Effects of Sibutramine on Insulin Resistance, Metabolic Parameters and Abdominal Fat Mass

SİBUTRAMİNİN İNSÜLİN DİRENCİ, METABOLİK PARAMETRELER VE ABDOMİNAL YAĞ DOKUSU ÜZERİNE ETKİLERİ

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Abstract

Objective: Obesity is recognized as a major worldwide health problem. In particular, visceral fat accumulation is usually accompanied by insulin resistance or type 2 diabetes mellitus, hypertension, hypertriglyceridemia, high uric acid and low high-density lipoprotein cholesterol levels defined as metabolic syndrome. Metabolic syndrome is strongly associated with increased risk of cardiovascular morbidity and mortality. The objective of this study was to assess the effects of sibutramine therapy on body mass index (BMI), body fat distribution, visceral fat mass (VF) accumulation, insulin resistance and plasma lipid profile in central obese patients.

Material and Methods: Demographic, biochemical and anthropometric measurements, insulin resistance that was calculated by using homeostasis model assessment of 43 obese patients treated with 15 mg/day sibutramine for 6 months were evaluated. Abdominal fat distributions were determined by ultrasound examination.

Results: Sibutramine treatment accompanied with life style changes (diet and exercise) demonstrated significant reductions in BMI ($p< 0.0001$), total body fat mass ($p< 0.01$), waist circumference ($p< 0.0001$), subcutaneous ($p< 0.05$) and VF ($p< 0.0001$), and HOMA-IR ($p< 0.01$). Serum total cholesterol ($p< 0.05$) and triglyceride ($p< 0.05$) levels reduced significantly after the sibutramine treatment. BMI was inversely associated with HOMA-IR.

Conclusion: Sibutramine is a well-tolerated drug and may improve metabolic abnormalities in insulin resistance syndrome. In addition, it may have beneficial effects by preventing the progression of diabetes and cardiovascular diseases.

Key Words: Sibutramine; body mass index; insulin resistance

Özet

Amaç: Obezite tüm dünyada yaygın bir sağlık sorunu olarak tanınmaktadır. Özellikle visseral yağ birikimi genellikle metabolik sendrom denilen insülin direnciyle, tip 2 diabetes mellitusla, hipertansiyonla, hipertrigliseridemiya ile yüksek ürik asit ve düşük yüksek dansiteli lipoprotein kolesterol seviyeleriyle birlikte seyretmektedir. Metabolik sendrom artmış kardiyovasküler morbidite ve mortaliteyle güçlü bir bağlantı içindedir. Bu çalışmanın amacı santral obez hastalarda sibutramin tedavisinin beden kitle indeksi (BKİ)'ne, vücut yağ dağılımı ve visseral yağ birikimi üzerine, insülin direnci ve plazma lipid düzeni üzerine olan etkilerinin belirlenmesidir.

Gereç ve Yöntemler: Altı ay süreyle sibutramin (15 mg/gün) tedavisi alan 43 obez hastanın demografik, biyokimyasal ve antropometrik ölçümleri, insülin direnci değerlendirildi. Abdominal yağ dağılımı ultrasonografi ile belirlendi.

Bulgular: Yaşam stili değişikliği (diyet ve egzersiz) ile birlikte olan sibutramin tedavisi BKİ'de ($p< 0.0001$), total yağ kitlesinde ($p< 0.01$), bel çevresinde ($p< 0.0001$), subkutanöz ($p< 0.05$) ve visseral yağ kitlesinde ($p< 0.0001$) anlamlı azalmalara neden oldu. Serum total kolesterol ($p< 0.05$) ve trigliserid ($p< 0.05$) seviyeleri sibutramin tedavisinden sonra belirgin azalma gözterdi. BKİ insülin direnciyle ters orantılıydı.

Sonuç: Sibutramin insülin direnci sendromunda metabolik bozukların iyileşmesine katkısı olan ve kolay uyum sağlanabilen bir ilaç olarak gözükmektedir. Ayrıca kardiyovasküler hastalıkların ve diyabetin ilerlemesine karşı olumlu etkileri olabilir.

Anahtar Kelimeler: Sibutramin; beden kitle indeksi; insülin direnci

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Abdominal fat accumulation, hypertension, dyslipidemia, and glucose intolerance are the components of metabolic syndrome that is strongly associated with increased risk of cardiovascular morbidity and mortality.[1-3] Abdominal VF accumulation was recognized as the

main determinant of components of this syndrome.[1] The relationship between abdominal fat accumulation and metabolic disorders was attributed to insulin resistance and the compensatory hyperinsulinemia, which may also contribute to arterial hypertension.[3-7]

Studies demonstrated that even a 5-10% weight loss of initial body weight was associated with an improvement in cardiovascular risk factors.[8-12] Even though lifestyle modifications including diet and exercise regimens are still considered the cornerstones of obesity management, in a considerable number of patients these approaches are of limited success. Pharmacological agents may be useful adjuncts to exercise and diet therapy, especially when obesity is associated with metabolic and vascular risk factors, because aggressive weight management for these patients is crucial.

Sibutramine has a dual physiological action influencing both sides of the energy balance equation. It reduces food intake by enhancing satiety and increases metabolic rate during weight loss. Clinical trials report that 2/3 of patients taking sibutramine lose 5% weight and the drug may enhance the maintenance of weight loss.[13]

To our knowledge there are only a few prospective studies regarding the effects of sibutramine on visceral and abdominal adipose compartments and lipid parameters.[14-16] However, the studies concerning the effects of sibutramine on lipid metabolism have conflicting results. In this prospective study, we aimed to assess the effects of sibutramine therapy on BMI, body fat distribution, VF accumulation, insulin resistance and plasma lipid profile in central obese patients.

Material and Methods

Subjects

Forty-five obese patients (25 females, 20 males) who were admitted to our Obesity Clinic between April 2003 and April 2004 were consecutively enrolled in this prospective study. Before and after the study, all subjects were evaluated by an extensive physical examination. A standardized interview was conducted by trained researchers and detailed information on medical history was collected for each subject. Exclusion criteria included alcohol consumption, histories of liver disease, coronary artery and chronic kidney diseases, diabetes, cerebrovascular and peripheral vascular disease, hypothyroidism, chronic and acute inflammatory diseases, asthma, chronic bronchial diseases, smoking and use of all medications known to alter insulin secretion or action. No subject had any of the exclusion criteria mentioned above. Patients with diastolic blood pressure (DBP) > 95 mmHg, systolic blood pressure (SBP) > 140 mmHg and/or pulse rate > 100 beats/min were followed up and included in the study if they were stabilized with antihypertensive therapy. The current report represents an audit of an established clinical practice in our unit, for which our institutional ethics committee does not require a written approval form. However, patients gave consent to the investigations described as part of their normal medical care and an informed consent was obtained from all participants.

Anthropometric Measurements

All anthropometric measurements were done by the same physician on the day blood specimen was taken. Height, weight, and waist and hip circumferences were measured while the subjects wore underwear without shoes. Waist circumferences (WC) were measured at the mid point between the lower border of the rib cage and the iliac crest and hip circumferences were measured at the widest part of the hip region. BMI [(Body weight (kg)/height (m^2)] and waist-to-hip ratio (WHR) were calculated. Total body fat mass and fat-free mass was measured by bioelectric impedance analysis using a non-invasive hand-held machine (Bodystat®1500, UK). SBP and DBP were determined after 15 minutes of resting in sitting position and the mean value of two measurements were recorded.

Study Design

Each subject underwent a comprehensive nutritional evaluation by a dietitian. Each subject was instructed to follow a calorie-controlled meal plan with calorie restriction. Meal plans were based on the 1995 Exchange Lists for Meal Planning booked by The American Diabetes Association and The

American Dietetic Association.[17] Subjects were instructed to complete a 24-hour food record and the records were collected at each monthly visit. All the participants were instructed to walk briskly every day for 30 minutes for a week. Each patient received sibutramine 15 mg/day. The patients were prospectively evaluated for 6 months. Four patients reported constipation that was resolved after increasing the dietary fiber content. Two male patients who reported scrotal pain were excluded from the study and thus the study population consisted of 43 subjects.

Ultrasonographic Measurements

Ultrasonography (US) was carried out using GE logic α 200-ultrasound machine. The linear array probe (7.5 MHz) was used to measure the subcutaneous (SC) and preperitoneal (PP) abdominal fat layers. The subcutaneous minimum (SC_{min}) and preperitoneal maximum (PP_{max}) measurements were obtained from the region just below the xyphoid process, whereas the subcutaneous maximum (SC_{max}) and preperitoneal minimum (PP_{min}) fat layers were measured from the region just above the umbilicus.[18] The convex-array probe (3.5 MHz) was used for measuring visceral abdominal muscle and anterior wall of the aorta.[19] The patient was asked to suspend respiration during examination and special care was taken to keep the probe just touching the skin to prevent compression of fat layers. All measurements were performed by the same radiologist. The validity of US for the evaluation of visceral and SC fat thickness was also supported by another study.[20] Inter-operator and intra-operator mean variation coefficients of this method were about 7% and 5% respectively.[21]

Biochemical Analysis

Venous blood samples were drawn from the participants after 12 hours of fasting. For the measurement of postprandial glucose levels, venous blood samples were obtained 2 hours after a 587 kCal mixed meal (containing 75 g carbohydrate, 23 g fat, 20 g protein). Samples were collected in serum separator tubes, allowed to clot for 30 min, and centrifuged for 15 min at 2000 x g at room temperature. All biochemical measurements were performed on the same day. Commercial kits were used for the biochemical measurements. Serum glucose, triglyceride (TG), total cholesterol (TC), aspartat amino transferase (AST), alanine amino transferase (ALT) and gamma glutamyl transferase (GGT) measurements were performed by enzymatic methods and high-density lipoprotein-cholesterol (HDL-C) without precipitation by the liquid selective detergent homogeneous technique (Synchrone LX-20, Beckman Coulter, Fullerton, CA, USA). Low-density lipoprotein-cholesterol (LDL-C) levels were calculated by the Friedewald's formula. Insulin measurements were done by solid phase chemiluminescence immunoassay "IMMULITE ONE" (DPC Biosystems, CA, USA). Insulin resistance was calculated by homeostasis model assessment score that employs the formula: fasting insulin concentration (mU/L) x glucose (mmol/L) /22.5.[22] Individuals with HOMA-IR > 2.7 were considered insulin resistant.

Statistical analysis

Paired t-test and Pearson correlation analysis were used for statistical analyses. The data were expressed as means ± SD. Statistical significance was set at $p< 0.05$. Data were analyzed with the SPSS (Statistical Package for the Social Science, version 10.0).

Results

All patients (mean age for 25 females: 40.3 ± 10.6 year; 20 males: 40.4 ± 1.2 year) were insulin resistant (for each patient, HOMA-IR value ≥ 2.7). There were no significant differences in SBP, DBP, LDL-C, HDL-C, AST, ALT, GGT, fasting glucose, insulin levels, HOMA-IR index and WHR, SC_{min}, PP_{max}, PP_{min} (data were not shown for SC_{min} and PP_{min}) between measurements at baseline and at 6 months. Significantly lower BMI, waist, body weight, fat mass percent, VF, and SC_{max} measurements were observed at the end of the study compared with initial evaluations. There were significant decreases in postprandial glucose, TC, and TG levels after sibutramine treatment (Table 1 and 2).

Table 1. Biochemical characteristics of subjects.

	Sibutramine (n: 43)			
	Baseline	**At 6 months**	**p**	**t**
Fasting glucose (mg/mL)	102.3 ± 22.5	104.3 ± 19.1	NS	-0.8
Postprandial glucose (mg/mL)	120.6 ± 38.1	106.3 ± 17.4	0.03	2.3
Fasting insulin (mmol/L)	16.9 ± 11.5	13.7 ± 6.2	NS	1.5
TC (mg/L)	208.2 ± 51.5	188.4 ± 46.0	0.02	2.5
LDL-C (mg/mL)	125.0 ± 42.0	116.2 ± 31.8	NS	1.3
HDL-C (mg/mL)	51.1 ± 15.1	49.9 ± 13.4	NS	0.4
TG (mg/mL)	165.6 ± 89.0	137.0 ± 60.0	0.04	2.1
HOMA-IR	4.8 ± 1.2	4.7 ± 0.6	NS	1.4
AST (IU/L)	19.7 ± 9.5	17.4 ± 5.7	NS	1.3
ALT (IU/L)	19.3 ± 5.6	18.2 ± 5.8	NS	0.8
GGT (IU/L)	22.7 ± 9.2	21.2 ± 8.1	NS	0.9
SBP (mmHg)	132.7 ± 2.9	135.5 ± 2.4	NS	2.3
DBP (mmHg)	82.6 ± 2.07	80.07 ± 2.3	NS	1.7

p< 0.05, NS: Not significant
TC: Total cholesterol, TG: Triglyceride, AST: Aspartat amino transferase, ALT: Alanine amino transferase, GGT: Gamma glutamyl transferase, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low high-density lipoprotein-cholesterol, DBP: Diastolic blood pressure, SBP: Systolic blood pressure.

Table 2. Anthropometric characteristics of subjects.

	Sibutramine (n: 43)			
	Baseline	**At 6 months**	**p**	**t**
Waist (cm)	101.2 ± 10.6	94.5 ± 9.8	0.0001	6.1
WHR (cm)	0.91 ± 0.1	0.88 ± 0.1	NS	1.8
BMI (kg/m^2)	36.7 ± 5.4	34.5 ± 5.4	0.0001	6.5
Body weight (kg)	90.8 ± 14.7	85.3 ± 13.6	0.0001	7.9
Fat mass %	44.1 ± 5.8	41.7 ± 7.4	0.01	2.6
VF (cm)	49.7 ± 14.1	37.1 ± 12.6	0.0001	4.6
SC_{max} (cm)	21.6 ± 6.1	19.4 ± 6.0	0.02	2.7
PP_{max} (cm)	7.0 ± 3.0	6.3 ± 4.3	NS	0.9

p< 0.05, NS: Not significant
WHR: Waist-to-hip ratio, BMI: Body mass index, VF: Visceral fat mass, $PP_{max:}$ Preperitoneal maximum, $SC_{max:}$ Subcutaneous maximum.

While BMI was positively correlated with body weight (r= 0.62; p< 0.05), it was inversely associated with HOMA-IR (r= -0.70, p< 0.05). Fat mass was positively related with TG (r= 0.65; p< 0.05). There was a positive correlation between serum SC_{max} and VF (r= 0.75; p< 0.05). No significant correlation was present between other parameters.

Discussion

Obesity is a multifactorial, chronic disorder and it has reached epidemic proportions worldwide. Obese patients have an increased risk for the development of coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, and various types of cancers, cerebrovascular events, osteoarthritis, restrictive pulmonary disease, and sleep apnea. Moreover, metabolic syndrome is classified as a spectrum of abnormalities including abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, and prothrombotic and proinflammatory state. The increase in relative risk for the development of

type 2 diabetes is positively associated with BMI.[23] The intra-abdominal fat layer has significance as a determinant of hypertriglyceridemia and insulin resistance.[24,25] In particular, VF accumulation is usually accompanied by insulin resistance or type 2 diabetes mellitus, hypertension, hypertriglyceridemia, low HDL-C cholesterol level to define metabolic syndrome.[26-28] VF is metabolically active with a high rate of free fatty acid (FFA) turnover and is relatively resistant to insulin in individuals with abdominal obesity. VF provides FFA for the liver and other tissues.[29] In contrast, lipolysis of the SC fat layer is more sensitive to the inhibitory effect of insulin that regulates re-esterification of FFA to form TG.[30,31] Consequently, we may suggest that there is a positive correlation between obesity and increased overall mortality. Fortunately, a modest weight loss of 5-10% of initial body weight improves all the multiple risk factors mentioned above.[32] Therefore, efforts to lose weight are particularly important in the high-risk obese population, especially to avoid metabolic syndrome. In general, reducing energy intake and increasing energy expenditure are used for weight loss as two distinct strategies. When weight loss is achieved, the maintenance of weight reduction appears as an additional problem. Some auxiliary medical factors may support the patients to initiate and maintain weight loss.

Sibutramine among the new generation drugs for weight management and offers an improvement in the long-term control of weight loss as an adjunct to diet and exercise. It displays anti-obesity actions by influencing both noradrenergic and serotonergic pathways within the hypothalamus. Therefore, sibutramine enhances the feeling of fullness. In addition, this drug has a thermogenic effect that increases energy expenditure. Central stimulation of efferent sympathetic nerves activates thermogenesis via β_3-adrenoceptors, whereas the hypophagic effect is mainly mediated via α_1-adrenoceptors.[33,34] Reports indicated that sibutramine-treated obese high risk patients achieved 4.6% weight loss after 1 year of follow-up. Besides, sibutramine was successful for the reduction of BMI by 5.99%, waist circumference by 6.62% and total body fat content by 5.42% in these subjects.[35] In this study, there were significant decreases in BMI, body weight, waist circumference and fat mass percent, VF, and SC_{max} thickness. The results are consistent with some previous studies and confirm aforementioned interpretations.[14-16]

Computed tomography (CT) may be used in order to distinguish abdominal fat layers. Ionizing radiation and cost are the major disadvantages of CT limiting its clinical use. Magnetic resonance imaging (MRI), which is another way of determining abdominal fat layers, is an expensive and time-consuming method and also is not available in every setting. Recently, ultrasonographic examination was suggested as an alternative non-invasive, cheaper and reliable technique for measuring intra-abdominal fat thickness.[36] The method we used for measuring total adipose tissue mass based on bioelectrical impedance is closely correlated with hydrodensitometry even though it may not be as accurate as densitometric techniques.[37,38]

Some prospective studies showed significant improvements in serum lipid levels in patients treated with sibutramine[39,40] although the results of a recently published study conflicted with these results in spite of a reduction in VF thickness.[16] The favorable effect of sibutramine on VLDL-C and TC levels is durable.[41] The results of the current study demonstrated significant improvements in serum TC and TG levels. Moreover, we observed a significant improvement in postprandial glucose levels after weight loss by sibutramine treatment and BMI was inversely correlated with HOMA-IR index. These results enhance the antiatherogenic effect of sibutramine treatment.

During treatment, no changes were observed in the mean blood pressure and heart rate in hypertensive patients who were extensively controlled for one month before treatment. Safety of sibutramine in patients with hypertension was also demonstrated in some other studies.[16,42-44] The reassurance that results from the benefit of weight loss and decreased insulin resistance could counteract the mild increasing effect of the drug on blood pressure.

Two male patients who reported scrotal pain were withdrawn from the study. Urological consultation and examination did not reveal the cause of this side effect. The pain relieved following cessation of the treatment. According to our knowledge, this adverse effect was the first reported in the literature.

The major limitation of our study was the lack of a control group. Thus, evaluation of the effects of sibutramine on obesity in more detail was not possible. Our plan for the future is to conduct a placebo controlled prospective study.

In conclusion, the results of our study clearly indicate that sibutramine is effective in reducing BMI, waist, VF, SC measurements, serum TC and TG levels and insulin resistance in high-risk obese patients. Visceral adipose compartment is not only the best predictor of insulin resistance but also it is responsible for increased serum TC and TG levels. Sibutramine is a well-tolerated drug and may improve metabolic abnormalities in insulin resistance syndrome. Besides, it may have beneficial effects in the progression of diabetes and cardiovascular diseases.

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