Effects of One Year Treatment of Sibutramine on Insulin Resistance Parameters in Type 2 Diabetic Patients

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Received, May 13, 2010; Revised, August 30, 2010; Accepted, September 9, 2010; Published, September 10, 2010

ABSTRACT – Purpose. comparison of the effects of one year treatment with sibutramine compared to placebo on insulin resistance parameters, body weight, glycemic control, and lipid profile, in type 2 diabetic patients. **Methods.** two hundred and forty-six patients with uncontrolled type 2 diabetes mellitus in therapy with different oral hypoglycemic agents or insulin were enrolled in this study and randomised to take sibutramine 10 mg or placebo for one year. We evaluated at baseline, and after 3, 6, 9, and 12 months these parameters: homeostasis model assessment insulin resistance index (HOMA-IR), retinol binding protein 4 (RBP-4), resistin, visfatin, and high sensitivity-C reactive protein (Hs-CRP), body weight, body mass index (BMI), glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), fasting plasma insulin (FPI), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), and triglycerides (Tg). **Results.** a faster decrease of HOMA-IR, resistin, and RBP-4 was recorded with sibutramine compared to the control group. We observed a significant decrease of Hs-CRP in both groups, and a faster improvement of HbA_{1c}, FPG and PPG with sibutramine compared to the control group; furthermore we recorded a decrease of FPI, TC, LDL-C, body weight, and BMI in the sibutramine group, but not in the control group. **Conclusions.** sibutramine gave a faster improvement of insulin resistance parameters and glycemic control compared to placebo; furthermore sibutramine gave also an improvement of lipid profile, and body weight.

INTRODUCTION

Overweight and obesity are increasing health problems associated with cardiovascular disorders and premature mortality (1). Weight loss is the recommended first step in managing cardiovascular risk (2). Intensive programs aimed at reducing calories (3) intake and at increasing physical activity (4) have clearly shown to improve the metabolic control of obese diabetic patients. However, the behavioural approach is usually slow and not always sufficient to get the optimal targets of weight and metabolic control in obese diabetic patients and a pharmacological treatment has often to be planned in order to significantly and quickly reduce their high cardiovascular disease risk (5). Weight loss drugs added to conventional lifestyle changes may help to achieve and maintain adequate weight loss and improve insulin sensitivity. Currently, two molecules are licensed for use as antiobesity drugs: orlistat, a gastrointestinal lipase inhibitor, reduces weight by around 3 kg on average, and sibutramine, a monoamine-reuptake inhibitor, results in mean weight losses of 4 to 5 kg (6). Sibutramine hydrochloride monohydrate is a norepinephrine and serotonin reuptake inhibitor approved for the long-term management of obesity, in conjunction with a reduced calorie diet and behaviour modification, in patients unable to lose weight with diet and lifestyle changes alone. Sibutramine is rapidly metabolized by the hepatic cytochrome P450 system (CYP) generating two pharmacologic active metabolites which affect both food intake and energy expenditure (7).

The efficacy of sibutramine has been demonstrated in randomised trials in obese/overweight patients including those with type 2 diabetes mellitus (T2DM) (8-10). Furthermore, glycemic control was improved in randomised trials when sibutramine was added to diet and lifestyle advice for patients receiving conventional antidiabetic therapy (11). However preliminary data emerged from the SCOUT trial (12) showed that there was a 16% rise in the risk

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of non-fatal myocardial infarction or stroke in people taking sibutramine and for this reason recently European regulators have suspended the marketing authorisation for sibutramine, and the US Food and Drug Administration has restricted its licence.

We conducted a study on sibutramine just before the withdrawal of sibutramine licence, evaluating sibutramine effects on different parameters; our primary endpoint was to evaluate sibutramine effect on insulin resistance parameters in type 2 diabetic patients, but we also evaluated body weight, glycemic and lipid profile, and the onset of adverse events.

METHODS

Study design

This multicenter, randomised, double-blind, controlled study was conducted in the Internal Medicine and Therapeutics Department at the University of Pavia (Pavia, Italy) and in the Internal Medicine, Aging and Kidney diseases Department "G. Descovich" Atherosclerosis Study Center, at the University of Bologna (Bologna, Italy).

The study protocol was approved at each site by institutional review boards and conducted in accordance with the Declaration of Helsinki and its amendments.

Patients

We enrolled 246 Caucasian type 2 diabetic patients aged ≥ 18 of either sex (Table 1) according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines criteria (2), obese (body mass index [BMI] ≥30 kg/m^2) (13), and with uncontrolled T2DM [glycated hemoglobin (HbA_{1c}) > 8.0 %] in therapy with different oral hypoglycemic agents or insulin. Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic, or renal function, or severe anemia.

Table 1. General subjects characteristics at baseline in the study.

	Control group	Sibutramine group
N	121	125
sex (M/F)	60/61	63/62
age (years)	53 ± 6	51 ± 4
Sm. st. (M/F)	23/21	24/18
Diab. dur. (years)	4 ± 1	5 ± 2
Height (m)	1.70 ± 0.05	1.71 ± 0.06
Concomitant disease, n (%)	108 (89.3)	112 (89.6)
Hypertension	92 (85.2)	96 (85.7)
Hypercholesterolemia	36 (33.3)	39 (34.8)
Hypertriglyceridemia	6 (5.5)	4 (3.6)
Combined dyslipidemia	28 (25.9)	25 (22.3)
Concurrent medications, n (%)	109 (90.1)	114 (91.2)
ACE-I	28 (25.7)	30 (26.3)
ARBs	36 (33.0)	31 (27.2)
Calcium-antagonists	19 (17.4)	24 (21.0)
β-blockers	7 (6.4)	9 (7.9)
Diuretics	22 (20.2)	18 (15.8)
Statins	44 (40.4)	48 (42.1)
Fibrates	12 (11.0)	10 (8.8)
Omega-3	10 (9.2)	14 (12.3)
Acetylsalicylic acid	99 (90.8)	94 (82.5)
Ticlopidine	10 (9.2)	7 (6.1)

Data are expressed as means ± *SD* or *n* and *%*

Sm. st.: Smoking status; Diab. dur.: diabetes duration; ACE-I: angiotensin-converting enzyme-inhibitors; ARBs: angiotensin receptor blockers

Patients with cardiovascular disease (CVD) (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or past incidences of cerebrovascular conditions (stroke or TIA), history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia were also excluded. Women who were pregnant or breastfeeding or who might become pregnant (due to inadequate contraceptive precautions). All patients provided written informed consent to participate.

At the beginning of the study and for all the observational period, patients were taking different antidiabetic drugs. The complete list of the antidiabetic drugs taken is reported in Table 2.

Treatments

Patients were divided in two groups and assigned to receive, as addition to their current antidiabetic therapy, either sibutramine 10 mg (sibutramine group) or placebo (control group) for 12 months in a randomised, double-blind, controlled study. Both placebo, and sibutramine were supplied as identical-looking, opaque, white capsules in coded bottles to ensure the blind status of the study. Randomisation was performed by drawing of envelopes containing randomisation codes prepared by a statistician. A copy of the code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but it could have been broken for individual subjects in the event of an emergency. Medication compliance was assessed by counting the number of pills returned by patients at the time of their specified clinic visits. At baseline, we weighed participants and gave each patient a bottle containing a supply of study medication for at least 14 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.

Table 2. Antidiabetic agents before and during the study.

	Control group	Sibutramine group
N	121	125
OHA, n (%)	118 (97.5)	116 (92.8)
Sulphonylureas, n (%)	**28 (23.7)**	**25 (21.5)**
Glyburide	5 (17.9)	7 (28.0)
Glimepiride	17 (60.7)	14 (56.0)
Gliclazide	6 (21.4)	4 (16.0)
Biguanides, n (%)	**76 (64.4)**	**77 (66.4)**
Metformin	76 (100.0)	77 (100.0)
Glinides, n (%)	**17 (14.4)**	**20 (17.2)**
Repaglinide	12 (70.6)	15 (75.0)
Nateglinide	5 (29.4)	5 (25.0)
α-glucosidase inhibitors, n (%)	**19 (16.1)**	**12 (10.3)**
Acarbose	19 (100.0)	12 (100.0)
Thiazolidinediones, n (%)	**59 (50.0)**	**64 (55.2)**
Troglitazone	39 (66.1)	34 (53.1)
Rosiglitazone	20 (33.9)	30 (46.9)
Incretin-mimetics, n (%)	**9 (7.6)**	**11 (9.5)**
Exenatide	9 (100.0)	11 (100.0)
DPP-4 inhibitors, n (%)	**19 (16.1)**	**17 (14.6)**
Sitagliptin	12 (63.2)	11 (64.7)
Vildagliptin	7 (36.8)	6 (35.3)
INSULIN, n (%)	11 (9.1)	13 (10.4)
Analogue, n (%)	**9 (81.8)**	**9 (69.2)**
Lispro	6 (66.7)	7 (77.8)
Glulisine	3 (33.3)	2 (22.2)
Long-acting, n (%)	**5 (45.4)**	**7 (53.8)**
Glargine	2 (40.0)	2 (28.6)
NPH	3 (60.0)	5 (71.4)

Data are expressed as *n* or *%*

OHA: oral hypoglycemic agents; DPP-4: dipeptidyl peptidase-4 inhibitors; NPH: neutral protamine Hagedorn

A bottle containing placebo or the study medication for the next treatment period was given to participants each three months. At the same time, all unused medication was retrieved for inventory. Both placebo and medications were provided by each Hospital and were free of charge.

Diet and Exercise

Subjects began a controlled-energy diet (near 600 Kcal daily deficit) based on American Heart Association (AHA) recommendations (14) that included 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Patients were not treated with vitamins or mineral preparations during the study.

Standard diet advice was given by a dietitian. Every three months a dietitian provided instruction on dietary intake recording procedures as part of a behaviour modification program and then later used the subject's food diaries for counselling. 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 cycling. The recommended changes in physical activity throughout the study were assessed at each visit using the subject's activity diaries. Physical activity was evaluated using the Borg RPE Scale that measures perceived exertion (15).

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, and a 12-lead electrocardiogram. Blood pressure, and vital sign measurements were assessed twice per week for the first 12 weeks of treatment, and if there was a rise of > 10 mmHg, or heart rate > 10 bpm or weight loss > 2 kg after 4 weeks treatment patients were discontinued from the study. We evaluated at baseline, and after 3, 6, 9, and 12 months these parameters: homeostasis model assessment insulin resistance index (HOMA-IR), retinol binding protein-4 (RBP-4), resistin, visfatin, and high sensitivity-C reactive protein (Hs-CRP), body weight, BMI, HbA_{1c}, fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), fasting plasma insulin (FPI), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), and triglycerides (Tg).

In order to evaluate the tolerability assessments, all adverse events were recorded. All plasmatic parameters were determined after a 12-h overnight fast, with the exception of PPG, determined 2 hours after a standardized meal. Venous blood samples were taken for all patients between 08.00 and 09.00. We used plasma obtained by addition of Na2-EDTA, 1 mg/ml, and centrifuged at 3000 g for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for no more than 3 months. All measurements were performed in a central laboratory.

The HOMA-IR index was calculated as the product of basal glucose (mmol/l) and insulin levels (μU/ml) divided by 22.5 (16,17).

Retinol binding protein-4 was measured using a retinol binding protein-4 (Human) EIA kit (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA). The intra- and interassay CsV were less than 10% and less than 14%, respectively (18).

Resistin value was measured by a commercially available enzyme-linked immunoassay (ELISA) kit (BioVendor Laboratory Medicine, Brno, Czech Republic). Intra-assay CsV was 3.4% and inter-assay CsV was 5.9%, respectively (19).

Visfatin levels were measured by enzyme immunoassay (EIA) kit obtained from Phoenix Pharmaceuticals, Inc., (Burlingame, CA, USA). The intra- and interassay CsV were 10% and less than 14%, respectively (20).

High sensitivity C-reactive protein was measured with use of latex-enhanced immunonephelometric assays on a BN II analyser (Dade Behring, Newark, Delaware, USA). The intra- and interassay CsV were 5.7% and 1.3%, respectively (21).

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Glycated hemoglobin level was measured by an HPLC method (DIAMAT, Bio-Rad, USA; normal values 4.2-6.2%), with intra- and interassay CsV of < 2% (22). Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficients of variation of < 2% (23). Plasma insulin was assayed with Phadiaseph Insulin RIA (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay coefficients of variation: 4.6 and 7.3%, respectively) (24).

Total cholesterol and Tg levels were determined using fully enzymatic techniques (25-

26) on a clinical chemistry analyzer (HITACHI 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1.0 and 2.1 for TC measurement, and 0.9 and 2.4 for Tg measurement, respectively. High density lipoprotein-cholesterol level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid (27) intra- and interassay CsV were 1.0 and 1.9, respectively; LDL-C level was calculated by the Friedewald formula (28).

Statistical Analysis

An intention-to-treat analysis was conducted in patients who had received ≥ 1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received ≥ 1 dose of trial medication and had undergone a subsequent tolerability observation. Considering as clinically significant a difference of at least the 10% compared to the baseline and an alpha error of 0.05, the actual sample size was adequate to obtain a power higher than 0.80 for all measured variable. Continuous variables were compared by analysis of variance (ANOVA). Interaction effects were adjusted for additional potential confounders using analysis of covariance (ANCOVA). ANOVA was also used to assess significance within and between groups. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. The 1-sample t test was used to compare values obtained before and after treatment administration; 2-sample t tests were used for between-group comparisons (29). Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean ± standard deviation (SD). For all statistical analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Study sample

A total of 246 type 2 diabetic patients were enrolled in the study; of these, 24 patients did not complete the study and the reasons for premature withdrawal are explained in Figure 1. The characteristics of the patient population at study entry are shown in Table 1.

Insulin resistance parameters

A statistically significant decrease of HOMA-IR was recorded after 9, and 12 months ($p < 0.05$, and $p < 0.01$, respectively) compared to baseline in the group treated with sibutramine, and after 12 months ($p < 0.05$) in the control group without any significant difference between the groups (Table 4, and Figure 2).

Retinol binding protein-4 value was significantly decreased after 9, and 12 months ($p < 0.05$, $p < 0.02$, respectively) compared to baseline in the group treated with sibutramine and after 12 months in the control group. No differences were recorded between the two groups (Table 4, and Figure 2).

Resistin value was significantly decreased after 9, and 12 months ($p < 0.05$, and $p < 0.01$, respectively) compared to baseline in the group treated with sibutramine, and after 12 months in the control group ($p < 0.05$). We did not observe any significant differences between the two groups (Table 4, and Figure 2).

We did not observe any significant variation of visfatin in either group and no differences were recorded between the two groups (Table 4, and Figure 2).

Inflammatory state

A significant decrease of Hs-CRP value was obtained after 12 months in both groups ($p < 0.02$ with sibutramine, and $p < 0.05$ with placebo) compared to baseline without significant differences between the two groups (Table 4, and Figure 2).

Body weight and BMI

There was a significant decrease of body weight, and BMI after 9, and 12 months ($p < 0.05$, and $p < 0.01$, respectively) in the sibutramine group, while no statistically significant variations of BMI and body weight were observed in the control group. Furthermore, the body weight value obtained with sibutramine was significantly lower than the value obtained in the control group after 9, and 12 months ($p < 0.05$, and $p < 0.01$, respectively). Moreover the BMI value recorded in the group treated with sibutramine was significantly lower than the value obtained in the control group after 12 months ($p < 0.05$) (Table 3).

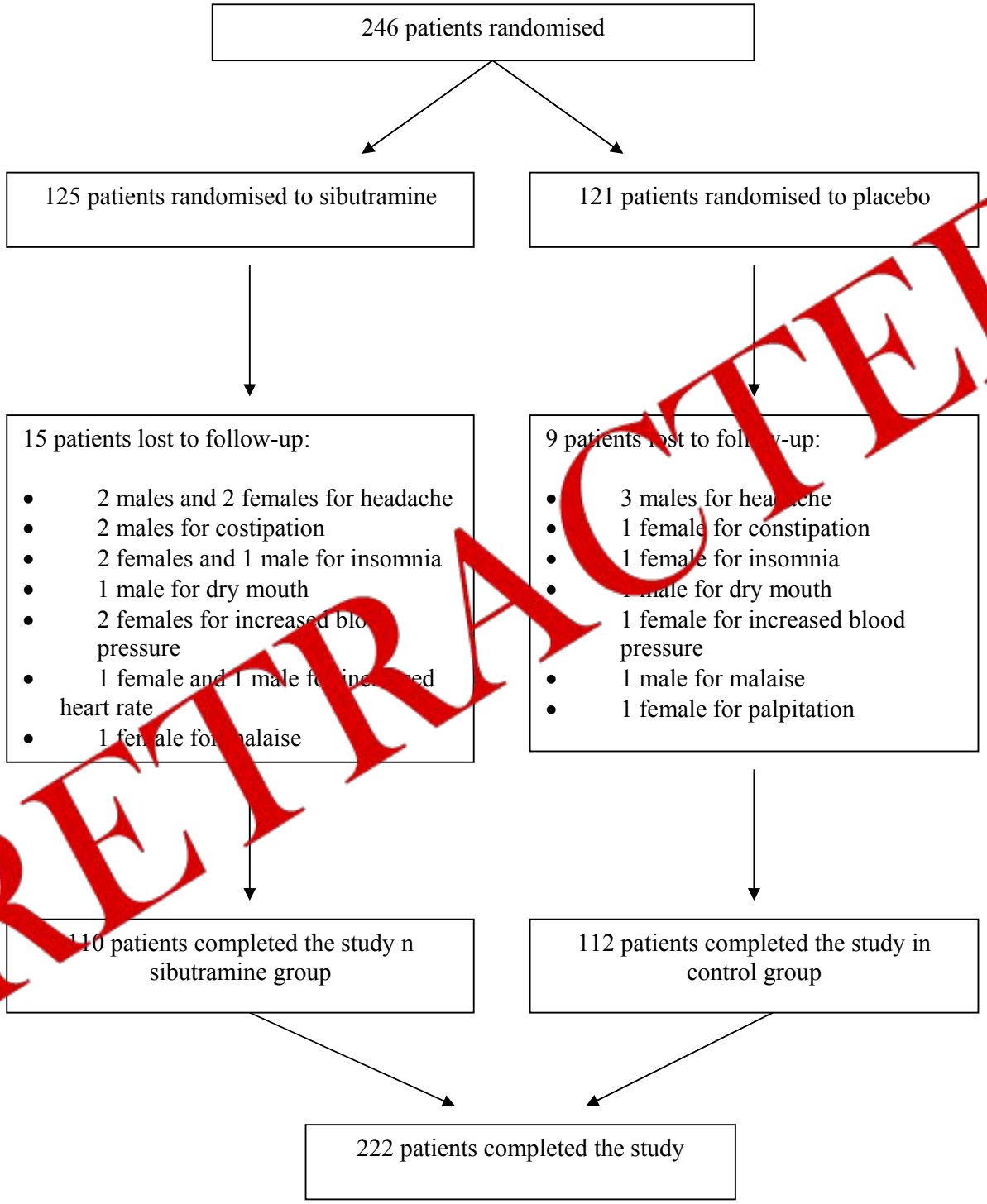

Figure 1. Study design

Glycemic parameters

We observed a statistically significant improvement of HbA_{1c} after 9 and 12 months ($p < 0.05$, and $p < 0.01$, respectively) compared to baseline in the control group and after 6, 9, and 12 months in the sibutramine group ($p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively). We did not record any significant differences between the two groups (Table 3).

There was a statistically significant decrease of FPG after 12 months ($p < 0.05$) compared to baseline in the control group and after 9, and 12 months in the sibutramine group ($p < 0.05$, and $p < 0.01$ respectively). No differences between the two groups were recorded (Table 3).

A significant decrease of PPG was reported after 12 months ($p < 0.05$) compared to baseline in the control group and after 9, and 12 months in the sibutramine group ($p < 0.05$, and $p < 0.01$ respectively). No differences between the two groups were obtained (Table 3).

There was a decrease of FPI after 12 months ($p < 0.05$) compared to baseline in the group treated with sibutramine not observed in the control group, even if we did not record any differences between the two groups (Table 4, and Figure 2).

Lipid profile

A significant decrease of TC, and LDL-C was observed after 12 months ($p < 0.05$, for both) with sibutramine, but not in the control group, while we did not observe any variations of Tg, or HDL-C neither in the control group nor in the sibutramine group. We did not obtain any significant differences between the two groups (Table 3).

Correlations

Stepwise multilinear regression analysis was undertaken to establish which anthropometric and metabolic factors could best predict the insulin-resistance (HOMA) improvement changes or which metabolic factors could best predict the anthropometric (BMI) improvement change. Significant predictors of change in insulin-resistance (HOMA) were RBP-4 and resistin concentration in sibutramine group ($r= 0.56$, $p < 0.05$, and $r= 0.62$, $p < 0.01$, respectively), and significant predictors of change in anthropometric value (BMI) were RBP-4 and resistin concentration in sibutramine group ($r= 0.58$, $p < 0.01$, and $r= 0.64$, $p < 0.01$, respectively).

DISCUSSION

We have already demonstrated in two our previous studies that sibutramine appears to be a tolerable and efficacious drug when added to pioglitazone for the global management of obese diabetic patients (30-31). Sibutramine appeared to give a better improvement of body weight compared to pioglitazone, while both drugs equally reduced blood pressures, improved glycemic control and HOMA index. Both pioglitazone and sibutramine gave a TC, LDL-C, and Tg decrease, while no HDL-C variations were observed (30).

In the current study we have recorded that both placebo and sibutramine added to the usual antidiabetic therapy taken before the beginning of the study, gave a similar improvement of glycemic control, even if sibutramine addition gave a faster improvement of glycemic parameters. We have also observed that sibutramine, but not placebo, gave an improvement of lipid profile, even if, at the end of the study, no significant differences between the two groups were observed. Furthermore we confirmed that sibutramine gave an improvement of body weight, according to what previously reported by our group (30).

Regarding insulin resistance, it has been reported in literature that in T2DM patients the HOMA-IR resulted to be increased compared to the normal glucose tolerance (NGT) subjects (32) and that exercise training can improve insulin sensibility (33). Data from our study showed that sibutramine gave a faster improvement of FPI and HOMA-IR compared to placebo, confirming what already reported in literature (29-30).

Compared to our previous studies, we have also evaluated some insulin resistance parameters, such as RBP-4, resistin, and visfatin. Regarding RBP-4, its concentration has been reported to be increased in subjects with obesity, insulin resistance or T2DM compared with lean subjects (34), even if the mechanisms by which RBP-4 induces insulin resistance are not well understood. On the other side, resistin is produced by mononuclear cells and activated macrophages: it has been demonstrated that overexpression of resistin decreases the ability of insulin to suppress hepatic glucose output or increase glucose uptake by muscle (35-37).

Table 3. Body weight, glycemic profile, and lipid profile data during the study.

	Sibutramine group					Control group				
	Baseline	**3 month**	**6 month**	**9 month**	**12 month**	**Baseline**	**3 month**	**6 month**	**9 month**	**12 month**
Weight (Kg)	97.7±11.4	96.5±10.7	94.2±9.2	90.4±7.1*$^{£}$	88.6±6.0**§	95.0±9.6	91.3±8.5	91.0±8.2	90.5±7.3	89.9±6.5
BMI (Kg/m^2)	33.4±3.2	33.0±3.0	32.2±2.7	30.9±2.1*	30.3±1.9**$^{£}$	32.8±3.1	31.6±2.5	31.[illegible]±2.4	[illegible].3±2.3	31.1±2.2
HbA_{1c} (%)	8.7±1.5	8.4±1.3	7.8±1.0*	7.5±0.8**	7.3±0.6^	8.6±1.4	8.4±1.3	8.[illegible]2	[illegible]±1.0*	7.5±0.8**
FPG (mg/dL)	144±20	135±15	128±12	124±10*	120±9**	141±18	139±[illegible]7	135±[illegible]	[illegible]1±13	126±11*
PPG (mg/dL)	185±29	174±24	169±22	165±20*	161±21**	182±27	178±[illegible]	175±2[illegible]	170±23	166±21*
TC (mg/dL)	224±28	218±23	211±21	206±17	197±15*	219±24	211±2[illegible]	214±22	208±18	210±20
LDL-C (mg/dL)	160±15	156±13	147±9	142±7	138±6*	15[illegible]±12	146±9	148±10	145±8	148±10
HDL-C (mg/dL)	43±7	42±6	43±7	44±7	41±6	45±8	47±9	47±9	44±8	44±8
Tg (mg/dL)	105±42	99±40	107±44	101±40	91±36	97±39	[illegible]3±36	95±37	91±35	90±32

Data are means ± SD

*p< 0.05 vs baseline; **p< 0.01 vs baseline; ^p< 0.001 vs baseline

$^{£}$p< 0.05 vs Control group; §p< 0.01 vs Control group

BMI: body mass index; HbA_{1c}: glycated hemoglobin; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides

Available data support also a role of resistin in determining an increase of inflammation and atherosclerosis (38). In our study we observed that sibutramine, added to the previously taken antidiabetic therapy, gave an improvement of RBP-4, and resistin faster than placebo, improving insulin resistance and glucose intolerance. It has been already reported that insulin resistance and hyperglycemia often co-exist with a cluster of risk factors for coronary artery disease and cardiomyopathy and that the over-production of free radicals in patients suffering from diabetes results in a state of oxidative stress, which leads to endothelial dysfunction and a greater risk of atherosclerosis (39). Reducing insulin resistance we obtain also an improvement of risk of cardiovascular events.

We have also analysed visfatin: visfatin was discovered as a secretory protein highly enriched in human visceral adipocytes, yet this protein is also expressed by liver, muscle, bone marrow and lymphocytes, where it was first identified as PBEF (pre-B-cell colony stimulating factor) (40-41). The expression and secretion of visfatin is increased during the development of obesity; however, in contrast with inflammatory cytokines, the rise in visfatin does not decrease insulin sensitivity. Instead, visfatin exerts insulin-mimetic effects in cultured adipocytes, hepatocytes and myotubes and lowers plasma glucose in mice (40). Visfatin binds to the insulin receptor with similar affinity but at a site distinct from insulin (40). In contrast with insulin, visfatin levels do not change with feeding and fasting (40). It remains to be determined if visfatin acts in concert with insulin to regulate metabolism and whether such interaction occurs via endocrine or paracrine mechanisms. In our study neither placebo nor sibutramine improved visfatin levels.

Table 4. Insulin resistance and inflammatory parameters during the study.

	Sibutramine group					Control group				
	Baseline	**3 month**	**6 month**	**9 month**	**12 month**	**Baseline**	**3 month**	**6 month**	**9 month**	**12 month**
n	125	119	116	112	110	121	117	115	114	112
sex (M/F)	63/62	61/58	59/57	58/54	56/54	60/61	59/58	5[illegible]/57	57/57	55/57
Sm. st. (M/F)	24/18	22/18	21/18	21/17	21/17	23/21	22/[illegible]	22/2[illegible]	21/21	20/21
FPI (µU/mL)	24.9±7.2	24.0±6.8	23.3±5.9	22.4±5.4	21.2±5.0*	23.7±6.1	23.4±6.[illegible]	23.[illegible]±5.[illegible]	22.8±5.6	22.5±5.5
HOMA-IR	8.9±5.1	8.0±4.5	7.4±4.1	6.9±3.6*	6.3±3.5**	8.3±4.7	8.1±4.6	7.8±4.4	7.4±4.1	7.1±3.8*
RBP-4 (µg/mL)	43.9±11.8	41.4±10.2	37.6±9.4	36.4±9.0*	35.0±8.6$^{\$}$	41.6±10.3	[illegible].2±10.1	38.7±9.6	37.1±9.1	35.8±8.9*
Resistin (ng/mL)	7.1±2.5	6.9±2.3	6.4±1.9	6.0±1.7*	5.5±1.5**	6.9±2.3	6.8±2.2	6.5±2.0	6.4±1.9	6.2±1.8*
Visfatin (ng/mL)	17.9±6.5	16.9±6.0	16.6±5.8	16.5±5.7	[illegible]±5.5	17.8±6.[illegible]	17.3±6.1	17.5±6.2	16.9±6.0	16.7±5.9
Hs-CRP (mg/L)	2.6±1.8	2.2±1.4	2.1±1.3	1.9[illegible]	1.7±1.[illegible]	2.4±1.6	2.3±1.5	2.2±1.4	2.1±1.3	1.9±1.2*

Data are means ± SD

*p< 0.05 vs baseline; $^{\$}$p< 0.02 vs baseline; **p< 0.01 vs baseline

FPI: fasting plasma insulin; HOMA-IR: homeostasis model assessment insulin resistance index; RBP-4: retinol binding protein-4; Hs-CRP: high sensitivity-C reactive protein.

Regarding inflammatory parameters, Hs-CRP has been shown to independently predict myocardial infarction, stroke and peripheral artery disease (42-43). In our study both sibutramine and placebo improved this parameter.

Regarding adverse reactions we did not observe any significant differences between the group treated with sibutramine, and the group treated with placebo; the reported adverse effects were headache, constipation, insomnia, dry mouth, increased blood pressure, increased heart rate, depression, malaise, palpitation. All the events were reported as mild or moderate. This was in line with what already reported by our group in two previous studies (44-45); sibutramine intake was not associated to any cardiovascular effects and was generally well tolerated.

This was in contrast with what recently reported by unpublished data from the sibutramine cardiovascular outcomes trial (SCOUT) (12). This six year trial of 10000 mostly European patients, which began in December 2002, showed a 16% rise in the risk of non-fatal myocardial infarction or stroke in people taking sibutramine. We think that the reason of these differences between our results in adverse effects and SCOUT results is that patients enrolled in the SCOUT trial had a history of cardiovascular disease and diabetes, and that 90% of these patients would not have been eligible for sibutramine under the current label.

The controversity between our study and the SCOUT trial is similar to the one reported on the clinical use of sulfonylurea, tolbutamide, on cardiovascular disease reported in 1970 by University Group Diabetes Programme (UGDP) (46).

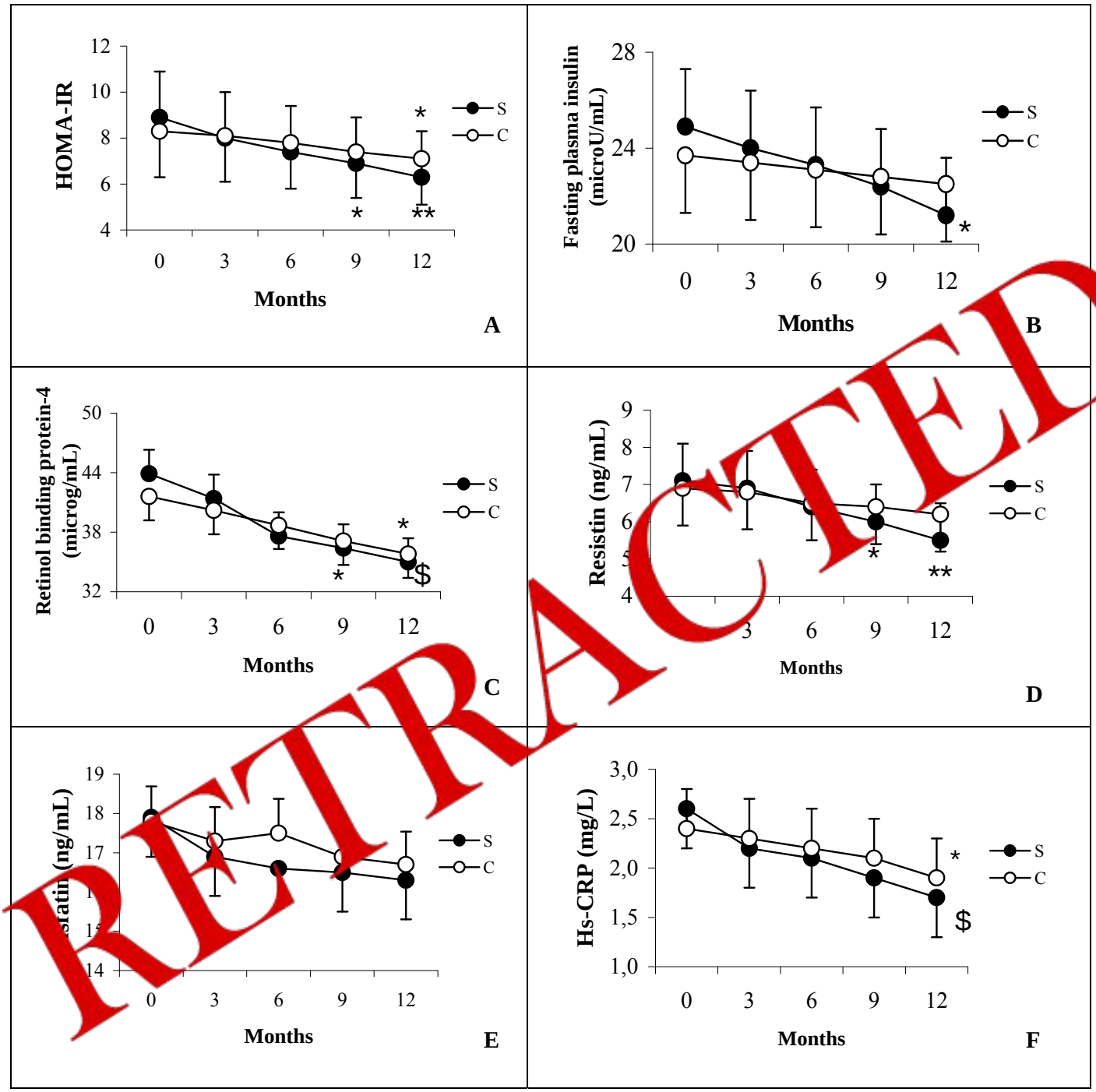

Figure. 2. Inflammatory and insulin resistance parameters variations during the study *p< 0.05 vs baseline; $p< 0.02 vs baseline; **p< 0.01 vs baseline HOMA-IR: homeostasis model assessment insulin resistance index; FPI: fasting plasma insulin; RBP-4: retinol binding protein-4; Hs-CRP: high sensitivity-C reactive protein.

The study found cardiovascular disease mortality was higher in patients given tolbutamide than those given insulin (12.7% vs 6.2%). These findings remained in controversy as United Kingdom Prospective Study (UKDPS 33 & 34) (47) showed reduction in cardiovascular effects of sulfonylureas.

Of course our study has some limitations: for example we did not evaluate if the beneficial effects on glycemic control, body weight, lipid

profile and insulin resistance parameters were sustained after the cessation of therapy. Another limitation is that we evaluated only a limited number of insulin resistance biomarkers, more parameters should be considered to evaluated an effective improvement of insulin resistance.

However, at the best of our knowledge, this is the first study investigating the effect of sibutramine on insulin resistance and inflammatory parameters.

CONCLUSIONS

All data considered we can safely conclude that sibutramine gave a faster improvement of glycemic control and of insulin resistance parameters compared to placebo. Sibutramine gave also an improvement of lipid profile, and body weight not observed with placebo.

AKNOWLEDGEMENTS

The authors certify that have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

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