Clinical Efficacy of Orlistat Therapy in Overweight and Obese Patients With Insulin-Treated Type 2 Diabetes

A 1-year randomized controlled trial

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OBJECTIVE — Weight loss improves glycemic control, lipid profiles, and blood pressure in patients with type 2 diabetes. However, successful long-term weight loss is difficult for these patients, particularly those treated with insulin. The aim of this study was to assess the effect of orlistat, a gastrointestinal lipase inhibitor, on weight loss, glycemic control, and cardiovascular risk factors in overweight or obese insulin-treated type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — This study was a 1-year multicenter, randomized, double-blind, placebo-controlled trial of orlistat (120 mg three times a day) or placebo combined with a reduced-calorie diet in overweight or obese adults (BMI 28–40 kg/m^2) with type 2 diabetes treated with insulin alone or combined with oral agents, but with suboptimal metabolic control (HbA_{1c} 7.5–12.0%). Outcome measurements included changes in body weight, glycemic control, blood pressure, and serum lipids.

RESULTS — After 1 year, the orlistat group lost significantly more weight (−3.89 ± 0.3% of baseline body weight, means ± SE) than the placebo group (−1.27 ± 0.3%, $P < 0.001$). Orlistat treatment, compared with placebo, produced greater decreases in HbA_{1c} (−0.62 ± 0.08 vs. −0.27 ± 0.08%, $P = 0.002$), fasting serum glucose (−1.63 ± 0.3 vs. −1.08 ± 0.3 mmol/l, $P = 0.02$), and the required doses of insulin and other diabetic medications. Orlistat also produced greater improvements than placebo in serum total cholesterol ($P = 0.0002$) and LDL cholesterol concentrations ($P = 0.001$) and LDL/HDL ratio ($P = 0.01$).

CONCLUSIONS — Orlistat therapy produces clinically significant weight loss, with improvements in glycemic control and cardiovascular disease risk factors, in overweight or obese patients with type 2 diabetes who have suboptimal metabolic control with insulin therapy.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Most patients with type 2 diabetes are obese (1), a factor that makes it more difficult to achieve glycemic control with insulin or oral hypoglycemic agents (2) and increases the risk of micro- and macrovascular complications (3). Therefore, weight loss is a fundamental component of therapy for overweight and obese patients with type 2 diabetes (3–7). However, successful long-term weight management is more difficult in obese patients with type 2 diabetes than in obese individuals who do not have diabetes (8). Weight loss may be especially challenging for insulin-treated patients because insulin therapy is associated with greater weight gain than that associated with oral hypoglycemic therapy (9–12). Moreover, weight gain increases insulin resistance and thereby increases the amount of exogenous insulin needed to control hyperglycemia (13).

The limited success in achieving long-term weight loss in patients with type 2 diabetes by conventional diet therapy has led to increased interest in adjunctive pharmacotherapy for weight management. Data from several randomized controlled clinical trials in patients with type 2 diabetes have demonstrated that antiobesity agents enhance weight loss (14,15). However, these trials were conducted in patients treated with oral hypoglycemic agents only. It is not known whether pharmacological therapy for weight management might also be useful for managing overweight or obese patients with type 2 diabetes who require insulin therapy.

This 1-year placebo-controlled multicenter investigation was conducted to assess the clinical efficacy of orlistat in treating overweight or obese patients with type 2 diabetes who were receiving insulin therapy, either alone or in combination with one or more oral agents. The aim of this study was to test the hypothesis that orlistat plus diet therapy causes greater weight loss and improvements in

glycemic control and cardiovascular disease risk factors than diet alone.

RESEARCH DESIGN AND METHODS

Study design

This multicenter, double-blinded, randomized, placebo-controlled 1-year trial was conducted in 43 centers in the U.S. The study consisted of a 2-week screening phase followed by a 52-week treatment phase. Patients who met the criteria for inclusion in the study (see below) were randomized to receive a reduced-calorie diet plus either 120 mg orlistat or placebo three times daily. To ensure balance with respect to initial glycemic control in the two treatment arms, patients were stratified into two groups based on HbA_{1c} levels ≤10.0 or >10.0%. The study was conducted in compliance with the Declaration of Helsinki. The study protocol was approved by the institutional review board at each center, and written informed consent was obtained from each subject.

Patients

Men and women, aged 40–65 years, were eligible for the study if they met the following criteria: BMI 28–43 kg/m^2 and a stable weight (<3 kg weight change) for 3 months before study entry, treatment with a stable daily dose (±10%) of insulin for 6 weeks before study entry, and an HbA_{1c} of 7.5–12.0% at screening. Women with childbearing potential were required to have a negative serum pregnancy test at screening and to use an acceptable form of contraception throughout the study. Patients were excluded from the study if their diabetes treatment included a thiazolidinedione or if their diabetic medications, with the exception of insulin, had changed during the 12 weeks before screening. Other exclusion criteria were a medical history or presence of renal, hepatic, or endocrine disorders that could affect the results of the study, previous bariatric surgery, use of approved or experimental weight reduction medications or treatments, presence of malabsorption syndrome, presence of bulimia or laxative abuse, or presence of disorders that could affect compliance with the requirements of the study.

Treatment regimen

Patients were instructed to take the study drug by mouth three times daily with their main meals for 52 weeks. Patients were also instructed to take a multivitamin at least 2 h before or after the evening dose of the study drug. Medication compliance was assessed by counting the number of capsules returned at each study visit. Patients were considered compliant if capsule consumption was at least 70% of the prescribed dose and were withdrawn from the study if compliance was <60%.

All patients were maintained on a nutritionally balanced energy deficit diet designed to induce a weight loss of 0.25–0.5 kg per week. The diet contained ~30% of calories as fat, 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day of cholesterol. At the baseline visit, patients received diet instructions from a registered dietitian. Additional dietary instruction was provided at predetermined intervals during the study, and dietary compliance was monitored by the use of dietary intake records. At week 24, the prescribed caloric intake was further reduced by 200 kcal/day (with a minimum caloric intake of at least 1,200 kcal/day) to compensate for reduced energy requirements induced by weight loss. Lifestyle and behavioral modification literature were available to all patients throughout the study. Patients were encouraged to participate in moderate physical activity.

Assessments

All subjects underwent a comprehensive medical evaluation that included a medical history and physical examination, an electrocardiogram, laboratory tests, and a serum pregnancy test for women of childbearing potential. After the start of double-blind treatment, subjects were seen every 2–4 weeks for study assessments, procedures, and dietary instruction. Primary efficacy variables were weight loss and changes in HbA_{1c}. Patients were weighed at least twice at each assessment until two consecutive measurements were within 0.5 kg of each other, and the average of the two measurements was recorded. Assessment of glycemic control included HbA_{1c} (normal range 4.3–6.1%), fasting serum glucose, and dosage of diabetes medications. Fasting glucose was measured at each visit. Serum HbA_{1c} was measured at baseline and at weeks 12, 24, 36, and 52. Investigators were instructed to try to maintain stable doses of insulin and other diabetes medications, but they had the option to adjust doses (see below). Secondary efficacy parameters were serum lipid levels, blood pressure, and waist circumference. Serum lipids (total, LDL, and HDL cholesterol, triglycerides, and LDL/HDL ratio) were determined at baseline and at weeks 24 and 52. Waist circumference was measured at baseline and at weeks 24 and 52 with a spring-loaded calibrated measuring tape.

Diabetes medication changes

Dose adjustments of diabetes medications as well as the addition and discontinuation of medications were recorded. Criteria for changes in medication doses were standardized across study centers and based on symptoms or evidence of hypo- or hyperglycemia. Diabetes medications were decreased according to the following criteria: symptoms or documented evidence of hypoglycemia on two occasions within 1 week at home (home blood glucose measurement <3.33 mmol/l [60 mg/dl]) or on one occasion measured by the investigator (<2.78 mmol/l [50 mg/dl]), with or without symptoms of hypoglycemia. Diabetes medications were increased if blood glucose concentration was >19.4 mmol/l (350 mg/dl) at any time, if HbA_{1c} had increased by >2.0% from baseline to week 12 or was >12.0%, or if HbA_{1c} had increased by >0.2% from baseline to week 24 or was >10.2%. Adjustments in medications were made at any time except during the 2 weeks before randomization.

Statistical analysis

The two primary end points of the study were changes in HbA_{1c} and changes in weight. Groups were compared for both parameters using a Holm's sequential rejection procedure. Using this method, *P* values were calculated for each end point. Then, the end point with the smaller *P* value was chosen and, if this *P* value was >0.025, it was considered an insignificant change from baseline and was rejected. However, if the *P* value was <0.025, it was accepted as significant. From here, the other primary end point *P* value was examined. If this was <0.05, then both primary end points were considered significant. As presented later, this was the case for the change in body weight and HbA_{1c}. The number of subjects enrolled into this study was estimated to be sufficient to provide a statistical power of at least 80% to detect differences between treatment groups of a 2.1-kg change in body weight and a 0.5% change in HbA_{1c}, with an α level of 0.025 for each of the

Table 1—*Clinical characteristics at randomization*

	Placebo	Orlistat
n	269	266
Sex		
Male	118 (44)	116 (44)
Female	151 (56)	150 (56)
Race		
Caucasian	196 (73)	189 (71)
African-American	43 (16)	45 (17)
Asian	2 (1)	5 (2)
Other	28 (10)	27 (10)
Age (years)	58.0 ± 0.5	57.8 ± 0.5
Weight (kg)	101.8 ± 1.0	102.0 ± 1.0
Height (cm)	168.9 ± 0.6	168.5 ± 0.6
BMI	35.6 ± 0.3	35.8 ± 0.2
HbA_{1c} (%)	8.99 ± 0.07	9.01 ± 0.07
Fasting glucose (mmol/l)	11.16 ± 0.2	10.91 ± 0.2
Daily dosages of diabetes medications		
Insulin (units/day)	84.0 ± 6	71.3 ± 1
Sulfonylurea (mg/day)	67.6 ± 6.5	60.75 ± 7.0
Metformin (mg/day)	1,207 ± 105	1,287 ± 104
Diabetes medications (%)		
Insulin only	69.9	72.9
Insulin + metformin	16.0	12.8
Insulin + sulfonylurea	10.0	6.8
Insulin + metformin + sulfonylurea	3.3	4.5

Data are *n* (%) or means ± SE, unless otherwise indicated.

two primary efficacy variables and assuming a 40% withdrawal rate. An intent-to-treat analysis was conducted using the data from all patients who had at least one postbaseline efficacy observation. All efficacy variables were analyzed using the last-observation-carried-forward technique. The null hypothesis—that the expected mean weight loss and change from baseline in HbA_{1c} at the end of 1 year of double-blind treatment did not differ significantly between the placebo and orlistat treatments—was tested using ANOVA and ANCOVA. Similar analyses were applied to the secondary efficacy variables. Differences between groups in the frequency distributions of weight loss, changes in HbA_{1c}, and changes in diabetes medications were tested by use of the Cochran-Mantel Haenszel method.

RESULTS

Clinical characteristics

A total of 550 patients were enrolled in the study and randomized to double-blind treatment with orlistat ($n = 274$) or placebo ($n = 276$). The intent-to-treat population consisted of 266 and 269 subjects in the orlistat and placebo groups, respectively, who received at least one dose of medication and had body weight or HbA_{1c} assessments. The characteristics of the patient population at study entry were similar in the two treatment groups (Table 1). The treatment groups were well matched for sex and distribution of racial and ethnic groups. Diabetes medications at baseline are also shown in Table 1. Mean daily doses of insulin were 71 ± 1 and 84 ± 6 units/day for the orlistat and placebo groups, respectively. Despite these relatively large insulin doses, mean values for HbA_{1c} and fasting serum glucose at baseline (Table 1) indicated inadequate glycemic control. The baseline serum lipid concentrations were indicative of the dyslipidemia characteristic of type 2 diabetes, namely low HDL cholesterol and elevated triglyceride and LDL cholesterol concentrations.

Of the intent-to-treat population, 137 in the orlistat group (51.5%) and 128 (47.6%) in the placebo group completed 52 weeks of treatment. Overall, 54% of placebo-treated and 50% of orlistat-treated patients withdrew prematurely from the study. The reasons for premature withdrawal during the double-blind treatment period are shown in Table 2. More orlistat- (13%) than placebo-treated patients (8%) discontinued treatment because of an adverse event, whereas a lower percentage of orlistat- than placebo-treated patients (37 vs. 46%) withdrew for other reasons.

Table 2—*Summary of reasons for premature withdrawal from study*

Reason for withdrawal	Placebo	Orlistat
n	276	274
Adverse event	22 (8)	35 (13)
Non-safety	126 (46)	102 (37)
Insufficient therapeutic response	1	1
Protocol violation	7	3
Refused treatment*	79	55
Failure to return	35	36
Other	4	7
Total	148 (54)	137 (50)

Data are *n* (%). Percentages are based on total randomized population, including seven patients in the placebo group and eight patients in the orlistat group who were excluded from the intent-to-treat population because there were no efficacy assessments. *Including "did not cooperate" and "withdrew consent."

Body weight

Changes in body weight during the study are shown in Fig. 1. Both relative and absolute weight loss at 52 weeks were greater in the orlistat than in the placebo treatment group (−3.76 ± 0.26 vs. −1.22 ± 0.3% of baseline body weight and −3.89 ± 0.27 vs. −1.27 ± 0.28 kg for the orlistat and placebo treatment groups, respectively; $P < 0.001$). The difference in weight loss between the two treatments was apparent by 8 weeks after randomization, with a steeper rate of weight loss in orlistat- than in placebo-treated subjects. More subjects treated with orlistat (32.7%) than placebo (13.0%) lost ≥5% of their baseline body weight ($P < 0.0001$) (Fig. 2). More subjects treated with orlistat (10.2%) than

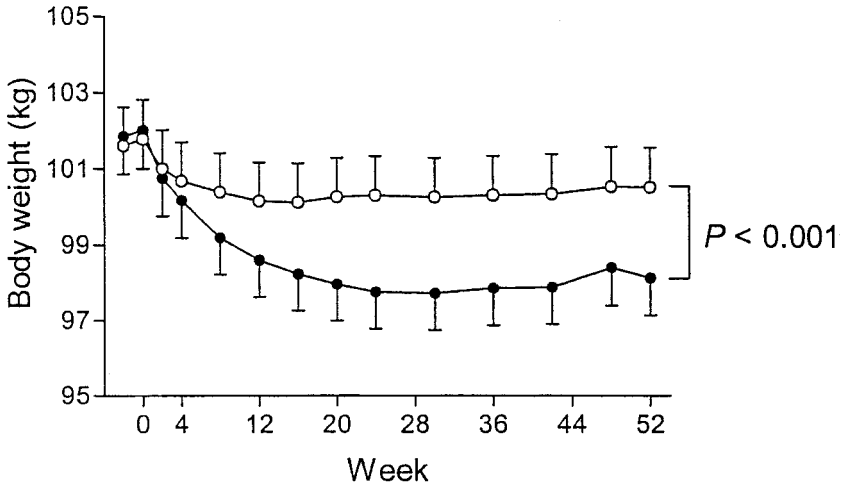

Figure 1—*Mean body weight change (± SE) during 1 year of double-blind treatment with placebo (○) or 120 mg orlistat (●). P < 0.001, least-squares mean difference from placebo in the change from baseline over 52 weeks.*

placebo (3.7%) lost ≥10% of their baseline body weight ($P < 0.001$). Waist circumference was similar in orlistat and placebo groups at baseline (113.1 ± 0.7 and 113.9 ± 0.8 cm, respectively) but decreased more after 52 weeks of treatment in the orlistat group than in the placebo group (−5.27 ± 0.7 and −2.54 ± 0.4 cm, respectively; $P < 0.0001$).

Glycemic control

After the initiation of treatment, subjects in both groups experienced a prompt reduction in fasting serum glucose levels, as shown in Fig. 3. During the 1-year trial, there was a greater decrease in fasting serum glucose concentration in the orlistat- than in the placebo-treated group (−1.63 ± 0.3 vs. −1.08 ± 0.3 mmol/l, $P = 0.02$). The decline in serum HbA_{1c} levels after 52 weeks of treatment (Fig. 4) was greater in the orlistat than in the placebo group (−0.62 ± 0.08 vs. −0.27 ± 0.08%, $P = 0.002$). Furthermore, 51.7% of orlistat-treated patients achieved a reduction in HbA_{1c} of ≥0.5%, as compared with 39.9% in the placebo group ($P = 0.008$). A reduction in HbA_{1c} ≥1.0% was also achieved by a significantly greater proportion of patients in the orlistat than in the placebo group (31.7 vs. 21.8%, respectively, $P = 0.013$). At the end of 1 year, 46% of participants receiving orlistat and diet achieved HbA_{1c} <8%, whereas for placebo and diet, 35% of participants achieved this value. Of patients on orlistat, 13% achieved HbA_{1c} <7%.

As previously described, there were 115 participants in the placebo group and 93 participants in the orlistat group who withdrew from the study. Among those who withdrew, the average length of time patients remained in the study was 127 days in the placebo group and 115 days in the orlistat group, and the baseline values for HbA_{1c} were 9.02 and 9.07%, respectively. The least-square mean changes for HbA_{1c} were −0.29% for placebo and −0.72% for orlistat, with a highly significant difference that was −0.42% ($P = 0.0063$). There were 128 patients in the placebo group and 137 patients in the orlistat group who completed 360 days for placebo or orlistat. The baseline values for HbA_{1c} were 9.00 and 8.91% for the placebo and orlistat groups, respectively, with least-square mean changes for HbA_{1c} of −0.25% for placebo and −0.56% for orlistat and a difference between groups of −0.31% ($P = 0.0438$). Thus, the response of glucose control to placebo plus diet versus orlistat plus diet was very similar in those who withdrew before completing 1 year of treatment compared with those who completed the study.

The greater reduction in HbA_{1c} produced by orlistat treatment was not entirely dependent on the magnitude of weight loss. ANOVA, adjusting the change in HbA_{1c} at 1 year for the corresponding percent change in body weight at 1 year (the covariate), was used to examine whether there was a significant effect of orlistat treatment on HbA_{1c} concentrations that was separate from the effect of orlistat on weight loss. After adjusting for differences in weight loss, the mean change in HbA_{1c} remained significantly different between groups (−0.56 vs. −0.32% for the orlistat and placebo treatment groups, respectively, $P = 0.04$).

Changes in diabetes medications

There was a statistically significant ($P = 0.0001$) difference between treatment groups in the frequency distribution of diabetes medication changes (Table 3). A greater reduction in insulin dose was associated with orlistat than with placebo treatment (−8.1 vs. −1.6 units/day, $P = 0.007$). A greater proportion of patients achieved ≥5% reduction of insulin dose

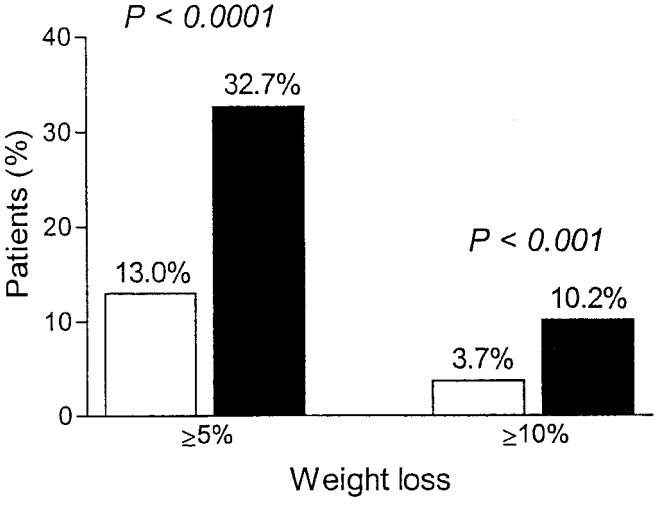

Figure 2—*Frequency distribution of percent change from initial body weight after 1 year of treatment with placebo (□) or 120 mg orlistat (■). Intent-to-treat population.*

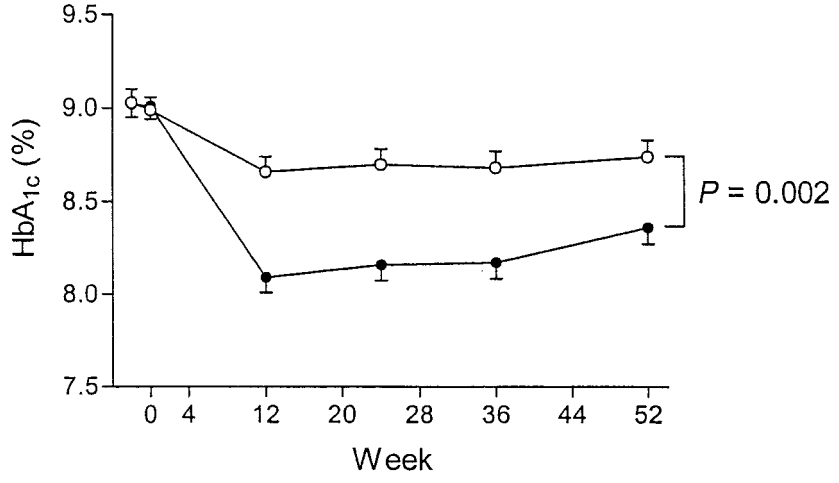

Figure 3—*Fasting serum glucose levels over time with placebo (○) or 120 mg orlistat (●). P = 0.02, least-squares mean difference from placebo in the change from baseline over 52 weeks.*

in the orlistat treatment group compared with placebo (41 vs. 31%, $P < 0.001$), whereas fewer patients in the orlistat than in the placebo group increased their insulin dose by ≥5% (12 vs. 26%, $P < 0.001$). Dose changes in other diabetes medications are also shown in Table 3. More orlistat- (41.3%) than placebo-treated patients (30.9%) decreased the dose or discontinued at least one oral diabetes medication during the study; conversely, dose increase or the addition of at least one new diabetes medication occurred less frequently in orlistat- (14.7%) than in placebo-treated patients (31.7%) ($P < 0.0001$). There was a greater reduction in sulfonylurea dose in the orlistat group compared with placebo. Changes in metformin dose were not different between groups.

In this study, investigators were required to change the antidiabetic regimen at week 24 if there was an increase in HbA_{1c} of ≥0.2% from baseline or if HbA_{1c} remained >10.2%. These treatment modifications may have diminished differences in serum HbA_{1c} concentration between treatment groups because more subjects randomized to placebo than orlistat required increases in antidiabetic medications to control glycemia, whereas medication reductions occurred more frequently in the orlistat group. To account for this intervening variable, an analysis of changes in HbA_{1c} concentration was performed that excluded values obtained after any changes in antidiabetic medication were made. This analysis found that the decrease in HbA_{1c} from baseline to the time at which medication changes were made was greater in the orlistat- than in the placebo-treated group (−0.77 vs. −0.26%, $P = 0.022$).

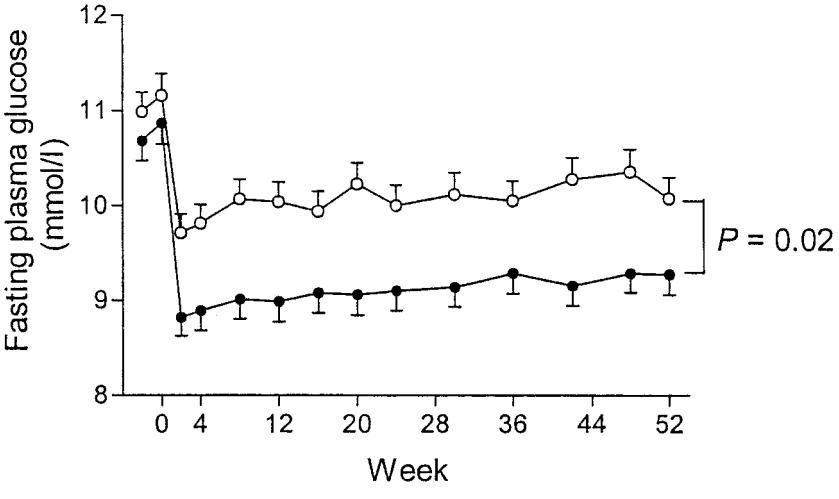

Figure 4—*HbA_{1c} over 1 year of double-blind treatment with placebo (○) or 120 mg orlistat (●). P = 0.002, least-squares mean difference from placebo in the change from baseline over 52 weeks.*

Cardiovascular risk factors: blood pressure and serum lipid levels

Changes in blood pressure and serum lipid concentrations after 52 weeks of treatment are shown in Table 4. At 52 weeks, total and LDL cholesterol and the LDL/HDL ratio decreased significantly more in orlistat- than in placebo-treated patients. After statistical adjustment for the effect of weight loss on changes in serum lipid concentrations by ANCOVA, the change in total cholesterol over 1 year of treatment was significantly greater in the orlistat compared with the placebo group (adjusted means −4.12 vs. 2.07%, respectively; $P < 0.0001$). Similarly, the mean reduction in LDL cholesterol, adjusted for percent weight loss, was significantly greater in the orlistat compared with the placebo group (−8.61 vs. 3.75%, $P < 0.0001$). Changes in serum triglyceride and HDL cholesterol concentration and blood pressure were not significantly different between treatment groups.

Adverse events

Gastrointestinal events were the most commonly reported adverse event in both groups and were reported more frequently in orlistat- (80%) than in placebo-treated patients (62%) ($P < 0.05$). Most patients with gastrointestinal events reported a single episode, and most gastrointestinal events in both treatment groups were of mild to moderate intensity. Episodes of hypoglycemia occurred in a greater proportion of orlistat- than placebo-treated patients (16.9 and 9.7%, respectively, $P < 0.05$). In the majority of patients, hypoglycemic symptoms were mild to moderate, with blood glucose levels ranging from 2.2 to 6.9 mmol/l. Only four patients (one in the placebo and three in the orlistat group) required medical intervention due to hypoglycemia. The incidence of adverse events related to other organ systems was similar in placebo- and orlistat-treated subjects.

CONCLUSIONS — Weight loss is the cornerstone of treatment for overweight or obese patients with type 2 diabetes. However, long-term weight loss is difficult to achieve by conventional diet therapy in

obese patients with diabetes, particularly those who are treated with insulin (8,10,16). The current study was undertaken to examine the clinical efficacy of orlistat, a gastrointestinal lipase inhibitor (17), in combination with a reduced-calorie diet, in overweight or obese patients with type 2 diabetes who were being treated with insulin. Orlistat plus diet therapy produced significantly greater weight loss and improvement in glycemic control than diet therapy alone. Treatment with orlistat plus diet also lowered the dose requirement for insulin more than placebo plus diet and produced greater reductions in total and LDL cholesterol and LDL/HDL cholesterol ratio.

Previous orlistat clinical trials in nondiabetic obese patients have demonstrated that greater weight loss is achieved with orlistat than placebo therapy after 1 year of treatment (18,19). Data from 1-year randomized controlled trials conducted in diabetic patients treated with either sulfonylurea (15) or metformin therapy (20) suggest that orlistat produces less weight loss in persons with type 2 diabetes than in nondiabetic individuals. However, the relative difference in weight loss between orlistat and placebo treatment appears to be consistent in diabetic and nondiabetic subjects (15,18–20).

The longitudinal 10-year assessment of patients in the U.K. Prospective Diabetes Study found that patients treated with insulin gained ~4.0 kg more and that those treated with sulfonylurea medications gained 2.2 kg more than patients assigned to diet therapy alone (9,16). Therefore, effective therapy of hyperglycemia with insulin and most oral hypoglycemic agents is associated with weight gain, which limits the effectiveness of weight loss therapy in diabetes. The mechanism(s) responsible for the lower weight loss in patients with type 2 diabetes than in nondiabetic subjects are not fully understood but may be related to weight gain induced by diabetes therapy. Weight gain associated with treatment of type 2 diabetes with insulin and most oral hypoglycemic medications is in part explained by reductions in urinary energy (glucose) losses and by decreased energy expenditure due to lowering the rate of gluconeogenesis (21,22). Other mechanisms, such as changes in energy intake, may also play a role.

Glycemic control

In most patients with type 2 diabetes, even modest amounts of weight loss have a substantial impact on glucose metabolism (23–26). However, not all patients with type 2 diabetes respond to weight loss. Watts et al. (27) found that weight loss in a subset of patients with type 2 diabetes was not associated with improvement in glycemic control; they attributed the poor response to more severe β-cell dysfunction. Typically, insulin therapy is initiated in patients with type 2 diabetes after failure of one or more oral agents and often reflects a progressive insulin deficiency. However, the results of the present study indicate that modest weight loss does enhance glycemic control in type 2 diabetic patients who are receiving insulin therapy. This benefit was greater with orlistat than placebo treatment.

A difference between the orlistat and placebo treatment groups in the reduction of HbA_{1c} levels was evident by 3 months and remained throughout the 1-year trial. In the current study, participants who were randomized to receive placebo treatment received the same dietary interventions directed at weight loss as the group randomized to orlistat. Although there was a significant difference in weight loss between groups, as described above, there was weight loss in the placebo-treated group and a decline from baseline in HbA_{1c}. Thus, in the current study, it should be considered that the group randomized to placebo medication did in fact receive an active intervention of increased nutritional counseling and that this lead to weight loss and improvement in glycemic control. This is in contrast to the natural history of type 2 diabetes, which is often characterized by a rise in both HbA_{1c} and weight (16). In the current trial, the magnitude of improvement in HbA_{1c} achieved with orlistat therapy exceeded that of the placebo group (least-square mean difference from placebo of 0.46%), and there was a 0.62% improvement in HbA_{1c} relative to the baseline value for the participants randomized to orlistat. This improvement is associated with meaningful reductions in the risk of microvascular complications (28). It is also similar in magnitude to the improvement produced by the addition of some oral diabetes medications to insulin therapy (29). Moreover, the improvement in HbA_{1c} observed with orlistat therapy was achieved despite the use of lower doses of insulin and oral hypoglycemic medications. Orlistat may also have long-term effects on glycemic control that are not solely attributable to the amount of weight loss. The mean change in plasma HbA_{1c} concentration at 1 year was signif-

Table 3—*Changes in diabetes medications after 52 weeks of treatment*

	Placebo	Orlistat	*P*
n	269	266	
Changes in daily dosages of diabetes medications			
Insulin (units/day)	−1.6 ± 1.7	−8.1 ± 1.5	0.007
Decrease in insulin dose ≥5.0%	31.0	41.2	0.0085
Increase in insulin dose ≥5.0%	25.7	11.8	0.000
Sulfonylurea (mg/day)	1.3 ± 4.1	−7.8 ± 6.2	0.037
Metformin (mg/day)	163 ± 66	190+ ± 65	0.343
Frequency distribution of medication changes over 52 weeks			0.000
No change in any medications	37.5	44.0	
Decreased dose or discontinued at least one medication	30.9	41.3	
Increased dose or added at least one medication	31.7	14.7	

Data are means ± SE or %.

Table 4—*Blood pressure and serum lipid levels at study entry and week 52 and changes over 52 weeks of treatment*

	Placebo	Orlistat	*P*
n	276	266	
Systolic blood pressure (mmHg)			
Initial	134.9 ± 0.9	135.1 ± 0.9	
52 weeks	134.0 ± 1.0	134.0 ± 1.0	
Change	−0.9 ± 1.0	−1.2 ± 1.0	0.948
Diastolic blood pressure (mmHg)			
Initial	80.9 ± 0.6	79.5 ± 0.5	
52 weeks	78.0 ± 0.5	77.2 ± 0.6	
Change	−1.0 ± 0.5	−2.3 ± 0.7	0.075
Total cholesterol (mmol/l)			
Initial	5.43 ± 0.07	5.49 ± 0.07	
Week 52	5.46 ± 0.08	5.20 ± 0.08	
Change	0.08 ± 0.07	−0.30 ± 0.07	0.002
Percent change	2.61 ± 1.21	−4.66 ± 1.07	
LDL cholesterol (mmol/l)			
Initial	3.30 ± 0.06	3.37 ± 0.06	
Week 52	3.18 ± 0.06	3.00 ± 0.06	
Change	−0.08 ± 0.05	−0.38 ± 0.05	0.001
Percent change	0.83 ± 1.9	−9.06 ± 1.5	
HDL cholesterol (mmol/l)			
Initial	1.07 ± 0.02	1.07 ± 0.02	
Week 52	1.12 ± 0.02	1.09 ± 0.02	
Change	0.05 ± 0.01	0.02 ± 0.01	0.247
Percent change	6.44 ± 1.29	3.95 ± 1.30	
LDL/HDL ratio			
Initial	3.27 ± 0.07	3.38 ± 0.08	
Week 52	2.98 ± 0.07	2.88 ± 0.07	
Change	−0.25 ± 0.06	−0.50 ± 0.07	0.013
Percent change	−3.50 ± 1.9	−10.11 ± 1.8	
Triglycerides (mmol/l)			
Initial	2.31 ± 0.08	2.33 ± 0.1	
Week 52	2.61 ± 0.17	2.47 ± 0.18	
Change	0.31 ± 0.13	0.18 ± 0.16	0.421
Percent change	17.27 ± 3.70	10.01 ± 3.41	

Data are means ± SE. Intent-to-treat population; last observation carried forward.

icantly greater in orlistat- than in placebo-treated subjects, even after statistically adjusting for the difference between treatments in weight loss. The mechanism for this effect is uncertain but may be related to differences in the composition of absorbed macronutrients between groups. Presumably, the percentage of absorbed calories derived from fat was lower in the orlistat than in the placebo treatment group.

Cardiovascular disease risk factors

Obesity and type 2 diabetes are associated with dyslipidemia, which increases the risk for cardiovascular disease (30). Therefore, decreasing total and LDL cholesterol is an important clinical target (31). Recently, Lamotte et al. (32) conducted a cost-benefit analysis of using orlistat in the treatment of type 2 diabetes, based upon a Markov model, using the previously published data of Hollander et al. (15). In the analysis by Lamotte et al., the cost-effectiveness of orlistat therapy was greater in obese type 2 diabetic patients with hypertension and hypercholesterolemia (3,462 Euro dollars/life-year gained), as compared with obese type 2 diabetic patients without these risk factors (19,986 Euro dollars/life-year gained). A formal cost-benefit analysis was not performed in the current trial. In the current trial, the decreases in serum total and LDL cholesterol concentrations were greater in patients treated with orlistat than in those treated with placebo. Moreover, our results demonstrate that part of the lipid-lowering effect associated with orlistat was independent of weight loss; reductions in total and LDL cholesterol remained significantly greater in the orlistat than in the placebo group after removing the effect of weight loss by ANCOVA. The mechanism responsible for this effect may be related to orlistat's inhibition of dietary cholesterol absorption (33).

Adverse effects

The adverse event profile for orlistat treatment in this trial was very similar to that previously reported for orlistat in obese nondiabetic subjects and diabetic patients treated with oral hypoglycemic agents (15,18). More patients treated with orlistat than placebo reported at least one occurrence of a gastrointestinal adverse event, which is related to the consumption of dietary fat and orlistat's inhibition of gastrointestinal lipase activity. Despite the greater number of gastrointestinal events in subjects treated with orlistat, the number of premature withdrawals from the study due to gastrointestinal events was similar in the placebo and orlistat groups. The incidence of nongastrointestinal adverse events was similar in the orlistat and placebo groups, with the exception of a greater frequency of hypoglycemia in orlistat- than in placebo-treated patients. These results underscore the need for careful glucose monitoring and appropriate reductions in insulin dose after starting orlistat and diet therapy in insulin-treated patients.

The results of the present study demonstrate the beneficial effects of orlistat therapy in the management of patients with insulin-treated type 2 diabetes. Orlistat plus diet therapy produced greater weight loss and improvements in glycemic control and serum lipid concentrations than placebo plus diet therapy, and these changes were sustained throughout 1 year of treatment. Efforts to achieve weight loss with pharmacological therapy should be considered as part of the treatment approach in overweight or obese patients with type 2 diabetes.

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