Turkish Journal of Endocrinology and Metabolism, (2003) 3 : 127-130 **ORIGINAL ARTICLE**

Effects of Sibutramine Assisted Weight Loss on Body Composition, Metabolic Parameters and Insulin Resistance

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To determine the effects of sibutramine in combination with hypocaloric diet and exercise on body composition, metabolic parameters and insulin resistance.

11 female, 1 male (aged 18-60 year) patients were enrolled. Sibutramine (10 mg/day), hypocaloric mixed diet and exercise were given. Analysis of antropometric measurements and bioimpedance measurements for estimating body composition, metabolic (uric acid, cholesterol, triglyceride, HDL-cholestrol) and hormonal (total and free testosterone, DHEAS, cortisol, growth hormone, prolactin) measurements and the determination of insulin resistance by euglycemic hyperinsulinemic clamp technique were done before and after the patients lost 10 % of their initial body weight.

After weight loss, decrease in body weight (from 102,0±4,9 to 89,8±4,4 p<0,001), waist circumference (from 110,0±2,7 to 97,9±3,6 p>0,001) WHR (from 0,85±0,02 to 0,79±0,02 p<0,05) were significant. In impedance measurements, decrease of body fat mass (from 48±2,2 % to 41,1±2,2 % p<0,001) increase of lean body mass (from 51,9±2,2 % to 58,6±2,1 % p<0,001) and decrease of level of uric acid (from 5,3±0,4 to 4,8±0,3 p<0,05), triglyceride (from 126,2±23,7 to 98,0±17,2 p<0,01), cortisol (from 18,9±1,9 to 11,6±1,0 p<0,05), C-peptide (4,7±1,0 to 2,6±2,6 p<0,05) and 120 min glucose concentration (from 107,5±3,5 to 9,1±6,3 p<0,05) were significant. In euglycemic hyperinsulinemic clamp study, whole body glucose disposal (M value) increased significantly (from 2,87±0,27 to 4,26±0,41 p<0,01).

Although the patients didn't reached ideal body weight, sibutramine assisted weight reduction of %10 caused meaningful reductions in BMI, WHR, triglyceride, fasting C-peptide, cortisol level and significant improvement in insulin resistance.

Key words: Weight loss, sibutramine, insulin resistance

Introduction

Obesity is a major chronic and multifactorial disorder characterized by excess accumulation of adipose tissue (1,2). It is associated with a number of complications including type 2 diabetes, dyslipidemia, cardivascular disease and hypertension. A weight loss of 5-10 % is associated with clinically meaningful reductions with respect to all comorbidities (3).

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Non-pharmacological treatment modalities such as diet and increased physical activity, constitute the basis of treatment for obese patients. However, adequate weight loss is seldom attained with these approaches (4). Sibutramine is a centrally- acting agent which enhances satiety and thermogenesis by inhibiting noradrenaline and serotonin re-uptake (5-7). It is appropriate for patients who are unable to loose weight by diet and exercise.

The aim of this study was to evaluate the effects of sibutramine in combination with hypocaloric diet, exercise on metabolic parameters and body composition and insulin resistance.

Method

A total of 12 obese subjects (11 female, 1 male, mean age 42.2±2.7) with BMI>30 kg/m^2 were recruited from obesity outpatient clinic in Osmangazi University, Medical School, Division of Endocrinology. Subjects with hypertension, diabetes mellitus or cardiovascular disease or major systemic diseases were excluded. All patients gave informed consent. Study protocol included initial physical examination, (blood pressure and heart rate), electrocardiogram, as well as blood hematology and chemistry, analysis of antropometric and impedance examinations and the calculation of insulin resistance as peripheric glucose disposal by euglycemic hyperinsulinemic clamp tecnique. Then Sibutramine 10 mg/day in combination with hypocaloric mixed diet (1000-1400 kcal/d) and exercise were given. Exercise was initially planned as 30 min/ d, then 45 min/d fast walking. The patients were evaluated every month until a reduction of 10 % of their initial body weight occured. Then they were reevaluated for all interventions that applied beginning of the study.

All blood samples were taken after over-night fast. OGTT performed with 75 gr, blood samples obtained at 0. and 120. minute for glucose. Glucose, cholesterol, triglyceride, HDL, uric acid (Bohringer Manheim-Hitahci 917 Analyzer), C-peptide, free and total testosterone, cortisol, DHEASO4 growth hormone, prolactin (BioDPC Immilite 2000 Analyzer) measurements were performed.

Antropometry: Weight and height were measured in street light clothes without shoes. Waist circumference was measured at the level midway lateral rib margin and iliac crest. Hip circumference was determined as the maximum value over the buttocs.

Impedance: Body fat mass, lean mass, water and basal metabolic rate (BMR) were determined using bioelectric impedance analysis (Biostat 1500 Bioelectric Impedance Analyzer System) at postvoiding, fasting state.

Insulin resistance: Insulin sensivity was assessed by the use of the euglycemic hyperinsulinemic clamp tecnique as previously described (8). Subjects were studied after an overnight (10-12 h) fast. Briefly an intravenous catheter was inserted into for antecubital vein for infusion of insulin and glucose, and a second catheter was inserted into dorsal hand vein for blood sampling. The hand was then placed in a warming box thermostatically controlled at 60 Co to arterialize the blood and allowed to equilibrate for 30 min before baseline samples for glucose and insulin were obtained. Infusion pump (Abbott-Shaw Life Care 4) was used to infuse 20 % dextrose (Eczacıbaşı Baxter) and insulin (Novo Nordisc Actrapid 100 IU). Insulin was administered 127.6 mU/m^2 for 1st min, 113.6 mU/m^2 for 2nd min, 101.2 mU/m^2 for 3rd min, 90,2 mU/m^2 for 4th min, 80.2 mU/m^2 for 5th min, 71.4 mU/m^2 for 6th min, 63.6 mU/m^2 for 7th min, 56.8 mU/m^2 for 8th min, 50.4 mU/m^2 for 9th min, 45 mU/m^2 for 10th min. Then insulin was infused constant rate of 40 mU/m^2 until 120th min. Dextrose infusion was started at 4th min 2 mg/kg, 2,5 mg/kg after 10th min. Arterialized blood samples were obtained every 10 min. Blood glucose levels were maintained between ± 10% initial blood glucose level.

Calculation: Dextrose infusion rates were collected in 5 coupled groups except 10th and 120th min during clamp study. These values were converted to mg/kg.dk every each 20 min to find whole body glucose uptake rate (M-value). The values below 4mg/kg.dk (M-value) was considered as insulin resistant state for each patients.

Statistics: Statistical analysis was performed with the aid of SPSS 10.0 version using paired t-test and multivariate analysis. Parametric data were expressed as arithmetic mean ± and a p- value <0,05 was considered statistically significant.

Results

Of the 12 obese patients, 1 patient was excluded due to sibutramine side effects, constipation and dry mouth. Evalutions were made with 11 patients (10 female, 1 male, mean age 42.2±2.7 years). Patients achieved 10% weight loose in 9- month duration (9.1±2.0)

Before and after weight loss, decrease in waist hip ratio (WHR) (from 0.85±0.02 to 0.79±0.02 p<0.05), BMI (from 38.5±1.9 to 33.4±1.7 p<0.001), waist (from 110±2.7 to 97.9±3.6 p<0.001), and hip (from 128.7±4.4 to 121.3±3.5 p<0.001) were significant. In body composition after weight loss, decrease of body fat mass (from 48%±2.2 to 41.1% 2.2 p<0.05) and increase of lean mass (from 51.9%±2.2 to 58.6%±2.1 p<0.05) were significant (table 1). No changes in systolic (from 119.5± 2.5 to 120.4±3.3 p>0.05) and diastolic (from 75.4±3.1 to 75.0±3.1 p>0.05) blood pressure, heart rate (from 85.0±2.2 to 83.8±1.5 p>0.05) were observed during the study.

Table 1. Changes in antropometry and empedance after sibutramine use.

Before	After	p	
Weight (kg)	102±4.9	89.8±4.4	<0.001
BMI (kg/m^2)	38.5±1.9	33.4±1.7	<0.001
Waist (cm)	110.0±2.7	97.9±3.6	<0.001
Hip (cm)	128.7±4.4	121.3±3.5	<0.01
WHR	0.85±0.02	0.79±0.02	<0.05
Body fat (%)	48.0±2.2	41.1±2.2	<0.001
Lean (%)	51.9±2.2	58.6±2.1	<0.001
Water (%)	38.0±1.4	42.6±1.8	<0.01
BMR (kcal/day)	1630.5±78.3	1608.0±57.9	>0.05

The changes in triglyseride (from 126±23.7 to 98.0 ±17.2 p<0.05), uric acid (from 5.3±0.4 to 4.8±0.8 p<0.05) and cortisol (from 20.0±2.9 to 11.6±0.10 p<0.05) were significant. The changes in other metabolic parameters were not significant (Table 2). Improvement in fasting C-peptide (from 4.7±1.0 to 2.6±0.2 p<0.05), 120 min glucose (107.5±3.5 to 91.4±6.3 p<0.05) and whole body glucose uptake rate (M-value)(from 2.87±0.27 to 4.23±0.41 p<0.01) were significant (Table 3).

Table 2. Changes in lipid and hormon levels after sibutramine treatment.

	Before	After	p
Cholesterol (mg/dl)	203.4±7.9	189.2±9.0	>0.05
Triglyseride (mg/dl)	126.0±23.7	98.0±17.2	<0.01
HDL (mg/dl)	51.4±2.4	52.1±2.5	>0.05
LDL (mg/dl)	129.8±8.1	110.4±11.1	>0.05
Cholesterol/HDL	3.93±0.2	3.65±0.6	>0.05
Uric acid (mg/dl)	5.3±0.4	4.8±0.3	<0.05
Total testosterone (ng/dl)	61.63±14.63	58.58±14.15	>0.05
Free testosterone (pg/ml)	2.59±0.65	1.84±0.51	>0.05
$DHEASO_4$ (mg/dl)	190.2±40.9	156.9±34.9	>0.05
Growth hormone (ng/ml)	1.62±0.53	2.57±0.58	>0.05
Cortisol (mcg/dl)	18.9±1.9	11.6±1.0	<0.05
Prolactin (ng/dl)	10.9±1.5	9.39±1.31	>0.05

Table 3. Changes in insulin resistance after sibutramine treatment.

	Before	After	p
Fasting glucose (mg/dl)	93.8±3.5	91.3 ±2.0	>0.05
Fasting C-peptide (ng/ml)	4.7±1.0	2.6±0.2	<0.05
OGTT 120.min glukoz(mg/dl)	107.5± 3.5	91.4±6.3	<0.05
M-value (mg.kg/min)	2.87±0.27	4.23±0.41	<0.01

Discussion

Sibutramine is a combined serotonin (5-HT) and NA reuptake inhibitor that works predominantly through its two pharmacologically active metabolites which induce marked weight loss by affecting both food intake and energy expenditure. It enhances the physiological process of satiety and stimulates thermogenesis, increasing the efferent sympathetic activity in thermogenically active brown fat. There is a dose-related reduction in body weight with sibutramine up to 5-10 % below baseline (5-7,9,10). In our study, obese patients lost 10 % of their initial body weight with the assistance of 10 mg/day sibutramine. Despite a high overall incidence of reported adverse events (71-84 %) including dry mouth, constipation, and insomnia, only one patient was withdrown due to dry mouth and constipation. During sibutramine therapy, a small increase in heart rate and blood pressure occured and persisted as long as treatment was continued, but monitoring of our patients did not provide us any changes in these parameters. On the other hand, a weight loss of 5-10 % of initial weight had been demonstrated to cause a blood pressure lowering and normalisation of blood pressure observed even they didn't reach ideal body weight. Therefore, it is reasonable to suggest weight reduction counterbalanced the effect of sibutramine on blood pressure levels in our patients.

Insulin resistance and hyperinsulinemia are established as metabolic features of obesity (11). Therefore, we measured insulin mediated glucose disposal and examined its relationship with metabolic parameters in obese patients. All the patients included in this study were insulin resistant, as shown by means of hyperinsulinemic euglycaemic clamp technique. Sibutramine assisted loss of 10 % of body weight, improved insulin sensivity as M value was shown to be increased from 2.87 to 4.23 mg/kg.min. A concomitant improvement of peripheral glucose disposal and fasting C-peptide level as well as 120 min glucose concentration indicate amelioration of both insulin resistance and beta cell function. The degree of insulin resistance is closely associated with the lipoprotein metabolism. The reduction of serum triglyceride and uric acid levels accompanied substantial improvements in insulin sensivity, in our study. In contrast the reductions in total and LDL cholesterol were nonsignificant. Sibutramine, diet and exercise did not effect either total or LDL cholesterol levels despite the lower saturated fatty acid intake and weight loss; the expected reduction in total and LDL cholesterol concentrations from diet alone was reported to be approximately 10-12%. A more likely explanation for this, as reported other studies,

may be the enhanced conversion of VLDL to LDL cholesterol (2).

A weight loss of 10 % of body weight assisted by sibutramine was associated with meaningful reductions in BMI, WHR, body fat mass and improvement in lean body mass in our study. Abdominal body fat either overall or visceral has a strong and independent association with obesity and its related co-morbidities, particularly metabolic complications such as cardiovascular disease and type 2 diabetes (12). The reduction of WHR and the loss of body fat accompanied the improvements in peripheral insulin sensivity and triglyceride level in our patients. Therefore, sibutramine treatment in combination with diet and exercise was associated with improvements in cardiovascular and type 2 diabetes risk profiles.

Basal metabolic rate did not changed after weight loss in our patients. In fact, BMR is expected to fall with weight loss (9), but sibutramine inhibits neuronal reuptake of norepinephrine and serotonin at the receptor sites, which enhances peripheral noradrenaline function via β3 adrenoceptors (2). This effect prevents the decline in energy expenditure during weight loss.

In addition to all these metabolic benefits in our insulin resistant obese patients, cortisol levels were also decreased after weight reduction. Chronic endogenous cortisol excess even in a mild form, was shown to be related to central obesity and insulin resistance(13,14). Moreover, cessation of mild cortisol excess was reported to result in improvement in insulin resistance (15).

As a result, obesity is a major chronic health problem in adults. To maximize the benefits of sibutramine exercise and diet therapy was given to our patients. A weight reduction of 10 % assisted by sibutramine caused meningful reductions in BMI, waist/hip, triglyceride, fasting C-peptide and cortisol levels. The importance of all these findings together is its ability to ameloriate insulin sensitivity, the independent risk factor for cardiovascular disease, even without reaching ideal body weight.

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