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Sibutramine *versus* Metformin: assessment of anthropometric, lipid and glycemic parameters in obese and overweight high-risk patients

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ABSTRACT

Anthropometric, lipid and glycemic parameters were compared in obese or overweight high-risk patients. This double-blind trial included 16 obese and overweight patients who followed a standard calorie-controlled diet and received 15mg/day sibutramine or 1700mg/day metformin over three months. The changes observed in the sibutramine and metformin groups were, respectively: body mass index -6.0% and -4.0%; abdominal circumference -7.9% and -6.6%; fatty tissue -10.5% and -1.7%; total cholesterol -2.9% and -2.8%; LDL-C -0.01% and -0.1%; HDL-C -11.0% and -6.8%; total cholesterol/ HDL-C ratio +12.0% and +4.5%; HDL-C-to-LDL-C ratio -7.2% and -0.1%; triglycerides +14.0% and +22.3%; fasting glucose +4.3% and +1.4%; insulin -10.4% and -4.9%; HOMA -8.0% and -3.9%. Although the study was conducted with only 16 patients and the drugs were taken for only three months, we can see that sibutramine-treated obese or overweight high-risk patients showed a reduction of anthropometric parameters and better control of insulin resistance.
Keywords: Metformin. Sibutramine. Clinical study. Obesity treatment. Pharmacist

INTRODUCTION

The prevalence of chronic diseases such as obesity, diabetes and hypertension is increasing substantially in both developed and developing countries (WHO, 2005). In Brazil, it is estimated that 50.0% of the adult population is overweight and that 11.0% is obese (Gigante et al., 2009). Obesity, particularly when associated with excess abdominal fat (central obesity), increases the risk of cardiovascular morbidity and mortality (Yusuf et al., 2004; Canoy, 2010).

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Obese or overweight patients with associated comorbid conditions have a high risk of developing cardiovascular diseases, according to changes in anthropometric and cardio-metabolic parameters, inflammatory markers, serum adipokine levels and other indicators (Bogers et al., 2007; Tziomalos et al., 2009; Allende-Vigo, 2010). It has been shown that reductions in body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), inflammatory markers and glycaemia reduce the cardiovascular risk (Poirier et al., 2006; Fox et al., 2008; Tziomalos et al., 2009; Gomes et al., 2010).

The prevention and treatment of obesity begin with a change in lifestyle. However, lifestyle interventions alone frequently fail either to achieve or to maintain weight loss. Therefore, pharmacotherapy represents an important adjunct to lifestyle modification for the management of obesity (Snow et al., 2005) and, by 2010, only sibutramine and orlistat were approved by United States Food and Drug Administration (FDA) for long-term treatment of obesity (Tziomalos et al., 2009).

Sibutramine is an anorexiant that reduces food intake and induces weight loss by increasing satiety and suppressing appetite by inhibiting the reuptake of monoamines, primarily serotonin and noradrenaline and, to a lesser extent, dopamine (Rolls et al., 1998; Luque & Rey, 1999). However, sibutramine has been associated with increases in blood pressure and pulse rate, raising concerns about a potential increase in cardiovascular risk (Florentin et al., 2008).

In addition, the final results of the large-scale randomized trial SCOUT (Sibutramine Cardiovascular and Diabetes Outcome Study) showed that long-term (mean 3.4 year) treatment with sibutramine (10-15 mg/day) exposed subjects with pre-existing cardiovascular disease to a significantly increased risk of non-fatal myocardial infarction and non-fatal stroke, but not cardiovascular death or all-cause mortality (James et al., 2010).

On the other hand, metformin is an oral antidiabetic drug used in the treatment of type 2 diabetes mellitus (DM2), which has also been associated with anorexic effects. Metformin acts by decreasing the release of glucose by the liver and increasing peripheral glucose

uptake by raising the number of insulin receptors (Dunn & Peters, 1995; Bell & Hadden, 1997). The anorexic effect of metformin may be related to reduced insulin resistance, which promotes some changes in the energy balance and daily calorie requirement of the individual, or to changes in the regulation of the satiety center, possibly involving neuropeptide Y (Rouru et al., 1992, 1995).

Therefore, in this study we compared the changes in the anthropometric, lipid and glycemic parameters promoted by sibutramine and metformin in obese or overweight high-risk patients, in conjunction with a regulated diet.

MATERIALS AND METHODS

Protocol

In this double-blind trial, metformin (1700 mg/day) and sibutramine (15 mg/day) were compared for three months. The subjects were all outpatients at the Specialized Clinic for Obesity Treatment. Suitable subjects, identified by review of computerized medical records, were contacted personally or by telephone.

Inclusion criteria were as follows: BMI above 30 kg/m^2 or above 27 kg/m^2 associated with two or more comorbid conditions (dyslipidemia, hypertension, diabetes, osteoarthritis or sleep apnea), age ≥ 18 years and the patient must have participated in the nutritional education program for six months before the study and failed to reduce their body weight through dietary re-education. Exclusion criteria were: alcoholic, pregnant or lactating patients, patients with acquired immunodeficiency, viral liver infections or altered hepatic functions.

The participants that were eligible for the study, comprising 12 women and 4 men, were assigned to two groups, with 6 women and 2 men in each group. One group received one dose of sibutramine daily (15 mg/day Reductil®, lot 901308F01) and the other received metformin (1700 mg/day Glifage®, lot 1021133) twice a day, one dose after lunch and the other after dinner. Patients with high blood pressure at the beginning of the study were assigned to the metformin group, while the others were allocated randomly.

During the study, the patients were monitored by pharmaceutical interviews held on day 0 (baseline), 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 and 90. At the baseline, after 42 days and after 90 days of treatment, each patient was subjected to anthropometric, hemodynamic and metabolic measurements: weight (kg), height (m), BMI, abdominal circumference (cm), blood pressure (mmHg), fatty tissue (%), fasting glucose (mg/dL), insulin (μIU/mL), total cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL-C) (mg/dL), high-density lipoprotein cholesterol (HDL-C) (mg/dL), very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL), and triglycerides (mg/dL). Blood samples were collected in the morning, after each patient had fasted for at least 12h. All selected patients received a plan of dietary re-education containing, on average, 1800 calories per day and were monitored by a nutritionist.

During the study, patients were monitored by an endocrinologist, nutritionist and pharmacist. Visits were scheduled for before the first intake of the drug and then weekly up to 3 months of treatment. Each visit to the pharmacist included a physical examination and measurement of blood pressure, heart rate, weight, height and waist circumference. Any adverse events were reported as they were detected by the pharmacist or stated by the patient. The pharmacist gave the patient the necessary amount of drug for weekly consumption (7 days) and assessed the need for consultation with an endocrinologist and nutritionist. Only the pharmacist knew which drug was being administered to which patient.

Outcome Measure

Weight and height were measured with a Filizola® weighing balance and stadiometer. BMI was calculated as the ratio of weight (kg) to height (m) squared (Gokcel et al., 2002). Weight and height were measured with the patient in light clothes and without shoes. As recommended by the World Health Organization, the abdominal circumference was measured half way between the lowest rib and the iliac crest, after breathing out, with a measuring tape (Macdonald, 2000; Lean, 2001; Gokcel et al., 2002). The percentage of fatty tissue was assessed by measuring bioelectric impedance with a Prizum 101-A RJL apparatus with TBW electrodes (WHO, 2003). Insulin resistance was estimated by using the homeostasis model assessment (HOMA), derived from the following equation based on fasting plasma levels of glucose and insulin:

$$HOMA = [glucose\ (mg/dL) \times insulin\ (\mu UI/mL)] / (22.5 \times 18.0)$$

Ethics

The study protocol was approved by the Research Ethics Committee of the Specialized Clinic for Obesity Treatment, in accordance with the Declaration of Helsinki. The participants were included in the study after receiving detailed information and giving their informed written consent. In particular, they were informed that they would be taking metformin or sibutramine.

Statistics

The results were assessed as continuous variables (mean ± standard deviation) by Student´s *t*-test for independent data. Statistical significance was set at $p<0.05$. Analyses were performed with Statistical package for Social Sciences® (SPSS 11.5, 2002).

RESULTS

Both sibutramine and metformin were well tolerated and no subject discontinued the treatment because of adverse effects. Table I shows the anthropometric, lipid and glycemic parameters of the sibutramine and metformin groups. At the baseline, there was no significant difference between the groups in any parameter.

TABLE I. Changes in anthropometric, lipid and glycemic parameters in groups treated with 15 mg/day sibutramine or 1700 mg/day metformin

Parameter	Metformin Group (n=8)				Sibutramine Group (n=8)				p#	CI (95%)#
	Baseline [mean (SD)]		Changea [mean (SD)] (%)		Baseline [mean (SD)]		Changea [mean (SD)] (%)			
Age (years)	38.9	(11.5)	-		30.2	(9.7)	-		0.128	(-2.8, 20.1)
BMI (kg/m2)	37.2	(5.8)	-4.0	(2.3)	32.0	(2.4)	-6.0	(4.7)	0.149	(-1.2, 6.8)
Abdominal circumference (%)	117.1	(14.3)	-6.6	(3.6)	103.7	(4.5)	-7.9	(3.6)	0.475	(-2.5, 5.2)
Fatty tissue (%)	38.6	(8.5)	-1.7	(6.2)	34.2	(8.0)	-10.5	(12.4)	0.096	(-1.8, 19.3)
Total cholesterol (mg/dL)	185.1	(16.4)	-2.8	(11.7)	208.1	(30.8)	-2.9	(13.9)	0.991	(-13.7, 13.9)
LDL-C (mg/dL)	105.3	(23.1)	-0.1	(31.6)	133.3	(35.7)	-0.01	(18.51)	0.994	(-27.9, 27.7)
HDL-C (mg/dL)	49.2	(13.8)	-6.8	(7.8)	57.0	(22.5)	-11.9	(9.1)	0.249	(-4.0, 14.2)
Total cholesterol-to-HDL-C ratio	4.0	(0.8)	+4.5	(11.6)	4.0	(1.1)	+12.0	(23.1)	0.423	(-12.0, 27.1)
HDL-C-to-LDL-C ratio	0.5	(0.2)	-0.1	(26.1)	0.5	(0.4)	-7.2	(31.2)	0.630	(-38.0, 23.8)
VLDL-C (mg/dL)	30.6	(18.1)	+22.3	(59.0)	17.8	(4.0)	+13.4	(49.1)	0.748	(-49.3, 67.1)
Triglycerides (mg/dL)	153.0	(90.4)	+22.3	(59.0)	89.2	(19.9)	+14.6	(48.5)	0.781	(-50.3, 65.6)
Fasting glucose (mg/dL)	90.5	(12.9)	+1.4	(9.2)	91.2	(4.8)	+4.3	(13.5)	0.618	(-15.4, 9.5)
Insulin (µIU/mL)	12.6	(5.7)	-4.9	(44.4)	7.4	(2.8)	-10.4	(22.2)	0.755	(-32.1, 43.2)
HOMA	3.0	(1.7)	-3.9	(46.7)	1.7	(0.6)	-8.0	(27.5)	0.835	(-37.0, 45.1)

a Mean percent change from start to finish (%).
# Test for difference between metformin and sibutramine group, except for age.
SD = standard deviation; statistical significance was set at $p<0.05$.

DISCUSSION

The average BMI of the metformin group was 37.2 kg/m^2 and that of the sibutramine group was 32.0 kg/m^2. These patients received non-pharmacological treatment (diet and physical activity) for obesity before beginning the study, but without satisfactory results. Thus, we decided to offer them drug treatment, to assist them in losing weight.

The patients showed reductions in BMI and waist circumference, but the sibutramine group achieved better results than the metformin group (Table 1). However, this result was not statistically significant. In the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) (James et al., 2000), sibutramine showed a decrease in anthropometric parameters when associated with a controlled diet and exercise.

Gokcel et al., (2002) reported decreases of 13.6% and 9.9% in BMI after treatment with 20 mg/day of sibutramine and 1700 mg/day of metformin, respectively. These changes were greater than in our study; however, Gokcel et al., (2002) prescribed these drugs for six months, while in our study the drugs were prescribed for three months and with a lower dose of sibutramine (15 mg/day). Several authors report that a 5-10% reduction in body weight lowers the cardiovascular risk for obese patients (Goldstein, 1992; Williamson et al., 1995).

The waist circumference has an important role in the development of hyperinsulinemia and insulin resistance in obese patients. Some studies have shown this parameter to be a risk factor for the development of dyslipidemia and coronary artery disease (Rexrode et al., 1998; Lean et al., 1998). Table 1 shows reductions in the waist circumference of both groups. These were lower than those found by Gokcel et al. (2002), but may be considered clinically relevant, given the shorter period of treatment and lower sibutramine dose in the present study.

As discussed by other authors (Williamson et al., 1995; Polonsky et al., 1996; Hauner, 1999), the reduction of anthropometric parameters provides significant improvements in insulin resistance and lipid profile and reduces the risk of developing cardiovascular disease. In this study, the changes in the lipid parameters were not statistically significant (Table 1). After four weeks of treatment with sibutramine and lifestyle changes, Weeke et al. (2010) observed that obese and overweight high-risk patients experienced reductions in all lipid parameters. On the other hand, Bray et al. (1999) did not observe any reduction in LDL-C.

The present study shows that HDL-C levels decreased after three months of treatment with sibutramine and metformin (Table 1). In the Sibutramine Cardiovascular OUTcomes (SCOUT) trial (James et al., 2010; Weeke et al., 2010), HDL-C decreased 1.4% on average after four weeks of sibutramine treatment, dietary advice and exercise. Shechter et al. (2006) showed no increase in HDL-C levels following four weeks of sibutramine therapy. In contrast, assessments of the use of sibutramine for 12 and 24 months showed increases in HDL-C of around 8.0-11.0% higher than placebo (Apfelbaum et al., 1999; James et al., 2000). In addition, Levin & Dunn-Meynell (2000) suggested that the HDL-C increases were greater than expected from the weight loss alone, and identified sibutramine as an inducer of HDL-C, independently of the effects of weight changes. However, recent meta-analyses showed that the effect of sibutramine on HDL-C levels was not significant (Apfelbaum et al., 1999).

According to McNulty et al. (2003), total cholesterol and LDL-C did not show any significant change during treatment with sibutramine. However, HDL-C showed significant rises with doses of 15 or 20mg/day of sibutramine, while the total cholesterol/HDL-C ratio fell. The HDL-C/LDL-C ratio can be used to assess the reduction of cardiovascular risk. In this study, there was no change in either the HDL-C/LDL-C ratio or the total cholesterol/HDL-C ratio during the period of treatment. Weeke et al. (2010) observed that after four weeks of treatment with sibutramine and lifestyle changes, the ratio HDL-C: LDL-C increased in obese patients, with or without DM2, but these results were due to the significant reduction of LDL-C in all patients, with or without DM2.

In spite of the reduction in BMI, our study showed an increase in the levels of triglycerides (TG) in patients using sibutramine (15 mg/day) and metformin (1700 mg/day). McNulty et al. (2003) did not observe changes in TG levels in the obese patients who used placebo or 15 mg/day of sibutramine, but did observe a significant fall in TG in patients who used 20 mg/day of sibutramine. In addition, a meta-analysis found that sibutramine promoted a significant reduction in TG levels, compared to placebo, especially after six months of treatment (Rucker et al., 2007). Therefore, the unexpected result in our study might be related to the reduced period of sibutramine treatment (three months) or increased mobilization of adipose tissue.

Changes in the lipid profile can help to decrease cardiovascular risk. In addition, a central distribution of fat increases the risk of cardiovascular morbidity and mortality (Yusuf et al., 2004). Our study shows a significant reduction in the percentage of fatty tissue only in individuals who used sibutramine (Table 1). Faria et al. (2005) found a reduction of 5.3% in fatty tissue; however, those patients received metformin combined with sibutramine (10 mg/day) for six months.

Overweight and obesity increase the risk of developing DM2 (Yusuf et al., 2004; Hauner et al., 2003), while patients with impaired glucose tolerance or impaired fasting glucose may reduce the risk of developing DM2 after weight loss (Tuomilehto et al., 2001; Knowler et al., 2002). This may be because insulin resistance often coexists with central obesity and weight loss improves this condition, reducing the associated metabolic disorders (Pi-Sunyer, 1996).

The insulin resistance was assessed by HOMA. Metformin improved insulin resistance and glucose mobilization, but the fall in the HOMA value was about 50.0% less than that with sibutramine (Table 1); it should be emphasized that the obese patients in the present study had no DM2, so the results obtained were more modest in the metformin group. On the other hand, the lowering of insulin resistance in the sibutramine group reflected decreased insulin secretion (10.4% vs. 4.9%; Table 1), but this drug has a different mechanism of action from that of metformin, not intervening directly in the action of this hormone.

Sari et al. (2010) obtained similar results to those in this study, with 10.0% reduction in HOMA after three months of treatment with 15mg/day sibutramine. These results suggest that weight loss improves the use of insulin, consequently reducing its secretion. Other studies confirm that the improvement in insulin resistance promoted by sibutramine depends on the reduction of body weight (Mclaughlin et al., 2001; Tambascia et al., 2003).

Despite hypertension being more prevalent in obese or overweight patients (Yusuf et al., 2004), sibutramine is contraindicated in patients with coronary disease, history of stroke, heart disease or arrhythmia (Klein et al., 2004). Therefore, sibutramine has some limitations, but in our study this drug achieved better reduction in anthropometric parameters than metformin, as expected, and this was decisive for the better glycemic profile of patients in the sibutramine than in the metformin group.

The limitations of this study are related to the small population sample and the prescription of drugs for only three months, so that comparison with other studies, in which the same drugs were assessed for 6, 12 or 24 months, may be of limited value. Moreover, no patients with DM2 were diagnosed, so glycemic control by metformin may have been reduced.

In addition, after SCOUT, the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA) recommended the suspension of marketing authorizations for sibutramine in 2010 (Scheen, 2010; FDA, 2010) and the Brazilian National Agency for Sanitary Surveillance (ANVISA) issued new regulations for greater control over the prescription of sibutramine, in 2010 (ANVISA, 2010) and 2011 (ANVISA, 2011).

Metformin and sibutramine treatments were well tolerated during our study. Despite the disappointing results on lipid profile, sibutramine showed a reduction of anthropometric parameters and control of insulin resistance, making it a therapeutic option to be considered in obese patients with DM2 or glucose intolerance, as long as the limitations on its prescription are respected. However, it should be noted that this study covered only 3 months of treatment.

Metformin, as expected by the researchers, led to slightly less improvement in the anthropometric measures than sibutramine. However, its worse performance in the glucose profile should be interpreted with caution, given the small sample size (8 patients in each group) and short time of drug use (3 months). Furthermore, no patient in the study had been diagnosed with DM2. However, the BMI and waist circumference results in the metformin group qualify it as an option for the treatment of obese patients with DM2.

RESUMO

Sibutramina versus Metformina: avaliação dos parâmetros antropométricos, lipídicos e glicêmcios em pacientes obesos e sobrepeso de alto risco

Comparar os parâmetros antropométricos, lipídicos e glicêmicos em pacientes obesos ou sobrepeso de risco elevado. Estudo duplo cego com 16 pacientes obesos ou em sobrepeso de risco elevado que receberam tratamento com dieta mais 15mg/dia de sibutramina ou 1700mg/dia de metformina durante três meses. As mudanças nos parâmetros avaliados no grupo sibutramina e metformina foram: índice de massa corporal (-6,0% vs. -4,0%), circunferência abdominal (-7,9% vs. -6,6%), tecido adiposo (-10,5% vs. -1,7%), colesterol total (-2,9% vs. -2,8%), LDL-C (-0,01% vs. -0,1%), HDL-C (-11,0% vs. -6,8%), razão colesterol total/HDL-C (12,0% vs. 4,5%), razão HDL-C/LDL-C (-7,2% vs. -0,1%), triglicerídeos (14,0% vs. 22,3%), glicemia de jejum (4,3% vs. 1,4%), insulina (-10,4% vs. -4,9%), HOMA (-8,0% vs. -3,9%). Embora o estudo tenha sido conduzido com somente 16 pacientes e o uso dos medicamentos ter sido por apenas três meses, pode-se observar que o tratamento com sibutramina em pacientes obesos ou sobrepeso de risco elevado mostrou uma redução nos parâmetros antropométricos e melhor controle na resistência a insulina.

Palavras-chave: Metformina. Sibutramina. Estudo Clínico. Tratamento da obesidade. Farmacêutico.

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