Effects of Sibutramine in Obese Female Subjects With Type 2 Diabetes and Poor Blood Glucose Control

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OBJECTIVE — In this study, we evaluated the efficacy of sibutramine in combination with hypoglycemic drugs in obese type 2 diabetic women whose glucose levels were poorly regulated.

RESEARCH DESIGN AND METHODS — Female patients with type 2 diabetes, poorly controlled glucose levels, and HbA_{1c} >8% were randomly assigned to one of two groups. In addition to their prescribed hypoglycemic agents (maximum doses of sulfonylureas and metformin), one group ($n = 30$) received a placebo twice daily for 6 months and the other ($n = 30$) received sibutramine 10 mg b.i.d. for the same period.

RESULTS — One patient in the sibutramine group was excluded during the study period because of hypertension; thus, a total of 29 data sets were analyzed for this group. In the placebo group, five patients had to be excluded because of low treatment efficacy, leaving a total of 25 who completed the study. Comparing the changes that occurred over 6 months in the sibutramine and placebo groups, the former showed significantly greater reductions in fasting blood glucose ($P < 0.0001$), second-hour postprandial blood glucose ($P < 0.0001$), insulin resistance ($P < 0.0001$), waist circumference ($P < 0.0001$), BMI ($P < 0.0001$), HbA_{1c} ($P < 0.0001$), diastolic blood pressure, pulse rate, uric acid levels, and all elements of the lipid profile except HDL cholesterol and apolipoprotein A1.

CONCLUSIONS — The addition of sibutramine to oral hypoglycemic therapy resulted in significant weight loss and improvement in metabolic parameters in this patient group. Sibutramine is an effective adjunct to oral hypoglycemic therapy in obese women with type 2 diabetes.

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Most patients with type 2 diabetes are obese, dyslipidemic, and insulin-resistant (1,2). In most cases, high doses of hypoglycemic drugs and statins or fibrates are required, and it is usually difficult to regulate metabolic parameters. Modification of dietary habits and subsequent weight loss can improve glycemic control, insulin level, and lipid profile findings (3,4); however, unfortunately, diet restriction alone usually does not lead to adequate weight loss (3,5,6).

Previous studies have shown that tight glycemic control reduces the long-term complications of the disease. The U.K. Prospective Diabetes Study (UKPDS) showed that a 1% reduction in the average HbA_{1c} level was associated with a 21% reduction in risk for any end point related to diabetes, 37% for microvascular complications, and 14% for myocardial infarction (7,8). The subgroup analysis of the simvastatin (4S) study showed that reducing the level of LDL cholesterol decreased cardiovascular mortality in diabetic patients (9).

Recent studies on dexfenfluramine and fluoxetine have revealed that weight reduction with these agents improves glucose control and reduces HbA_{1c}, BMI, and blood pressure (10–12). Sibutramine is an anti-obesity drug that induces satiety and thermogenesis (13). Administration of sibutramine has been shown to reduce weight gain, lower the levels of nonesterified fatty acids, decrease hyperinsulinemia, and reduce insulin resistance (IR) in obese diabetic *ob/ob* mice (14). In a recent investigation, we found that sibutramine decreased IR and BMI in nondieting obese women (15).

In this study, we evaluated the tolerability and efficacy of sibutramine (10 mg b.i.d.) in combination with dietary restrictions and oral hypoglycemic drugs in obese women with type 2 diabetes and poor glucose level control. Outcome was assessed based on improved glycemic control and positive changes in dyslipidemia and BMI.

RESEARCH DESIGN AND METHODS

— This double-blinded rank-randomized placebo-controlled prospective study was conducted at the Baskent University Endocrinology and Metabolism Clinic, which is a referral-based clinic, and all of the women studied were referred because of poor glucose control. A total of 60 female patients with type 2 diabetes, poor glucose control, HbA_{1c} >8%, and BMI >30 kg/m^2 who were taking maximum doses of metformin (2,550 mg/day) and sulfonylureas (gliclazide [320 mg/day] or glipizide [20 mg/day]) were enrolled. None of the patients had previously been on other weight-loss drugs or intensive weight-loss programs. We excluded patients with type 1 diabetes, obesity of endocrine origin other than that associated with type 2 diabetes, uncontrolled hypertension (sys-

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Abbreviations: apo, apolipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; lipo(a), lipoprotein(a).

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg), or glaucoma, and we also excluded pregnant women and patients who were using β-adrenergic blockers, antidepressants, monoamine oxidase inhibitors, or any drug that might affect appetite or body weight. The subjects gave their informed consent to participate.

Patients were randomly assigned to either the sibutramine 10 mg b.i.d. group ($n = 30$; mean age 46.93 ± 1.62 years) or the placebo group ($n = 30$; mean age 49.28 ± 1.34 years), and neither the physician nor the patient knew the group to which they were assigned. They received this treatment in addition to their prescribed diet and hypoglycemic drugs. All patients were taking maximum doses of sulfonylurea and metformin throughout the study.

At baseline, a physician examined each individual and measured her weight, height, and waist circumference. Each patient was placed on a diet of 25 kcal/kg ideal body weight. Under the recommended regimen, patients would intake ~50% of the calories from carbohydrates, 30% from lipids, and 20% from proteins. They received a list of those foods that were permitted and not permitted, along with recommended portions and possible combinations.

Visits were scheduled before the medication was started and then monthly throughout 6 months of treatment. At each visit, the patient underwent a physical examination and had her blood pressure, heart rate, weight, height, and waist circumference measured. Any problems or adverse events were recorded as they were detected by the physician or stated by the patient. Weight and height were measured with the individual in light clothes and without shoes. Waist circumference was measured with the patient standing, and the measurement was taken at the midpoint between the highest point of the iliac crest and the lowest limit of the costal margin at the mid-axillary line. Blood pressure and heart rate were recorded in the morning as the mean of three resting readings after 5 min in the seated position.

Blood chemistry and electrocardiography examinations were performed before the beginning of the medication and after 6 months of treatment. Blood samples were collected in the morning after each patient had been fasting for at least 8 h. To measure the postprandial glucose level, a second blood sample was drawn 2 h after ingestion of 75 g glucose. Levels of plasma glucose, total cholesterol, HDL cholesterol, and triglycerides were determined by the calorimetric method, using a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Mannheim, Germany). LDL cholesterol and VLDL cholesterol levels were calculated using the Friedwald formula. Insulin was measured in an AXSYM autoanalyzer (Abbott Laboratories, Abbott Park, IL), using the microparticle enzyme immunoassay method. Apolipoprotein (apo) A1, apoB, and lipoprotein(a) [lipo(a)] were quantitated by the immunoturbidimetric method in a Roche/Hitachi 912 autoanalyzer (Roche Diagnostics). IR was calculated using the homeostasis model assessment (HOMA) of IR (formula: glucose × insulin/22.5).

Statistical testing was done with Student's *t* test analysis and homogeneity of variance checked by Levene's test using SPSS version 9.05 (SPSS, Chicago, IL). All results were expressed as the means ± SEM, and $P < 0.05$ was considered significant.

RESULTS — In the sibutramine group, one patient developed hypertension and was withdrawn from the study, 11 patients reported dry mouth, and 16 reported constipation. In the placebo group, five patients had to be excluded and switched to insulin therapy because of low treatment efficacy. Thus, a total of 25 subjects in the placebo group completed the study. The sulfonylurea and metformin doses remained unchanged throughout the study period in both groups because none of the patients had problems with hypoglycemia.

Findings after 6 months of treatment showed that sibutramine produced greater weight reduction than placebo (9.61 ± 1.37 kg loss vs. 0.91 ± 0.53 kg gain, respectively; $P < 0.0001$). The mean reduction in BMI was significantly greater in the sibutramine group than in the placebo group (3.92 ± 0.54 kg/m^2 decrease vs. 0.36 ± 0.21 kg/m^2 increase, respectively; $P < 0.0001$). Waist circumference also decreased significantly more in the sibutramine group (8.04 ± 3.43 cm decrease vs. 0.92 ± 0.49 cm increase, respectively; $P < 0.0001$).

Fasting and postprandial glucose levels fell significantly below baseline (124.88 ± 8.58 and 102.24 ± 51.99 mg/dl, respectively; $P < 0.0001$) in patients treated with sibutramine, but they did not change significantly in the placebo group. Mean HbA_{1c} values dropped by 2.73 ± 0.01% ($P < 0.0001$), and IR calculated by HOMA fell by 7.09 ± 0.81 ($P < 0.0001$) in the sibutramine group, but these parameters remained unchanged in the placebo group.

In the sibutramine-treated patients, fasting and postprandial blood glucose, insulin, total cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, lipo(a), apoB, uric acid levels, IR, HbA_{1c}, waist measurement, BMI, diastolic blood pressure, and pulse rate all fell significantly over the 6 months of treatment. These patients' HDL cholesterol, apoA1, and systolic blood pressure did not change significantly. In the placebo-treated patients, only fasting and postprandial glucose, LDL cholesterol, and HbA_{1c} decreased significantly. Patient characteristics at baseline are shown in Table 1, and the differences between the changes that occurred in the sibutramine- and placebo-treated groups from baseline to 6 months are summarized in Table 2.

CONCLUSIONS — Type 2 diabetes is a worldwide, growing health problem that affects >150 million people. Nonpharmacological treatment modalities, such as weight loss and increased physical activity, represent the basis of treatment for obese patients with this disease. The efficacy of these approaches has been demonstrated by numerous studies and was summarized in recent reviews (16,17); however, adequate weight loss is seldom attained with diet therapy alone (3,5,6).

In the present study, the addition of 10 mg sibutramine b.i.d. to the treatment regimen led to significant weight loss and improvement in metabolic parameters. However, the weight reduction observed was less than that noted with the same dose of sibutramine in nondiabetic patients after the same period of treatment (13 vs. 9.6 kg, respectively) (A.G., H.K., E.M.E., N.T., N.B.T., N.G., unpublished study). This confirms other authors' findings that obese diabetic patients achieve less weight reduction than nondiabetic obese patients taking sibutramine (18,19). The reason for this is unknown,

Table 1—*Patient characteristics at baseline*

Characteristic	Sibutramine	Placebo
Duration of diabetes (years)	8.45 ± 0.55	8.30 ± 0.59
Glipizide + metformin users	17	14
Gliclazide + metformin users	12	11
Fasting blood glucose (mg/dl)	251.45 ± 4.83	249.80 ± 4.47
Postprandial blood glucose (mg/dl)	269.79 ± 11.90	277.08 ± 4.80
Insulin level (μU/ml)	17.85 ± 1.15	18.90 ± 1.01
HOMA IR	11.08 ± 0.73	11.67 ± 0.68
HbA_{1c} (%)	9.96 ± 0.01	9.76 ± 0.01
Total cholesterol (mg/dl)	218.69 ± 8.87	216.44 ± 5.40
HDL cholesterol (mg/dl)	45.76 ± 1.75	45.92 ± 1.56
LDL cholesterol (mg/dl)	132.86 ± 6.64	137.60 ± 6.09
VLDL cholesterol (mg/dl)	39.93 ± 3.52	37.48 ± 2.91
Triglycerides (mg/dl)	200.10 ± 17.66	188.04 ± 14.56
Lipo(a) (mg/dl)	20.22 ± 4.31	19.99 ± 4.01
apoA1 (mg/dl)	138.57 ± 4.29	139.42 ± 4.33
apoB (mg/dl)	105.30 ± 4.15	108.43 ± 4.28
Uric acid (mg/dl)	5.72 ± 0.24	5.69 ± 0.25
Body weight (kg)	95.57 ± 3.41	95.48 ± 2.84
BMI (kg/m^2)	39.30 ± 1.36	37.40 ± 0.99
Waist (cm)	109.59 ± 1.46	107.84 ± 2.51
Systolic blood pressure (mmHg)	129.07 ± 4.82	130.03 ± 3.89
Diastolic blood pressure (mmHg)	86.67 ± 2.50	87.11 ± 2.54
Heart rate (beats per min)	79.78 ± 1.70	78.95 ± 1.32

Data are means ± SEM or *n*.

but some investigators believe it is caused by sulfonylurea therapy, which is known to promote weight gain (19). We should also consider the likelihood of excessive weight gain with insulin therapy had these patients been put on insulin, which would have been the next step toward improving metabolic control.

Our results showed statistically significant improvement in glycemic control in the sibutramine-treated patients. Fasting and postprandial blood glucose levels, IR, and HbA_{1c} decreased to a greater degree in this group than in the placebo group. These significant differences are in all likelihood related to the weight loss that occurred in the sibutramine-treated individuals. HbA_{1c} also decreased significantly in the placebo group, and the reason for this could be the "Hawthorne effect," which is described as follows: patients enrolled in any trial invariably show an improvement in glycemic control because of the greater attention paid to them and because they may also want to show their interest in the study. Recent epidemiological studies and prospective therapeutic trials have revealed that glycemic control reduces the microvascular and macrovascular complications of diabetes in patients with either type of the disease. Every 1% reduction in HbA_{1c} decreased cardiac complications from 9 to 40%, depending on the population and type of diabetes (7,8,20,21).

Our sibutramine-treated patients also showed a greater reduction in waist circumference, which is reportedly correlated with the level of abdominal visceral adipose tissue and associated metabolic variables (22). We found that weight loss with sibutramine produced a significant positive change in the lipid profile of obese patients with type 2 diabetes. Total cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, lipo(a), and apoB decreased significantly, although there were no significant changes in HDL cholesterol and apoA1 levels. Because reduction of LDL cholesterol has been shown to be associated with reduced cardiovascular morbidity and mortality in diabetic patients (9), our results indicate that sibutramine is of significant potential benefit relative to cardiovascular risk in obese women with type 2 diabetes.

Previous studies have noted small rises in blood pressure and modest increases in heart rate in sibutramine-treated patients (23,24). These effects of the drug result from its mechanism of action as a norepinephrine and serotonin reuptake inhibitor (13). In the present investigation, patients who took sibutramine showed significant reductions in diastolic blood pressure and heart rate. It is noteworthy that only one patient was withdrawn as a result of hypertension.

In summary, our results show that the addition of sibutramine to oral hypoglycemic therapy leads to significant weight loss and improved metabolic parameters in this patient group. Sibutramine was well tolerated by our study population. In our opinion, this drug is an effective and safe adjunct to oral hypoglycemic therapy in obese women with type 2 diabetes.

Table 2—*Comparison of the mean changes that occurred from baseline to 6 months in the sibutramine- and placebo-treated groups*

Characteristic	Sibutramine	Placebo	*P*
Fasting blood glucose (mg/dl)	124.88 ± 8.58	15.76 ± 3.89	<0.0001
Postprandial blood glucose (mg/dl)	102.24 ± 51.99	32.88 ± 6.13	<0.0001
Insulin level (μU/ml)	5.66 ± 0.97	0.68 ± 0.43	<0.0001
HOMA IR	7.09 ± 0.81	0.31 ± 0.28	<0.0001
HbA_{1c} (%)	2.73 ± 0.01	0.53 ± 0.01	<0.0001
Total cholesterol (mg/dl)	28.08 ± 4.93	7.68 ± 5.04	<0.008
HDL cholesterol (mg/dl)	0.97 ± 1.58	0.01 ± 1.10	>0.05
LDL cholesterol (mg/dl)	20.92 ± 4.66	13.32 ± 3.94	>0.05
VLDL cholesterol (mg/dl)	8.68 ± 2.58	0.01 ± 2.58	<0.02
Triglycerides (mg/dl)	46.76 ± 13.09	0.36 ± 7.26	<0.08
Body weight (kg)	9.61 ± 1.37	0.91 ± 0.53*	<0.0001
BMI (kg/m^2)	3.92 ± 0.54	0.36 ± 0.21*	<0.0001
Waist (cm)	8.04 ± 3.43	0.92 ± 0.49*	<0.0001

Data are means ± SEM. *Increases (all others are decreases).

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