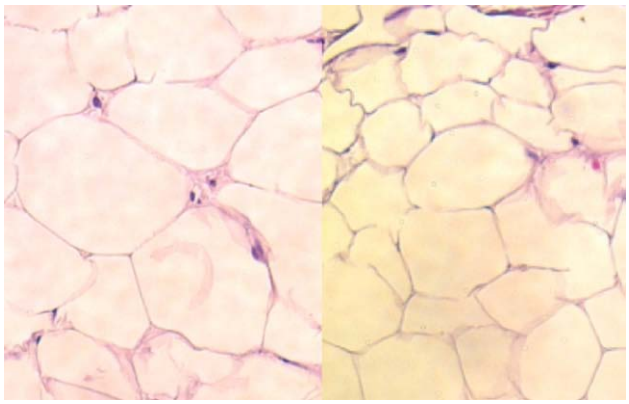

Fig. 2. Posttreatment visceral fat cell size after less than 5% reduction in body weight (left panel) vs a 5% to 10% reduction in body weight (right panel). Images were taken from 2 severely obese women matched for age and baseline BMI. Visceral fat cells were approximately 40% smaller in women who lost 5% to 10% of their initial body weight (right panel) compared with those who lost less than 5% of their initial body weight (left panel).

5% to 10% of initial body weight results in significant decreases in fat cell size in this population.

3.5. Degree of weight loss required to improve metabolic parameters

Changes in insulin, glucose, and CRP concentrations over the course of the trial are reported in Table 3. Insulin and glucose concentrations decreased significantly from baseline by 59% and 10%, respectively, in 5% to 10% weight loss group. Insulin and glucose remained unchanged in the less than 5% weight loss group when baseline values were compared with values posttreatment. No changes in CRP concentrations for either group were observed.

3.6. Relationship between adipokines, fat cell size, and metabolic parameters

Lower leptin concentrations were related to reduced body weight ($r = 0.74$, $P = .004$), decreased BMI ($r = 0.72$, $P = .01$), and smaller subcutaneous ($r = 0.62$, $P = .03$) and visceral fat cell size ($r = 0.63$, $P = .02$). Reduced resistin concentrations were associated with decreased body weight ($r = 0.66$, $P = .01$), lower BMI ($r = 0.61$, $P = .03$), and smaller visceral fat cell size ($r = 0.76$, $P = .01$). Adiponectin was not significantly correlated with any of these variables. Lower insulin concentrations were related to smaller subcutaneous ($r = 0.62$, $P = .03$) and visceral ($r = 0.82$, $P = .01$) fat cell size. Likewise, decreased glucose concentrations were related to smaller subcutaneous ($r = 0.56$, $P = .04$) and visceral ($r = 0.58$, $P = .04$) adipocyte size.

4. Discussion

This study shows that a decrease in body weight, as small as 5% from baseline, can improve circulating adipokine profiles and decrease adipocyte size in severely obese women. More specifically, we report here increases in the beneficial adipokine, adiponectin, and decreases in the less favorable adipokines, leptin and resistin, in women who lost at least 5% of their initial body weight. This degree of weight loss also resulted in significant reductions in both subcutaneous and

Table 3
Metabolic parameters of subjects grouped according to percentage of weight loss

	Weight loss group	Baseline[a]		Posttreatment		Change (%)		P value[b]
		Mean	SEM	Mean	SEM	Mean	SEM	
Insulin (μU/mL)	<5% Weight loss	23	±5	15	±3	−31.0	±13.5	.10
	5%-10% Weight loss	28	±6	9	±2	−58.9	±10.1	.04
Glucose (mg/dL)	<5% Weight loss	106	±16	96	±4	−4.6	±8.5	.46
	5%-10% Weight loss	93	±6	83	±4	−10.2	±4.0	.04
hs-CRP (mg/L)	<5% Weight loss	22	±10	17	±9	−26.7	±18.0	.15
	5%-10% Weight loss	14	±2	7	±2	−28.7	±25.6	.16

hs-CRP indicates high-sensitivity C-reactive protein.

[a] Baseline values were not significantly different between weight loss groups for insulin, glucose, or CRP: independent-samples t test.

[b] Within-group differences comparing baseline to posttreatment: paired-samples t test.

visceral fat cell size. Improvements in adipocyte physiology were associated with reductions in glucose and insulin, which may indicate protection from metabolic disease in this high-risk population.

Circulating adiponectin levels are a significant predictor of future diabetes [11]. Findings from a recent clinical trial demonstrate that a 1000-ng/mL increase in adiponectin is associated with a 16% reduction in the rate of progression to diabetes in obese subjects [12]. The antidiabetic effect of adiponectin has been shown to be due, in part, to its ability to increase fatty acid oxidation in muscle and to stimulate glucose uptake in the liver [13,14]. Results from the present study indicate that adiponectin levels increased by approximately 20% in severely obese women who achieved a 5% reduction in body weight (9-kg decrease from baseline). When expressed in absolute terms, this degree of weight loss raised adiponectin levels by 1618 ng/mL from baseline, which corresponds to an approximately 25% reduction in the rate of progression to diabetes [12]. Results from other studies in this area report discrepant findings [15]. In a recent trial by Madsen et al [15], it was shown that a minimum weight loss of 10% (12-kg reduction from baseline) was required to significantly elevate adiponectin concentrations in grade II obese individuals (mean BMI, 37 kg/m^2). A reason for why a greater degree of weight loss was required in the study by Madsen et al [15] is not apparent. One possible explanation may be that adiponectin responds differently in grade III obese individuals (mean BMI in the present study was ~50 kg/m^2) when compared with grade II obese individuals. Another explanation may be that significant shifts in adiponectin are related to absolute decreases (kilogram reduction) instead of relative decreases (percentage reduction) in body weight. More specifically, because both of these studies observed an approximately 10-kg loss of weight, it can be hypothesized that, once the body sheds a minimum of 10 kg, adiponectin will be significantly increased. This hypothesis will require confirmation in other human trials examining these effects in grade I, II, and II obese individuals before solid conclusions can be reached.

This degree of weight loss also corresponded to reductions in circulating concentrations of leptin and resistin. Adipocytes are the most important source of leptin, and plasma levels of leptin are tightly correlated to adipose tissue mass [4]. Augmented leptin levels amplify CHD risk by increasing platelet aggregation and arterial thrombosis [16]. Whether leptin is directly related to the progression of type 2 diabetes mellitus remains uncertain [17]. As for resistin, circulating levels are positively correlated to body fat content [5]. In humans, resistin may play a role in diabetes progression by interfering with hepatic insulin signaling [18]. Resistin may also mediate CHD risk by promoting endothelial dysfunction and angiogenesis [19]. We show here that circulating levels of these proatherogenic adipokines decrease dramatically in response to minor weight loss (5% from baseline) in severely obese women. Leptin and resistin levels decreased by 37% and 27%, respectively, in those who lost at least 5% of their initial body weight, but remained unchanged in the group that did not meet this weight loss threshold. To our knowledge, the *minimum* degree of weight loss required to lower leptin and resistin levels in obese subjects has not been evaluated previously. As such, there are no data to which to compare the present findings. Nevertheless, these findings suggest that a minor drop in weight, as small as 5% from baseline, can ameliorate adipokine profile, which may protect against metabolic disease in this population.

Reductions in visceral and subcutaneous fat cell size were also observed in the subjects who lost a minimum of 5% of their initial body weight. Obesity is characterized by increased fat mass, which is primarily due to enlarged adipocytes. The enlargement of adipocytes is associated with significant changes in metabolic functions, most notably, adipokine synthesis and release. Recent evidence indicates that large adipocytes synthesize lower quantities of adiponectin and higher amounts of leptin and resistin when compared with smaller adipocytes [20,21]. The present study demonstrates that significant reductions in visceral and subcutaneous fat cell size can be observed with only a 5% drop in weight. Because adipocytes from both depots were approximately 40% smaller in the group that lost more weight, these findings also indicate that subcutaneous and visceral adipocytes lose similar amounts of fat during the initial stages of weight loss. We also show here that visceral fat cells in obese women are approximately 20% smaller than subcutaneous adipocytes. Similar findings have been reported by Michailidou et al [22]. Furthermore, these declines in visceral fat cell size were correlated to decreased leptin and resistin concentrations, whereas reduced subcutaneous fat cell size was related to lower leptin concentrations. Interestingly, there was no relationship between smaller fat cells and augmented adiponectin concentrations, which may have occurred because of the small sample size of the study. Nevertheless, such findings suggest that small reductions in body weight (5% from baseline) can decrease both visceral and subcutaneous fat cell size, in turn producing beneficial modulations in adipokine profile. Because adipocyte size has been identified as a significant predictor of type 2 diabetes mellitus [23], these findings further strengthen our conclusion that this small amount of weight loss is protective against disorders related to obesity.

Improvements in adipose tissue physiology were also related to beneficial changes in metabolic indicators. Insulin and glucose concentrations decreased dramatically in the group that lost more weight, but remained unchanged in the group that did not meet the 5% weight loss threshold. Decreased insulin and glucose concentrations were correlated to smaller fat cells in both subcutaneous and visceral depots. It is well established that large adipocytes are less responsive to the stimulating effect of insulin on the metabolism and uptake of glucose [24]. In view of this, the reductions in adipocyte size observed in the present study may have contributed to enhanced insulin action and greater

clearance of glucose from the circulation. Therefore, a reduction in adipocyte size resulting from this small degree of weight loss may be directly linked to reductions in glucose and insulin levels, indicating an improvement in metabolic risk profile.

In summary, we show here that a minimum degree of weight loss, equivalent to 5% of initial body weight, can improve adipokine profile and decrease fat cell size in severely obese women. Because these changes in adipose tissue physiology were related to reductions in the severity of certain obesity-associated risk factors, this degree of weight loss may be set forth as an initial target goal for weight loss therapy in this population group.

Acknowledgment

We are grateful for the help of Emily Church during the analysis phase of the study. The authors have no conflicts of interest to report.

Departmental grant: Kinesiology and Nutrition, University of Illinois, Chicago.

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