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Orlistat and Cardiovascular Risk Profile in Hypertensive Patients With Metabolic Syndrome: The ARCOS Study

Maria Teresa Zanella
Marcelo Hiroshi Uehara
Artur Beltrame Ribeiro
Marcelo Bertolami
Ana Claudia Falsetti
Mirela A. Yunes
for the ARCOS Study Investigators

Divisions of Endocrinology (MTZ, MHU) and Nephrology (ABR), Federal University of São Paulo; Service of Cardiology (MB), Instituto Dante Pazzaneze de Cardiologia; and Roche Laboratories (ACF, MAY), São Paulo, SP.

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ABSTRACT

Weight loss improves metabolic abnormalities and reduces cardiovascular risk in obese hypertensive patients. To evaluate the impact of a sustained weight loss on coronary risk, 181 hypertensive patients with metabolic syndrome underwent to orlistat therapy, 120 mg, t.i.d., plus diet for 36 weeks. During therapy, Framingham risk scores (FRS) were calculated for determination of coronary heart disease risk in ten years. Body mass index decreased from 35.0 ± 4.2 to 32.6 ± 4.5 kg/m^2 (p< 0.0001) and waist circumference from 108.1 ± 10.1 to 100.5 ± 11.1 cm (p< 0.0001), at the end of the study period (week 36). Systolic and diastolic blood pressure showed reductions after the two first weeks, which were maintained up to the end of the study. A clear shift to the left in FRS distribution curve occurred at the end of the study, compared to baseline, indicating a reduction in coronary risk. Over all patients at risk, 49.2% moved to a lower risk category. A weight loss ≥ 5% occurred in 64.6% of all patients, associated with improvement in glucose metabolism. Among those with abnormal glucose metabolism, 38 out 53 patients (71.7%) improved their glucose tolerance (p< 0.0005). In conclusion, long-term orlistat therapy helps to reduce and maintain a lower body weight, decreasing risk of coronary disease and improving glucose metabolism, thus protecting against type 2 diabetes. **(Arq Bras Endocrinol Metab 2006;50/2:368-376)**

Keywords: Central obesity; Orlistat; Weight reduction; Cardiovascular risk; Framingham risk score

RESUMO

Avaliação do Risco Cardiovascular em Pacientes Obesos Hipertensos com Síndrome Metabólica: Estudo ARCOS.

A perda de peso melhora as anormalidades metabólicas e reduz o risco cardiovascular em pacientes obesos hipertensos. Com o objetivo de avaliar o impacto da perda de peso mantida sobre o risco coronariano, submetemos 181 pacientes hipertensos com síndrome metabólica à terapia com orlistat, 120 mg, três vezes ao dia, mais dieta, por um período de 36 semanas. Durante a terapia, foram calculados os *scores* de risco de Framingham (FRS) para a determinação do risco de doença cardíaca coronariana em dez anos. Ao final do período de estudo (semana 36), o índice de massa corpóreo diminuiu de 35,0 ± 4,2 para 32,6 ± 4,5 kg/m^2 (p< 0,0001) e a circunferência da cintura de 108,1 ± 10,1 para 100,5 ± 11,1 cm (p< 0,0001). As pressões sistólica e diastólica mostraram reduções após as primeiras duas semanas, que se mantiveram até o final do estudo. Um deslocamento evidente para a esquerda na curva

ARCOS Investigators: Maria Teresa Zanella, Marcelo Bertolami, Abrahão Afiune, João C. Rocha, Marcia G. Nunes, Décio Mion Jr, Rogério A. Mullinari, Paulo César Jardim, Marco A. Albernaz, José Egidio Oliveira, Mauro Dinato, João Toniolo Neto, José Márcio Ribeiro, Roberto Franken.

de distribuição do FRS ocorreu no final do estudo, em comparação com os valores basais, indicando redução no risco coronariano. Do total de pacientes em risco, 49,2% passou para uma categoria de risco menor. Ocorreu perda de peso ≥ 5% em 64,6% de todos os pacientes, associada com melhora no metabolismo da glicose. Entre os 53 pacientes com metabolismo de glicose anormal, 38 (71,7%) melhoraram sua tolerância à glicose (p< 0,0005). Em conclusão, terapia de longa duração com orlistat auxilia a reduzir e manter mais baixo o peso corpóreo, reduzindo o risco de doença coronária e melhorando o metabolismo da glicose e protegendo, dessa maneira, contra o diabetes tipo 2. **(Arq Bras Endocrinol Metab 2006;50/2:368-376)**

Descritores: Obesidade central; Orlistat; Redução de peso; Risco cardiovascular; *Score* de risco de Framingham.

HYPERTENSION IS A MAJOR risk factor for all clinical manifestations of atherosclerosis in both sexes at all ages (1). A 36-year follow-up of individuals aged 35–64 years in the Framingham Heart Study showed that hypertensive patients have an excess risk of coronary heart disease, stroke, peripheral artery disease, and heart failure compared with patients with normal blood pressure. Part of the excessive cardiovascular risk in hypertensive patients is due to the presence of the metabolic syndrome (2), a cluster of cardiovascular risk factors closely linked to insulin resistance (3). Hypertension, dyslipidemia, and glucose intolerance promote accelerated atherogenesis and correcting them stabilizes lesions and slows its progression. Because the burden of metabolic risk factors accompanying hypertension is promoted by weight gain leading to visceral adiposity and insulin resistance, weight control is of paramount importance (4-6).

Several studies have shown that weight loss improves metabolic abnormalities and reduces cardiovascular risk in obese hypertensive patients (7-9). However, weight reduction and the long-term maintenance of lower body weight can be difficult to achieve, and not many obese patients maintain the short-term weight losses achieved following dietary restriction (10-12). Pharmacological treatment promoting long-term weight reduction and improving insulin resistance-related risk factors may benefit many overweight hypertensive patients at risk of vascular events. Orlistat acts as an inhibitor of pancreatic, gastric, carboxyl ester lipase, which consequently results in both, decreased absorption of fat and emission of unabsorbed cholesterol and triacylglycerols. The intake of excess dietary fat is one of the leading causes of obesity, and the above-described systemic effect should facilitate weight loss in obese subjects. Orlistat therapy, in conjunction with diet, has been shown to result in significantly greater weight loss and improvement in risk factors than diet alone among obese patients at high risk of coronary events (13,14). The primary objective of this study was to further investigate the impact of long-term body weight reduction with orlistat on the risk of a coronary event trough the determination of Framingham Risk Score in hypertensive patients with metabolic syndrome.

PATIENTS AND METHODS

Patients

In this study, 181 patients were included in the intention to treat (ITT) efficacy analysis population. Eligible patients were of both sex, 18–70 years of age, with a BMI > 25 and < 45 kg/m² and systolic blood pressure ≥ 130 and < 180 mmHg. Patients should also present at least two of the following factors to characterize the occurrence of metabolic syndrome: waist circumference in men ≥ 94 cm and women ≥ 80 cm; plasma triglycerides ≥ 150 and < 400 mg/dl or fasting plasma glucose ≥ 100 and < 126 mg/dl. Patients on antihypertensive drugs should be receiving in the past two months the same dosage of angiotensin converting enzyme inhibitors, calcium antagonists, angiotensin II antagonists, diuretics or beta-blockers.

Exclusion criteria included: total cholesterol ≥ 240 mg/dl; diastolic blood pressure ≥ 110 mmHg; smoking or smoking cessation within past 6 months; history or presence of significant renal, hepatic, cardiac or psychiatric disorders; weight loss > 3 kg in the three months prior to screening, participation in a weight-loss program (diet or pharmacological) during the past 3 months, previous surgery for obesity; endocrine disorders, excepting patients with impaired glucose tolerance or treated hypothyroidism. Patients with acute or chronic severe diseases possibly affecting the absorption, metabolism or excretion of the trial medication, or impairing the evaluation of patient safety and the outcome of the clinical trial (such as AIDS, tumor diseases, cardiac insufficiency) were also excluded. Drugs administered for the first time or withdraw during the past 6 months, which have a significant impact on the body weight (such as serotoninergically acting drugs, antidepressants, central adrenergically acting substances, substances inhibiting digestion and absorption, thyroid hormones and corticosteroids) were not allowed. Patients in use of oral hypolipidemic agents,

oral hypoglycaemic agents or insulin, at any time, were also excluded. Lactating women, pregnant women or of childbearing potential not applying a reliable method of contraception, were not allowed in this study.

Protocol design

The study was conducted as a multicenter, open-label, non-comparative in 14 clinical research sites between 2002 and 2003, during 36 weeks with 11 visits within this period. After selection, patients were initially seen in two visits with two weeks interval and every 4 weeks thereafter. In the first visit patients were submitted to a complete physical examination, with weight, height, waist circumference and blood pressure determinations and all other inclusion/exclusion criteria were checked.

Patients included in the study were instructed to take a 120 mg capsule of orlistat, orally, together with the major meals (breakfast, lunch, and dinner) during 36 weeks. Body weight, body mass index, waist circumference and blood pressure were recorded at every study visit. Waist circumference was measured halfway between the lower rib margin and the iliac crest in the stand position after a normal expiration. Systolic and diastolic blood pressures were taken after a 5-min resting in the sitting position by standard sphygmomanometry.

Fasting blood glucose and plasma lipid profile, including total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides, were determinate at visit 1, just before introducing the study medication, at visits 4 (week 8), 6 (week 16), 8 (week 24) and 11 (week 36), at the end of the study. An oral glucose tolerance test (OGTT) with blood glucose determination before and 2 hours after an oral glucose load of 75 g was performed before therapy (visit 1) and at the end of the study period. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were assessed using an autoanalyser and respective reagents (Cobas-Miraplus, Roche). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula [LDL-C mg/dL= TC in mg/dL – (TGmg/dL/5 + HDL-C mg/dL)]. Blood glucose was measured using the glucose-oxidize methodology.

Ninety three patients were submitted to an abdominal computed tomography (CT), both before and at the end of the study period. Since CT was performed in more than one clinical research site, to reduce the variability of the abdominal fat measurement, the thickness of the visceral and subcutaneous fat was preferred to the measurement of the abdominal fat areas. Only one axial cut was performed, 5 cm below the xiphoid process and the thickness of two fat plans were determined in centimeters. The subcutaneous fat was measured, at the middle line, between the posterior wall of the skin and the anterior wall of the subjacent muscular plan. The thickness of the visceral fat was measured between the posterior wall of the abdominal muscle and the anterior wall of the aorta. This linear measurement of the visceral fat has been shown to have a good correlation with the area of the visceral fat at CT (15).

Framingham risk score (FRS) (16), based on age, sex, total cholesterol, HDL-cholesterol, blood pressure values, smoking habits and presence or absence of diabetes, were calculated at visits 1, 4, 6, 8 and 11 for determination of coronary heart disease (CHD) risk in ten years.

During the entire 36-week study period, all patients were prescribed a reduced-calorie diet (~500 kcal/day deficit) containing 30% of calories from fat and not more than 300 mg of cholesterol per day. Participants received dietary counseling every 2 weeks in the first month and monthly thereafter and were also encouraged to walk during 30 minutes every day in addition to their usual physical activity.

The study protocol was approved by the Ethical Committee of each hospital where the study has been conducted, and all patients signed an informed consent.

Statistical methods

This was a prospective, multi-centre, open-label study. The following tests were used: analysis of covariance (ANCOVA) to investigate the significance of changes within the whole group and between subgroups over time. The ANOVA, paired *t*-test, Wilcoxon signed rank sum test, Pearson (*r*) correlation coefficient, Cochran-Mantel-Haenszel test, and Chi-square tests were also used. Mean and standard deviation (SD) of the numerical variables are reported. A two tailed $p< 0.05$ was considered significant.

RESULTS

The demographic characteristics and the cardiovascular risk profile of the intention-to-treat (ITT) population studied are shown in table 1. This study analyzed the results of 181 hypertensive patients, the majority of them female (84%) with age ranging from 25–65 years old and BMI ranging from 27–44 kg/m^2. The presence of hypertension, abdominal obesity associated with high levels of tryglicerides and/or low levels

Table 1. Demographic and clinical characteristics of the study population.

Age (years)	48 ± 9.3
Weight (kg)	89,8 ±13.6
Systolic Blood Pressure (mmHg)	143 ±12.2
Diastolic Blood Pressure (mmHg)	91 ± 8.6
Body Mass Index (kg/m)	35.0 ± 4.2
Waist circumference (cm)	108.1 ± 10.1
Fasting Blood Glucose (mg/dl)	102.6 ±13.0
Total cholesterol (mg/dl)	203.0 ± 26.1
HDL-cholesterol (mg/dl)	43.5 ± 9.8
LDL-cholesterol (mg/dl)	124.3 ± 30.7
Triglycerides (mg/dl)	188.2 ± 82.0

of high-density lipoprotein (HDL)-cholesterol and/or impaired fasting glycemia characterized the occurrence of metabolic syndrome in all patients of this population. Antihypertensive medication administered during the study period included calcium channel blockers (35%), diuretics (32.8%), renin-angiotensin blocking agents (27.1%) beta blockers (16.9%) and other agents (6.2%). Fifty nine patients (32.6%) were off antihypertensive medication.

From the 181 patients included, 155 completed the treatment (85%). The most common causes of premature discontinuation were refusal of treatment (n= 9; 34%), protocol violation (n= 6; 23%) and adverse event or intercurrent illness (n= 3; 11.5%)

The intention to treat analysis demonstrated that, during orlistat therapy, as shown in figure 1, body weight decreased significantly up to week 16, from 89.8 ± 13.6 kg to 84.3 ± 13.7 kg (p< 0.0001), with no significant changes thereafter, reaching 83.3 ± 14.3 kg at the end of the study. A mean reduction of 7.3 ± 7.1% was observed for the whole population. As a consequence, body mass index decreased from the Baseline value of 35.0 ± 4.2 to 32.6 ± 4.5 kg/m^2 (p< 0.0001) and waist circumference from 108.1 ± 10.1 to 100.5 ± 11.1 cm (p< 0.0001), at the end of the study period (week 36). Systolic and diastolic blood pressure showed a clear reduction after the first two weeks of therapy and reached the lowest values at week 8. No significant changes have been detected from week 2 to week 36, as demonstrated in figure 2. Similar responses of systolic blood pressure to therapy were observed in the subgroups of patients on (n= 122) and off (n= 59) antihypertensive medication. In those on antihypertensive therapy systolic blood pressure decreased from 144.6 ± 22.0 to 134.9 ± 22.0 mmHg (p< 0.0001) after two weeks, reaching 133.9 ± 22.1 mmHg at the week 36. In those not taking antihypertensive drugs systolic blood pressure decreased from 139.2 ± 12.4 to 134.4 ± 12.7 mmHg (p< 0.0001) after two weeks, reaching 131.6 ± 12.2 mmHg at the end of the study.

For all patients, the distribution of the calculated Framingham Risk Score (FRS), which is the risk of coronary heart disease in 10 years (16), before and at the end of orlistat therapy, is depicted in figure 3. A beta-density distribution was fitted to the distributions of the FRS, at weeks 0 and 36, with descriptive purposes. It was observed a clear shift to the left in the FRS distribution at the end of the study period, when compared to distribution observed at baseline. These curves indicate a reduction in the risk of a coronary event in 10 years, particularly in those patients at higher risk categories in the beginning of the study. Although a small change was observed in the mean of the calculated FRS for the whole population (from 8.0 ± 5.2% to 6.8 ± 4.4%), there was a significant difference between the risk distribution at weeks 0 and 36 (p= 0.0037). The proportions of patients in the categories that are considered of intermediate risk (≥ 10% – < 20%) and high risk (≥ 20%) of a coronary heart disease in 10 years reduced from 36.4% and 5.8% before therapy to 19.7% and 3.4%, respectively, by the end of the study period. In contrast, the proportions of patients in the low (≥ 5% and < 10%) and very low risk (< 5%) categories increased from 27.2% to 40.1% and from 30.6% to 36.7% respectively. Of the 120 patients in the low, intermediate and high-risk classes, 49.2% moved to a lower risk category, 45.0% remained in the same category and only 5.8% moved to a higher risk category. Of the 54 patients in the lower risk category, nine (16%) moved to the moderate risk category.

In the whole group, the thickness of subcutaneous fat at CT decreased from 3.23 ± 1.04 cm at baseline to 3.0 ± 0.97 (p< 0.002) at the end of the study period while the thickness of the visceral fat was reduced from 7.61 ± 3.39 to 6.52 ± 3.04 cm (p< 002), within the same period. No significant correlation was found between changes in abdominal fat and changes in FRS.

Patients were also divided, according to the percentage of body weight lost, in three other categories: < 5%, ≥ 5% – <10% and ≥ 10%. It was observed a weight loss ≥ 5% in 64.6% of all patients studied. Table 2 shows that the changes that occurred in the cardiovascular risk factors during orlistat therapy were dependent on the amount of weight lost. At the end of the study, patients who lost more then 5% of the initial body weight showed significant reductions in waist circumference, systolic blood pressure, fasting glycemia and, total cholesterol, LDL-cholesterol and triglycerides.

In all patients, fasting glycemia was lower than 126 mg/dl at baseline. From 151 patients who were submitted to an oral glucose tolerance test, 98 (64.9%)

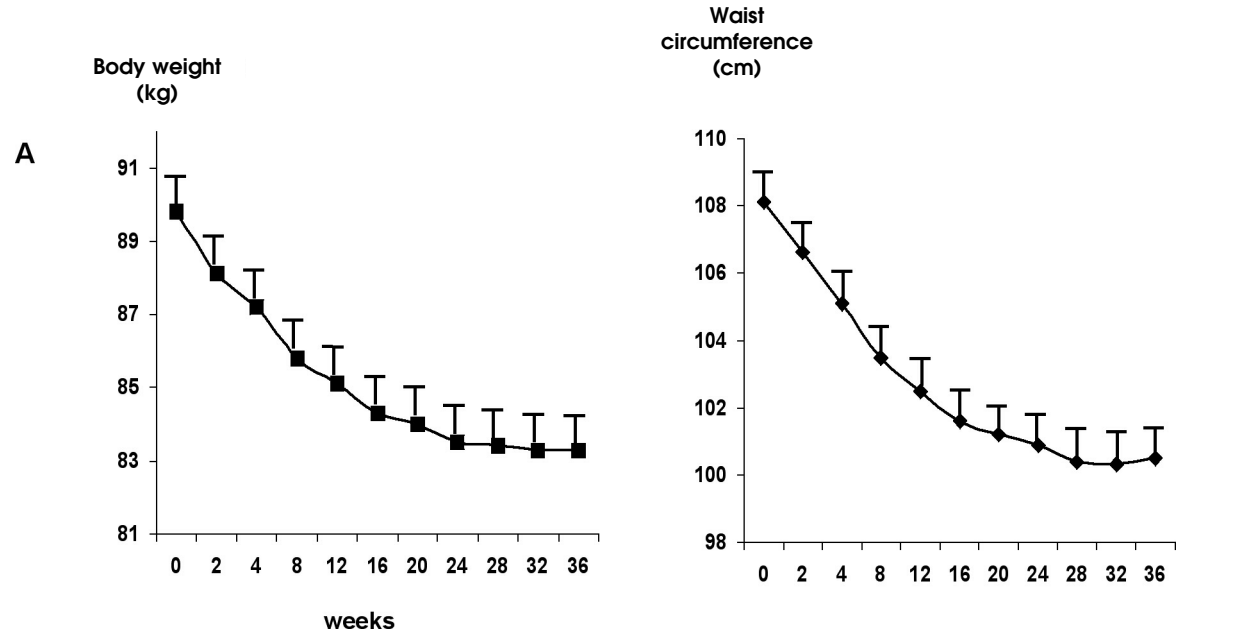

Figure 1. (A) Body weight. **(B)** Waist circumference reductions during a 36-week orlistat plus diet therapy (mean ± SE).

presented a normal glucose tolerance, with blood glucose levels at 120 minutes after glucose load < 140 mg/dl; 36 (23.8%) had impaired glucose tolerance (blood glucose ≥ 140 mg/dl and < 200 mg/dl) and 17 (11.3%) had diabetes (blood glucose ≥ 200 mg/dl). However, as fasting glucose were lower than 126 mg/dl, all patients were considered non-diabetics for FRS calculation purpose, once for risk stratification OGTT has not been indicated.

Compared to those with normal glucose tolerance, patients with blood glucose levels ≥ 140 mg/dl at 120 minutes of OGTT had only higher fasting blood glucose (108.8 ± 11.6 mg/dl vs. 97.8 ± 12.1 mg/dl; p< 0.05) with similar body mass index, waist circumference, blood pressure and plasma lipid profile. At the end of the study period, from 36 patients with impaired glucose tolerance, 23 (63.9%) showed normal blood glucose levels, 9 (25%) remained with impaired glucose tolerance and 4 (11.1%) developed diabetes, detected only by OGTT. From the 17 patients with diabetes at OGTT at baseline, 6 (35.3%) showed normal glucose tolerance test at the end of the study, 9 (52.9%) presented with glucose intolerance and only 2 (11.7%) remained with diabetes at OGTT after therapy. Overall, of the 53 patients with abnormal glucose metabolism, 38 (71.7%) improved their glucose tolerance. From the 98 patients with normal glucose tolerance test 15 (15.3%) developed glucose intolerance and one developed diabetes. The Cochran-Mantel-Haenszel statistics showed that the changes in patients' distribution toward classes of better glucose tolerance were significant (p< 0.0005). There was also an association (chi-square) between decrease in body weight ≥ 5% and improvement in glucose tolerance (p< 0.001).

DISCUSSION

Modest weight loss of 5–10% body weight has been shown to improve insulin sensitivity and other cardiovascular risk factors across a wide range of patient groups (17-20). However, maintenance of the weight losses, which is difficult to achieve with usual weight management programs (21), is required for sustained improvements in coronary heart disease risk factors. Initial studies with orlistat have indicated that this treatment is effective and well tolerated and provide long-term benefits in the management of weight loss in obese individuals (22-24). This was confirmed in our study, which demonstrates that such health benefits can be achieved in an obese population with uncontrolled hypertension and other features of the metabolic syndrome. The significant decrease in body weight observed throughout the 16 weeks of treatment was maintained up to 36 weeks of therapy. Furthermore, 64.6% of all patients on orlistat therapy could maintain more than 5% body weight reduction

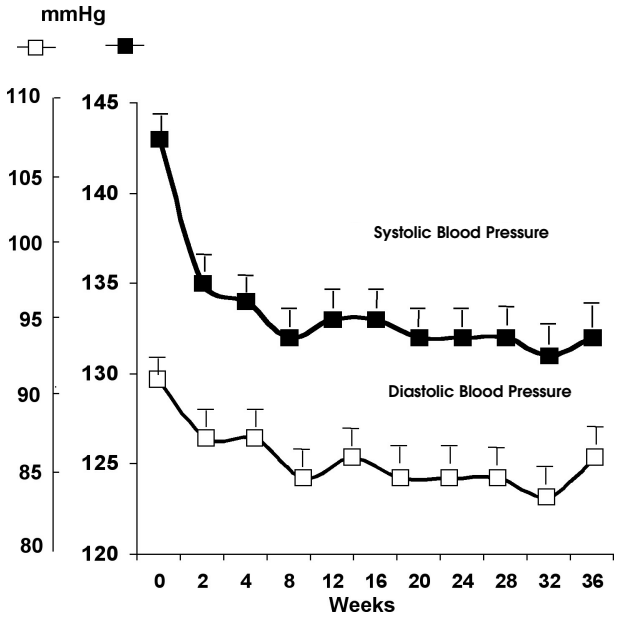

Figure 2. Systolic and diastolic blood pressure reduction during a 36-week orlistat plus diet therapy.

up to the end of the study period. This finding is important as the potential benefits to the obese individual increase the longer the weight reduction can be maintained (7).

Central adiposity is a well-known cardiovascular risk factor (25). Several studies have shown that changes in waist circumference correlate well with changes in visceral adipose tissue and thus with changes in risk factors (4,5,26). In this study, the marked 7% and 10% reduction in waist circumference in the two groups of patients, which lost 5% and 10% of the initial body weight, respectively, indicates that orlistat-related weight loss is accompanied by a decrease in visceral fat.

The reduction in body weight with orlistat in our patients resulted in a significant reduction in the Framingham Risk Score (FRS), with 49.2% patients in the low, intermediate and high-risk categories moving to a lower risk category. Since patients included in this study were not smokers or had overt diabetes, the only two variables that could have changed the FRS were total cholesterol and blood pressure, once HDL-cholesterol did not show significant alterations and glucose tolerance is not considered in FRS calculation.

The most pronounced reductions in blood pressure occurred very early in the study, during the first two weeks of therapy, associated with a mean small change in body weight. Also a mean reduction near 5% was observed in systolic blood pressure even

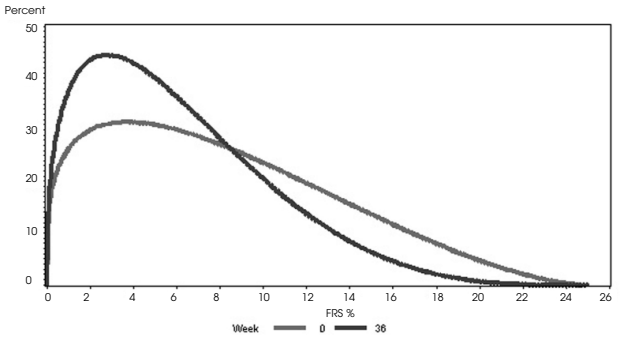

Figure 3. Beta density distribution fitted to the distributions of the FRS, before (week 0) and after 36 weeks of orlistat plus diet therapy (week 36).

in the group of patients showing a body weight reduction less than 5%. A better adherence to antihypertensive medication could be the reason for the prompt response of blood pressure to therapy. However, a significant early fall in blood pressure was also observed in patients who were not on antihypertensive therapy. Considering that no changes in antihypertensive medication were performed throughout the study period, these observations raise the hypothesis that not all changes in blood pressure can be attributed exclusively to weight loss. Changes in dietary components and/or in other metabolic factors, occurring with the initial weight loss, may be contributors to the early improvements observed in blood pressure (27), although the degree of blood pressure reduction is marked influenced by the degree of weight reduction.

The occurrence of insulin resistance in the metabolic syndrome increases the risk of developing impaired glucose tolerance and type 2 diabetes. Besides being a risk factor for the progression to type 2 diabetes, impaired glucose tolerance, defined by abnormal values of blood glucose concentrations 2 hours after an oral glucose load, is also considered an independent risk factor for cardiovascular disease. A metaregression analysis of 20 studies concluded that nondiabetic degrees of fasting and postprandial hyperglycemia were associated with cardiovascular disease (28). Thus, the decrease in 2-hour plasma glucose indicates not only a reduced diabetes risk but also a lower risk for cardiovascular disease. A number of studies (6,29) show that the risk of developing type 2 diabetes is closely linked to the presence and duration of overweight and obesity. In contrast, reduction in the incidence of type 2 diabetes with lifestyle changes has previously been demonstrated. The Finnish Diabetes Prevention Study (DPS) and

Table 2. Cardiovascular risk factors before and after a 36-week orlistat plus diet therapy in subgroups of patients divided according to changes in body weight.

		Weight Loss Categories			
		< 5% (n= 64) (35.4%)	**≥ 5% – <10% (n= 69) (38.1%)**	**≥ 10% (n= 48) (26.5%)**	**p****
Body Mass Index (kg/m^2)	Baseline	35.5 ± 4.5	35.3 ± 4.2	35.2 ± 3.7	ns
	Final	34.9 ± 4.5	32.4 ± 4.0*	30.1 ± 3.3*	
	Δ%	-1.7	-8.2	-14.5	0.0001
Waist circumference (cm)	Baseline	110.1 ±11.7	107.1 ± 9.0	107.4 ± 9.2	ns
	Final	106.0 ±11.7	99.0 ± 9.4*	95.7 ± 9.2*	
	Δ%	-3.7	-7.6	-10.9	0.0002
Systolic Blood Pressure (mmHg)	Baseline	141.8 ± 12.0	143.0 ± 13.3	143.0 ± 10.9	ns
	Final	134.9 ± 14.5*	132.4 ± 19.4*	128.9 ± 14.3*	
	Δ%	-4.9	-7.4	-9.8	0.03
Diastolic Blood Pressure (mmHg)	Baseline	90.3 ± 8.4	91.3 ± 9.5	91.3 ± 7.5	ns
	Final	87.8 ± 8.6	86.2 ± 10.8*	85.0 ± 10.4*	
	Δ%	-2.8	-5.6	-6.9	ns
Fasting Blood Glucose (mg/dl)	Baseline	100.4 ± 14.8	104.0 ± 12.1	103.4 ± 11.7	ns
	Final	102.0 ± 26.1	95.3 ± 13.1*	90.4 ± 13.0*	
	Δ%	2.5	-7.5	-11.5	0.017
Total Cholesterol (mmHg)	Baseline	204.7 ± 28.7	202.0 ± 23.4	202.3 ± 26.4	ns
	Final	199.7 ± 34.1	184.2 ± 31.3*	182.9 ± 34.9*	
	Δ%	-1.9	-8.5	-10.1	0.0007
HDL-cholesterol (mmHg)	Baseline	42.8 ± 8.7	43.4 ± 8.4	44.7 ± 12.6	ns
	Final	42.4 ± 9.2	44.7 ± 8.3	44.7 ± 11.7	
	Δ%	1.8	4.7	4.0	ns
LDL-cholesterol (mmHg)	Baseline	125.3 ± 34.8	121.5 ± 27.0	124.7 ± 31.2	ns
	Final	121.0 ± 32.4	109.8 ± 29.0*	111.3 ± 32.6*	
	Δ%	0.1	-9.0	-8.9	ns
Triglycerides (mg/dl)	Baseline	202.7 ± 77.2	182.2 ± 79.6	177.4 ± 90.3	
	Final	186.5 ± 95.8	153.9 ± 63.1*	136.5 ± 74.7*	
	Δ%	-2.7	-9.7	-13.3	ns

* p< 0.05 vs. baseline; **comparisons between groups.

the Diabetes Prevention Program (DPP) have shown that modest weight loss achieved by lifestyle changes (diet and exercise) can significantly reduce the risk of developing type 2 diabetes in obese patients with impaired glucose tolerance (IGT) (30,31). The benefits of adding orlistat to life style changes were previously demonstrated in the XENDOS Study (32). In a 4-year, double-blind, prospective study, 3,305 obese patients with normal or impaired glucose tolerance were randomized to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. Compared with lifestyle changes and placebo, orlistat plus lifestyle changes for 4 years produced greater weight loss and reduced by 52% the incidence of type 2 diabetes in subjects with impaired glucose tolerance. The present study also showed that orlistat therapy and a dietary program resulted in a weight loss greater than 5% in 64.6% of all obese hypertensive patients and improved glucose tolerance in a subpopulation at higher risk for developing type 2 diabetes. From 53 patients with impaired glucose tolerance or diabetes, detected by an oral glucose tolerance test, 38 (71.7%) improved their glucose tolerance. In contrast, only 15 (15.3%) out 98 patients with normal glucose tolerance developed impaired glucose tolerance.

In summary, orlistat treatment resulted in a high proportion of obese hypertensive patients that could maintain more than 5% reduction in initial body weight for 36 weeks. This was associated with coronary risk reduction and improvement in glucose metabolism in those with impaired glucose tolerance. Thus, dietary modification plus orlistat therapy should, therefore, be considered as an option for the treatment of hypertensive patients with metabolic syndrome. It might help to reduce the need for multiple drug therapy in these patients, usually requiring a polypharmacy treatment strategy to avoid type 2 diabetes and to reduce cardiovascular risk.

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Endereço para correspondência:

Maria Teresa Zanella
Rua Leandro Dupret 365
04025-002 São Paulo, SP
E-mail: tereza.zanella@hrim.com.br