Modest Weight Loss and Reduction in Waist Circumference After Medical Treatment Are Associated With Favorable Changes in Serum Adipocytokines

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Modest weight loss if maintained is associated with significant metabolic benefits and reduction in cardiovascular risk. Adipose tissue secretes cytokines believed to contribute to the pathogenesis of insulin resistance and cardiovascular risk. We therefore observed the effect of modest weight loss on serum adipocytokines and their relationship with changes in anthropometric and metabolic parameters within a period of 6 months in the setting of a routine obesity hospital clinic after various medical treatments. In this prospective, nonrandomized, nonblinded observational study, patients were first given treatment (sibutramine or orlistat) as decided by the treating clinician and then allocated into 1 of 2 groups according to the treatment prescribed. The first group included 21 Caucasian nondiabetic female subjects, with a mean (±SD) age of 43 ± 11 years and a mean body mass index (BMI) of 46 ± 8.6 kg/m^2; subjects were treated with sibutramine 10 or 15 mg/d for weight loss. The second group included 20 Caucasian nondiabetic female subjects, mean age 42 ± 9 years and mean BMI 45.2 ± 5.2 kg/m^2; orlistat was introduced after 1 month on a low-fat (≤30%) diet in this group. Blood pressure and anthropometric measurements were performed before and after weight loss by a single observer. Serum glucose, insulin, lipid profile, C-reactive protein (CRP), resistin, leptin, and adiponectin were measured before and after weight loss on a fasting sample. After 6 months, the sibutramine group had a modest mean weight loss of 5.4% ($P = .0001$), and waist circumference was reduced by 4.5 ± 1.4 cm. There was a decrease in serum resistin, leptin, and CRP levels, and a rise in serum adiponectin ($P < .05$). Change (%) (Δ) in BMI (ΔBMI%) was associated with Δinsulin(%) ($P = .02$, $r = 0.53$) and Δleptin(%) ($P = .01$, $r = 0.58$). Change in waist was associated with Δinsulin(%) ($P = .005$, $r = 0.75$) and Δresistin(%) ($P = .03$, $r = -0.55$). The orlistat-treated group had a mean weight loss of 2.5%. Although this group did not show significant change in metabolic parameters, surprisingly there was a greater decrease of resistin ($P = ..02$) associated with comparable (%) increase in adiponectin and (%) reduction of waist circumference and CRP. We conclude that modest weight loss (>5%) after medical treatment in a routine obesity hospital clinic is associated with improvements in insulin sensitivity and lipid profile. Modest weight loss is also associated with potentially favourably changes in serum adipocytokines, particularly in a rise of serum adiponectin. Reduction of waist circumference is associated with a change in serum resistin.

OBESITY IS ASSOCIATED with metabolic, hormonal, and neuroendocrine abnormalities. Central obesity is a powerful risk factor for the development of insulin resistance, hypertension, hyperlipidemia, and atherogenesis.[1-4] Weight reduction results in an improvement or elimination of these obesity-related comorbid conditions.[5,6] Weight loss of 5% or even less has been shown to reduce health risks, and metabolic improvements are related to the magnitude of weight loss.[7] We still do not know if there is a threshold under which there are not health benefits after weight loss. Different modes of weight loss may result in some differences in health benefits achieved. Lifestyle modifications with a low-fat diet and orlistat—an inhibitor of gastric and pancreatic lipases[8]—are associated with a reduction in blood pressure and serum triglycerides, and with improvement of insulin sensitivity.[9] This medical approach results also in a reduction of low-density lipoprotein (LDL)-cholesterol without significant change of high-density lipoprotein (HDL)-cholesterol.[10] Sibutramine, a potent reuptake inhibitor of noradrenaline and serotonin, inhibits food intake and is believed to stimulate thermogenesis by activating the β3 system in brown adipose tissue. Sibutramine therapy is associated with a mild increase in blood pressure, increased HDL-cholesterol, decreased triglycerides, and improved insulin sensitivity.[11]

Adipose tissue is now known to express and secrete a variety of novel adipocytokines that have been implicated in the development of insulin resistance and atherosclerosis.[12] Adipocytes secrete a variety of polypeptides, such as leptin, resistin, and adiponectin. Balanced production of adipocytokines plays an important role in maintaining homeostasis of glucose and lipid metabolism. Dysregulation of adipocytokine production is directly involved in the pathophysiology of the metabolic syndrome, and normalization of plasma concentrations of adipocytokines reverses the phenotype of the metabolic syndrome.[13,14] Leptin is an afferent signal molecule that interacts with the appetite and satiety centers in the brain to regulate body weight and it contributes to energy expenditure and to the regulation of food intake. The relationship of leptin to insulin sensitivity and components of the metabolic syndrome showed leptin to be positively associated with body mass index (BMI), fasting insulin, and mean blood pressure after adjusting for age and sex.[15] Weight loss after a hypocaloric diet for 6 months in women has been shown to decrease leptin levels.[16] Adiponectin, a 30-kd adipocytokine, has antidiabetic and antiatherogenic properties.[17,18] Hypoadiponectinaemia is associated with the development of obesity-related metabolic syndrome, including insulin-resistant diabetes and atherosclerosis.[17] Circulating adiponectin concentrations are decreased in obese individuals and the reduction is believed to have a role in the pathogenesis of atherosclerosis and cardiovascular disease associated with obesity and other components of the metabolic syndrome.[12,19,20] Plasma adiponectin concentrations are lower in patients with

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diabetes and ischemic heart disease.[21,22] Weight loss after gastric partition surgery has been shown to increase serum adiponectin levels in a mixed gender population.[23] Finally resistin, a novel 12.5-kd cysteine-rich protein, has been proposed to be the link between obesity and insulin resistance.[24] In a study using 32 adipose tissue samples and quantitative polymerase chain reaction (PCR), there was an increased amount of resistin mRNA in abdominal depots compared with thigh depots, suggesting an increased risk for type 2 diabetes as a result of central obesity and higher resistin levels.[25] Resistin was also reported as a cysteine-rich adipose tissue–specific secretory factor that blocks adipocyte differentiation.[26]

The aim of this study was to assess the effect of modest weight loss on serum adipocytokine changes and their association with anthropometric and cardiovascular risk factors, achieved in the setting of a routine obesity hospital clinic using the medical treatments available.

MATERIALS AND METHODS

Patient Recruitment

The study was approved by the East Birmingham Research and Ethics Committee and written consent was obtained from all patients. This was a prospective, nonrandomized, nonblinded, parallel-group, observational study within the setting of a routine obesity hospital clinic. Patients were first given treatment (sibutramine or orlistat) as decided by the treating clinician and were then approached by the observing research doctor; those who consented were subsequently allocated into 1 of 2 groups according to the treatment prescribed. Exclusion criteria were history of cardiovascular disease, stroke, type 2 diabetes, uncontrolled blood pressure (>160/100 mm Hg), and smoking during the previous 6 months, or currently taking on angiotensin-converting enzyme (ACE) inhibitors, diuretics, glucocorticoids, oral combined contraceptives, or psychoactive drugs.

Lifestyle Interventions and Treatment

The first group included 21 Caucasian nondiabetic women, with a mean age of 43 ± (SD) 11 years and BMI of 46 ± 8.6 kg/m^2. Subjects were treated for weight loss with sibutramine 10 or 15 mg/d (in the morning) for 6 months. In 6 patients the initial dose of 10 mg sibutramine was increased to 15 mg by the treating physician because of inadequate response (defined as <2-kg weight loss after 4 weeks of treatment). The sibutramine-treated group was prescribed a 600-kcal deficit diet by the dietitian of the obesity clinic and received instructions in behavioral change techniques. A second group of 20 Caucasian nondiabetic women, age 42 ± 9 years and BMI 45.2 ± 5.2 kg/m^2, from the obesity clinic were treated with a low-fat diet and orlistat (120 mg 3 times per day) for 6 months. In this group patients were prescribed a hypocaloric diet containing roughly 30% of energy as fat (≤30%) together with instruction in behavioral change techniques by the dietitian in the clinic. These 20 patients managed to loose 2 kg of weight after the first month on diet and subsequently they were put on orlistat 120 mg three times per day by the treating physician. At the beginning and at the end (6 months) of the study each subject had anthropometric measurements and serum samples taken, after an overnight fast, for the purposes of the research study by the observing research physician. Samples were centrifuged, and stored in freezers (−80°C) until analyses were performed. All patients included in the study were compliant with the treatment and were encouraged to increase their activity levels aiming for a minimum of a three 30-minute fast walking sessions per week. All patients were seen by the dietitian at the end of the first and third month of treatment and by the treating physician at the end of the third month. Dose increases in the sibutramine-treated patients and initiation of orlistat treatment after the first month were done by the registered general practitioner according to the recommendations of the treating hospital physician.

Anthropometry

Weight in kilograms was measured on the nearest 0.1 kg on a beam balance with the subject without shoes and only light clothing. Height in meters was measured to the nearest 1 mm using a stadiometer attached to the balance. Waist circumference in centimeters was taken in duplicate with a 6-mm wide flexible tape and was the minimum between the costal margin and iliac crest. All measurements were taken with the subject standing and in the horizontal plane position.

Biochemistry

Fasting plasma glucose, triglycerides, and total and HDL-cholesterol (all in millimoles per liter) were measured, using the Roche P800 analyzer (Roche, Basel, Switzerland), by enzymatic determination. LDL-cholesterol was calculated using the Friedwald formula.[27] C-reactive protein (CRP) (milligrams per liter) was measured with a highly sensitive in-house enzyme-linked immunosorbent assay (ELISA). Fasting insulin (milli-international units per liter) was determined using the Medgenic immunoenzymetric assay by Biosource-Europe SA (Nivelles, Belgium). Insulin sensitivity was derived from fasting glucose and insulin data, using the homeostasis model assessment (HOMA) mathematical model.[28] Insulin sensitivity was expressed as (HOMA-S%) = ([22.5/fasting insulin × fasting glucose] × 100). Fasting serum leptin concentrations (nanograms per milliliter) were determined using the radioimmunoassay procedure (RIA) by Linco Research (St Charles, MO). Fasting serum adiponectin was also measured using the Linco RIA. Fasting resistin concentrations (nanograms per milliliter) were determined using the ELISA by Phoenix (Belmont, CA).

Statistical Analysis

Data are described as the mean ± SD in the case of normal distribution and as median and interquartile range in the case of non-Gaussian distribution (Tables 1 and 2). SPSS statistical software (SPSS Inc, Chicago, IL) was used for statistical analysis.[29] Paired *t* test (if normally distributed) and Wilcoxon ranked test (in case of non-Gaussian distribution data) were used to assess the change of variables with different weight loss methods. Correlation analysis between variables (X) before and after weight loss and between percentage (%) changes of variables ([Δ × %] = 100 × [Xmonth 6 − Xday 1]/Xday 1) was done using the Spearman correlation. Changes of variables in the tables are presented as mean percentage (%) change.

RESULTS

Effect of Modest Weight Loss on Adipocytokines and Other Metabolic Parameters

After 6 months on sibutramine, the first group (Table 1) had a 5.4% weight loss ($P = .0001$) and waist circumference change of 3.6% ($P = .002$). Analysis revealed that the modest change of weight improved significantly insulin sensitivity (HOMA-S%) ($P = .03$), increased HDL-cholesterol by 13.8% ($P = .01$), decreased triglycerides by 9.4% ($P = .02$), and decreased CRP by 9.7% ($P = ..03$). Sibutramine increased systolic and diastolic blood pressures, but changes were not statistically significant ($P > .05$). We also observed statistically significant changes ($P < .05$) in serum adipocytokines (Table

Table 1. Pre- and Post-Weight Loss Data and Mean Changes (%) in Metabolic Parameters and in Serum Adipocytokines After 5.4% Weight Loss in the Sibutramine-Treated Group

	Baseline	Post-Weight Loss	Change (%)	*P* Value
n (females)	21			
Age (yr)	43 ± 11			
Weight (kg)	130.2 ± 26.1	123.1 ± 22.7	−5.4%	.0001
BMI (kg/m^2)	46 ± 8.6	43.4 ± 7.4	−5.4%	.0001
Waist circumference (cm)	133.1 ± 18	128.6 ± 16.6	−3.6%	.002
Systolic blood pressure (mm Hg)	131.7 ± 21.3	135.8 ± 20.9	+1.9%	.647
Diastolic blood pressure (mm Hg)	80.4 ± 12.5	84.9 ± 9.9	+2.3%	.264
Fasting plasma glucose (mmol/L)	5.5 ± 0.9	4.9 ± 0.8	−6.4%	.079
Insulin (mIU/L)	23 (13–32)	18 (12–25)	−9%	.117
HDL-cholesterol (mmol/L)	1.1 ± 0.2	1.3 ± 0.3	+13.8%	.011
LDL-cholesterol (mmol/L)	3 ± 0.7	2.9 ± 0.6	−4.7%	.443
Total cholesterol (mmol/L)	4.9 ± 0.6	4.6 ± 0.4	−5.8%	.062
Triglycerides (mmol/L)	1.5 ± 0.6	1.1 ± 0.5	−9.4%	.022
HOMA-S%	14.05 (10.2–35.15)	25.5 (17.35–32.7)		.03
Leptin (ng/mL)	29.7 ± 13.4	21.4 ± 9.1	−22%	.021
Resistin (ng/mL)	11.9 ± 3.6	9.3 ± 3.2	−16.8%	.020
Adiponectin (μg/mL)	4.3 (2.7–5.9)	5.1 (4–8.8)	+27%	.042
CRP (mmol/L)	5 (4.2–10.1)	4 (3.5–5.9)	−9.7%	.031

NOTE. Data are expressed as means ± SD and median (interquartile range) values according to their distribution.

1), with a 22% decrease in serum leptin ($P = .02$), 16.8% decrease in serum resistin ($P = .02$), and 27% increase in serum adiponectin ($P = .04$).

The orlistat-treated group, after an initial 2-kg weight loss on the low-fat diet only in the first month (Table 2), at the end of 6 months treatment, had a weight loss of 2.5% ($P = ..002$) and waist change of 2.32% ($P = .08$). Further analysis revealed that there was a trend towards increase in HDL-cholesterol and serum adiponectin and a decrease in serum leptin, insulin, and CRP, but these changes were not statistically significant ($P > .05$). Surprisingly resistin was decreased significantly on orlistat treatment ($P = .009$), even with lower weight loss achieved in this group.

Correlation of Changes in BMI and Waist Circumference With Metabolic Parameters and Serum Adipocytokines Before and After Weight Loss

Spearman correlation between variables revealed that the change (%) in BMI (ΔBMI%) was associated with Δinsulin(%) ($P = .02$, $r = 0.53$) and Δleptin(%) ($P = ..01$, $r = 0.58$). Change (Δwaist%) of waist circumference with weight loss was associated with Δinsulin(%) ($P = .005$, $r = 0.75$) and Δresistin(%) ($P = .03$, $r = -0.55$). Δinsulin(%) was associated with Δleptin(%) ($P = .008$, $r = .61$). Rise in HDL-cholesterol during weight loss did not correlate with adiponectin. There were no other significant correlations between anthropometric

Table 2. Pre- and Post-Weight Loss Data and Mean Changes (%) in Metabolic Parameters and in Serum Adipocytokines After 2.5% Weight Loss in the Orlistat-Treated Group

	Baseline	Post-Weight Loss	Change (%)	*P* Value
n (females)	20			
Age (yr)	42 ± 9			
Weight (kg)	128 ± 18	124.8 ± 17.7	−2.5%	.002
BMI (kg/m^2)	45.2 ± 5.2	44 ± 5	−2.5%	.002
Waist circumference-cm	137.5 ± 10	134.4 ± 2.1	−2.3%	.080
Systolic blood pressure (mm Hg)	137.5 ± 18.6	126.2 ± 13.7	−6.4%	.221
Diastolic blood pressure (mm Hg)	87.7 ± 8.3	76.3 ± 7	−9.7%	.205
Fasting plasma glucose (mmol/L)	5.9 ± 1.4	5.4 ± 0.9	−3.6%	.110
Insulin (mIU/L)	22.9 ± 9.4	21.9 ± 9.9	−4.3%	.674
HDL-cholesterol (mmol/L)	1.1 ± 0.2	1.4 ± 0.6	+3.4%	.357
LDL-cholesterol (mmol/L)	2.7 ± 0.8	2.6 ± 0.6	−1.8%	.732
Total cholesterol (mmol/L)	4.7 ± 0.5	4.6 ± 0.7	−1.2%	.863
Triglycerides (mmol/L)	1.7 ± 0.7	1.7 ± 0.6	−1.6%	.806
HOMA-S%	16.7 (9.5–37.2)	18.9 (15.7–29.6)		.362
Leptin (ng/mL)	22.3 ± 8	21.4 ± 9.6	−4.7%	.638
Resistin (ng/mL)	12 ± 3.5	6.5 ± 2.6	−36%	.005
Adiponectin (μg/mL)	3 (1.8–7)	4.4 (2.8–8)	+24%	.212
CRP (mmol/L)	4.2 (2–10.1)	3.6 (2.1–8.9)	−8%	.315

NOTE. Data are expressed as means ± SD and median (interquartile range) values according to their distribution.

parameters and adipocytokines or between the adipocytokines ($P > .05$).

Finally, in the orlistat-treated group, due to minimum weight loss achieved, Spearman correlations showed that change in waist circumference was associated with change in resistin ($P = ..05$, $r = -0.825$) and was the only significant correlation in this group between all variables ($P > ..05$).

DISCUSSION

Weight loss is associated with favorable changes in cardiovascular risk factors.[30] Even modest weight loss following lifestyle changes or medical treatment has beneficial effects on several cardiovascular risk factors.[31] The present data, as previous studies, have demonstrated the different beneficial effects of sibutramine and orlistat on anthropometric and metabolic parameters after weight loss.[10,11,32] Most obese patients receive medical treatment in obesity hospital clinics with the aim of achieving realistic weight loss, in order to reduce their cardiovascular risk. This is the first report of the effects of modest weight loss on serum adipocytokines concentrations after the initial 6 months of medical treatment and their association with anthropometric and cardiovascular risk factors. This study was a nonrandomized, nonblinded, observational study. It was conducted by using the 2 different medical approaches available for patients under the realistic conditions of a routine hospital obesity clinic. The first (sibutramine) is not reliant on successful change of diet by patients, whereas orlistat treatment relies on patient adherence to a low-fat (≤30% fat) diet. Because this study was not blinded, it is not possible to compare outcomes directly between treatments.

However, after a modest weight loss of 5.4% on sibutramine, in 21 obese Caucasian female patients, there were significant changes in lipid profile, rise in HDL-cholesterol, reduction in triglycerides, reduction of CRP, and rise of insulin sensitivity. Furthermore, there were favorable changes in serum adipocytokines. Modest weight loss was associated with significantly reduced serum leptin and increased serum adiponectin levels. Although resistin changes in this group were significant, the effect of sibutramine treatment on serum resistin needs further study by comparison with a control group. Some of these data are supported by previous studies using different methods. One study using gastric partition surgery, in a mixed male and female population, observed a 46% increase in serum adiponectin after achieving a 21% reduction in mean BMI.[30] Another study of 102 moderately obese females (mean BMI, 29.5 ± 0.5) looking at the effects of weight loss in blood pressure found a significant reduction of serum leptin levels after weight loss.[33,34]

Furthermore, weight change on sibutramine was associated with insulin and leptin changes during weight loss. Previous studies, using a very-low-calorie diet, have shown that a low serum leptin level at baseline could predict the weight reduction and maintenance after 1 year.[34] The role of leptin as a predictor of weight loss requires further research. From experimental data we know that during the development of obesity and progression to diabetes mellitus, there is increased ability of insulin to stimulate glucose oxidation and to stimulate lipid synthesis in obese animals compared to normals.[35] Adiponectin has been associated with insulin sensitivity and HDL-cholesterol in recent studies.[36] One of these analyzed the association in 262 nondiabetic individuals between serum adiponectin and insulin sensitivity measured by euglycemic clamp and found that high adiponectin predicts insulin sensitivity, a relationship which affects not only insulin-stimulated glucose disposal but also lipoprotein metabolism.[37] Resistin change was not associated with BMI change but was correlated with waist circumference change, supporting previous data that resistin concentrations are related to visceral/central obesity.

A minimal 2.5% weight change after orlistat treatment did not result in any statistically significant changes in metabolic parameters and this was also not associated with significant changes in serum adipocytokines. The reason for lack of success in weight loss in this group may be because this approach relies on effective behavior modification by the patient who should be able to achieve lifestyle changes. Surprisingly, orlistat treatment, even after a minimal weight loss of 2.5%, achieved a greater reduction in serum resistin levels compared to that achieved in the sibutramine group and this was associated with comparable (as percentage) reduction in waist circumference and serum CRP, as well as a rise of serum adiponectin levels. Changes in serum resistin levels were associated with changes in waist circumference in both groups and were more significant in the group that lost the least weight. Resistin has been suggested to be the link between obesity and diabetes by a mechanism that is still not clear.[24]

In conclusion, these preliminary data show that even modest weight loss with sibutramine is able to produce significant changes in serum adipocytokines, insulin sensitivity, and HDL-cholesterol. Serum resistin is associated with central obesity, but baseline serum insulin level was the best predictor of the change of BMI and waist circumference. Orlistat treatment resulted in less weight loss with no significant changes in most cardiovascular risk factors, but was able to achieve comparable (%) changes of waist circumference and this was associated with greater reduction in serum resistin. Further studies are needed to compare the specific effect of each medical treatment on serum adipocytokines and to assess the diet effect after modest weight loss.

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