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Small weight loss on long-term acarbose therapy with no change in dietary pattern or nutrient intake of individuals with non-insulin-dependent diabetes

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OBJECTIVES: To see if the long-term treatment of non-insulin dependent diabetes (NIDDM) with the α-glucosidase inhibitor acarbose affects food intake and body weight.
DESIGN: Randomized, double-blind, placebo-controlled, parallel design clinical trial of 12 months duration.
SUBJECTS: Subjects with NIDDM in four treatment strata: 77 on diet alone, 83 also treated with metformin, 103 also treated with sulfonylurea and 91 also treated with insulin.
MEASUREMENTS: Two 3 day diet records were obtained before randomization to acarbose or placebo therapy, and additional 3 day diet records were obtained at 3, 6, 9 and 12 months after randomization. Body weight was also measured at these times.
RESULTS: Of the 354 subjects randomized, 279 (79%) completed at least 9 months of therapy and, of these, 263 (94%) provided at least one diet record during the baseline period and two diet records during the treatment period. After one year, subjects on acarbose had lost 0.46 ± 0.28 kg, which differed significantly from the 0.33 ± 0.25 kg weight gain on placebo ($P = 0.027$). The difference in weight change between acarbose and placebo did not differ significantly in the different treatment strata. Being in the study had significant effects on diet, including a reduction in energy intake from 1760–1700 Kcal/d ($P < 0.05$), a reduction in simple sugars intake from 18.5–17.4% of energy ($P < 0.001$), and reductions in the number of different foods consumed (33–30, $P < 0.001$) and the number of meals eaten per day (4.7–4.3, $P < 0.001$). However, compared to placebo treatment, acarbose had no effect on energy intake, nutrient intakes, or dietary patterns.
CONCLUSIONS: In subjects with NIDDM on weight-maintaining diets, long-term acarbose therapy results in a small weight loss, but has no effect on energy or nutrient intakes. The weight loss induced by acarbose may be due partly to reduced doses of concomitant oral agents and insulin and partly to energy loss due to increased colonic fermentation.

Keywords: acarbose; humans; diabetes; colonic fermentation; body weight

Introduction

Acarbose is the first of a new class of drugs, the α-glucosidase inhibitors, now available in many countries for the treatment of diabetes mellitus. α-glucosidases are enzymes present on the brush border of the small intestine which hydrolyze di- and oligosaccharides, derived from the diet and from the luminal digestion of starch by pancreatic amylase, into their component monosaccharides.[1] Since only monosaccharides can be transported across the cell membranes of intestinal cells, inhibition of α-glucosidases reduces carbohydrate absorption and reduces postprandial glucose responses. Hence, acarbose improves blood glucose control by reducing the rise of blood glucose after eating.[2,3]

A potential advantage of acarbose is that, unlike sulfonylureas and insulin,[4] long-term use has been reported to result in weight loss.[3] The reason for this is not clear. At certain doses, acarbose may reduce food intake in some strains of animals.[5,6] However, only one study assessed the effect of acarbose on food intake in humans,[7] and showed that acarbose treatment resulted in a small reduction in fat intake and an increase in carbohydrate, with no significant difference in energy intake. This study involved only 27 subjects treated with acarbose or placebo for eight weeks each, with food intake being assessed with a single 2–5 d diet record at the end of each period. Thus, it is not possible to determine whether the changes in fat and carbohydrate intake induced by

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acarbose are temporary. In addition, energy intake is very variable from day-to-day within individuals,[8] and this study probably only had enough power to detect a change in energy intake of >201 Kcal/d, which represented >12% of mean energy intake. In view of the results of animal studies, it would be of interest to know if acarbose induced more subtle changes in energy intake in humans. Therefore, our purpose was to determine the effect of long-term acarbose treatment on the nutrient intake and dietary patterns of a large number of subjects with non-insulin-dependent diabetes.

Methods

The results reported here were obtained as part of a multicenter trial of acarbose in the treatment of non-insulin dependent diabetes (NIDDM). The primary purpose of the study was to determine the effect of acarbose on blood glucose control and these results were reported elsewhere.[2] One of the secondary purposes of the study was to determine the effect of acarbose on nutrient intake. Subjects with NIDDM of at least six months duration with normal renal and liver function treated by diet alone, diet plus metformin, diet plus sulfonylurea or diet plus insulin were recruited from seven participating centers (Vancouver, Calgary, Edmonton, London, Toronto, Montreal and Halifax). They had to have a glycosylated hemoglobin (HbA1c) >7.0%, except for subjects on diet alone where the HbA1c had to be >6.5%. Subjects on thiazide diuretics or β-blockers for hypertension, lipid-lowering drugs, those with gastrointestinal disease, and those taking drugs likely to alter gastrointestinal motility or absorption were excluded.

Subjects were seen by a dietitian and placed on a weight-maintaining diet for a six week pre-treatment period, during which time, two 3 d diet records were obtained. After this, subjects were randomly assigned to receive either acarbose or placebo for one year. The initial dose was 50 mg with the first bite of each meal three times daily. On subsequent visits the dose was titrated upwards to 100 mg and then 200 mg three times daily. The dose was increased if postprandial plasma glucose was greater than 10 mmol/L, and adjusted according to the patient's tolerance. Subjects were seen at three month intervals when they provided a fasting blood sample, were weighed and handed in a 3 d diet history.

Subjects were instructed about how to record a 3 d diet history by the dietitian at each study center. All food and drink consumed on 1 weekend day and 2 weekdays were recorded into booklets provided to the subjects. The diet records were reviewed for accuracy with the subjects by the dietitians who then coded the diets using a standard computer program provided to each center. The database was derived from the Canadian Condensed nutrient file[9] which contains data for 18 nutrients for about 650 foods. The database was supplemented with data on simple sugars, dietary fiber and glycemic index. Information about simple sugars came from manufacturer's information or other food composition tables.[10] Dietary fiber values were derived from food tables[10] or direct analysis using standard methods.[11] The values in the database for carbohydrate were adjusted to reflect available carbohydrate. Glycemic index values were derived from literature values or estimated as previously described.[12] The coded diets were sent on floppy diskette to Toronto, where they were compiled.

Values for the intakes of fat, protein and carbohydrate are expressed in grams and % of energy. Cholesterol, vitamin and mineral intakes were expressed as total amounts and as amounts per 1000 Kcal. Diet glycemic index was the weighted average of the glycemic index of each carbohydrate food consumed, with the weighting based on the proportion of total carbohydrate contributed by the food, as previously described.[13] To determine the pattern of food intake several calculations were performed. The total number of different foods listed in each 3 d food record was recorded. The number of meals per day was estimated as follows: in the booklets provided for recording food intake, there were six separate time intervals for each day, breakfast, midmorning, lunch, afternoon, dinner and evening. If any food or drink was recorded in one of these spaces, it was counted as a meal; thus, the maximum number of possible meals per day was six. Since acarbose was consumed only with main meals, we also calculated the percent of total daily energy, protein, fat, carbohydrate and fiber which was consumed in the three main meals of the day.

Three hundred and fifty-four patients were randomized to receive either acarbose or placebo; 77 were treated with diet alone, 83 with diet plus metformin, 103 with diet plus sulfonylurea and 91 with diet plus insulin. The clinical characteristics of the subjects at randomization are shown in Table 1. For the purposes of this paper, the data for the subjects in the four concomitant treatment strata were pooled for added statistical power. Since the purpose of this paper was to determine the long-term effect of acarbose on body weight and diet, subjects were excluded from analysis if they did not complete at least nine months of the study, and if they did not provide at least three of the six diet records called for in the protocol. Of the 354 subjects randomized, 279 (79%; 130 acarbose, 149 placebo) took the study medication for at least nine months, and all of these were included in the statistical analysis of body weight. For the 11 subject who dropped out between 9 and 12 months (6 on placebo and 5 on acarbose), body weight at nine months was taken to be their weight at 12 months. Subjects included in the statistical analysis of diet included the 263 individuals for whom at least one 3 d diet record during the baseline period, and at least two 3 d

diet records during the treatment period were available. Of the 1578 diet records possible according to the protocol (each of the 263 subjects was expected to hand in six 3 d food records) 1449 (92%) were actually obtained. Fifty-five (55) of the 526 baseline diet records (11%), and 74 of the 1052 post-randomization diet records (7%) were missing. The baseline diet records were pooled to provide a single average value for each subject. The single baseline and 4 post-randomization diet records were arranged in a 5×263 matrix with 74 missing values. The missing values were imputed using Rubin's non-iterative method.[14]

Change in dosage of oral agents or insulin was considered to be a possible cause of weight change. Thus, change in insulin dose was calculated as the change in mean total daily insulin dose from baseline. Subjects on oral agents whose blood glucose control deteriorated were sometimes switched to a different oral agent or insulin; thus, the dose of concomitant oral agent was considered a discrete variable: namely either a reduction, an increase or no change. A switch to another drug due to poor glucose control was considered as a dose increase. Body weight, insulin dose and dietary variables were subjected to statistical analysis by repeated measures analysis of variance with a nested design, examining for the effects of treatment, time and the interaction between treatment and time.[15] To see if the effect of acarbose treatment on mean body weight change differed in the different concomitant treatment strata, a second two-way analysis of variance was performed examining for study treatment, concomitant treatment stratum and their interaction. The numbers of subjects on acarbose and placebo with an increase, decrease and no change in dose of concomitant oral agents was compared by chi-squared test. The results are given as means ± s.e.m. Differences were considered significant if $P < 0.05$.

Results

As reported elsewhere,[2] acarbose therapy significantly reduced postprandial plasma glucose responses to a standard test meal and significantly improved overall glycemic control as assessed by glycosylated hemoglobin (HbA1c). The maximum fall in HbA1c was attained by six months of therapy and remained fairly constant thereafter. The results for HbA1c summarized on Table 2 are slightly different than in the original report because two baseline values were used and fewer subjects are included in the analysis. However, the focus of this paper is the effect of acarbose on body weight and food intake.

Being in the study resulted in a change in body weight in both the acarbose and placebo groups. In the placebo group, body weight fell initially, but returned to exceed the baseline value by 12 months, whereas in the acarbose group, the weight loss was maintained over the entire 12 month period (Figure 1). For the 149 subjects treated with placebo, mean body weight at baseline, 3, 6, 9 and 12 months was 81.1 ± 1.3, 80.7 ± 1.3, 80.9 ± 1.3, 81.2 ± 1.3 and 81.4 ± 1.3 kg, respectively. In the 130 subjects treated with acarbose, mean body weight at baseline, 3, 6, 9 and 12 months was 84.5 ± 1.5, 83.8 ± 1.5, 83.5 ± 1.5, 83.8 ± 1.5 and 84.0 ± 1.5 kg, respectively. Analysis of variance showed that the mean weight change from baseline of subjects taking acarbose was greater than that of the

Table 1 Characteristics of study subjects at randomization

	Diet alone (n = 77)	*Metformin (n = 83)*	*Sulfonylurea (n = 103)*	*Insulin (n = 91)*
Age (y)	57.2 ± 1.1	57.4 ± 1.1	58.4 ± 0.9	56.6 ± 0.9
Sex (M : F)	48 : 29	53 : 30	58 : 45	52 : 39
BMI (kg/m^2)	28.8 ± 0.5	29.4 ± 0.6	27.8 ± 0.4	30.2 ± 0.5
Diabetes duration (y)	5.2 ± 0.6	8.8 ± 0.6	9.4 ± 0.7	12.9 ± 0.8

Values are means ± s.e.m.

Table 2 Effects of acarbose and placebo therapy on glycemic control

		Diet alone	*Metformin*	*Sulfonylurea*	*Insulin*
Number of subjects:	Acarbose	25	30	39	28
	Placebo	29	35	39	38
Baseline HbA1c (%):	Acarbose	6.97 ± 0.32	8.19 ± 0.31	8.15 ± 0.23	7.69 ± 0.17
	Placebo	6.72 ± 0.20	7.76 ± 0.25	8.02 ± 0.22	7.84 ± 0.19
Treatment Hb1Ac (%):	Acarbose	6.11 ± 0.21	6.83 ± 0.83	6.92 ± 0.20	6.92 ± 0.17
	Placebo	6.75 ± 0.22	7.37 ± 0.26	7.77 ± 0.19	7.49 ± 0.21
HbA1c change:	Acarbose	−0.86 ± 0.29	−1.35 ± 0.24	−1.23 ± 0.23	−0.78 ± 0.16
	Placebo	0.02 ± 0.18	−0.39 ± 0.25	−0.25 ± 0.18	−0.35 ± 0.19
		(*P* = 0.01)	(*P* = 0.009)	(*P* = 0.002)	(*P* = 0.11)

Values are means ± s.e.m.
Baseline HbA1c is the mean of two baseline samples; Treatment HbA1c is the mean of three values (at 6, 9 and 12 months of therapy); *P*-values represent the significance of the difference between the changes on acarbose and placebo.

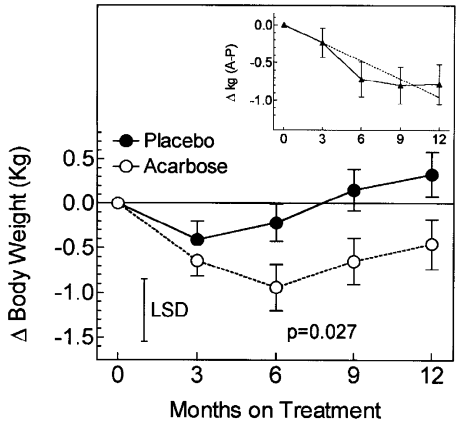

Figure 1 Change in weight from baseline in subjects randomized to receive treatment with placebo or acarbose. Values are means ± s.e.m. LSD: length of bar shows the least significant difference between individual means. Inset: difference between mean weight changes in acarbose and placebo groups. Error bars represent the pooled SEM of the data for the acarbose and placebo groups, multiplied by $\sqrt{2}$. The dotted line represents the regression line for the five points.

placebo group ($P < 0.027$; Figure 1). In addition, there was a significant interaction between the effects of time and treatment ($P = 0.018$) indicating that the pattern of weight change with time in subjects with acarbose was different from that in subjects on placebo.

The difference between the change in weight on placebo and acarbose indicates the effect of acarbose on weight independent of the study effect (Figure 1, inset). After six months of therapy the weight loss on acarbose was 0.72 kg, corresponding to a rate of weight loss of 0.12 kg/mon. Between 6 and 12 months, no further weight loss occurred. However, it is not possible to be confident as to whether the rate of weight loss on acarbose is constant with time or not. Assuming a constant rate of weight loss over 12 months, the rate of weight loss, determined from the slope of the regression line of weight loss on month, is 0.08 kg/mon (Figure 1, inset). Since a loss of 1 kg of body weight requires a negative energy balance of 6500 Kcal,[16] the rate of weight loss on acarbose over the first six months, 0.12 kg/mon, is accounted for by an energy deficit of 26 Kcal/d. A linear rate of weight loss of 0.08 kg/mon over 12 months, is accounted for by an energy deficit of 17 Kcal/d.

Mean weight changes from baseline in the different treatment strata are shown in Figure 2. There was a significant effect of concomitant treatment stratum on weight change ($P = 0.013$) with subjects on metformin losing more weight than the other groups. However, in each concomitant treatment stratum, subjects on acarbose lost more weight than those on placebo. Weight loss on acarbose was greatest for the insulin treatment stratum. However, analysis of variance showed no significant interaction between the effect of acarbose and concomitant treatment ($P = 0.30$) indicating that the magnitude of weight loss on acarbose did not differ significantly in the different treatment strata.

Acarbose therapy was associated with significant reductions in the dosage of concomitant therapy. Twice as many subjects on placebo had their dose of sulfonylurea or metformin increased compared to subjects on acarbose, while more on acarbose had their dose decreased (Figure 3). The difference was significant for sulfonylurea alone ($P = 0.011$), metformin alone ($P = 0.044$) or the two treatment groups combined ($P = 0.0007$). Subjects on placebo plus insulin had no change in insulin dose (-0.6 ± 1.3 U/d), whereas those on acarbose had their dose of insulin reduced by 7.7 ± 2.5 U/d ($P = 0.0037$).

Being in the study had significant effects on nutrient intakes and dietary patterns, but, except for a small, temporary effect on starch intake, the changes in subjects receiving acarbose were not significantly different from those in subjects receiving placebo. This indicates that acarbose treatment, *per se*, had virtually no effect on diet. There was a significant effect of time on energy intake; namely energy intake fell at three months in both acarbose and placebo groups, and remained below baseline until the end of the study (Figure 4). There was no effect of treatment on energy intake and no significant time × treatment interaction (Table 3). There were trends for fat,

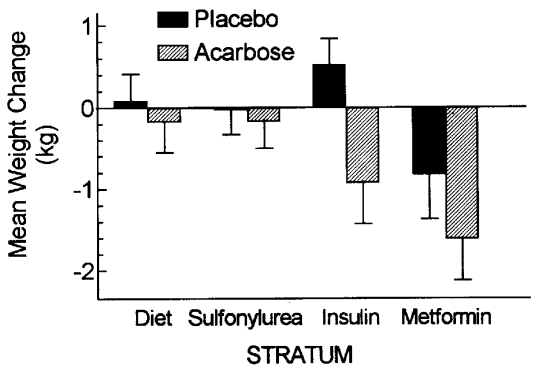

Figure 2 Weight change from baseline on acarbose or placebo treatment in the four different treatment strata. Values are means ± s.e.m.

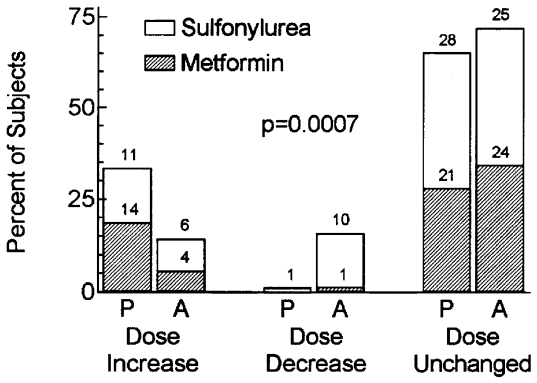

Figure 3 Percent of subjects in the sulfonylurea and metformin treatment strata randomized to placebo (P) or acarbose (A) whose dose of concomitant drug was increased, decreased or remained constant. Values at the top of each bar represent the number of subjects represented. For both groups combined, $\chi^2 = 14.6$ ($P = 0.0007$).

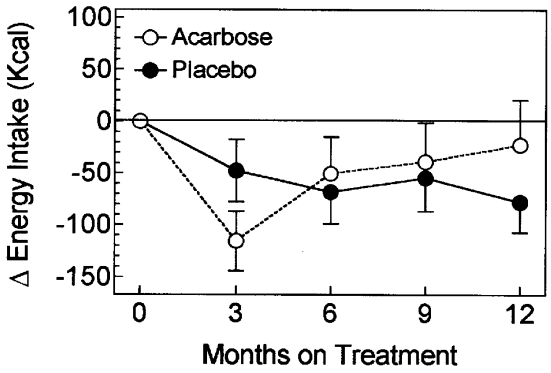

Figure 4 Change in energy intake from baseline in subjects randomized to receive treatment with placebo or acarbose. Values are means ± s.e.m.

protein and carbohydrate intakes, in grams, to parallel energy intake; thus, when expressed as a % of energy, there were no significant changes in fat, protein or total carbohydrate intakes throughout the study (Table 3). The only energy-containing nutrient whose intake, expressed as a % of energy, fell significantly during trial was simple sugars (Table 3), but the change was not different in the acarbose and placebo groups. The intake of starch, expressed as a % of energy increased significantly during the study, and there was a significant interaction between the effects of time and treatment ($P = 0.05$, Table 3). The interaction was due to the fact that at three months, subjects on acarbose had increased starch intake to a greater extent than those on placebo. However, at 6, 9 and 12 months the difference in starch intake from baseline was similar for the acarbose and placebo groups (Table 3).

Acarbose had no significant effect on dietary patterns relative to placebo, namely the changes which occurred during the study were the same in the subjects taking acarbose and placebo. The number of different foods and the number of meals eaten per day fell to reach a minimum at six months, which values were maintained for the duration of the trial (Table 4). Since the number of meals per day was reduced, the proportion of total energy consumed during the three main meals of the day increased from 84.5 to ~88% (Table 4), and a similar effect was seen for fat, protein, carbohydrates and fiber (not shown). Again, these effects were seen equally in subjects on acarbose and placebo.

Thiamin, riboflavin, niacin and folate intakes did not vary significantly during the study, and there was no effect of acarbose relative to placebo (not shown). Mean vitamin C and potassium intakes, respectively, fell from ~70 and 1890 mg/1000 Kcal at baseline to 63 and 1840 mg/1000 Kcal between 6 and 12 months ($P = 0.025$ and 0.0015, respectively). On the other hand, mean vitamin A intake increased from ~840 retinol equivalents (RE)/1000 Kcal to 940 RE/1000 Kcal at 6–12 months ($P = 0.038$). The changes in vitamin C, potassium and vitamin A intakes in subjects on acarbose were the same as those in subjects on placebo.

Table 3 Energy, macronutrient and dietary fiber intakes and diet glycemic index at baseline and at 3, 6, 9 and 12 months post randomization to acarbose or placebo treatment

	Acarbose					*Placebo*					*Time*	*Drug*	*T × D*
	Base	*3 month*	*6 month*	*9 month*	*12 month*	*Base*	*3 month*	*6 month*	*9 month*	*12 month*	$F_{(4,970)}$	$F_{(1,261)}$	$F_{(4,970)}$
Energy (Kcal)	1753 ± 42	1641 ± 41	1703 ± 42	1714 ± 48	1731 ± 53	1761 ± 39	1714 ± 39	1693 ± 39	1707 ± 40	1683 ± 33	2.76*	0.00	1.58
Protein (% energy)	20.1 ± 0.3	20.5 ± 0.3	20.5 ± 0.3	20.3 ± 0.3	20.7 ± 0.3	19.6 ± 0.3	20.0 ± 0.3	19.6 ± 0.3	19.9 ± 0.3	20.1 ± 0.3	2.34	3.79	0.35
Total fat (% energy)	32.8 ± 0.6	31.4 ± 0.6	32.3 ± 0.6	33.0 ± 0.6	32.7 ± 0.6	32.5 ± 0.6	32.9 ± 0.6	32.7 ± 0.6	32.7 ± 0.6	32.6 ± 0.6	0.72	0.11	1.91
Carbohydrate (% energy)	46.4 ± 0.6	47.5 ± 0.6	46.5 ± 0.6	46.1 ± 0.6	45.9 ± 0.6	47.1 ± 0.6	46.4 ± 0.6	47.2 ± 0.6	46.7 ± 0.6	46.6 ± 0.6	1.01	0.24	1.97
Sugars (% energy)	18.6 ± 0.5	18.0 ± 0.5	17.8 ± 0.5	17.2 ± 0.5	17.7 ± 0.5	18.4 ± 0.5	17.7 ± 0.5	17.2 ± 0.5	17.3 ± 0.5	17.3 ± 0.5	5.21**	0.23	0.33
Starch (% energy)	27.8 ± 0.5	29.4 ± 0.5	28.8 ± 0.5	28.9 ± 0.6	28.2 ± 0.5	28.7 ± 0.4	28.8 ± 0.4	30.0 ± 0.4	29.5 ± 0.5	29.3 ± 0.5	3.41*	1.37	2.38*
Fiber (g)	17.1 ± 0.5	15.9 ± 0.5	15.9 ± 0.6	15.8 ± 0.6	16.0 ± 0.7	17.6 ± 0.6	17.1 ± 0.5	17.5 ± 0.6	17.0 ± 0.6	16.6 ± 0.5	2.44*	2.11	0.71
Glycemic index	85.6 ± 0.4	85.9 ± 0.5	85.2 ± 0.4	86.3 ± 0.5	84.9 ± 0.5	85.4 ± 0.4	85.2 ± 0.5	85.7 ± 0.4	84.9 ± 0.5	85.0 ± 0.5	1.05	0.35	2.32

Values are means ± s.e.m. Carbohydrate represents total carbohydrate minus dietary fiber.
$n = 122$ for acarbose and $n = 141$ for placebo. Right three columns give the F values from analysis of variance for the effect of time, treatment (drug) and the interaction between time and

Table 4 Dietary patterns at baseline and at 3, 6, 9 and 12 months post randomization into acarbose or placebo treatment

	Acarbose					*Placebo*					*Time*	*Drug*	*T* × *D*
	Base	*3 month*	*6 month*	*9 month*	*12 month*	*Base*	*3 month*	*6 month*	*9 month*	*12 month*	$F_{(4,970)}$	$F_{(1,261)}$	$F_{(4,970)}$
No. foods	32.8 ± 0.7	31.6 ± 0.6	30.4 ± 0.6	30.3 ± 0.7	30.8 ± 0.7	32.6 ± 0.6	31.0 ± 0.6	30.0 ± 0.6	30.0 ± 0.6	29.6 ± 0.6	17.72*	0.51	0.56
No. meals	4.7 ± 0.1	4.6 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	4.5 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	16.52*	0.02	0.97
% Kcal 3 m	84.9 ± 0.8	87.2 ± 0.8	88.0 ± 0.8	88.1 ± 0.8	87.9 ± 0.8	84.5 ± 0.7	86.1 ± 0.8	86.9 ± 0.9	87.9 ± 0.8	88.0 ± 0.8	15.19*	0.25	0.67

Values are means ± s.e.m.
No. foods = number of different foods listed on diet record; No. meals = number of meals per day; % Kcal 3 m = % of total energy contained in the three main daily meals.
$n = 122$ for acarbose and $n = 141$ for placebo. Right three columns give the F values from analysis of variance for the effect of time, treatment (drug) and the interaction between time and

Discussion

The results of this study are consistent with those of previous studies in showing that acarbose therapy results in a small amount of weight loss in subjects with NIDDM. The weight loss did not appear to be due to a detectable effect of acarbose on energy or nutrient intakes, nor dietary patterns in subjects with NIDDM. In addition, the results are of interest because they illustrate how diabetic subjects interpret the dietary advice given to them by registered dietitians in major diabetes treatment centres in Canada.

The present conclusion that acarbose therapy resulted in a small but statistically significant weight loss appears to differ from the primary report of the results of this study,[2] where it was stated that body weight was 'stable' during the 12 month study period on acarbose therapy (84.5 ± 1.2 kg at baseline to 84.2 ± 1.6 kg after 12 months). The reason for this is that body weight was not a primary or secondary endpoint of the study, and, thus, in our original paper, the data for body weight were not subjected to statistical analysis. The mean body weights reported here differ slightly from the original report because in the current analysis we excluded subjects who did not finish the study. The effect of acarbose on body weight becomes apparent when, as in this paper, the changes in weight from baseline are evaluated in the same way as the other efficacy variables.[2]

The results of this study are not consistent with animal studies which suggest that, in some strains of rat, certain doses of acarbose reduce food intake.[5,6] The reason why acarbose should cause a reduction in food intake is unclear. By inhibiting the absorption of carbohydrates, acarbose would be expected to increase the bulk of intestinal contents and reduce energy absorption. These effects would be expected to increase food intake to maintain energy balance; for example feeding cellulose to rats leads to increased food intake.[6] In some animal studies, acarbose has been shown to stimulate food intake.[17,18] In the present study, we saw no evidence of any effect at all of acarbose, at doses of up to 600 mg/d, on energy intake of subjects with NIDDM.

Tuomilehto *et al*[7] concluded from an 8 week cross-over study in 27 subjects with NIDDM, that acarbose treatment slightly decreased fat intake. We also saw a small reduction in fat intake and an increase in starch intake at three months in the acarbose group which did not occur on placebo (Table 3). However, the fall in fat intake was not significant, and the changes in fat and starch intakes had disappeared by 6 months. In Tuomilehto's study fat intake fell from 38.2% of energy at baseline to 32.1% on acarbose ($P < 0.05$). However, placebo treatment was also associated with a reduction in fat intake to 35.0%, but it is not indicated whether this value is significantly different from fat intake on acarbose or at baseline. Thus, the change in fat intake on acarbose noted by Tuomilehto *et al*[7] could be due to

an effect of being in the study, rather than a true effect of acarbose. This would be consistent with the present results where there were a number of significant changes in diet during the study, but these were the same in the acarbose and placebo groups.

Acarbose therapy was associated with a significant weight loss compared to placebo, even though there was no difference in energy intake. The weight loss was seen in the face of improved glucose control which might be expected to increase body weight because of reduced excretion of glucose, and hence energy, in the urine. Increased physical activity could contribute to weight loss, but there is no reason why acarbose would increase physical activity, and it is unlikely that the randomly selected acarbose and placebo groups would have different exercise patterns by chance since each group consisted of >100 subjects. The use of acarbose in combination with other hypoglycemic agents, allowed a reduction in the dose of the concomitant medication. Both sulfonylurea and insulin therapy cause weight gain.[4] Thus, the significant reductions in the dose of insulin and sulfonylurea associated with acarbose therapy may have contributed to the weight loss, particularly in the insulin treatment stratum. However, metformin does not cause weigh gain.[4] Indeed, in the present study, subjects on metformin alone lost weight. Thus, a reduction in metformin dose cannot explain the weight loss in subjects on metformin plus acarbose. In addition, weight loss was also seen in subjects treated with acarbose alone.

Weight loss on acarbose therapy could also be due to a reduction in feed efficiency. Acarbose causes a dose-dependent malabsorption of carbohydrate.[19] Malabsorbed carbohydrate is fermented in the colon with the production of gases and short chain fatty acids.[20] The gases are the source of the major side-effect of acarbose, flatulence. The short chain fatty acids, acetate, propionate and butyrate, are absorbed from the colon,[21] providing a mechanism whereby energy from malabsorbed carbohydrate can be salvaged. Digestible carbohydrates normally provide about 4 Kcal/g. However during colonic fermentation, energy from carbohydrate is not completely retrieved by the host because some is lost to colonic bacteria, heat, gases and faeces. It has been estimated that the energy obtained from carbohydrates which are completely fermented in the colon, about 2 Kcal/g, is only about 50% of that obtained from carbohydrates absorbed from the small intestine.[22] Thus, the daily energy deficit on acarbose treatment necessary to account for the observed weight loss, 26 Kcal/d over six months, or 17 Kcal/d over 12 months, can be provided by the malabsorption of 13 or 8.5 g carbohydrate per day, respectively, or about 4–6.5% of total carbohydrate intake. It seems very reasonable to ascribe this amount of carbohydrate malabsorption to acarbose, since even on a normal diet, it has been estimated that 5–10% of dietary carbohydrate is normally malabsorbed, and enters the colon.[23–26]

Recent studies illustrate the fact that individuals with diabetes find it difficult to make long-term changes in their diets.[27] It is likely that subjects with diabetes are no different from other people in this respect. The subjects in this study probably received dietary advice more frequently than most people with diabetes. During the eight week run-in period before the study, subjects recorded their diets for three days and received at least two sessions of nutrition counseling according to Canadian Diabetes Association recommendations.[28] After randomization, subjects recorded their diets and received nutrition counseling at least once every three months, and often more frequently, because they visited the diabetes centres once a month to pick up their study medication and to have blood glucose measured for dose adjustments. The frequent dietary counseling was associated with a number of changes in diet which are of interest. The number of meals consumed each day fell significantly during the study, resulting in a larger proportion of total energy being consumed in the three main meals of the day (Table 4).

The major sustained change in nutrient intake by subjects in this study was a reduction in simple sugars intake. There was no change in fat intake. Restriction of both fat and simple sugars are goals of diet therapy for persons with NIDDM. Reduced fat intake is advised to facilitate weight reduction and lower blood lipids and hence the risk for ischaemic heart disease.[29,30] Avoidance of sugar is part of the traditional diabetes diet[31] which persons with diabetes expect. Patients with diabetes are advised to avoid foods rich in simple sugars, particularly drinks, because of their high carbohydrate and energy content per serving. For example a cup of apple juice, has nearly twice as much carbohydrate, $\sim$32 g, as a medium (150 g) apple, $\sim$17 g.[9] Reduced use of fruit juice and fruit drinks may, in part, explain the reduction in the number of different foods consumed and the reduction in simple sugars, vitamin C and potassium intakes in both the acarbose and placebo groups. However, the rationale for avoiding simple sugars is not clear. Low simple sugars intake is associated with a high body mass index.[32] Many foods rich in simple sugars produce lower blood glucose responses than foods high in starch.[31,33] There is an inverse correlation between sugars intake and fat intake in the general population[34] and it may be difficult to reduce both sugars and fat intakes.

Conclusions

It is concluded that, in subjects with non-insulin-dependent diabetes following weight maintaining diets, long-term acarbose therapy results in a small weight loss, but has no effect on food or nutrient intake. The weight loss induced by acarbose may be

due partly to reduced doses of concomitant oral agents and insulin and partly to energy loss due to increased colonic fermentation.

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