Effects of Moderate Weight Loss and Orlistat on Insulin Resistance, Regional Adiposity, and Fatty Acids in Type 2 Diabetes

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OBJECTIVE — Moderate weight loss is recommended for overweight and obese patients with type 2 diabetes, and conjunctive use of weight loss medication has been advocated. The current study examined weight loss–dependent and –independent effects of the intestinal lipase inhibitor orlistat at 6 months of treatment, using behavioral intervention (Int) combined with randomized, double-blinded, placebo (P)-controlled treatment with orlistat (O).

RESEARCH DESIGN AND METHODS — Metabolic control, insulin sensitivity (IS), regional fat distribution, and fat content in liver and muscle were measured in 39 volunteers with type 2 diabetes in whom all antidiabetic medication was withdrawn 1 month preceding randomization. Weight loss was equivalent in the Int+O and Int+P groups, respectively (-10.3 ± 1.3 vs. $-8.9 \pm 1.1\%$), and there were identical decreases in visceral adipose tissue (VAT), fat mass (FM), thigh adiposity, and hepatic steatosis.

RESULTS — Weight loss resulted in substantial improvement ($P < 0.001$) in HbA_{1c} (-1.6 ± 0.3 vs. $-1.0 \pm 0.4\%$; NS between groups). IS improved significantly more with orlistat ($\Delta 2.2 \pm 0.4$ vs. $\Delta 1.2 \pm 0.4$ mg · min^{-1} · kg^{-1} fat-free mass [FFM]; $P < 0.05$), and plasma free fatty acid (FFA) levels were strongly correlated with IS ($r = 0.56$; $P < 0.001$). Orlistat caused greater reductions in fasting plasma FFA ($\Delta -154 \pm 22$ vs. $\Delta -51 \pm 33$ μmol/l; $P < 0.05$), insulin-suppressed FFA ($\Delta -119 \pm 23$ vs. $\Delta -87 \pm 34$ μmol/l; $P < 0.05$), and fasting plasma glucose (FPG; -62 ± 9 vs. -32 ± 8 mg/dl; $P = 0.02$). Changes in HbA_{1c} were correlated with ΔIS ($r = -0.41$; $P < 0.01$) but not with weight loss per se.

CONCLUSIONS — At equivalent weight loss, conjunctive use of orlistat resulted in greater improvement in FFA levels and IS.

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Type 2 diabetes has an especially strong association with obesity (1,2), and the increased prevalence of type 2 diabetes closely parallels that of obesity (3). Findings from bariatric surgery indicate that substantial weight loss can markedly improve type 2 diabetes (4,5), yet even modest weight loss induces clinically important improvements (6,7), leading to a consensus that a target weight loss of ~5–10% be achieved (8,9). Conjunctive use of weight loss medication has been recommended (10,11).

Orlistat is an intestinal lipase inhibitor approved for management of obesity. In type 2 diabetes, orlistat therapy has led to greater improvement than placebo in glycemic control and larger reductions in antidiabetic medications (12–14), and orlistat reduced progression from impaired glucose tolerance to type 2 diabetes (15). These improvements are ascribed to weight loss (12), although there has been speculation that orlistat might have effects independent of weight loss (13,15). However, because orlistat acts as an intestinal lipase inhibitor and is not considered to have direct systemic effects (16,17), responsible mechanisms are unclear. The current study was undertaken to address the metabolic effects of orlistat used as monotherapy in type 2 diabetes and to determine whether there are effects that occur independently of weight loss.

RESEARCH DESIGN AND METHODS

— This was a single center, randomized, double-blinded, placebo-controlled, clinical trial of a behavioral weight loss intervention combined with orlistat (Int+O) or placebo (Int+P) in overweight and obese patients with type 2 diabetes. The goal was to achieve at least a 7% weight loss. Research volunteers were recruited from the general community by advertisement. Inclusion criteria were *1*) type 2 diabetes, *2*) BMI >27 kg/m^2, *3*) stable current weight, and *4*) good general health other than type 2 diabetes. In

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Abbreviations: CT, computed tomography; EGP, endogenous glucose production; FFA, free fatty acid; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose; IS, insulin sensitivity; L/S ratio, liver-to-spleen ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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

Table 1—*Clinical characteristics at baseline and after 6 months of weight loss intervention in type 2 diabetes*

	Int + O			Int + P		
	Baseline	6 months	Change	Baseline	6 months	Change
Weight (kg)	99 ± 3.5	87 ± 3.3*	−10.1 ± 1.4	102 ± 3.6	92 ± 3.5*	−9.4 ± 1.3
BMI (kg/m^2)	34.0 ± 1.0	30.4 ± 1.0*	−3.6 ± 0.5	35.9 ± 1.1	32.8 ± 1.1*	−3.3 ± 0.4
FPG (mg/dl)	196 ± 11	123 ± 6	−62 ± 9†	158 ± 8	126 ± 8*	−32 ± 8
HbA_{1c} (%)	8.13 ± 0.30	6.48 ± 0.24*	−1.65 ± 0.31	7.82 ± 0.3	6.85 ± 0.37*	−0.97 ± 0.39
Fasting insulin (μU/ml)	16.3 ± 2.6	9.7 ± 1.0*‡	−4.9 ± 1.2	18.3 ± 1.8	14.7 ± 1.6*	−3.6 ± 1.2
Fasting FFA (μmol/l)	691 ± 24	517 ± 23*‡	−154 ± 22†	705 ± 35	658 ± 28	−51 ± 33
Triglyceride	206 ± 26	147 ± 15*	−59 ± 22	164 ± 14	123 ± 12*	−41 ± 8
HDL cholesterol	44 ± 2	42 ± 2	−2.0 ± 2.0‡	47 ± 2	51 ± 3†	4 ± 2
LDL cholesterol	129 ± 7	110 ± 7*‡	−19 ± 4‡	128 ± 5	124 ± 6	4 ± 3

Data are means ± SE. *$P < 0.01$ for baseline vs. 6 months (paired); †$P < 0.05$ for baseline vs. 6 months (paired); ‡$P < 0.05$ for orlistat vs. placebo.

research volunteers, prior antidiabetic medications were withdrawn and, considering the decrease in insulin secretion with progressive duration of type 2 diabetes (18,19), participation was restricted to those with known duration of type 2 diabetes of ≤5 years. Individuals receiving insulin, maximal dose combinations of sulfonylurea and metformin, or thiazolidinediones were excluded. The protocol was approved by the University of Pittsburgh Institutional Review Board, and volunteers gave written informed consent.

After enrollment in the study, participants discontinued any prior metformin or sulfonylurea therapy during a 4-week baseline period, but volunteers in whom fasting plasma glucose (FPG) ≥250 mg/dl developed during baseline or the subsequent 6-month intervention were withdrawn from the study.

Weight loss interventions

A 24-h dietary recall was obtained twice during baseline and near completion of 6 months' intervention (version 4.05_33; Nutrition Data Systems for Research, Minneapolis, MN). Nutritional therapy was based on healthy food selections (8), emphasizing reduced fat consumption (≤30% of daily calories) and restriction of portions to create a daily negative energy balance of ~500 kcal/day. Volunteers met with a nutritionist weekly. In addition, participants were encouraged to gradually increase physical activity (40–60 min of moderate intensity physical activity such as walking or cycling).

After baseline assessments, participants were randomized to receive orlistat (120 mg before each meal) or placebo. Pill counts were obtained monthly to monitor medication compliance. A daily multivitamin supplement was provided. FPG was measured monthly at clinic visits, and HbA_{1c} was measured at baseline and at 6 months.

Insulin sensitivity

After baseline, participants underwent measurement of insulin sensitivity (IS) and body composition using methods previously described (20). A primed continuous infusion of 6,6-$^2H_2$ glucose was given to measure endogenous glucose production (EGP) and glucose utilization (R_d) (20). Systemic indirect calorimetry was performed (DeltaTracI; Sensormedics, Anaheim, CA) to measure resting rates of energy expenditure and glucose and lipid oxidation (21). A 4-h continuous infusion of insulin was administered at 40 mU · m^{-2} · min^{-1} using the glucose clamp procedure (22); plasma glucose was allowed to decrease until euglycemia was achieved.

Body composition assessments

Weight and height were measured using a calibrated scale. To measure fat mass (FM) and fat-free mass (FFM), dual-energy X-ray absorptiometry was performed, as previously described (23). Computed tomography (CT) was used to assess the degree of liver steatosis, to measure the cross-sectional area of adipose tissue in the abdomen and midthigh, and to evaluate thigh muscle attenuation as previously described (20). A liver-to-spleen ratio (L/S ratio) of CT attenuation values <1 is considered to represent fatty infiltration of the liver (24).

Analysis and calculations

Glucose, insulin, plasma free fatty acid (FFA), lipoproteins, and plasma glucose enrichment with 6,6-$^2H_2$ glucose were measured as previously described (20). Rates of glucose appearance and R_d during fasting and insulin infusion conditions were calculated using steady-state and non–steady-state equations, respectively (25). Rates of glucose and lipid oxidation were calculated using indirect calorimetry equations (21).

Statistics

Data are presented as means ± SE. ANOVA was used to examine the effects of group and treatment. A P value <0.05 was considered significant.

RESULTS

Weight loss and metabolic control

Baseline clinical characteristics of the 39 volunteers who completed 6-month assessments are shown in Table 1. At baseline, the two groups were closely matched for age (50.3 ± 1.9 and 52.1 ± 1.6 years for Int+O and Int+P, respectively), sex distribution (12 women and 5 men in Int+O; 14 women and 8 men in Int+P), weight, BMI, baseline HbA_{1c}, and other clinical characteristics as listed. The two groups were also well matched for other body composition variables and had similar insulin resistance, as will be presented subsequently. At 6 months, a mean weight loss of ~10% was achieved, and this was similar in the two groups. As shown in Fig. 1, the rate of weight loss was quite similar in the two groups, and the percentage of research volunteers who lost <5, 5–10, and >10% of baseline weight was similar; ~40% of participants

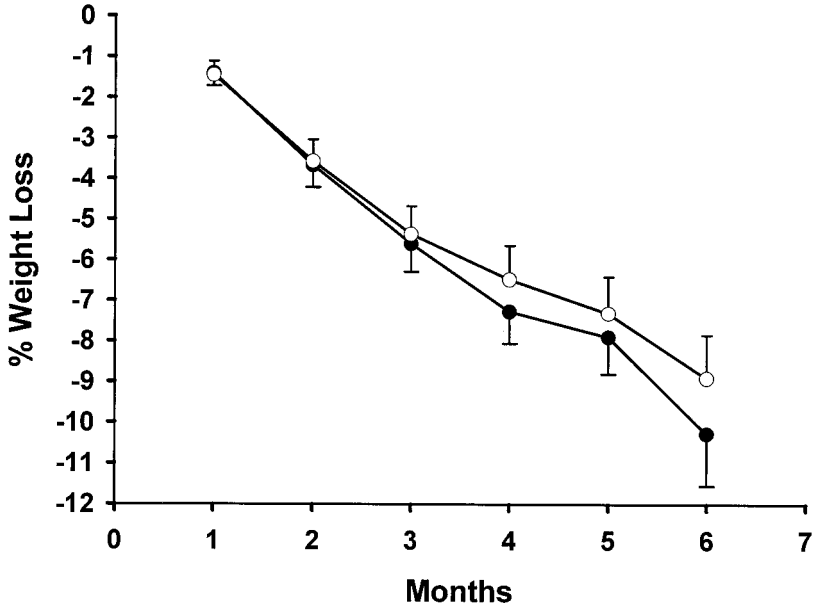

Figure 1— *The percentage of weight loss from baseline weight in volunteers with type 2 diabetes is shown for those randomized to Int + P (○) and to Int + O (●).*

achieved >10% weight loss, and 20% of participants in each group lost <5% of baseline weight. Based on pill counts at each clinic visit, compliance with orlistat and placebo was 94 ± 3 and 87 ± 3%, respectively.

The effects of weight loss on several parameters of metabolic control are also shown in Table 1. There was a highly significant decrease in HbA_{1c} in each group ($P < 0.001$). The decrement in HbA_{1c} was not significantly different between groups (−1.65 ± 0.31 and −0.97 ± 0.39% for Int+O and Int+P, respectively; $P = 0.15$). Values for FPG at 6 months were nearly identical in the two groups, but this represented a larger decrease from baseline values in the Int+O group ($P = 0.02$). The decrease in HbA_{1c} was significantly correlated with an improvement in IS ($r = 0.41$; $P < 0.01$) but was not significantly correlated with weight loss per se or changes in visceral adipose tissue (VAT) or other changes in regional adiposity. Similarly, the reduction in FPG was correlated with the improvement in IS ($r = 0.57$; $P < 0.01$) but was not significantly correlated with weight loss or changes in regional adipose tissue distribution.

At 6 months in the Int+P group, there was a significant decrease in fasting insulin, but fasting plasma FFA did not change significantly compared with baseline. At 6 months in the Int+O group, fasting values for insulin and FFA were significantly lower than at baseline, and there were significantly lower plasma FFAs in the Int+O group ($P < 0.01$). The decrease in fasting levels of plasma FFAs associated with use of orlistat remained statistically significant ($P < 0.01$) after adjusting for effects of weight loss.

With regard to lipoprotein profiles, there was a significant and similar decrease in plasma triglyceride in the two groups but a greater decrease in LDL cholesterol in those receiving Int+O ($P < 0.01$), which is consistent with prior studies (26). There was a modest and significant increase in HDL cholesterol in the Int+P group but not in the Int+O group. A nonsignificant decrease in systolic blood pressure was observed by 6 months in both groups (−3 ± 2 and −4 ± 2 mmHg for Int+O and Int+P, respectively), whereas there was a significant decrease in diastolic blood pressure (−6 ± 2 and −5 ± 2 mmHg for Int+O and Int+P, respectively; both $P < 0.01$).

Regarding side effects, 10 of the volunteers randomized to Int+O noted adverse gastrointestinal effects of loose or oily stools or increased flatus. Similar adverse effects were noted by six of the volunteers randomized to Int+P. No one withdrew from the study due to adverse effects of the medication.

Noncompleters

A total of 52 individuals were randomized to intervention and 39 completed 6 months and postintervention body composition and metabolic assessments. The data on these 39 volunteers form the basis of this report. Of the 13 volunteers who withdrew from intervention, 9 had been randomized to orlistat and 4 to placebo. Of the 13 volunteers who withdrew (6 from Int+O and 2 from Int+P), 8 individuals did so because FPG exceeded 250 mg/dl; prior pharmacologic treatment was resumed. The other five volunteers who withdrew (three from Int+O and two from Int+P) did so because of inability to attend weekly intervention visits. In those who withdrew because of FPG, withdrawal was at 10 ± 2 weeks from randomization and mean weight loss was 3.9 ± 1.1 kg (−4.2 ± 1.2%), which was not different from the average weight loss in the overall group. However, in those who withdrew from the study, an increase in FPG of 14 ± 10 mg/dl occurred despite weight loss. At baseline, those who were later withdrawn from the study due to FPG level had a higher HbA_{1c} than those completing the 6-month intervention (10.2 ± 0.3 vs. 7.9 ± 0.2%; $P < 0.001$) and higher FPG (241 ± 10 vs. 168 ± 6 mg/dl; $P < 0.001$). Similarly, fasting C-peptide (2.5 ± 0.3 vs. 3.1 ± 0.2 ng/ml) and baseline IS (2.44 ± 0.33 vs. 3.66 ± 0.30 $mg \cdot min^{-1} \cdot kg^{-1}$ FFM) tended to be lower ($P = 0.12$–0.15). Baseline weight, BMI, VAT, and plasma FFA were similar in those who withdrew from the study.

Weight loss and body composition

Consistent with the similarity in baseline BMI between groups, other baseline values for body composition, as shown in Table 2, were also quite similar, with comparable values for FM and VAT; the mean values of VAT were nearly twice the thresholds identified as posing increased metabolic risk (27). At 6 months, loss of VAT was ~26% of baseline and identical in the two groups. There was a 22 and 17% loss of FM in the Int+O and Int+P groups, respectively. There were also significant decreases in abdominal subcutaneous adipose tissue (SAT) and in the superficial and deep subdivisions of SAT, and these were closely matched in the Int+O and Int+P groups. Adipose tissue distribution in the lower extremities was similar at baseline and had comparable decreases at 6 months.

Table 2—*Body composition at baseline and after 6 months of weight loss intervention in type 2 diabetes*

	Int + O			Int + P		
	Baseline	6 months	Change	Baseline	6 months	Change
VAT (cm^2)	243 ± 24	176 ± 21*	−67 ± 14	254 ± 19	193 ± 17*	−66 ± 9
SAT (cm^2)	426 ± 23	176 ± 21	−68 ± 18	450 ± 31	384 ± 31	−67 ± 10
Superficial SAT (cm^2)	187 ± 20	169 ± 18	−18 ± 5	205 ± 19	177 ± 18	−28 ± 6
Deep SAT (cm^2)	207 ± 11	172 ± 11	−34 ± 7	231 ± 20	199 ± 19	−32 ± 7
Thigh SAT (cm^2)	108 ± 10	89 ± 11	−20 ± 4	129 ± 14	108 ± 12	−22 ± 7
SFAT (cm^2)	17.4 ± 1.4	14.2 ± 1.6	−3.1 ± 0.9	21.0 ± 2.3	17.4 ± 1.9	−3.6 ± 1.3
Muscle attenuation (CT Hounsfield units)	45.2 ± 0.7	46.6 ± 0.8*	1.5 ± 0.5	45.4 ± 0.7	46.3 ± 0.8	0.9 ± 0.5
Liver attenuation (CT Hounsfield units)	46.7 ± 2.5	58.9 ± 1.5	12.2 ± 2.3	42.8 ± 3.0	53.4 ± 2.2*	10.6 ± 2.1
L/S ratio	0.95 ± 0.04	1.15 ± 0.03*	0.20 ± 0.05	0.84 ± 0.05	1.04 ± 0.05	0.20 ± 0.04

Data are means ± SE. *$P < 0.05$; baseline vs. 6 months. SFAT, subfascial adipose tissue of the thigh.

One aspect of body composition of particular emphasis in the current study was hepatic steatosis. At baseline, for the entire cohort, mean L/S ratio was <1.0, indicative of fatty liver. In the two groups, 64 and 73% of the Int+O and Int+P groups, respectively, had L/S ratio <1.0. There was a highly significant effect of weight loss to increase the L/S ratio to mean values >1.0 in both groups. The increment for the L/S ratio was 26%, similar to the change in VAT, and was equivalent in the two groups. In those with fatty liver, there was an increase in L/S ratio, whereas in those without fatty liver at baseline, values for L/S ratio did not change despite comparable weight loss. The change in L/S ratio was correlated significantly with the change in VAT ($r = -0.38$; $P < 0.05$) but was not significantly correlated with percentage weight loss ($r = -0.28$; $P = 0.1$) or other weight loss parameters of adiposity. Baseline values for skeletal muscle CT attenuation values, a biophysical characteristic that reflects lipid content (28), were comparable at baseline in the two groups; after 6 months of intervention, these values increased slightly and similarly in the two groups.

Weight loss and IS

Baseline values for EGP (3.04 ± 0.13 vs. 2.72 ± 0.10 mg · min^{-1} · kg^{-1} FMM for Int+O and Int+P, respectively; NS) and resting energy expenditure (35.7 ± 1.2 vs. 36.2 ± 1.1 kcal/kg FFM) were similar in the two groups. There was not a statistically significant change in rates of EGP at 6 months compared with baseline (Δ0.01 ± 0.09 vs. Δ0.10 ± 0.13 mg · min^{-1} · kg^{-1} FMM). There was, however, a significant decrease in resting energy expenditure at 6 months, which was similar in the two groups (−3.3 ± 1.0 vs. −2.5 ± 0.7 kcal/kg FFM), and this is consistent with known effects of weight loss (29). Fasting values for systemic respiratory quotient were similar at baseline and decreased significantly at 6 months in the Int+P group (0.79 ± 0.001 vs. 0.77 ± 0.01; $P < 0.01$) but did not change in the Int+O group (0.79 ± 0.01 vs. 0.80 ± 0.01; NS).

Insulin-stimulated R_d was similar at baseline in the two groups, as shown in Table 3 and in Fig. 2*A* and *B*. At baseline, in response to insulin infusion, there were only slight increases in R_d above fasting rates, indicative of severe insulin resis-

Table 3—*Insulin-stimulated systemic glucose metabolism and IS at baseline and after 6 months of weight loss intervention in type 2 diabetes*

	Int + O			Int + P		
	Baseline	6 months	Change	Baseline	6 months	Change
Clamp						
R_d (mg · min^{-1} · kg^{-1} FFM)	4.23 ± 0.70	6.38 ± 0.79*	2.15 ± 0.39†	3.46 ± 0.27	4.66 ± 0.43*	1.20 ± 0.43
RQ	0.85 ± 0.01	0.87 ± 0.01*	0.02 ± 0.01	0.82 ± 0.01	0.84 ± 0.01*	0.02 ± 0.01
G Ox (mg · min^{-1} · kg^{-1} FFM)	2.80 ± 0.28	3.08 ± 0.27*	0.27 ± 0.34	2.03 ± 0.24	2.43 ± 0.24*	0.38 ± .17
G Non Ox (mg · min^{-1} · kg^{-1} FFM)	1.43 ± 0.54	3.46 ± 0.63*	1.95 ± 0.37	1.15 ± 0.14	2.39 ± 0.34*	0.90 ± 0.40
Lip Ox (mg · min^{-1} · kg^{-1} FFM)	0.98 ± 0.12	0.67 ± 0.08*	0.31 ± 0.13	1.29 ± 0.16	0.97 ± 0.11*	−0.31 ± 0.08
EGP (mg · min^{-1} · kg^{-1} FFM)	1.39 ± 0.20	0.61 ± 0.16*	0.78 ± 0.25	1.01 ± 0.14	0.54 ± 0.14	−0.47 ± 0.11*
(% suppression)	(55 ± 6)	(82 ± 4)	(27 ± 8)	(63 ± 5)	(82 ± 5)	(18 ± 5)
FFA (μmol/l)						
Mid-clamp	312 ± 18	171 ± 11*	−109 ± 18†	330 ± 22	249 ± 20*	−81 ± 24
End-clamp	225 ± 26	77 ± 10*	−119 ± 23†	263 ± 33	176 ± 31*	−96 ± 34

*$P \leq 0.05$ for baseline vs. 6 months; †$P < 0.05$ for Int + O vs. Int + P. G Ox, glucose oxidation; G Non Ox, glucose nonoxidative metabolism; Lip Ox, lipid oxidation; RQ, respiratory quotient.

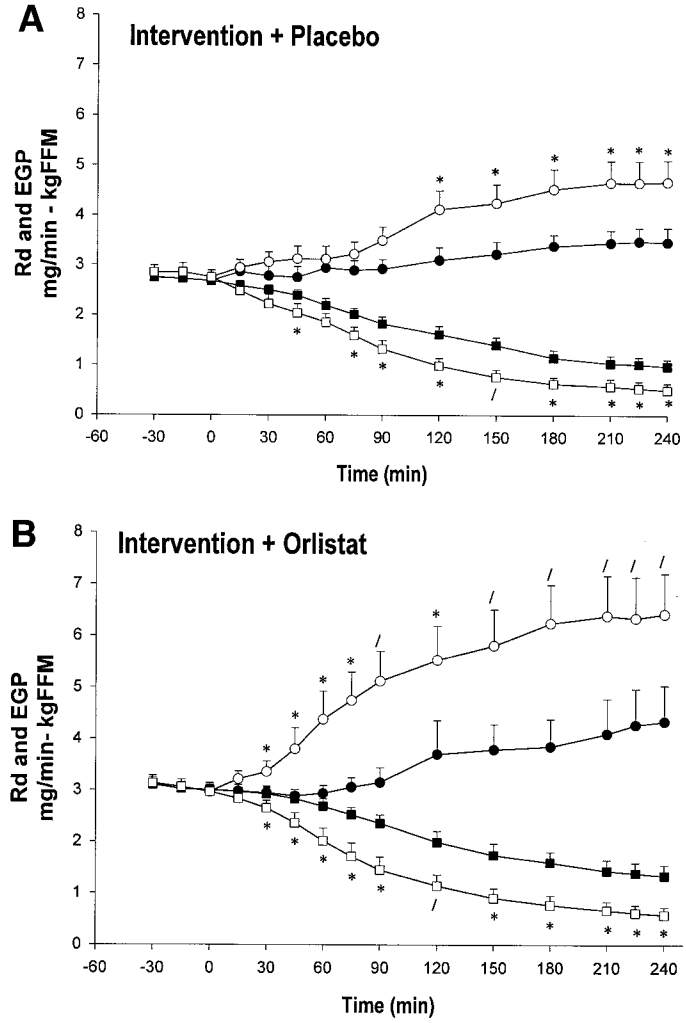

Figure 2—A: *Data from volunteers with type 2 diabetes randomized to Int + P.* B: *Data from volunteers with type 2 diabetes randomized to Int + O. Baseline values for* R_d (●) *and EGP* (■) *after an overnight fast (−30 to 0 min) and during a 4-h insulin infusion (40 mU · min^{-1} · m^{-2}) are plotted with values at 6 months for* R_d (○) *and EGP* (□). *There were significant postintervention changes in* R_d *and EGP in both groups, and the changes in* R_d *were greater after randomization to Int + O .*

tance. However, IS increased significantly after weight loss, by 63 ± 12 and 44 ± 15% in the Int+O and Int+P groups, respectively. Improvements in R_d (ΔR_d) were strongly correlated with percentage weight loss ($r = 0.62$; $P < 0.001$). In multivariate analysis, ΔR_d was significantly correlated with changes in BMI, VAT, and weight, but percentage weight loss was the strongest single correlate of the change in IS.

There was a greater improvement in IS in the Int+O group ($P < 0.05$). Values for R_d were significantly correlated with plasma FFA during fasting conditions ($r = -0.36$; $P < 0.001$) and plasma FFA during clamp conditions ($r = -0.56$; $P < 0.0001$). There was greater suppression of FFA in the Int+O group than in the Int+P group after weight loss, as shown in Fig. 3. Mostly, this reflected a significant treatment effect of orlistat to lower fasting levels of FFA as well as differences that persisted during the clamp conditions. The increase in R_d was most clearly manifested by an increase in nonoxidative glucose metabolism. There was a significant increase in insulin-stimulated respiratory quotient and a significant decrease in rates of lipid oxidation during post–weight loss changes; these changes were similar in the two groups.

There was a significant improvement in insulin suppression of EGP, as also shown in Fig. 2*A* and *B*. The improved suppression of EGP by insulin was similar in the two groups and was significantly correlated with changes in VAT and weight. The correlation was strongest for weight loss ($r = 0.40$; $P < 0.05$). Improved suppression of EGP was also strongly related to the improvement in HbA_{1c} ($r = 0.55$; $P < 0.001$).

Dietary assessments

There were no significant differences in nutritional patterns between groups at baseline, with respect to estimated daily calories (2,264 ± 124 vs. 2,101 ± 178 kcal/day for Int+O and Int+P, respectively) and fat and carbohydrate intake; fat accounted for 36–38% of daily calories. At 6 months, there was a significant reduction in daily caloric consumption (−502 ± 176 and −568 ± 174 cal/day for Int+O and Int+P, respectively) and there were significant differences between groups in patterns of macronutrient consumption. Those randomized to Int+P reduced calorie intake but not the relative proportions of fat (−4 ± 2%) and carbohydrate (1 ± 2%). Among volunteers randomized to Int+O, there was a more selective reduction in fat intake (−10 ± 4%) with a higher relative percentage of carbohydrate intake (9 ± 3%).

Because the mechanism of action of orlistat is to reduce the absorption of triglyceride by ~30%, data on ingested amounts do not fully reflect amounts of fat that are actually absorbed. Therefore, the estimated effect of Int+O was a 50% decrease in total fat intake (98 ± 8 vs. 43 ± 8 g/day; $P < 0.001$).

CONCLUSIONS— It is recommended that overweight and obese individuals with type 2 diabetes achieve at least modest weight loss to improve metabolic control and lessen cardiovascular risk (8,9). In the current study, a mean weight loss of ~10% was achieved, using individualized nutritional counseling, behavioral interventions, moderate intensity physical activity, and randomization to double-blinded, placebo-controlled, conjunctive use of orlistat or placebo. There was substantial improvement in glycemic control; at 6 months, HbA_{1c} was decreased by 1.6 ± 0.3 and 1.0 ± 0.4% in the orlistat and placebo groups, respectively. This improvement occurred without use of other pharmacologic approaches to control hyperglycemia and

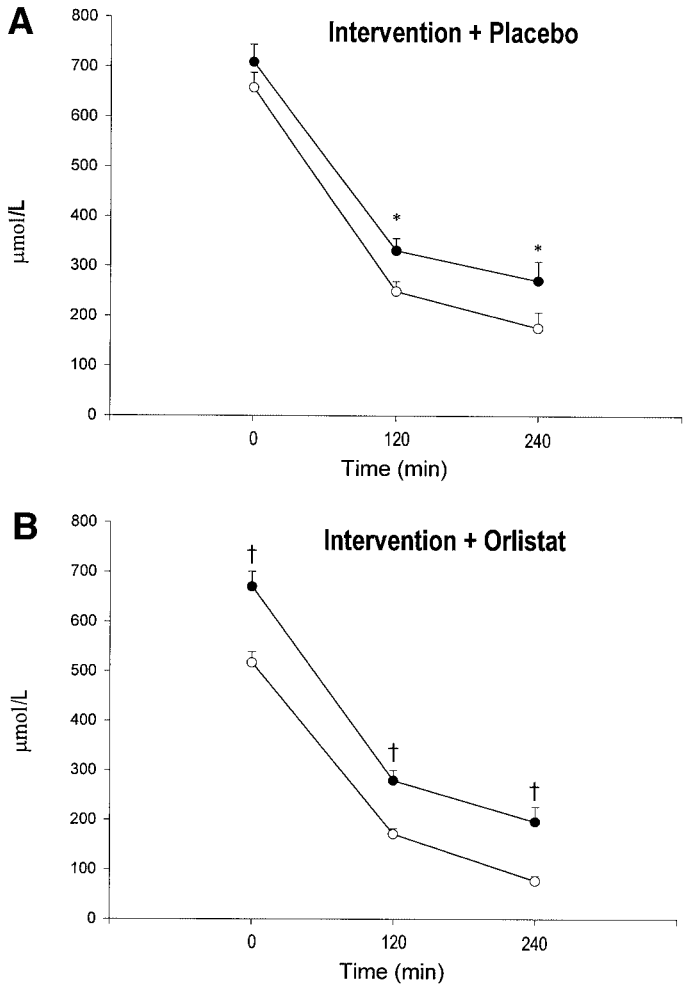

Figure 3— A: *Data from volunteers randomized to Int + P.* B: *Data from volunteers randomized to Int + O. Baseline for plasma FFA (●) and during a 4-h insulin infusion and are plotted with corresponding values at 6 months (○). There were significant postintervention changes in plasma FFA in both groups. The changes were greater with Int + O.* *$P < 0.05$; †$P < 0.01$.

is quite comparable to the effects of a 5–10% weight loss on HbA_{1c} earlier reported by Wing et al. (7) and equivalent to or greater than what is typically obtained with pharmacologic monotherapy (30). However, not all volunteers were able to reduce FPG with weight loss, and eight participants needed to resume antidiabetic medications. This has been previously noted (31) and is related to a longer duration of diabetes and more severely impaired insulin secretion. In our study, failure of hyperglycemia to respond to weight loss was associated with higher baseline values for HbA_{1c} and FPG.

In the participants who were able to complete 6 months of weight loss intervention, there was substantial improvement in IS, in suppression of EGP by insulin, and in suppression of FFA. It is interesting to note that improvement in glycemic control was more strongly related to improved IS than to weight loss per se or loss of specific aspects of regional adiposity. This association is consistent with the strong role that insulin resistance has in the pathogenesis of type 2 diabetes.

Even though weight loss was quite similar in the orlistat and placebo treatment groups, and despite highly comparable changes in regional adiposity, including nearly identical decrements of VAT, hepatic steatosis, and skeletal muscle fat content, improvement in IS was significantly greater with orlistat therapy. Prior studies have not directly examined the effects of orlistat on IS measured by a criterion method such as euglycemic insulin infusion. Improved IS is clearly a desirable metabolic effect of weight loss, and prior studies have found this is related to negative energy balance as well as loss of adipose tissue (32–34). However, because the rates and amounts of weight loss in the orlistat and placebo arms of the intervention were highly comparable, these important factors do not account for the differential effect. However, a differential treatment effect on plasma FFA likely did contribute to differences in IS.

There was greater reduction in fasting and insulin-suppressed plasma FFA in those receiving orlistat. Plasma FFA levels were a strong correlate of IS both before and after weight loss. There are convincing data that plasma levels of FFA modulate severity of insulin resistance in type 2 diabetes (35–37). The effect of orlistat to lower FFA more than placebo was significant after statistical adjustment for weight loss. This effect of orlistat is, to our knowledge, a novel observation. Plasma levels of FFA were not assessed during prior large clinical trials of orlistat treatment in those with type 2 diabetes (12–14) or in nondiabetic volunteers (15,26). There is a recent report that a single dose of orlistat, given before a relatively high fat content meal in overweight patients with type 2 diabetes, is associated with lower postprandial levels of plasma FFA compared with placebo (38).

Orlistat is an intestinal lipase inhibitor and inhibits absorption of ~30% of ingested triglyceride, which is the mechanism leading to weight loss (16). In the three prior multicenter trials of orlistat therapy in type 2 diabetes, weight loss at 6 months was ~6% among sulfonylurea-treated volunteers (12), ~4% among insulin-treated volunteers (13), and ~5% among those receiving metformin therapy (14), and in each of the above trials, weight loss was generally 2–4% greater with orlistat than placebo. The mean loss of nearly 10% of baseline weight in the current study is greater than in the trials cited above, but the behavioral interventions were more intensive, with weekly individual sessions. Frequency of behavioral visits is an important determinant of weight loss (10).

Fatty liver or hepatic steatosis has been reported to occur commonly in overweight and obese patients with type 2 diabetes (39), and among the research volunteers in the current study, we found that 70% had fatty liver at baseline. A mean weight loss of nearly 10% led to a

20% mean improvement in the L/S ratio, indicative of clear improvement in fatty liver (40). A prior study by Ryysy et al. has shown that fatty liver in type 2 diabetes contributes importantly to the severity of hepatic insulin resistance (41). In the current study, we observed improved insulin suppression of EGP after weight loss, and this was correlated with the improvements in HbA_{1c} and FPG.

In summary, a successful behavioral intervention of nutrition and physical activity changes resulted in a mean weight loss of nearly 10% among a group of overweight and obese research volunteers with type 2 diabetes. This had a clear and clinically significant effect to reduce hyperglycemia, dyslipidemia, and blood pressure and was associated with a marked improvement in hepatic and peripheral tissue insulin resistance. In those receiving orlistat, despite weight loss equivalent to those receiving a placebo medication, there was a greater reduction in fasting hyperinsulinemia and plasma FFA and a greater improvement in IS. The greater reduction in plasma FFA achieved with orlistat therapy would seem to be the major factor responsible for greater improvement in IS. Further investigation is needed to understand the mechanism for lowering of plasma FFA with orlistat therapy, though this likely is related to effects on triglyceride absorption and postprandial lipemia because this medication is not systemically absorbed. The effect of orlistat to lower FFA and improve IS is more than accountable for by weight loss per se and may translate into independent clinical benefits. This, too, was beyond the scope of the present study, and the current indication to use orlistat remains to enhance weight loss in the treatment of the comorbidities of obesity.

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