

Role of Orlistat in the Treatment of Obese Patients With Type 2 Diabetes

A 1-year randomized double-blind study

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OBJECTIVE — Obesity is an important risk factor for type 2 diabetes. Weight loss in patients with type 2 diabetes is associated with improved glycemic control and reduced cardiovascular disease risk factors, but weight loss is notably difficult to achieve and sustain with caloric restriction and exercise. The purpose of this study was to assess the impact of treatment with orlistat, a pancreatic lipase inhibitor, on weight loss, glycemic control, and serum lipid levels in obese patients with type 2 diabetes on sulfonylurea medications.

RESEARCH DESIGN AND METHODS — In a multicenter 57-week randomized double-blind placebo-controlled study, 120 mg orlistat or placebo was administered orally three times a day with a mildly hypocaloric diet to 391 obese men and women with type 2 diabetes who were aged >18 years, had a BMI of 28–40 kg/m², and were clinically stable on oral sulfonylureas. Changes in body weight, glycemic control, lipid levels, and drug tolerability were measured.

RESULTS — After 1 year of treatment, the orlistat group lost $6.2 \pm 0.45\%$ (mean \pm SEM) of initial body weight vs. $4.3 \pm 0.49\%$ in the placebo group ($P < 0.001$). Twice as many patients receiving orlistat (49 vs. 23%) lost $\geq 5\%$ of initial body weight ($P < 0.001$). Orlistat treatment plus diet compared with placebo plus diet was associated with significant improvement in glycemic control, as reflected in decreases in HbA_{1c} ($P < 0.001$) and fasting plasma glucose ($P < 0.001$) and in dosage reductions of oral sulfonylurea medication ($P < 0.01$). Orlistat therapy also resulted in significantly greater improvements than placebo in several lipid parameters, namely, greater reductions in total cholesterol, ($P < 0.001$), LDL cholesterol ($P < 0.001$), triglycerides ($P < 0.05$), apolipoprotein B ($P < 0.001$), and the LDL-to-HDL cholesterol ratio ($P < 0.001$). Mild to moderate and transient gastrointestinal events were reported with orlistat therapy, although their association with study withdrawal was low. Fat-soluble vitamin levels generally remained within the reference range, and vitamin supplementation was required in only a few patients.

CONCLUSIONS — Orlistat is an effective treatment modality in obese patients with type 2 diabetes with respect to clinically meaningful weight loss and maintenance of weight loss, improved glycemic control, and improved lipid profile.

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Abbreviations: ANCOVA, analysis of covariance; GI, gastrointestinal; LSM, least-squares mean; PT, prothrombin time.

Obesity is a significant cause of type 2 diabetes (1,2). It is also the most important modifiable factor for this disease in both men and women (3). The incidence of type 2 diabetes rises with increasing severity of obesity, and also with weight gain per se, independent of baseline BMI (4). In addition, the incidence of type 2 diabetes is closely associated with a particular pattern of regional body fat distribution (5,6), specifically, with excess adipose tissue centrally localized in the abdominal (particularly visceral) region (7). Individuals with this predominant pattern of fat accumulation are more insulin resistant than those with excess gluteofemoral adipose tissue (8,9).

Modest weight loss (5–10% of initial body weight) improves glycemic control in patients with type 2 diabetes (10). In addition, modest weight loss may reduce or even eliminate the need for hypoglycemic agents and may lessen the severity of cardiovascular disease risk factors, which are typically altered in patients with type 2 diabetes (11). Obese individuals experience difficulty in achieving clinically significant weight loss by dietary restriction alone (12), and this problem is compounded in obese diabetic patients because sulfonylureas and insulin both promote weight gain (13).

A number of pharmacologic agents have been used in obese patients in combination with dietary interventions to produce weight loss, but these generally short-term approaches have proven to be largely unsuccessful (14,15). Furthermore, most of the drugs used in these trials act on the central nervous system to suppress appetite, and owing to the risk of serious complications (16), their use has been withdrawn or is strictly regulated.

Orlistat is the first of a new class of antiobesity agents, the lipase inhibitors, developed for the long-term management of obesity and its associated comorbidities. A dose-dependent reduction in dietary fat absorption is produced by orlistat, with a maximum 30% inhibition of fat absorption with a dosage of 120 mg t.i.d. (17). By selectively inhibiting the absorption of dietary fat (18), orlistat is directed toward

one of the putative causes of obesity, namely, excess dietary fat intake (19). Previous short-term studies have shown that orlistat plus diet is more effective in reducing weight compared with diet alone (20,21). The aim of the present multicenter study was to investigate the long-term weight loss efficacy of orlistat, 120 mg t.i.d., in obese patients with type 2 diabetes maintained on oral sulfonylureas and to determine whether this treatment improves glycemic control and lipid status more than dietary treatment alone.

RESEARCH DESIGN AND METHODS

Study design

This multicenter double-blind randomized placebo-controlled trial was conducted in 12 centers in the U.S. During a 5-week single-blind placebo lead-in period, patients who had been receiving oral sulfonylurea medications for the previous 6 months were prescribed a nutritionally balanced mildly hypocaloric weight-loss diet (~30% of calories as fat, 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day of cholesterol).

The criteria for randomization and entry into the double-blind treatment were as follows: 1) completion of the placebo and diet lead-in period with a drug compliance of at least 70% based on counting placebo capsules, 2) HbA_{1c} of 6.5–10% at screening, 3) fasting plasma glucose level of 5.6–12.2 mmol/l at the end of the 4th week of the lead-in period, and 4) blood levels of fat-soluble vitamin above the lower limit of the normal reference range. During the placebo lead-in period, patients received an oral hypoglycemic agent (either glypizide or glyburide) at doses determined by their physician. During the 2 weeks before randomization, patients were maintained on a constant dose of oral hypoglycemic agent for the remainder of the lead-in period, to be changed only by protocol after randomization (see below). Randomization was stratified according to weight loss and glucose control during the placebo lead-in period: 1) weight loss \leq 2.0 kg, glucose 5.6–8.9 mmol/l; 2) weight loss \leq 2.0 kg, glucose 9.0–12.2 mmol/l; 3) weight loss $>$ 2.0 kg, glucose 5.6–8.9 mmol/l; and 4) weight loss $>$ 2.0 kg, glucose 9.0–12.2 mmol/l. Patients were randomized after the lead-in period to receive 120 mg orlistat or matching placebo three times a day taken with meals in conjunction with a mildly

hypocaloric diet (–500 kcal/day deficit) for a total of 52 weeks.

The study protocol was approved by each of the centers' institutional review boards and was conducted in accordance with the revised Declaration of Helsinki. All patients provided written informed consent.

Patients

Obese patients of either sex (aged $>$ 18 years) were eligible for inclusion in the study if they had a BMI of 28–40 kg/m², were on an oral hypoglycemic drug therapy for at least 6 months before the study, and had a stable plasma glucose level on a second-generation sulfonylurea agent (glyburide or glypizide) as the only hypoglycemic agent at entry into the trial. Patients were excluded if they were pregnant, lactating or of child-bearing potential and not taking adequate contraceptive measures, or if they had any clinically relevant condition that might affect the outcome of the study (e.g., psychiatric disorders, substance abuse, cholecystitis, pancreatic disease, uncontrolled hypertension). Patients were also excluded if they had significant complications associated with diabetes, weight loss of $>$ 4 kg during the previous 3 months, a history of recurrent nephrolithiasis or symptomatic cholelithiasis, gastrointestinal (GI) surgery for weight reducing purposes, or a history of bulimia or laxative abuse or if they had taken any drug that might influence body weight or plasma lipids during the 8 weeks before the study initiation.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, measurements of vital signs, electrocardiogram, laboratory parameters, and body weight. All vitamin supplements were discontinued, and patients were instructed on the dietary requirements of the study and procedures for completing food intake records. Efficacy and safety assessments were conducted weekly during the placebo lead-in period and after randomization at weeks 1 and 2 and then every 2–4 weeks for the remainder of the treatment period.

Efficacy measures

The primary efficacy parameter was weight loss. Patients were weighed at least twice at each assessment until two consecutive measurements were within 0.5 kg of each other; the average of the two measurements was recorded. Secondary efficacy param-

eters were glycemic control, lipid levels, and waist circumference. Waist circumference was measured at baseline and at weeks 24 and 52 with the use of a spring-loaded calibrated measuring tape.

Assessments of glycemic control included changes from baseline (day 1 of randomization) in levels of HbA_{1c}, fasting plasma glucose, and insulin, as well as the need for upward or downward adjustment of the dose of oral sulfonylurea medication over time. Criteria for changing sulfonylurea dose were standardized across study centers and were based on symptoms or plasma glucose evidence of hypo- or hyperglycemia. Fasting glucose was measured at each visit; HbA_{1c} was measured at baseline and at weeks 12, 24, 36, and 52; insulin levels were assessed at baseline and weeks 24 and 52. Measurement of HbA_{1c} was performed at the University of Minnesota Laboratory.

Assessment of lipid status included changes from baseline (day 1 of randomization) to weeks 24 and 52 in the following serum lipid parameters: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, the LDL-to-HDL ratio, VLDL cholesterol, and apolipoprotein B.

Tolerability assessments

All adverse events were recorded. To ensure consistency across centers in identifying and labeling GI events, a detailed dictionary of standard terms was developed to describe defecation patterns. Standard laboratory procedures included hematology, clinical chemistry, urinalysis, and fecal-occult blood (Roche Biomedical Laboratories, Raritan, NJ). Measurements of vitamins A, D (measured as 25-OH vitamin D), E, and β -carotene were also carried out. These procedures were undertaken by a central laboratory (Medical Research Laboratories, KY). Prothrombin time (PT), used as an index of vitamin K status, was measured locally. Investigators were promptly notified if plasma levels of vitamins A, D, or E, PT, or beta-carotene were below the reference range but were blinded to the actual values. Additional diet counseling and a standardized commercially available vitamin supplement were provided when necessary if two consecutive vitamin measurements were below the reference range.

Statistical analysis

An intent-to-treat analysis was conducted in patients who had received at least one dose of study medication and had a subsequent

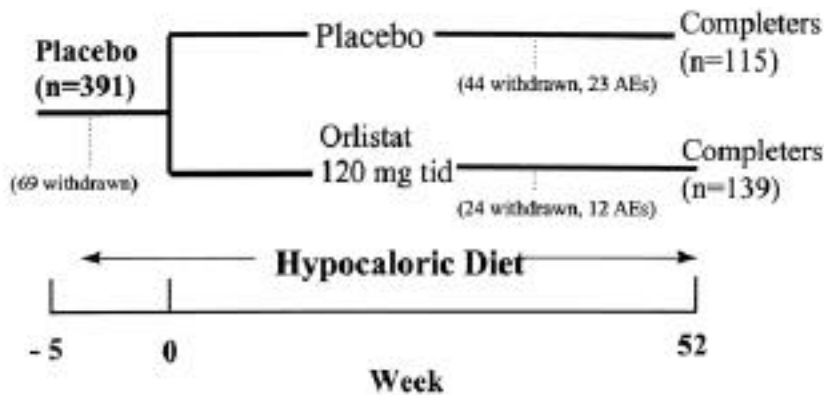


Figure 1—Study protocol. AEs, adverse events.

efficacy observation. Patients were included in the safety analysis if they had received one dose of trial medication after randomization and had a subsequent safety observation.

The null hypothesis that the expected mean weight change from baseline to the end of 1 year of double-blind treatment did not differ significantly between the placebo and orlistat treatments was tested using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models (22). Similar analyses were applied to the secondary efficacy parameters. The statistical significance of the independent effects of treatment and weight loss on the secondary efficacy parameters was determined by ANCOVA, using weight loss as the covariate. The placebo-adjusted 95% CI of orlistat treatment effect, based on the least-squares mean (LSM), was also determined.

RESULTS — A total of 391 patients were enrolled in the study. Of these, 322 completed the 5-week placebo lead-in and were randomized to double-blind treatment with orlistat ($n = 163$) or placebo ($n = 159$) (Fig. 1). There were 254 patients who completed the study (73% in the placebo group and 85% in the orlistat group). The reasons for premature withdrawal during the double-blind treatment period included adverse events, loss to follow-up, noncompliance ($n = 4$), administrative, protocol violations, and treatment failure. The characteristics of the patient population at study entry, shown in Table 1, were similar in the two treatment groups.

Body weight changes

Weight loss, expressed as the percentage reduction in body weight throughout the 1 year of treatment is shown in Fig. 2. During the 5-week placebo lead-in period, both groups lost an equivalent amount of weight

(mean \pm SEM, 2.24 ± 0.14 and 2.07 ± 0.15 kg in the placebo and orlistat groups, respectively). The difference in weight loss between the two treatments became apparent 4 weeks after randomization, with orlistat-treated patients losing weight at an appreciably faster rate than placebo-treated patients. At 57 weeks after study initiation, patients in the orlistat group had lost $6.2 \pm 0.5\%$ of their initial body weight vs. $4.3 \pm 0.5\%$ in the placebo group (intent-to-treat analysis). The LSM difference between treatment groups (2.4 kg) was statistically significant ($P < 0.001$). Nearly identical values were obtained from the population included in the completers analysis: 6.3 ± 0.4 vs. $4.2 \pm 0.5\%$ change from initial body weight in the orlistat and placebo groups, respectively. When expressed as kilograms of weight lost from initial body weight, the same pattern of results was obtained, namely, significantly greater weight loss in the orlistat compared with the placebo

group (6.19 ± 0.51 vs. 4.31 ± 0.57 kg, $P < 0.001$; intent-to-treat analysis).

Categorical analysis indicated that twice as many receiving orlistat lost $\geq 5\%$ of their initial body weight (48.8 vs. 22.6% , $P < 0.001$) (Fig. 3). Similarly, more patients in the orlistat group than in the placebo group lost $\geq 10\%$ of their initial body weight (17.9 vs. 8.8% , $P = 0.017$).

Glycemic control

During the placebo lead-in period, mean fasting plasma glucose levels decreased in both the orlistat and placebo groups (0.98 ± 0.13 and 1.16 ± 0.13 mmol/l, respectively). From randomization to the end of treatment, mean fasting plasma glucose decreased in the orlistat group by an additional 0.02 ± 0.14 mmol/l but increased by 0.54 ± 0.15 mmol/l in the placebo group ($P < 0.001$). In a subset of patients with a fasting plasma glucose ≥ 7.77 mmol/l at the start of double-blind treatment, there was a significantly greater decrease in fasting plasma glucose levels in the orlistat group than the placebo group after 52 weeks of treatment (-0.47 ± 0.19 vs. 0.36 ± 0.27 mmol/l increase for orlistat vs. placebo, respectively; $P < 0.001$). After 52 weeks of treatment, mean fasting insulin levels had also decreased by $5.2 \pm 4.4\%$ in orlistat-treated patients, compared with a $4.3 \pm 6.3\%$ increase in the placebo group. However, this difference was not statistically significant.

From the beginning of the lead-in period to the time of randomization, mean HbA_{1c} levels decreased to a similar extent in both treatment groups to $\sim 7.5\%$ at the time

Table 1—Characteristics of patient population at study entry

Parameter	Placebo	Orlistat (120 mg t.i.d.)
<i>n</i>	159	162
Sex (M/F)	85/74	79/83
Age (years)	54.7 ± 9.7	55.4 ± 8.8
Race		
White	140	141
Black	9	13
Hispanic	6	4
Other	4	4
Weight (kg)	99.7 ± 15.4	99.6 ± 14.5
Height (cm)	170.9 ± 9.5	169.6 ± 9.5
BMI (kg/m ²)	34.0 ± 3.4	34.5 ± 3.2
Fasting plasma glucose (mmol/l)	9.09 ± 1.87	8.85 ± 1.68
HbA _{1c} (%)	8.2 ± 1.07	8.05 ± 0.98

Data are means \pm SD.

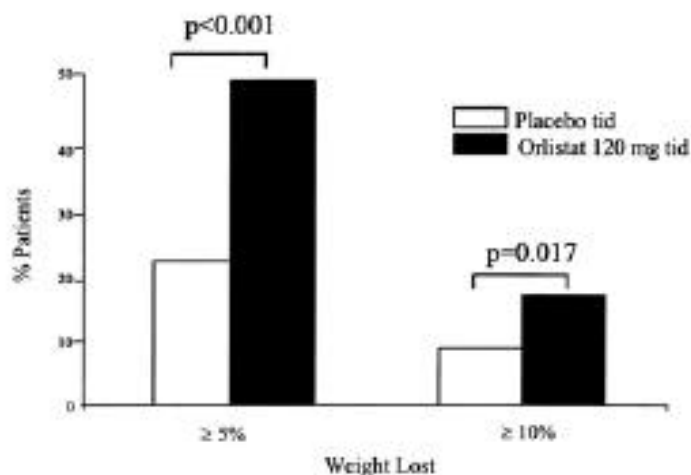


Figure 2—Mean percentage change (\pm SEM) from initial body weight.

of randomization. At 52 weeks after randomization, however, orlistat-treated patients had a further mean decrease in HbA_{1c} of $0.28 \pm 0.09\%$, compared with a mean increase of $0.18 \pm 0.11\%$ in the placebo group ($P < 0.001$). Moreover, in the subset of patients with HbA_{1c} levels $>8\%$ at the start of double-blind treatment, the orlistat group ($n = 41$) had a decrease of $0.53 \pm 0.18\%$, compared with a $0.05 \pm 0.29\%$ decrease in the placebo group ($n = 42$) ($P < 0.001$). In addition, the average dose of oral sulfonylurea medication decreased more in the orlistat group than in the placebo group (-23 vs. -9% , respectively; $P = 0.0019$). A total of 43.2% of orlistat-treated patients decreased the amount of oral sulfonylureas, compared with 28.9% of the placebo group, and 11.7% of orlistat-treated patients discontinued sulfonylurea medication. Also, 15 placebo-treated patients (8.8%) withdrew from the trial prematurely because of elevated plasma glucose levels on three or more occasions, despite maximal doses of sulfonylurea medication, compared with only 5 (2.5%) in the orlistat group.

Serum lipids

Table 2 shows the changes in mean serum lipid levels during the trial. During the lead-in period, there were similar decreases in most of the lipid parameters in both treatment groups. After randomization, however, orlistat-treated patients demonstrated improved serum lipids compared with placebo, with statistically significant differences for total cholesterol, LDL cholesterol, LDL-to-HDL ratio, triglycerides, and apolipoprotein B (Table 2).

The patients in both treatment groups were categorized according to whether they

1) lost $>10\%$ of their initial weight, 2) lost 5–10% of their initial weight, or 3) lost $<5\%$ of their initial weight or gained weight. Selected metabolic changes across drug treatments and categories of weight loss are shown in Fig. 4. As indicated in Fig. 4A, HbA_{1c} improved progressively with increasing weight loss with no significant drug treatment effect that was independent of weight loss. However, as shown in Fig. 4B and 4C, orlistat treatment reduced LDL cholesterol and total cholesterol, respectively, significantly more than placebo within all three levels of weight loss.

Anthropometry

After 52 weeks of therapy, mean waist circumference decreased significantly more in the orlistat-treated group than in the placebo group (-4.8 ± 0.5 vs. -2.0 ± 0.5 cm, $P < 0.01$).

Tolerability

Adverse events occurred at a similar overall incidence in both treatment groups. However, there were more GI events associated with orlistat. There were 79% of patients in the orlistat group versus 59% in the placebo group who experienced at least one GI event. The majority of patients on orlistat experienced one or two of these events. GI events occurred early during treatment, were mild to moderate in intensity, were generally transient, and resolved spontaneously. The number of patients who withdrew because of GI events was seven in the orlistat group versus two in the placebo group. There were seven types of GI events that were identified as being almost exclusively related to orlistat treatment (occurring with an incidence rate of at least 5% and in twice as many patients in the orlistat versus placebo group): flatus with discharge (40.1%), oily spotting (32.7%), fecal urgency (29.7%), fatty/oily stool (19.8%), oily evacuation (14.3%), fecal incontinence (11.8%), and increased defecation (11.1%).

Non-clinically relevant changes in a number of laboratory parameters occurred at a similar incidence in both treatment groups. There was no evidence for the development of gallstones or renal stones after orlistat treatment. Mean plasma levels of vitamins A, D, and E and beta-carotene remained within the reference range throughout the study. After 52 weeks of treatment, mean vitamin E and beta-carotene levels were significantly lower in the orlistat group compared with the placebo group ($P < 0.001$). However, there was no significant change in the vitamin

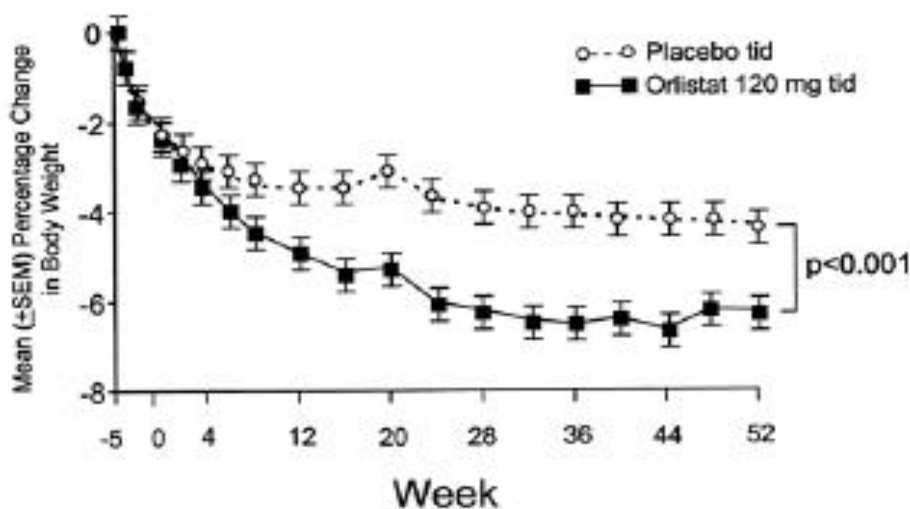


Figure 3—Frequency distribution of percentage change from initial body weight to end of 1 year.

Table 2—Change in lipid parameters after treatment with 120 mg orlistat or placebo three times a day

	Change from baseline (day 1)		LSM% difference from placebo or actual change	P value
	Orlistat	Placebo		
Total cholesterol (mmol/l)	-0.08 ± 0.05	0.39 ± 0.06	-9.14	<0.001
LDL cholesterol (mmol/l)*	-0.13 ± 0.05	0.22 ± 0.06	-12.79	<0.001
HDL cholesterol (mmol/l)	0.06 ± 0.01	0.08 ± 0.01	-1.20	0.486
LDL-to-HDL ratio	-0.26 ± 0.05	-0.02 ± 0.06	-0.30	<0.001
Triglycerides (mmol/l)	-0.01 ± 0.07	0.21 ± 0.08	-10.62	0.036
VLDL cholesterol (mmol/l)	-0.02 ± 0.03	0.08 ± 0.04	-0.09	0.059
Apolipoprotein A-1 (mg/l)	47.99 ± 7.72	58.23 ± 9.37	-10.43	0.341
Lipoprotein(a) (mg/l)	10.23 ± 8.08	-6.70 ± 7.93	16.06	0.141
Apolipoprotein B (mg/l)	-43.66 ± 17.22	75.4 ± 16.57	-108.80	<0.001

Data are means ± SEM. *Measured by ultracentrifugation.

E-to-LDL ratio in either group. As a consequence of having two or more consecutive low vitamin levels, vitamin D supplementation was instituted in 7% of placebo-treated patients and 17% of orlistat-treated patients; vitamin E supplementation was given to 1% of both treatment groups; and 9% of the orlistat group received beta-carotene supplementation. All patients receiving supplementation attained normal levels with treatment, and no patients were withdrawn because of low vitamin values. In addition, mean PT values, used as a surrogate marker of vitamin K, were not different between the orlistat and placebo groups and did not fall below the reference range.

CONCLUSIONS — This study showed that orlistat plus diet therapy produced an average weight loss of ~6 kg (6% of body weight) in patients with type 2 diabetes. Moreover, this loss was significantly greater than that seen with diet therapy alone and was maintained for 1 year. Weight loss of this magnitude has been reported to improve glucose tolerance, increase insulin sensitivity, improve lipid profiles, and reduce the requirement for hypoglycemic therapy (23–27). In the present study, orlistat plus diet not only improved glycemic control more than diet alone, but it also lowered the dose requirement for sulfonylurea therapy and had favorable effects on total cholesterol, LDL cholesterol, the LDL-to-HDL cholesterol ratio, and apolipoprotein B levels. It is noteworthy that the loss of ~4% of body weight in the placebo group had little impact on HbA_{1c}. This finding is consistent with a critical threshold weight loss of ≥5% for improved glycemic control (10).

While weight loss and exercise are the first recommended line of treatment for

most patients with type 2 diabetes, weight loss is very difficult to achieve and maintain in obese patients in general, and even more so in patients with type 2 diabetes on sulfonylurea medication (25). Furthermore, Watts et al. (28) have demonstrated that a

subset of patients with type 2 diabetes did not improve glycemic control with weight loss, perhaps owing to severe or long-standing β-cell deficiency. Nevertheless, the moderate weight loss achieved in this study was associated with HbA_{1c} improvement

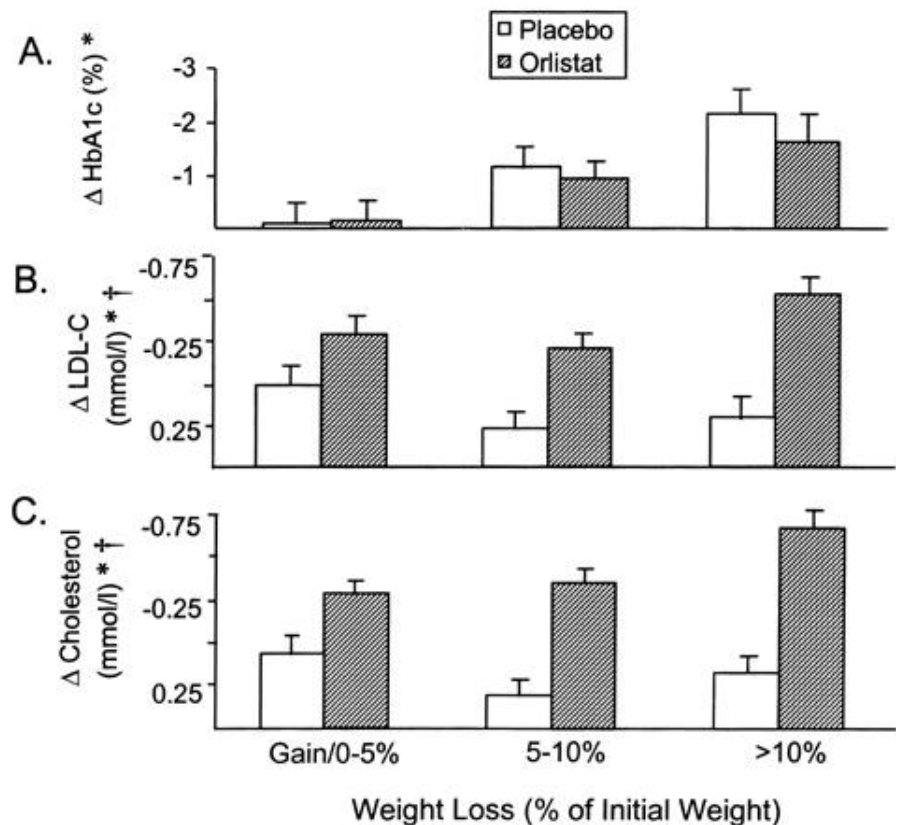


Figure 4—A: Mean ± SEM changes in HbA_{1c} (%) from initial value to end of 1-year treatment with placebo or orlistat across three categories of weight change (% of initial body weight). B: Mean ± SEM change in LDL cholesterol (LDL-C) (mmol/l) from initial value to end of 1-year treatment with placebo or orlistat across three categories of weight change (% of initial body weight). C: Mean ± SEM change in total cholesterol (mmol/l) from initial value to end of 1-year treatment with placebo or orlistat across three categories of weight change (% of initial body weight).

comparable to that seen in studies with antidiabetic drugs such as acarbose (29).

The significance of the present study, therefore, is that a new pharmacologic therapy, with an entirely new mechanism of action, has a beneficial effect on lipids and HbA_{1c} as a measure of glycemia, lasting for 1 year in patients with type 2 diabetes that is greater than the benefit derived from diet alone. Orlistat works on one of the putative causes of obesity, namely, dietary fat (19), rather than by suppressing food intake. The health benefits of orlistat in these patients were accomplished with a modest weight loss of ~6% of initial body weight. The impact of orlistat on several lipid parameters was independent of the magnitude of weight loss and was greater in orlistat-treated compared with placebo-treated patients in every category of weight loss (Fig. 4). This independent pharmacologic lipid-lowering effect of orlistat is probably related to the mechanism of action in reducing the absorption of dietary fat. On the other hand, there is no apparent pharmacologic basis for differential effects of treatment with orlistat compared with placebo on parameters of glycemic control beyond the fact that more patients lost a greater amount of weight in the orlistat-treated group and the relationship between degree of weight loss and improvement in glycemic control is well-established.

One of the other findings of note in this study is the significantly greater decrease in waist circumference in the orlistat versus the placebo group. Despres and others (9,30) have shown that waist circumference is more closely correlated with the volume of visceral adipose tissue than the waist-to-hip ratio or total body fat mass. It is possible that a greater loss of visceral adipose tissue, as reflected indirectly in the decrease in waist circumference, contributed to the improvement in glycemic status in the orlistat group (30). Reductions in visceral adipose tissue are associated with improved glycemic control and enhanced insulin action (30); however, a singular causative relationship can only be established by more direct measurements of insulin sensitivity and visceral fat content. The mechanisms underlying the observed independent impact of orlistat on several cardiovascular disease risk factors beyond the simple effect of weight loss per se warrant further investigation.

Orlistat was generally well tolerated. Despite significantly more GI events related to its mode of action to increase undigested fat passing through the intestine, the overall

incidence of adverse events was similar in the orlistat and placebo groups. Indeed, the withdrawal rate due to adverse events was even greater in the placebo group than the orlistat group. Inhibition of fat absorption could lead to the development of deficiencies in fat-soluble vitamin. To investigate this possibility, all vitamin preparations were discontinued 8 weeks before the trial, and plasma levels of fat-soluble vitamin and beta-carotene generally remained within the reference range throughout the study. Vitamin E and beta-carotene levels were lower in the orlistat group compared with the placebo group during the trial; however, when corrected for changes in LDL, vitamin E was not different between the orlistat and placebo groups. On a few occasions for a small number of patients, consecutive low vitamin levels were recorded, and vitamin supplementation was instituted. In all these patients, vitamin levels normalized by the end of the study. It is worth noting that it is standard medical practice for obese patients on a hypocaloric diet to receive vitamin supplements.

Over the years, many approaches to weight loss have been tried. Most of them have been ineffective and some have proven to be dangerous. During the past several years the serotonergic appetite-suppressant drugs have been shown in several trials to be effective in enhancing weight loss and improving glycemic control (31). Recently, however, the drugs used in these trials, fenfluramine and dexfenfluramine, were withdrawn because of serious complications and side effects. Sibutramine, a recently approved centrally acting serotonin and noradrenaline reuptake inhibitor, has been shown to facilitate greater weight loss than placebo in patients with type 2 diabetes but had no significant effect on glycemic control, although the observed increase in plasma glucose after 12 weeks of treatment was lower with sibutramine than placebo (32).

There are several points that make this study significant. Orlistat is a new pharmacologic therapy that uses an entirely new mechanism of action for achieving weight loss. It is also the first long-term large scale study of pharmacological therapy in obese patients with type 2 diabetes. In this study, orlistat had a greater beneficial effect on glycemia and lipids for 1 year than did treatment with diet alone. The fact that the drug is well tolerated and has a good safety record is especially important in this therapeutic category.

In conclusion, this study confirms that orlistat is effective for up to 1 year, enabling obese patients with type 2 diabetes to achieve clinically meaningful weight loss, while at the same time enhancing glycemic control, thereby reducing the dose requirement for oral hypoglycemic medications and improving several lipid parameters. Such findings appear to offer a new perspective for the management of obese patients with type 2 diabetes.

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References

- Higgins M, D'Agostino R, Kannel W, Cobb J, Pinsky J: Benefits and adverse effects of weight loss: observations from the Framingham Study. *Ann Intern Med* 19:758–763, 1993
- Pi-Sunyer F: Weight and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 63 (Suppl. 3):426S–429S, 1996
- Colditz G, Willett W, Rotnitzky A, Manson J: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481–486, 1995
- Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961–969, 1994
- Carey V, Walters E, Colditz G, Solomon C, Willett W, Rosner B, Speizer F, Manson J: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the Nurses' Health Study. *Am J Epidemiol* 145:614–619, 1997
- Bjorntorp P: Abdominal fat distribution and the metabolic syndrome. *J Cardiovasc Pharmacol* 20 (Suppl. 8):S26–S28, 1992
- Kissebah AH, Peiris AN: Biology of regional body fat distribution: relationship to non-insulin-dependent diabetes mellitus. *Diabetes Metab Rev* 5:83–109, 1989
- Bjorntorp P: Regional obesity and NIDDM. *Adv Exp Med Biol* 34:279–285, 1993
- Despres J: Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 9:452–459, 1993
- Wing R, Koeske R, Epstein L, Nowalk M, Gooding W, Becker D: Long-term effects of modest weight loss in type II diabetic patients. *Arch Intern Med* 147:1749–1753, 1987

- 1987
11. Meigs JB, Singer DE, Sullivan LM, Dukas KA, D'Agostino RB, Nathan DM, Wagner EH, Kaplan SH, Greenfield S: Metabolic control and prevalent cardiovascular disease in non-insulin-dependent diabetes mellitus (NIDDM): the NIDDM Patient Outcome Research Team. *Am J Med*102:38-47, 1997
 12. Hanefeld M, Fischer S, Schmechel H, Rothe G, Schulze J, Dude H, Schwanebeck U, Julius U: Diabetes Intervention Study: multi-intervention trial in newly diagnosed NIDDM. *Diabetes Care*14:308-317, 1991
 13. United Kingdom Prospective Diabetes Study (UKPDS): 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ*310:83-88, 1995
 14. Pi-Sunyer F: Short-term medical benefits and adverse effects of weight loss. *Ann Intern Med*119:722-726, 1993
 15. National Task Force on the Prevention and Treatment of Obesity: Long-term pharmacotherapy in the management of obesity. *JAMA*276:1907-1915, 1996
 16. McCann U, Seiden L, Rubin L, Ricaurte G: Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. *JAMA*278:666-672, 1997
 17. Zhi J, Melia A, Guerciolini R, Chung J, Kinberg J, Hauptman J, Patel I: Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. *Clin Pharmacol Ther*56:82-85, 1994
 18. Hauptman JB, Jeunet FS, Hartmann D: Initial studies in humans with the novel gastrointestinal lipase inhibitor Ro 18-0647 (tetrahydrolipstatin). *Am J Clin Nutr*55 (Suppl. 1):309S-313S, 1992
 19. Jebb SA: Aetiology of obesity. *Br Med Bull* 53:264-285, 1997
 20. Tonstad S, Pometta D, Erkelens D, Ose L, Moccetti T, Schouten J, Golay A, Reitsma J, Del Bufalo A, Pasotti E: The effect of the gastrointestinal lipase inhibitor, orlistat, on serum lipids and lipoproteins in patients with primary hyperlipidaemia. *Eur J Clin Pharmacol*46:405-410, 1994
 21. Zhi J, Melia A, Funk C, Viger-Chougnet A, Hopfgartner G, Lausecker B, Wang K, Fulton J, Gabriel L, Mulligan T: Metabolic profiles of minimally absorbed orlistat in obese/overweight volunteers. *J Clin Pharmacol*36:1006-1011, 1996
 22. Winer BJ: *Statistical Principles in Experimental Design* 2nd ed. New York, McGraw-Hill, 1971
 23. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249-1258, 1995
 24. Henry RR, Brechtel G, Griver K: Secretion and hepatic extraction of insulin after weight loss in obese noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 66:979-986, 1988
 25. Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M: Relative effects of calorie restriction and weight loss in non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*77:1287-1293, 1993
 26. Pontiroli AE, Calderara A, Pacchioni M, Cassisa C, Pozza G: Weight loss reverses secondary failure of oral hypoglycaemic agents in obese non-insulin-dependent diabetic patients independently of the duration of the disease. *Diabetes Metab* 19:30-35, 1993
 27. Wing RR, Shoemaker M, Marcus MD, McDermott M, Gooding W: Variables associated with weight loss and improvements in glycemic control in type II diabetic patients in behavioral weight control programs. *Int J Obes*4:495-503, 1990
 28. Watts N, Spanheimer R, DiGirolamo M, Gebhart S, Musey V, Siddiq Y, Phillips L: Prediction of glucose response to weight loss in patients with non-insulin-dependent diabetes mellitus. *Arch Intern Med* 150:803-806, 1990
 29. Coniff RE, Shapiro JA, Robbins D, Kleinfield R, Seaton TB, Beisswenger P, McGill JB: Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM: a placebo-controlled dose-comparison study. *Diabetes Care* 18:817-824, 1995
 30. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres J: A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr* 64:685-693, 1996
 31. Marks SJ, Moore NR, Clark ML, Strauss BJG, Hockaday TDR: Reduction of visceral adipose tissue and improvement in metabolic indices: effect of dexfenfluramine in NIDDM. *Obes Res*4:1-8, 1996
 32. FDA Pink Sheet. 9/26/96 FDA's Endocrinologic and Metabolic Drugs Advisory Committee Review of New Drug Application for Sibutramine. Washington, DC, U.S. Govt. Printing Office, Sept. 26, 1996