

# Effects of Weight Loss With Orlistat on Glucose Tolerance and Progression to Type 2 Diabetes in Obese Adults

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**Background:** Orlistat is a gastrointestinal lipase inhibitor that reduces dietary fat absorption by approximately 30%, promotes weight loss, and may reduce the risk of developing impaired glucose tolerance and type 2 diabetes in obese subjects.

**Objective:** To test the hypothesis that orlistat combined with dietary intervention improves glucose tolerance status and prevents worsening of diabetes status more effectively than placebo.

**Methods:** We pooled data from 675 obese (body mass index, 30-43 kg/m<sup>2</sup>) adults at 39 US and European research centers in 3 randomized, double-blind, placebo-controlled multicenter clinical trials. Subjects received placebo plus a low-energy diet during a 4-week lead-in period. On study day 1, the diet was continued, and subjects were randomized to receive placebo 3 times a day (n=316) or treatment with orlistat, 120 mg 3 times a day (n=359), for 104 weeks. A standard 3-hour oral glucose tolerance test was performed on day 1 and at the end of treatment.

**Main Outcome Measures:** The categorical assessment of glucose tolerance status (normal, impaired, dia-

betic) and changes in status from randomization to end of treatment were the primary efficacy measures. The secondary measures were fasting and postchallenge glucose and insulin levels.

**Results:** The mean length of follow-up was 582 days. Subjects who were treated with orlistat lost more weight (mean ± SEM, 6.72 ± 0.41 kg from initial weight) than subjects who received placebo (3.79 ± 0.38 kg; *P* < .001). A smaller percentage of subjects with impaired glucose tolerance at baseline progressed to diabetic status in the orlistat (3.0%) vs placebo (7.6%) group. Conversely, among subjects with impaired glucose tolerance at baseline, glucose levels normalized in more subjects after orlistat treatment (71.6%) vs placebo (49.1%; *P* = .04).

**Conclusions:** The addition of orlistat to a conventional weight loss regimen significantly improved oral glucose tolerance and diminished the rate of progression to the development of impaired glucose tolerance and type 2 diabetes.

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**M**ORE THAN 50% of Americans are overweight or obese, with 20% classified as obese (body mass index [BMI] [calculated as weight in kilograms divided by the square of height in meters] [BMI] ≥ 30), according to recently established National Institutes of Health body weight guidelines.<sup>1</sup> An important consequence of excessive adiposity is type 2 diabetes mellitus,<sup>2,3</sup> a condition that is associated with an increased risk of mortality and morbidity.<sup>4</sup> Furthermore, the incidence and prevalence of obesity and diabetes are increasing worldwide, especially in developing and newly industrialized nations. The estimated 80 million persons with diabetes in 1990 is expected to double by the year 2000, becoming a global

epidemic, and the major part of the increase will occur in developing countries.<sup>3</sup> Over 12 million Americans are now overweight or obese and have type 2 diabetes.<sup>3</sup>

The primary treatment for type 2 diabetes is weight loss.<sup>1</sup> Weight reduction of 5% to 10% improves serum glucose and insulin levels,<sup>5,6</sup> and intentional weight loss of a similar degree lowers diabetes-related mortality risk.<sup>7</sup> Although an untested hypothesis, a widely held view among diabetes and obesity experts is that a relatively small long-term loss of body weight might lower rates of deterioration in glucose tolerance and the development of new diabetes in high-risk obese subjects. While the evidence for the short-term beneficial effects of weight loss on carbohydrate metabolism is compelling, firm experimental

## SUBJECTS AND METHODS

### SUBJECTS

The present study was a pooled analysis of three 2-year randomized placebo-controlled clinical trials<sup>9,10</sup> in which 675 obese individuals (BMI, 30-43) received either orlistat, 120 mg 3 times daily, or placebo 3 times daily with a mildly low-energy diet for 1 year; subjects who were treated for 2 years had a weight maintenance diet in the second year. Data from these clinical trials were pooled to increase the sample size to attain greater statistical power: the individual studies were powered to test the statistical significance of differences in weight loss between treatments rather than secondary measures of efficacy, such as glucose tolerance. Subjects were recruited, evaluated, and monitored at 39 clinical research centers in the United States and Europe between 1992 and 1995. Entry criteria included age greater than 18 years, BMI of 30 to 43, adequate contraception in women of childbearing potential, and absence of weight loss (>4 kg) in the previous 3 months. Subjects were excluded if they had stopped smoking within the past 6 months; had significant cardiac, renal, hepatic, gastrointestinal, psychiatric, or endocrine disorders; had drug-treated type 2 diabetes; had a history or presence of substance abuse; had excessive intake of alcohol; or concomitantly used medications that alter appetite or lipid levels. The initial demographic characteristics of the subjects were similar in all 3 studies.

### STUDY DESIGN

The effects of weight loss and orlistat on measures of glucose metabolism were analyzed retrospectively from

pooled data from three 2-year, double-blind, randomized, placebo-controlled clinical trials. The protocols from these investigations differed minimally and are described in greater detail elsewhere.<sup>8-10</sup> Only those subjects assigned to receive either orlistat, 120 mg 3 times daily, or placebo for 2 full years were included. Thus, subjects who were switched from one treatment to another at the end of year 1 were not included in the analysis. Subjects were placed on a low-energy diet that provided 30% of energy intake as fat during a 4-week, single-blind placebo lead-in period. Energy intake in year 1 was prescribed for each patient on the basis of his or her estimated daily maintenance energy requirement (1.3 × calculated basal metabolic rate) minus 2083 to 3333 kJ/d (500-800 kcal/d). During year 2, a weight-maintaining diet was prescribed.

Weight change during the 4-week lead-in period was used as a measure of the potential to lose weight, and subjects were stratified accordingly at randomization to ensure an even distribution between treatment groups of individuals who lost less than 2 kg vs 2 kg or more during the run-in period. After the 4-week placebo lead-in period, subjects were randomized on study day 1 to receive placebo or orlistat, 120-mg capsules 3 times per day with their 3 main meals for 52 or 104 weeks. Each subject provided written informed consent before entry into the trial. The study protocol was reviewed and approved by the institutional review boards or research ethics committees of each investigational site.

### ASSESSMENTS

The initial screening visit (ie, week -4) included a medical history, physical examination, body weight evaluation,

evidence in support of the hypothesis that effective medical treatment of obesity delays or prevents the onset of type 2 diabetes is lacking. Testing this hypothesis requires a large and thoroughly evaluated obese cohort combined with effective dietary and medical therapies that are applied over long periods.

The recent US<sup>8</sup> and European<sup>9</sup> multicenter evaluations of the lipase inhibitor orlistat demonstrated that in obese subjects partial inhibition (approximately 30%) of dietary fat absorption combined with behavioral treatment promotes significant weight loss and weight maintenance over 2 years. The aim of the present study was to evaluate critically, in the pooled multicenter orlistat clinical trial population, the hypothesis that relatively small long-term body weight loss significantly improves glucose tolerance and reduces the rate of diabetes onset in obese subjects.

## RESULTS

### SUBJECTS

The study design and disposition of the subjects over 2 years are shown in the **Figure**. A total of 675 subjects completed the 4-week placebo lead-in period and were randomized to receive double-blind treatment with placebo

(n=316) or orlistat, 120 mg (n=359); each subject had at least 1 follow-up visit, including a repeated OGTT. Since the present study is a meta-analysis of subjects who had at least 1 follow-up assessment of glucose tolerance, consideration of the dropout rate from the initiation of double-blind treatment is more relevant than that from enrollment into the study. Reasons for withdrawal from the study included entry violations (clinical or laboratory findings incompatible with study entry that were not available until after the patient had begun the study), lack of cooperation, administrative considerations (changes in subjects' lives making continuation impractical or impossible), adverse events (clinical adverse events or adverse laboratory findings), protocol violations, loss to follow-up, and refusal of treatment. There were no significant differences in the withdrawal rates across the individual studies or across the possible treatment end points.

The mean duration of treatment was 587 and 577 days for the orlistat and placebo groups, respectively. The end point of treatment was 2 years for 217 subjects (68.7%) and 246 subjects (68.5%) in the placebo and orlistat groups, respectively. The characteristics of the study population at randomization were similar in the 2 treatment groups (**Table 1**). The characteristics of the study populations for whom treatment end point occurred at 26, 52, or 104 weeks were also similar.

electrocardiogram, and clinical chemistry, thyroid function, hematology, and urinalysis laboratory tests. A 3-hour oral glucose tolerance test (OGTT) with a 75-g oral glucose load was performed at the time of randomization (day 1), 26 weeks (one study only), 52 weeks, and/or 104 weeks. The OGTT that most closely coincided with the time at which the patient's participation in the study ended was used for the end-point analysis. Glucose tolerance was classified according to the 2-hour serum glucose values as described by the World Health Organization.<sup>11</sup> The criterion for normal glucose tolerance was a 2-hour glucose value of less than 7.8 mmol/L (140 mg/dL). Impaired glucose tolerance (IGT) was defined as a 2-hour glucose level of 7.8 to 11.0 mmol/L (140-199 mg/dL), and diabetes was defined as a 2-hour glucose level of 11.1 mmol/L (200 mg/dL) or higher. For classification purposes, 2-hour post-glucose-challenge serum glucose values are more robust than fasting glucose levels owing to variation among subjects in the number of hours the subjects fasted prior to the test. A recent study also reports greater sensitivity of the glucose tolerance test compared with fasting glucose levels in predicting progression to type 2 diabetes.<sup>12</sup>

Body weight was evaluated every 2 weeks until week 16, every 4 weeks until the end of year 1, and every 8 weeks thereafter for the 2-year studies. Measurements taken after the subjects' last OGTT measurements were excluded.

#### STATISTICAL ANALYSIS

An end-point analysis was applied in which each subject's last OGTT at 26, 52, or 104 weeks was taken to be the treatment end point. An analysis of the intent-to-

treat population was applied, as recommended in the Consolidated Standard of Reporting Trials guidelines.<sup>13</sup> Since the analysis of the impact of treatment depended on the results of the OGTT performed at the end of treatment, statistical analyses were performed on those subjects who had baseline and follow-up OGTT and body weight measurements. Prior to pooling the data from the individual studies and for the specific treatment end points, the initial characteristics as well as the outcomes were checked for similarity across cohorts. The characteristics of the subjects in the 3 individual studies as well as the characteristics of subjects whose treatment end points occurred at 26, 52, and 104 weeks were not significantly different.

The hypothesis that changes from baseline in body weight and oral glucose tolerance were greater in the orlistat treatment group was tested using analysis of variance models with the study protocol (the 3 individual studies) and treatment as factors.<sup>14</sup> This analysis was applied to the fasting glucose and insulin values and the integrated areas under the curves (AUCs) for the 3-hour glucose and insulin responses to oral glucose, which were calculated according to the trapezoidal rule. Data are presented as mean  $\pm$  SEM. Categorical analyses of the frequency distributions of weight loss and shift in OGTT status were performed with use of  $\chi^2$  analysis.<sup>15</sup> The glucose and insulin AUCs were compared across the treatment groups by 2-way analyses of covariance using treatment (placebo or orlistat) and diabetes status (normal, impaired, or diabetic) as grouping variables, with baseline values as covariates. Additional analyses are described in the "Results" section. For all statistical analyses,  $P < .05$  was considered statistically significant. No adjustments were made for multiple comparisons.

#### WEIGHT LOSS

Obese subjects in the orlistat group achieved a weight loss of  $6.72 \pm 0.41$  kg over the study period (ie, from week -4) compared with a weight loss of  $3.79 \pm 0.38$  kg for obese subjects in the placebo group ( $P < .001$ ). Expressed as percentage of weight change from initial body weight, the orlistat group lost significantly more weight than the placebo group ( $6.8\% \pm 0.4\%$  vs  $3.9\% \pm 0.4\%$ ;  $P < .001$ ). Analysis of the frequency distribution of weight loss indicated that 52.9% of subjects in the orlistat group lost 5% or more of initial body weight and 30.1% lost 10% or more of initial weight, while 37.7% of subjects in the placebo group lost 5% or more of initial body weight and 16.5% lost 10% or more of initial weight ( $P < .001$  for orlistat vs placebo for both  $\geq 5\%$  and  $\geq 10\%$  weight loss).

#### GLUCOSE TOLERANCE

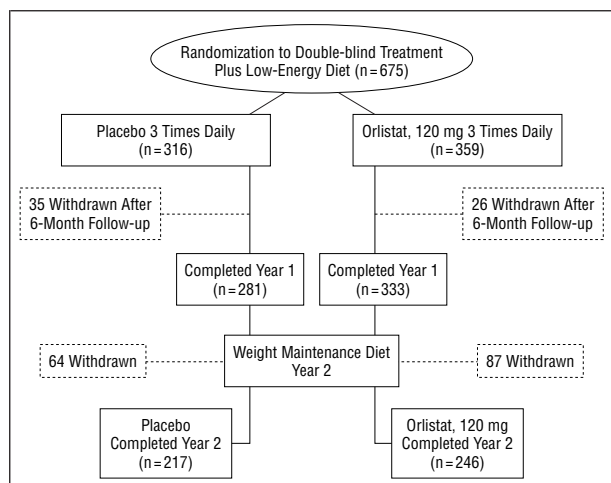
On day 1 (randomization), 5.3% of the orlistat group and 4.4% of the placebo group met the diagnostic criteria for diabetes mellitus. Impaired glucose tolerance at baseline was present in 18.7% and 16.8% of subjects in the orlistat and placebo groups, respectively. Thus, the baseline distribution among the categories of glucose tolerance was similar in the 2 treatment groups. The baseline

distributions were also similar across the 3 individual studies and among the cohorts for whom the treatment end point occurred at 26, 52, or 104 weeks.

Changes in glucose tolerance status are shown in **Table 2**. The distribution of changes in glucose tolerance status was not significantly different in the cohorts for whom the treatment end point occurred at 26, 52, or 104 weeks. Changes in glucose tolerance status were significantly different between the subjects who were categorized as normal or impaired at baseline ( $P = .04$ ). For subjects with abnormal glucose tolerance at baseline, a greater proportion who received orlistat vs placebo had improved glucose tolerance status after treatment, whereas deterioration in glucose tolerance (normal to IGT or diabetes, or IGT to diabetes) occurred in a greater proportion of subjects receiving placebo. For example, of the subjects with IGT at baseline, 71.6% who were treated with orlistat had normal glucose tolerance at the end of treatment compared with 49.1% in the placebo group ( $P = .04$ ), whereas 3.0% who were treated with orlistat progressed to diabetic status vs 7.6% in the placebo group.

#### SERUM GLUCOSE AND INSULIN LEVELS

Fasting serum glucose levels and glucose AUCs at baseline were progressively greater in subjects with IGT vs



Study design and disposition of subjects.

**Table 1. Demographic Characteristics for the Intent-to-Treat Population From the Start of the Placebo Lead-in Period (Week 4)**

Characteristic	Placebo (n = 316)	Orlistat, 120 mg (n = 359)
Male/female, No.	49/267	69/290
Race, No.		
White	278	316
African American	28	36
Hispanic	9	5
Asian	1	2
Age, mean ± SEM, y	44.3 ± 0.7	43.9 ± 0.6
Weight, mean ± SEM, kg	99.8 ± 0.9	99.0 ± 0.6
Body mass index, mean ± SEM, kg/m <sup>2</sup>	36.0 ± 0.9	35.6 ± 0.1

**Table 2. Change in Oral Glucose Tolerance Status From Baseline to End of Treatment**

Status at Baseline	Treatment	Status at End Point, No. of Subjects (%)			P*
		Normal	Impaired	Diabetic	
Normal	Placebo	219 (88.0)	27 (10.8)	3 (1.2)	.04
	Orlistat	255 (93.4)	18 (6.6)	0 (0)	
Impaired	Placebo	26 (49.1)	23 (43.4)	4 (7.6)	.04
	Orlistat	48 (71.6)	17 (25.4)	2 (3.0)	
Diabetic	Placebo	2 (14.3)	2 (14.3)	10 (71.4)	.19
	Orlistat	3 (15.8)	8 (42.1)	8 (42.1)	

\* Refers to significance of  $\chi^2$  for distribution of end-point status within each category of baseline status.

normal subjects, and greater in subjects with diabetes vs subjects with IGT. Fasting glucose levels decreased more among those subjects receiving orlistat vs placebo, whether subjects were normal or had IGT at baseline (**Table 3**). Fasting serum insulin levels and the insulin AUCs at baseline were progressively greater in subjects with IGT vs normal subjects.

Analysis of the insulin levels in the orlistat and placebo groups revealed significant interaction terms for the baseline-by-treatment interaction. Baseline insulin lev-

els tended to be higher among nondiabetic subjects in the placebo vs orlistat group. However, within the group of subjects categorized as diabetic at baseline, the mean fasting insulin level was roughly 2-fold lower among subjects receiving orlistat vs placebo. This suggests more advanced beta-cell dysfunction and more severe diabetes at baseline in the orlistat group.<sup>16,17</sup> With this baseline difference taken into account, the magnitude of change in the insulin AUC was comparable among subjects with diabetes in the placebo and orlistat groups. The improvement in the insulin AUC was significantly greater in the orlistat vs placebo group in the subjects with normal glucose tolerance at baseline ( $P = .03$ ; Table 3). Fasting glucose levels decreased significantly more in both the normal and impaired groups treated with orlistat compared with placebo (Table 3), while the glucose AUC decreased significantly more only in the normal group treated with orlistat vs placebo ( $P < .001$ ).

Further analyses were applied to the changes in glucose tolerance in order to evaluate the extent to which observed treatment effects are dependent on the greater weight loss produced by orlistat vs placebo. Analysis of covariance was applied to the 2-hour serum glucose values (which are the basis for glucose tolerance classification) using weight change as the covariate. Within the impaired group, the treatment difference was not significant after adjustment for weight change, whereas within the normal group a significant treatment effect persisted ( $P = .003$ ) after adjusting for differences in weight loss between the treatment groups.

#### COMMENT

The clinical and public health implications of the obesity-related risk for diabetes are important: over 16.6 million Americans have type 2 diabetes, and twice as many have IGT, a condition that progresses to type 2 diabetes at a rate of 6% per year.<sup>18</sup> Measures that prevent diabetes or improve glucose homeostasis are therefore central to reducing morbidity and mortality as well as augmenting quality of life and reducing national health care costs.

In the present analysis, we pooled data from 3 similar multicenter, randomized, double-blind orlistat trials to test the hypothesis that relatively small long-term body weight loss significantly improves glucose tolerance and reduces the rate of diabetes onset in obese subjects. Our observations strongly support this hypothesis. Compared with the placebo group, the orlistat group lost more weight (mean difference from placebo, approximately 3 kg), experienced improved categorical glucose tolerance status, and showed improved serum insulin and glucose levels.

The lowering of serum insulin levels observed in the present investigation may be clinically important since earlier studies have linked fasting serum insulin levels to ischemic heart disease risk, insulin resistance, and obesity-related hypertension.<sup>19</sup> The trend for reduced fasting and postchallenge serum insulin levels with treatment thus suggests that weight loss produced by orlistat combined with dietary and lifestyle intervention may improve the insulin resistance syndrome.<sup>20</sup>

**Table 3. Fasting Serum Insulin and Glucose Levels and Oral Glucose Response Areas Under the Curve (AUCs) at Randomization and After Treatment\***

Categorical Status	Study Period	Insulin, pmol/L		Glucose, mmol/L (mg/dL)		P‡				
		Fasting	AUC†	Fasting	AUC†	Insulin		Glucose		
						Fasting	AUC	Fasting	AUC	
Normal										
Placebo	Baseline (day 1)	85 ± 10	2231 ± 85	5.23 ± 0.03 (94 ± 1)	37.1 ± 0.4 (668 ± 7)					
	Follow-up	89 ± 5	2384 ± 118	5.20 ± 0.04 (94 ± 1)	37.7 ± 0.5 (679 ± 9)					
	Change	+4 ± 9	+152 ± 88	-0.04 ± 0.04 (-1 ± 1)	+0.7 ± 0.4 (+13 ± 7)					
Orlistat	Baseline (day 1)	81 ± 10	2305 ± 81	5.26 ± 0.04 (95 ± 1)	37.9 ± 0.4 (683 ± 7)					
	Follow-up	74 ± 3	2169 ± 86	5.09 ± 0.04 (92 ± 1)	36.6 ± 0.5 (659 ± 9)					
	Change	-7 ± 3	-136 ± 75	-0.16 ± 0.04 (-3 ± 1)	-1.4 ± 0.4 (-25 ± 7)	.40	.03	.02	<.001	
Impaired										
Placebo	Baseline (day 1)	110 ± 17	3566 ± 341	5.60 ± 0.09 (101 ± 2)	51.0 ± 0.7 (919 ± 13)					
	Follow-up	130 ± 24	3590 ± 311	5.70 ± 0.13 (103 ± 2)	48.7 ± 1.6 (877 ± 29)					
	Change	+20 ± 12	+24 ± 189	+0.10 ± 0.04 (+2 ± 1)	-2.3 ± 1.3 (-414 ± 23)					
Orlistat	Baseline (day 1)	102 ± 8	3426 ± 281	5.79 ± 0.11 (104 ± 2)	50.3 ± 0.7 (906 ± 13)					
	Follow-up	88 ± 7	2959 ± 222	5.37 ± 0.07 (97 ± 1)	44.5 ± 1.0 (802 ± 18)					
	Change	-14 ± 7	-467 ± 188	-0.42 ± 0.05 (-8 ± 1)	-5.7 ± 1.0 (-103 ± 18)	.07	.35	.01	.14	
Diabetic										
Placebo	Baseline (day 1)	179 ± 59	4138 ± 725	6.87 ± 0.30 (124 ± 5)	71.4 ± 2.5 (1286 ± 45)					
	Follow-up	129 ± 19	3401 ± 460	7.04 ± 0.32 (127 ± 6)	69.9 ± 3.5 (1259 ± 63)					
	Change	-50 ± 47	-737 ± 457	+0.17 ± 0.16 (+3 ± 2)	-1.5 ± 2.1 (-27 ± 38)					
Orlistat	Baseline (day 1)	97 ± 13	3230 ± 369	7.05 ± 0.27 (127 ± 5)	72.0 ± 2.3 (1297 ± 41)					
	Follow-up	131 ± 19	2750 ± 213	7.23 ± 0.58 (130 ± 10)	68.3 ± 4.8 (1230 ± 86)					
	Change	+34 ± 15	-480 ± 333	+0.17 ± 0.42 (+3 ± 8)	-3.8 ± 3.6 (-68 ± 64)	.02	.59	.97	.68	

\*All values are expressed as mean ± SEM.

†The AUC units are picomoles per liter per 3 hours and millimoles per liter per 3 hours for insulin and glucose, respectively.

‡The difference between placebo and orlistat in the change from baseline to follow-up (least square means).

The data from the present study suggest that improvements in glucose tolerance depend on relatively small changes in body weight. The improved glycemic control secondary to weight loss and the difficulty of maintaining weight loss are highlighted by the recent study of Wing et al.<sup>21</sup> Lifestyle interventions, including diet, exercise, and behavior modification, produced a mean 4.5-kg weight loss at 6 months of treatment and lowered the risk of developing type 2 diabetes in subjects who either were normal or had IGT. However, the weight loss achieved in the first 6 months of treatment was largely regained by the end of the second year, and along with this relapse all physiological measures of glucose metabolism had returned to or exceeded their baseline levels. In the present study, the orlistat group maintained weight loss that was 3 kg greater than that in the placebo group at the end of year 2, which was statistically significant. Although this difference in weight loss was modest, it was associated with significantly improved glycemic control. Moreover, within the group of subjects who had normal glucose tolerance, the effect of orlistat treatment was statistically significant after adjusting for the effect of weight change alone.

Few earlier intervention studies carried out in a medical setting have directly tested the hypothesis that intervention fostering weight loss in obese individuals diminishes the progression from IGT to diabetes. Long et al<sup>22</sup> reported that morbidly obese persons with IGT who underwent gastric bypass surgery developed diabetes at a reduced rate of 0.15 cases per 100 person-years vs the expected rate of 5% to 6%. Preliminary analysis of data

from another study of the surgical treatment of obesity, the Swedish Obesity Study,<sup>23</sup> indicated that in the surgically treated group, 69% of cases of diabetes diagnosed at baseline were reclassified as nondiabetic at 2-year follow-up compared with 16% of cases reclassified in the control group, and 0.5% of subjects in the treated group who did not have diabetes at baseline developed diabetes over 2 years compared with 7.8% in the control group. However, results of these obesity surgery interventions that produced large weight loss (>20% of initial weight) in morbidly obese subjects may have limited practical application to the treatment of less severe obesity. The Diabetes Prevention Program is an ongoing prospective multicenter randomized clinical trial to assess the impact of several interventions on reducing the rate of onset of diabetes,<sup>24</sup> but the results of this trial are not yet available.

A limitation of the present study is the fact that the baseline OGTT was performed on day 1 (randomization) after a 4-week lead-in period of placebo plus a low-energy diet. It is very likely that changes in oral glucose tolerance, both categorical and quantitative, would have been even greater if the test had been performed at the initial visit. However, both treatment groups lost similar amounts of weight during this lead-in period, and there is no evidence that use of the baseline test from the point at which subjects were randomized is a source of bias, except to the extent that the number of subjects with IGT or diabetes prior to treatment was probably underestimated. Furthermore, subjects with significant existing heart disease and uncontrolled hypertension were excluded, which would lower the number of obese sub-

jects at risk of developing IGT or type 2 diabetes. Nevertheless, significant improvements were seen in both quantitative and categorical measures of glucose tolerance, which supports the concept that modest weight loss may reduce the risk of developing diabetes in obese subjects. Finally, this report is a retrospective meta-analysis of glucose tolerance data, and none of the individual studies was powered to study shifts in glucose tolerance. Shifts in glucose tolerance status were significantly different between the orlistat and placebo groups for subjects who were normal ( $P=.04$ ) and impaired ( $P=.04$ ) at baseline, but the number of subjects who progressed to diabetic status was very small. Accordingly, confirmation of the results of this meta-analysis by prospective trials specifically designed to address this issue is warranted.

## CONCLUSIONS

Our findings indicate that even modest pharmacologically facilitated weight loss produces important metabolic benefits. Antiobesity pharmacotherapy may therefore offer an additional therapeutic option for the prevention of diabetes, although further long-term studies are required. This study demonstrates that partial inhibition of fat absorption by orlistat in obese subjects produces sustained weight loss, significantly impacts glucose and insulin metabolism, and can significantly diminish the risk of deterioration of glucose tolerance. These observations collectively suggest that pharmacologic treatment with orlistat may be a useful adjunct to dietary and lifestyle interventions in preventing or delaying the onset of glucose intolerance or type 2 diabetes in obese subjects who are at risk.

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