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Sibutramine effect on metabolic control of obese patients with type 2 diabetes mellitus treated with pioglitazone

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Abstract

Thiazolidinediones are supposed to be the pharmacologic agents that more physiologically fight the insulin resistance, but a possible adverse effect may be a weight increase. The aim of the study was to test the efficacy and tolerability of sibutramine on the metabolic effect of pioglitazone in obese patients with type 2 diabetes mellitus. All enrolled patients were required to have been diagnosed as being diabetic for at least 6 months and did not have glycemic control with diet and oral hypoglycemic agents such as sulfonylureas or metformin, both to the maximum tolerated dose. After a run-in period in which the eligible patients took a fixed dose of pioglitazone (30 mg/d), the patients were randomized to receive also sibutramine (10 mg/d) or placebo for 6 months. We assessed body mass index, hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), lipid profile, lipoprotein parameters, and lipoprotein (a) at baseline and after 3 and 6 months. No body mass index change was observed after 3 and 6 months in the pioglitazone + placebo (pp) group. Significant decrease was present in the pioglitazone + sibutramine (ps) group after 3 ($P < .05$) and 6 months ($P < .01$) compared with the baseline values, and this variation was significant ($P < .05$) between groups. A significant HbA_{1c} decrease was observed after 3 ($P < .05$) and 6 months ($P < .01$) in both groups with respect to the baseline values. There was no difference in HbA_{1c} value between the 2 groups. No FPG, PPG, FPI, PPI, and homeostasis model assessment index change was observed at 3 months, whereas a significant decrease was present after 6 months ($P < .05$), in both groups with respect to the baseline values. There was no difference in FPG, PPG, FPI, PPI, and homeostasis model assessment index value between the pp and ps groups. No significant low-density lipoprotein cholesterol change was observed at 3 months, whereas a significant decrease was present after 6 months ($P < .05$), in both groups with respect to the baseline values. There was no difference in low-density lipoprotein cholesterol value between the pp and ps groups. No triglyceride variation was present at 3 and 6 months in the pp group and at 3 months in the ps group, whereas a significant decrease was observed at 6 months ($P < .05$) in the ps group with respect to the baseline values. There was no difference in triglyceride value between both groups. No high-density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) changes were present in both groups with respect to the baseline values. Sibutramine appears to be a tolerable and efficacious drug when added to pioglitazone for the global management of obese diabetic patients.

1. Introduction

The prevalence of obesity has been increasing dramatically in the last decades in the whole world, not only in industrialized countries, but also in developing areas [1]. Major direct complications of obesity are insulin resistance and type 2 diabetes mellitus, whose prevalence is also rapidly increasing worldwide, reaching a prevalence in adults of approximately 5% to 6% in Central Europe and in the United States and more than 50% in specific, genetically prone populations [2].

Intensive programs aimed at reducing calorie [3] intake and at increasing physical activity [4] have clearly been shown to reduce progression from obesity to diabetes and to improve the metabolic control of obese diabetic patients. However, the behavioral approach is usually slow and not always sufficient to get the optimal target of weight and metabolic control in obese diabetic patients; and a pharmacologic treatment has to be planned to significantly and quickly reduce their high cardiovascular

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disease risk [5]. Moreover, beyond metformin and the recently marketed exenatide, for the most part, antidiabetic agents have a neutral or harmful effect on body weight [6]. In fact, the insulin sensitivity improvement associated with the use of some antidiabetic drugs could lead to a further accumulation of adipose tissue [7], even if mainly located in the subcutaneous tissue and not in the more dangerous visceral one. This effect has been clearly demonstrated with efficacious insulin-sensitizing drugs acting on peroxisome proliferator–activated receptor–γ, such as thiazolidinediones [8].

In this context, we tested the efficacy and tolerability of sibutramine, a monoamine-reuptake inhibitor with body weight–reducing properties, on the metabolic effect of pioglitazone, a peroxisome proliferator–activated receptor–γ activator, in obese patients with type 2 diabetes mellitus.

2. Materials and methods

2.1. Study design

This multicenter, double-blind, randomized, controlled trial was conducted in the Department of Internal Medicine and Therapeutics at University of Pavia and in the "G. Descovich" Atherosclerosis Study Center, Internal Medicine, Aging and Kidney Disease Department at University of Bologna.

Subjects began a controlled-energy diet (nearly 600 kcal daily deficit) based on American Diabetes Association recommendations [9] containing 30% of calories as fat (6% saturated), 50% as carbohydrates, 20% as proteins, with a maximum cholesterol content of 300 mg/d, and 35 g fiber. Each center's standard diet advice was given by a dietitian and/or a diabetologist. Dieticians and/or diabetologists periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject's food diaries for counseling. During the study, there were 1 behavior modification session on weight-loss strategies (at baseline), 1 session at 3 and 6 months, and 2 seminars with all patients at 1 and 5 months. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 minutes, 3 to 5 times per week, or by exercise bicycle. The recommended changes in physical activity throughout the study were not assessed.

After a 3-month run-in period in which the eligible patients took a fixed dose of pioglitazone (30 mg/d, once a day), the patients were randomized to receive also sibutramine (10 mg/d, once a day) or placebo for 6 months (Fig. 1). Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in cases of an emergency. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Sibutramine or placebo was supplied as matching opaque white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we weighed participants and gave them a bottle containing a supply of study medication for at least 100 days. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. A bottle containing the new study medication for the next treatment period was given to participants every 3 months. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

2.2. Patients

We recruited diabetic patients of either sex who were eligible for inclusion in the study if they had type 2 diabetes mellitus according to the American Diabetes Association criteria [10]. All were required to have been diagnosed as being diabetic for at least 6 months and did not have glycemic control with diet and oral hypoglycemic agents such as sulfonylureas or metformin, both to the maximum

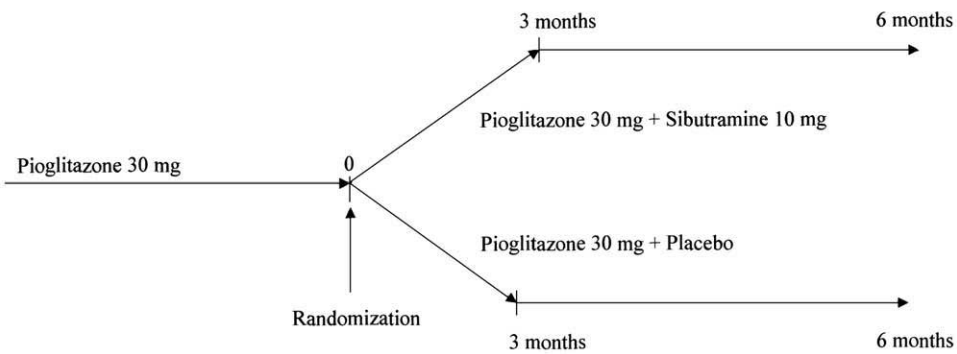

Fig. 1. Study design.

Table 1
Oral hypoglycemic agents (sulfonylureas and metformin) before the study randomization

Name	Pioglitazone + placebo	Pioglitazone + sibutramine
	Dose	Dose
Sulfonylureas		
Glimepiride	4.0 ± 2.0	5.0 ± 1.0
Gliclazide	200 ± 40	160 ± 80
Glyburide	12.5 ± 2.5	12.5 ± 2.5
Biguanides		
Metformin	2250 ± 750	2250 ± 750

Data are means ± SD; all group differences are nonsignificant.

tolerated dose (Table 1). All patients had a fasting C-peptide level greater than 1.0 ng/mL. They were obese patients (body mass index [BMI] ≥30 kg/m^2) [11].

Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with *impaired liver function* (defined as plasma aminotransferase [aspartate aminotransferase ≥40 mU/mL and alanine aminotransferase ≥35 mU/mL and/or γ-glutamyltransferase ≥54 mU/mL]), *impaired kidney function* (defined as serum creatinine level ≥1.3 mg/dL), or anemia. Patients with unstable cardiovascular conditions (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months of study enrolment were also excluded. Women who were pregnant, lactating, or of child-bearing potential and not taking adequate contraceptive precautions were also excluded.

Participants comprised 64 men (49.2%) and 66 women (50.7%) aged 48 to 56 years. There were no significant differences between centers in sex distribution, age, diabetes duration, and diabetes treatment (Table 2).

At entry, 26 subjects (20.0%) were taking antihypertensive drugs (9 subjects, angiotensin-converting enzyme inhibitors [34.6%]; 8 subjects, calcium antagonists [30.8%]; 7 subjects, angiotensin II antagonists [26.9%]; and 2 subjects, α_1-antagonists [7.7%]).

Before the beginning of pioglitazone treatment, 95 subjects (73.1%) had an insufficient glycemic control (hemoglobin A_{1c} [HbA_{1c}] >7.0%) with metformin and 21 (16.2%) with sulfonylureas: 10 (47.6%) with glimepiride, 7 (33.3%) with gliclazide, and 4 (19.1%) with glyburide. Nine subjects (6.9%) did not tolerate metformin, and 5 subjects (3.8%) did not tolerate sulfonylureas: 2 subjects (40.0%) glimepiride, 2 (40.0%) gliclazide, and 1 (20.0%) glyburide. The distribution of antidiabetic treatments other than pioglitazone and of antidiabetic drug–intolerant subjects was not significantly different in the 2 considered groups. No patient was taking lipid-lowering or antiaggregation drugs.

All selected patients were randomized to receive sibutramine or placebo.

2.3. Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history,

Table 2
Baseline values and parameter changes at 3 and 6 months in both groups during the study

	Pioglitazone + placebo			Pioglitazone + sibutramine		
	Baseline	3 mo	6 mo	Baseline	3 mo	6 mo
n	64	–	–	66	–	–
Sex (M/F)	31/33	–	–	33/33	–	–
Age (y)	52 ± 4	–	–	51 ± 4	–	–
Body weight (kg)	101 ± 5	101 ± 4	100 ± 3	102 ± 6	99 ± 4*	96 ± 3**,†
BMI (kg/m^2)	31.8 ± 0.7	31.7 ± 0.6	31.2 ± 0.5	32.0 ± 0.9	30.2 ± 0.6*	29.3 ± 0.4**,†
SBP (mm Hg)	136.1 ± 5.0	135.3 ± 4.5	134.4 ± 5.2*	135.6 ± 3.5	135.1 ± 4.1	133.2 ± 4.4*
DBP (mm Hg)	85.9 ± 3.7	85.4 ± 3.6	84.2 ± 3.4*	86.9 ± 4.2	85.4 ± 4.0	84.0 ± 3.8*
HbA_{1c} (%)	8.3 ± 0.5	7.9 ± 0.4*	7.4 ± 0.3**	8.1 ± 0.4	7.6 ± 0.3*	7.2 ± 0.2**
FPG (mg/dL)	142 ± 9	131 ± 6	124 ± 5*	146 ± 10	136 ± 8	128 ± 7*
PPG (mg/dL)	168 ± 13	152 ± 11	139 ± 8*	165 ± 14	150 ± 12	135 ± 10*
FPI (μU/mL)	27.2 ± 5.4	24.4 ± 4.8	22.9 ± 3.7*	26.9 ± 5.0	24.2 ± 4.6	23.1 ± 3.8*
PPI (μU/mL)	68.5 ± 9.1	61.8 ± 8.8	54.2 ± 8.2*	67.2 ± 8.9	60.1 ± 8.6	51.7 ± 8.2*
HOMA index	9.6 ± 3.9	7.9 ± 3.3	7.0 ± 3.0*	9.4 ± 3.8	8.1 ± 3.5	7.2 ± 2.8*
TC (mg/dL)	188 ± 10	183 ± 9	177 ± 8*	186 ± 10	184 ± 10	171 ± 7*
LDL-C (mg/dL)	115 ± 14	110 ± 13	107 ± 11*	114 ± 13	110 ± 12	104 ± 10*
HDL-C (mg/dL)	43 ± 3	44 ± 4	44 ± 3	42 ± 4	41 ± 4	43 ± 5
Tg (mg/dL)	152 ± 25	146 ± 22	141 ± 21	158 ± 29	131 ± 22	124 ± 19*
Apo A-I (mg/dL)	127 ± 18	128 ± 20	129 ± 21	125 ± 19	123 ± 17	126 ± 18
Apo B (mg/dL)	112 ± 17	111 ± 15	109 ± 14	110 ± 13	109 ± 12	107 ± 10
Lp(a) (mg/dL)	18.4 ± 14.3	17.1 ± 13.6	17.4 ± 13.8	19.2 ± 13.1	18.6 ± 12.2	18.2 ± 12.1

Data are means ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol.

* $P < .05$ vs baseline.

** $P < .01$ vs baseline.

† $P < .05$ vs pioglitazone + placebo.

physical examination, vital signs, a 12-lead electrocardiogram, measurements of BMI, HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), lipid profile, lipoprotein parameters, and lipoprotein (a) (Lp[a]). All these evaluations were repeated after 3 and 6 months.

Changes in BMI, HbA_{1c}, lipid profile, lipoprotein parameters, and Lp(a) were the primary efficacy variables. Fasting plasma glucose, PPG, and homeostasis model assessment (HOMA) index were also used to assess efficacy. All plasmatic parameters were determined after a 12-hour overnight fast, except for PPG and PPI, which were determined 2 hours after lunch.

Laboratory parameters were measured with standardized methods, widely described elsewhere [12,13], in a central laboratory.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. The estimate of insulin resistance was calculated by HOMA index with the following formula: FPI (in microunits per milliliter) × FPG (in millimoles per liter)/22.5 [14]. Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula [15].

To evaluate the tolerability assessments, all adverse events were recorded at each visit.

2.4. Statistical analysis

An intent-to-treat analysis was conducted in patients who had received at least 1 dose of study medication and had a subsequent efficacy observation. Patients were included in the safety analysis if they had received 1 dose of trial medication after randomization and had a subsequent safety observation. The null hypothesis that the expected mean BMI, HbA_{1c}, FPG, PPG, FPI, PPI, HOMA, total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (Tg), apolipoprotein (Apo) A-I, Apo B, and Lp(a) change from baseline to the end of 6 months of double-blind treatment did not differ significantly between sibutramine and placebo treatments was tested using analysis of variance and analysis of covariance models [16]. The statistical significance of the independent effects of treatments on the other parameters was determined by analysis of covariance. A 1-sample *t* test was used to compare values obtained before and after treatment administration, and 2-sample *t* tests were used for between-group comparison. The Bonferroni correction for multiple comparison also was carried out.

Considering as clinically significant a difference of at least 10% compared with the baseline and an α error of .05, the actual sample size is adequate to obtain a power higher than 0.80 for all variables related to glucose metabolism (HbA_{1c}, FPG, PPG, FPI, PPI, and HOMA).

Statistical analysis of data was performed by means of the SPSS statistical software package for Windows (version 11.0; SPSS, Chicago, IL); data are presented as mean ± SD. For all statistical analyses, *P* less than .05 was considered statistically significant.

3. Results

3.1. Study sample

A total of 138 patients was enrolled in the trial. Of these, 130 completed the study: 64 (49.2%) were randomized to double-blind treatment with placebo and 66 (50.8%) with sibutramine. There were 8 patients (5 men and 3 women) who did not complete the study; and the reasons for premature withdrawal included protocol violation, loss to follow-up, and noncompliance.

3.2. Efficacy

3.2.1. Body mass index

No significant body weight change was observed in the run-in phase in both groups, and patients did not gain weight after starting pioglitazone. No body weight or BMI change was observed after 3 and 6 months in the pioglitazone + placebo (pp) group. Significant decrease was present in the pioglitazone + sibutramine (ps) group after 3 ($P < .05$) and 6 months ($P < .01$) compared with the baseline values, and this variation was significant ($P < .05$) between groups (Table 2).

3.2.2. Blood pressure

Both systolic and diastolic blood pressures significantly decreased in comparison with the baseline in both groups of treatment after 6 months from the randomization only ($P < .05$).

3.2.3. Glycemic control

A significant HbA_{1c} decrease was observed after 3 ($P < .05$) and 6 months ($P < .01$) in both groups with respect to the baseline values. No FPG and PPG change was observed at 3 months, whereas a significant decrease was present after 6 months ($P < .05$), in both groups with respect to the baseline values. Fasting plasma glucose and PPG did not show any significant change between the pp group and the ps group.

A significant FPI and PPI decrease was observed after 6 months ($P < .05$) in both groups with respect to the baseline values. No difference was found in FPI and PPI value between the pp and ps groups.

A significant HOMA index decrease was observed at 6 months ($P < .05$) compared with the baseline value in both groups. There was no difference in HOMA index value between the pp and ps groups (Table 2).

3.2.4. Lipid profile and lipoprotein variables

A significant LDL-C decrease was present after 6 months ($P < .05$) in both groups with respect to the baseline values. There was no difference in LDL-C value between the pp and ps groups.

A significant Tg decrease was observed at 6 months ($P < .05$) in the ps group with respect to the baseline

values. There was no difference in Tg value between both groups. No HDL-C, Apo A-I, Apo B, and Lp(a) changes were present in both groups with respect to the baseline values (Table 2).

4. Discussion

Antiobesity treatment is recommended for selected patients in whom lifestyle modification is unsuccessful and when patients need the psychologic support of quicker results in terms of weight loss to continue their diet [17]. Currently, 3 molecules are licensed for use as antiobesity drugs. Orlistat, a gastrointestinal lipase inhibitor, reduces weight by around 3 kg on average; sibutramine, a monoamine-reuptake inhibitor, results in mean weight losses of 4 to 5 kg; rimonabant, a CB1 endocannabinoid receptor antagonist, reduces weight by 4 to 5 kg on average [18]. For this study carried out on obese diabetic subjects, we used sibutramine because, in our patients, it is usually more tolerated than orlistat [19] and because rimonabant is yet not available in Italy.

Pioglitazone was chosen as alternative to the other hypoglycemic agents because it has insulin-sensitizing activity [13,20,21] and a plausible preventive effect on cardiovascular disease [22].

In full agreement with literature data [23], we observed that 6-month pioglitazone treatment is associated with a significant improvement of the metabolic control of the patients: HbA_{1c} = −11.2%, FPG = −12.7%, PPG = −17.3%, FPI = −15.8%, PPI = −20.9%, HOMA index = −27.1%, and LDL-C = −6.9%. The association of sibutramine to the pioglitazone treatment was related to a significant reduction of BMI (−9.2%, $P < .05$) and of Tg (−21.5%, $P < .05$), without improving the other tested parameters more than pioglitazone alone did. This result suggests that the sibutramine-related weight loss is not associated with a significant improvement of metabolic parameters in diabetic patients when insulin resistance is strongly reduced by an efficacious insulin-sensitizing agent.

Some authors suggest that the use of sibutramine could raise blood pressure and induce arrhythmias in some patients [24], maybe because of a paradoxical effect on the autonomic system [25]. However, in most cases, patients who lose 5% or more of initial body weight have a reduction in blood pressure, which correlates with the degree of weight loss [26]. Therefore, in a previous study carried out by our research unit [27] and in previous reports of other groups [28,29], sibutramine use was not related to a significant increase in systolic or diastolic blood pressure during 12 months of treatment with sibutramine, or to changes in heart rate, when patients have blood pressure adequately controlled by efficacious antihypertensive treatments. In the present report, on the contrary, we observed a slight but significant decrease in blood pressure in the sibutramine-treated patients as well.

While waiting for new add-on therapies that appear to specifically improve both metabolic control and body weight in diabetic patients [30], the association of sibutramine to a stable antihyperglycemic treatment could be considered an efficacious and safe approach to reach the desired therapeutic goals in this class of patients at high risk of cardiovascular disease.

Because of the small sample of selected patients in this study and the short duration of the study itself, the results should be extrapolated cautiously, especially those regarding treatment tolerability. In fact, recently, large attention has been posed on the possibility that thiazolidinediones use, and in particular rosiglitazone, could be associated with an increased rate of cardiovascular events: the different meta-analyses were inconclusive as to whether thiazolidinediones caused real adverse effects of myocardial ischemia; however, the US Food and Drugs Administration placed a black box warning on rosiglitazone to signal potential of myocardial infarction and heart-related deaths as a precautionary measure until analyses of all available data provide clarity [31]. Therefore, the main concern about thiazolidinediones (ie, congestive heart failure) is also a main contraindication for the use of these drugs [32], so that the exclusion criteria we applied are the general ones suggested by the scientific literature to be applied when prescribing thiazolidinediones in routine clinical practice [33]. The good control of blood pressure before the patient treatment is also maybe responsible for the good cardiovascular tolerability of sibutramine in our patients [27-29]. On the other side, pioglitazone could compensate for the eventual slight blood pressure increases associated with sibutramine treatments [34].

It could be also argued that, with our study design, it is hard to know if sibutramine alone could have influenced glycemia to the same extent as pioglitazone only because of the associated body weight reduction. However, from our data, it is clear that, although the sibutramine-treated group experienced a significant body weight reduction (not experienced by the placebo-treated group), it obtained a glycemic control improvement fully similar to that obtained in the placebo-treated group.

Finally, it seems relatively strange that, in the sibutramine group, the body weight decrease appears not to be associated with a parallel stronger improvement in glucose metabolism, as expected from previous data [19,27]. However, it could be argued that the insulin-sensitizing effect of pioglitazone could overbear the one obtained with the body weight reduction in the middle-short term. Of course, this is only a hypothesis; and the design of our study does not permit to give a final answer to this doubt.

In conclusion, in our study, sibutramine appears to be a tolerable and efficacious drug when added to pioglitazone for the global management of obese diabetic patients. Long-term studies should be carried out to assess whether a longer treatment duration is associated with a further improvement in body weight and cardiovascular risk profile of these patients.

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