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Improved glycemic control by acarbose therapy in hypertensive diabetic patients: effects on blood pressure and hormonal parameters

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Abstract

A double-blind, randomized, placebo-controlled study was carried out on 44 hypertensive type 2 diabetic subjects previously treated by diet associated or not with sulfonylurea to assess the effects of acarbose-induced glycemic control on blood pressure (BP) and hormonal parameters. Before randomization and after a 22-week treatment period (100 to 300 mg/day), the subjects were submitted to a standard meal test and to 24-h ambulatory BP monitoring (ABPM) and had plasma glucose, glycosylated hemoglobin, lipid profile, insulin, proinsulin and leptin levels determined. Weight loss was found only in the acarbose-treated group (75.1 ± 11.6 to 73.1 ± 11.6 kg, $P<0.01$). Glycosylated hemoglobin decreased only in the acarbose group (6.4 ± 1.7 to 5.6 ± 1.9%, $P<0.05$). Fasting proinsulin decreased only in the acarbose group (23.4 ± 19.3 to 14.3 ± 13.6 pmol/l, $P<0.05$), while leptin decreased in both (placebo group: 26.3 ± 6.1 to 23.3 ± 9.4 and acarbose group: 25.0 ± 5.5 to 22.7 ± 7.9 ng/ml, $P<0.05$). When the subset of acarbose-treated patients who improved glycemic control was considered, significant reductions in diurnal systolic, diastolic and mean BP (102.3 ± 6.0 to 99.0 ± 6.6 mmHg, $P<0.05$) were found. Acarbose monotherapy or combined with sulfonylurea was effective in improving glycemic control in hypertensive diabetic patients. Acarbose-induced improvement in metabolic control may reduce BP in these patients. Our data did not suggest a direct action of acarbose on insulin resistance or leptin levels.

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• Hyperinsulinemia

Introduction

Approximately half of all diabetic patients are also hypertensive. One major factor linking diabetes and hypertension is insulin resistance and/or hyperinsulinemia. Since this situation is associated with increased cardiovascular risk, antidiabetic agents - able to reduce hyperinsulinemia - are desirable for diabetic patients with hypertension. Obesity contributes to elevated insulinemia and is accompanied by high leptin levels (1,2).

Postprandial hyperglycemia, even in the absence of fasting hyperglycemia, has been shown to be an independent cardiovascular risk factor (3,4). The properties of the antidiabetic acarbose make this a promising agent for the treatment of patients presenting

hyperglycemia, hyperinsulinemia and hypertension. Inhibition of α-intestinal glucosidases by acarbose retards the absorption of ingested carbohydrates and attenuates postprandial hyperglycemia and hyperinsulinemia. A potential beneficial effect of the drug on insulin resistance due to the improvement in hyperglycemia and glucotoxicity may also contribute to reducing blood pressure (BP) in hypertensive diabetic patients. However, few data are available about the effects of acarbose on BP, particularly using 24-h ambulatory monitoring, and on other hormonal parameters, such as leptin levels (5).

The present study evaluated the effects of acarbose-induced glycemic improvement on BP and hormonal parameters in patients at increased cardiovascular risk.

Patients and Methods

Fifty hypertensive diabetic patients aged 40-65 years were initially recruited from the Diabetes and Hypertension Clinic of the Federal University of São Paulo. Written informed consent was obtained from the patients and the study was approved by the Institutional Ethics Committee. Inclusion criteria were type 2 diabetes, BP between 140/90 and 160/104 mmHg and body mass index (BMI) ≥27 kg/m^2. Diabetic patients were supposed to have been previously treated by diet alone or associated with sulfonylurea; if they were treated with sulfonylurea, this agent was maintained at the same dose throughout the study. The use of other oral antidiabetic agents and insulin was an exclusion criterion. Antihypertensive therapy was based on salt intake restriction and if pharmacological therapy was necessary (diastolic BP >105 mmHg after a 4-week washout) only dipyridinic calcium channel blockers (Adalat Oros®, Bayer, Leverkusen, Germany) were used due to their neutrality in terms of glucose metabolism (6); doses (30 to 60 mg/day) were maintained throughout the study period. Elevated serum creatinine and hepatic enzymes were also exclusion criteria. Eligible patients were those with fasting glycemia between 6.7 and 13.9 mmol/l and diastolic BP <95 mmHg at the end of the placebo period. Of 50 patients initially screened, 6 did not fulfill the inclusion criteria.

This 24-week randomized, placebo-controlled trial consisted of a 2-week placebo period when patient eligibility was determined, followed by a 22-week double-blind treatment period. Patients were advised about a normocaloric diet and exercise and received a placebo (half a tablet) twice a day until randomization. Before starting the treatment period, baseline anthropometric data were obtained, 24-h ambulatory BP monitoring (ABPM) was performed, and a blood sample for fasting plasma glucose, glycosylated hemoglobin, lipid profile, serum insulin, proinsulin and leptin determinations was taken. In addition, patients were submitted to a standard meal test. Forty-four patients were randomized to either the placebo group or the acarbose group. The initial medication dose was 50 mg (or half a tablet) twice a day, adjusted at weeks 4 and 8 to 50 and 100 mg twice a day, respectively, if fasting capillary glycemia was >6.7 mmol/l. Thus, a maximum dose of 300 mg/day (3 tablets) was reached in the acarbose group at week 8. Weight, office BP and fasting capillary glucose were checked at each follow-up visit (weeks 4, 8, 12, 16 and 22). Treatment was discontinued prematurely if fasting plasma glucose level remained ≥13.9 mmol/l on two consecutive visits. At the final visit, ABPM and laboratory procedures were repeated to detect changes from baseline. Patient compliance was evaluated by counting the remaining tablets. Office BP was measured during all visits at the same time of day by the same investigator, using a standard mercury sphygmomanometer with appropriate cuff size. Ambulatory BP was recorded over a 24-h period using automatic monitors (SpaceLabs 90202, Redmond, WA, USA),

set to record every 15 min during the day and every 30 min during the night. Time limits for day and night were set to coincide with the patient's usual sleeping hours. Night BP fall was calculated by the percent difference between day and night systolic BP. Standard meal tests, performed after a 10-h fast, consisted of the consumption of a liquid meal (Ensure®, Abbott, Columbus, OH, USA) with total energy of 251 kcal, containing 50% of energy as carbohydrate, 15% as protein and 35% as fat. The morning tablet should be taken during the meal test and postprandial blood samples were obtained 1 h after consumption for plasma glucose and hormonal determinations.

Laboratory data (glycosylated hemoglobin, lipid profile, albumin excretion rate, fasting and postprandial plasma glucose, insulin, proinsulin and leptin) were obtained at baseline and at the end of the treatment period. The insulin resistance index (IRI) was estimated by the homeostasis model assessment (7). Plasma glucose was determined by the glucose-oxidase method, glycosylated hemoglobin by HPLC (normal range: 2.5-4.3%) and triglyceride and cholesterol contents of lipoprotein fractions were measured enzymatically. Urinary albumin was measured in duplicate by immunoturbidimetric assay (UNIMATE 3 ALB®, Roche, Basel, Switzerland). Insulin, proinsulin and leptin were determined using a radioimmunoassay kit (Linco Research Inc., St. Charles, MO, USA). The coefficients of variation of the assays were <10%. Insulin cross-reactivity with proinsulin was <0.2%. Fasting reference values were 5-15 µU/ml for insulin and 7.9 ± 1.5 pmol/ml for proinsulin. Leptin values for men and women were 3.8 ± 1.8 ng/ml and 7.4 ± 3.7 ng/ml, respectively.

Statistical analysis was performed using the SigmaStat software package. Parametric and nonparametric tests were used to compare variables within (paired Student *t*-test or Wilcoxon rank test) and between groups (unpaired Student *t*-test or Mann-Whitney U-test). Correlation between BMI and leptin level was tested by the Pearson coefficient. The chi-square test was used to compare frequencies. The level of significance was set at $P<0.05$.

Results

Forty patients completed the study; two patients of each group were excluded due to unstable diabetic control. One patient of each group had hypoglycemic episodes, and their sulfonylurea doses were reduced. Complaints of flatulence (N = 6) and/or diarrhea (N = 3) among acarbose-treated patients were attenuated throughout the study and did not interfere with the medication used. Compliance ranged from 85-96% of the prescribed medication. The highest acarbose dose was given to 17 of 20 patients who completed the study.

At baseline, demographic, clinical and laboratory data were similar between groups (Table 1). A significant reduction in body weight was verified in the acarbose group (75.1 ± 11.6 *vs* 73.1 ± 11.6 kg, $P<0.01$) but not in the placebo group (80.2 ± 9.8 *vs* 79.3 ± 9.7 kg, $P = 0.10$); the same occurred with BMI (placebo group: 31.7 ± 3.9 *vs* 31.5 ± 3.7 kg/m^2, $P = 0.40$ and acarbose group: 30.3 ±

Table 1. Baseline characteristics of the groups of patients.

	Placebo group	Acarbose group
Number of patients (men/women)	20 (8/12)	20 (6/14)
Age (years)	62.0 ± 9.7	59.8 ± 8.2
Diabetes duration (months)	81 (6-174)	82 (6-240)
Diabetes treatment (diet/SU)	6/14	7/13
Hypertension duration (months)	136 (24-240)	126 (12-360)
Micro- or macroproteinuria (yes/no)	10/10	12/8
Diabetic retinopathy (yes/no)	2/18	3/17
Weight (kg)	80.2 ± 9.8	75.1 ± 11.6
BMI (kg/m^2)	31.7 ± 3.9	30.3 ± 2.9
Mean office BP (mmHg)	107.8 ± 6.7	101.7 ± 9.0
Fasting plasma glucose (mmol/l)	10.3 ± 3.8	9.6 ± 2.3
Glycosylated hemoglobin (%)	6.3 ± 2.1	6.4 ± 1.7
Creatinine (µmol/l)	84 ± 20	78 ± 16

Data are reported as means and standard deviations or median and range. Differences were nonsignificant. SU, sulfonylurea; BMI, body mass index; BP, blood pressure.

2.9 *vs* 29.8 ± 2.7 kg/m^2, P<0.05). In acarbose-treated patients, weight reduction was observed particularly in those under monotherapy (78.8 ± 10.2 *vs* 75.2 ± 8.3 kg, P<0.05) but not in those under combined therapy with sulfonylurea (73.1 ± 12.2 *vs* 72.0 ± 13.2 kg, P = 0.18). Fasting or postprandial glycemia did not differ between groups at randomization or at the end of the treatment period (Table 2). A significant improvement of glycosylated hemoglobin was observed only in acarbose-treated patients. A tendency to a lower increment of glycemia after the meal test was observed in the acarbose group at the end of treatment when compared with the initial increment. Groups had similar lipid and hormonal profiles at baseline. No change in triglycerides, total, LDL- and HDL-cholesterol, fasting and postprandial insulin levels or IRI was found at the end of the treatment period. IRI was reduced in 75% of acarbose-treated subjects in contrast to 45% in the placebo group (P = 0.11). Fasting proinsulin levels were decreased only in the acarbose group at the end of the study, but no difference was observed in postprandial values. The proinsulin/insulin ratio did not change at the end of the treatment periods (placebo group: 0.15 ± 0.13 to 0.14 ± 0.15, P = 0.77 and acarbose group: 0.24 ± 0.21 to 0.26 ± 0.34, P = 0.79). Leptin levels were found to be correlated with BMI in women (r = 0.50, P<0.05). Both groups had their leptin levels reduced at the end of treatment (placebo group: 26.3 ± 6.1 to 23.3 ± 9.4 ng/ml and acarbose group: 25.0 ± 5.5 to 22.7 ± 7.9 ng/ml, P<0.05).

Two patients from each group did not require antihypertensive medication during the placebo period. Office systolic, diastolic and mean BP levels of the acarbose group were slightly lower than those of the placebo group (Table 3). Both groups had their office BP reduced at the end of the study period, although only the placebo group reached statistical significance. Baseline BP levels obtained by ABPM did not differ between groups and no change in systolic, diastolic or mean BP levels was found in any period. Baseline heart rates and nocturnal BP falls

Table 2. Metabolic and hormonal data obtained before randomization and at the end of the treatment period.

	Placebo group			Acarbose group		
	Initial	Final	P	Initial	Final	P
Fasting glycemia (mmol/l)	10.3 ± 3.7	10.0 ± 3.5	0.63	9.6 ± 2.3	9.8 ± 4.6	0.78
Postprandial glycemia (mmol/l)	15.6 ± 5.2	15.6 ± 5.1	0.98	14.3 ± 3.6	13.8 ± 5.9	0.61
Glycemic increment (%)	54.0 ± 21.0	62.0 ± 56.0	0.57	49.0 ± 17.0	41.0 ± 25.0	0.07
Glycosylated hemoglobin (%)	6.3 ± 2.1	6.3 ± 2.0	0.15	6.4 ± 1.7	5.6 ± 1.9	0.03
Total cholesterol (mmol/l)	12.2 ± 2.2	11.8 ± 1.7	0.19	11.4 ± 1.8	11.1 ± 2.2	0.34
HDL-cholesterol (mmol/l)	2.0 ± 0.4	1.9 ± 0.4	0.44	2.2 ± 0.6	2.2 ± 0.4	0.56
LDL-cholesterol (mmol/l)	8.4 ± 2.5	8.2 ± 1.4	0.47	7.7 ± 1.7	7.4 ± 1.7	0.34
Triglycerides (mmol/l)	10.8 ± 4.6	10.3 ± 4.9	0.45	7.9 ± 3.1	8.6 ± 4.5	0.37
Fasting insulin (µU/ml)	21.7 ± 10.6	21.8 ± 12.9	0.97	23.4 ± 18.6	18.0 ± 11.8	0.16
Postprandial insulin (µU/ml)	62.5 ± 52.0	49.0 ± 29.8	0.31	52.7 ± 32.0	59.2 ± 53.2	0.67
IRI	9.4 ± 5.0	7.9 ± 3.4	0.90	9.8 ± 6.8	7.2 ± 4.2	0.10
Fasting proinsulin (pmol/ml)	32.3 ± 28.7	27.7 ± 18.0	0.37	23.4 ± 19.3	14.3 ± 13.6	0.03
Postprandial proinsulin (pmol/ml)	47.9 ± 35.9	54.4 ± 29.3	0.38	49.8 ± 29.8	40.6 ± 28.1	0.26
Leptin (ng/ml)						
Men	27.9 ± 6.9	26.9 ± 9.4	0.31	26.1 ± 5.1	23.4 ± 7.9	0.08
Women	25.8 ± 5.9	22.3 ± 7.4	0.01	24.6 ± 5.8	22.3 ± 8.1	0.01

Data are reported as means and standard deviations or median and range. IRI, insulin resistance index. P values refer to the comparison of initial and final results (Student *t*-test).

were also similar and did not change by the end of the study. A comparison between patients who lost weight (N = 11) or not (N = 9) during acarbose therapy showed no difference in BP values obtained by ABPM and no correlation between body weight and BP variations.

A subset of 11 patients from the acarbose group who achieved improvement in metabolic control (glycosylated hemoglobin fall) was analyzed separately. Duration of diabetes and initial plasma glucose levels were not different when compared to the remaining acarbose-treated patients; 64% showed a reduction in 24-h systolic BP (136.0 ± 6.0 to 132.1 ± 7.0 mmHg, P = 0.10) and 73% of this subset showed a reduction in 24-h mean BP (100.3 ± 6.0 to 97.6 ± 7.0 mmHg, P = 0.12). These reductions were statistically significant for diurnal systolic (138.0 ± 6.7 to 133.7 ± 7.2 mmHg, P<0.03), diastolic (83.0 ± 7.6 to 80.0 ± 7.2 mmHg, P<0.05) and mean BP (102.3 ± 6.0 to 99.0 ± 6.6 mmHg, P<0.05) at the end of the treatment period, but not for nocturnal values. The IRI of these patients tended to decrease during treatment (7.9 ± 4.6 to 6.0 ± 5.0, P = 0.14).

Discussion

The results of this study indicate beneficial effects of acarbose on glycemic control of type 2 diabetic patients previously treated with diet alone or associated with sulfonylurea, since a significant reduction in glycosylated hemoglobin (0.8%) was obtained. Large prospective studies, in which acarbose was administered as monotherapy or in combination with other antidiabetic agents, also showed improvement in glycemic con-

Table 3. Hemodynamic data obtained before randomization and at the end of the treatment period.

	Placebo group			Acarbose group		
	Initial	Final	P	Initial	Final	P
Office BP						
Systolic (mmHg)	148.5 ± 13.0	140.7 ± 12.0	0.02	140.2 ± 16.2	134.0 ± 11.9	0.13
Diastolic (mmHg)	87.6 ± 5.5	84.2 ± 5.4	0.01	82.5 ± 7.3	80.9 ± 4.5	0.32
Mean (mmHg)	107.8 ± 6.7	103.0 ± 6.8	0.02	101.7 ± 9.0	98.7 ± 6.3	0.17
ABPM						
24-h						
Systolic (mmHg)	138.0 ± 11.6	138.3 ± 11.1	0.86	134.4 ± 7.8	132.4 ± 9.0	0.15
Diastolic (mmHg)	81.5 ± 10.1	81.4 ± 7.9	0.96	80.1 ± 7.2	78.7 ± 7.7	0.16
Mean (mmHg)	101.4 ± 8.5	101.5 ± 6.6	0.94	99.2 ± 6.9	97.2 ± 7.7	0.06
Heart rate (bpm)	80.3 ± 8.2	78.9 ± 10.8	0.36	81.1 ± 8.0	79.8 ± 8.0	0.31
Day period						
Systolic (mmHg)	136.7 ± 8.1	134.2 ± 9.8	0.38	136.7 ± 8.2	134.2 ± 9.8	0.08
Diastolic (mmHg)	82.2 ± 7.4	80.7 ± 8.2	0.53	82.2 ± 7.4	80.7 ± 8.2	0.14
Mean (mmHg)	101.2 ± 7.0	99.1 ± 8.2	0.40	101.2 ± 7.0	99.1 ± 8.2	0.06
Systolic load (%)	36.4 ± 22.2	31.5 ± 22.9	0.49	31.5 ± 22.9	36.4 ± 22.2	0.14
Diastolic load (%)	23.2 ± 18.0	17.5 ± 18.1	0.32	17.5 ± 18.1	23.2 ± 18.0	0.10
Night period						
Systolic (mmHg)	130.8 ± 13.1	133.1 ± 13.1	0.42	127.0 ± 8.7	126.8 ± 10.1	0.92
Diastolic (mmHg)	74.7 ± 12.2	76.2 ± 9.5	0.39	72.7 ± 7.1	72.1 ± 7.7	0.62
Mean (mmHg)	94.8 ± 11.6	96.5 ± 9.1	0.44	91.9 ± 7.0	91.6 ± 8.5	0.84
Nocturnal BP fall (%)	8.3 ± 8.7	5.1 ± 8.1	0.25	7.7 ± 3.7	6.9 ± 4.8	0.25

Data are reported as means and standard deviations or median and range. BP, blood pressure; ABPM, ambulatory blood pressure monitoring. P values refer to the comparison of initial and final results (Student *t*-test).

trol (8,9). A noncontrolled study including 4,071 patients reported a 1.0 to 2.3% decrease in glycosylated hemoglobin (8), which was less in the PROTECT trial (9). The comparison of our findings with those of controlled studies, either *vs* placebo or *vs* a reference drug, showed similar reductions in glycosylated hemoglobin levels (10-12). In a multicenter European study, glycosylated hemoglobin dropped by 0.9% in patients on acarbose monotherapy and on acarbose treatment combined with sulfonylurea (10). Our benefit was even better if compared to the 0.3-0.6% reductions achieved in the UKPDS after 3 years of follow-up (13). The acarbose-induced decrease in glycosylated hemoglobin strongly suggests that total daily insulin secretion was reduced during the study period. In addition to glycosylated hemoglobin, the efficacy of acarbose was evaluated by the glycemic response to oral overload of nutrients. No standardization concerning the total energy to be consumed during a meal test is found in the literature. The Essen Study used a standardized breakfast containing a total energy of 372 kcal (11) but even higher caloric overloads have been reported. In our study, acarbose therapy was associated with a smaller increase in postprandial plasma glucose after an overload of 251 kcal, when compared with the placebo group. This may suggest that the groups of patients, with comparable responses to the meal test at baseline, became distinct following acarbose therapy. However, mean postprandial plasma glucose was not changed by this therapy, in agreement with some (13) but not all previous reports (10,11,14).

Based on potential hemodynamic benefits (5,15) related to the improvement in metabolic control, as expressed by decreased glycosylated hemoglobin, the effects of acarbose on BP of hypertensive diabetic patients were investigated. Some experimental studies have provided contradictory results (16,17). Comparison of baseline and final office BP showed that patients had their BP levels decreased throughout the study period, being statistically significant only for the placebo group. This suggests a white-coat effect, which seemed to be minimized at the final visit to the doctor. Based on 24-h ABPM, acarbose-treated patients did not reduce BP. Considering the hypothesis of a glycemic control-induced hypotensive effect, we analyzed the subset of 11 patients with reduced glycosylated hemoglobin. In contrast to the total group of acarbose-treated patients, those with improved glycemic control had a significant BP drop in the diurnal period and a borderline significant drop during the 24-h period, indicating a beneficial role of glycemic control on BP levels of diabetic hypertensive patients. The reason for BP reduction only during the day requires further investigation. Intensive monitoring of glucose and insulin levels, particularly during the postprandial period, could also help clarify this aspect. The lack of correlation between weight and BP variations is against a role of weight loss in BP reduction. Furthermore, when analyzing separately the subset of patients from the acarbose group who lost weight (N = 11), quite similar baseline and final BP levels were found. Thus, our data support the notion of a hypotensive effect derived mainly from the improvement in metabolic control and attenuation of insulin resistance. To explore this possibility, insulin concentration and the HOMA for insulin resistance were assessed. Reductions in postprandial insulinemia following acarbose therapy and improved insulin sensitivity in patients with impaired glucose tolerance were previously reported (18). However, our findings do not support the idea that acarbose could attenuate insulin resistance and, consequently, reduce insulin secretion by the beta cells. The fact that a considerable proportion of our patients were on sulfonylurea should have contributed to their unchanged insulin levels. When the benefits of acarbose and/or

tolbutamide were compared, acarbose monotherapy did not prove to reduce postprandial hyperinsulinemia and tolbutamide alone was associated with high postprandial insulin levels when compared to the combination with acarbose (12). Our finding of unchanged postprandial insulinemia in the acarbose group might be due to an opposite action of sulfonylurea favoring insulin secretion. Prevention of the weight gain that usually follows sulfonylurea administration, however, could be considered an advantage of the combination of acarbose in sulfonylurea-treated patients. Although the comparison of HOMA between groups does not indicate an acarbose-induced improvement in insulin sensitivity, considering the patients whose IRI was decreased, a higher number of acarbose-treated patients (75%) showed improved insulin sensitivity compared to placebo (45%).

The previously described correlation of insulin levels with leptin (19) was not seen in the present study. Adipose mass represents the major determinant of leptin levels (20). Although only the acarbose group exhibited weight loss, both groups of patients showed reduced leptin levels. The lack of an accurate method to evaluate alterations in body composition, mainly concerning percentage of adipose mass, does not allow further speculations.

Acarbose shows benefits in terms of the glycemic control of hypertensive diabetic patients previously treated with diet alone or combined with sulfonylurea. Size sample and combined therapy may have a limited ability to demonstrate plasma glucose and insulin responses to acarbose. The administration of acarbose to sulfonylurea-treated patients may prevent weight gain. Such effects are desirable taking into account the elevated cardiovascular risk of these patients. In addition, the improvement in metabolic control induced by acarbose may contribute to reducing BP as evaluated by 24-h ABPM. Our data do not suggest a direct action of acarbose on insulin resistance or leptin.

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