The Effect of Orlistat-Induced Weight Loss, Without Concomitant Hypocaloric Diet, on Cardiovascular Risk Factors and Insulin Sensitivity in Young Obese Chinese Subjects With or Without Type 2 Diabetes

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Background: We examined the weight-losing effect of orlistat treatment on insulin sensitivity and cardiovascular risk factors in a group of severely obese young Chinese patients with or without type 2 diabetes mellitus.

Methods: Obese patients with diabetes (n=33) and obese nondiabetic patients (n=27) were given orlistat, 120 mg 3 times daily, without a concomitant hypocaloric diet for 6 months (body mass index [calculated as weight in kilograms divided by the square of height in meter; kg/m^2] range, 27.8-47.4). The efficacy measures were (1) insulin sensitivity indices derived from the homeostasis model assessment and a composite measure of whole-body insulin sensitivity index; (2) glycemic control; (3) cardiovascular risk factors, including anthropometry, blood pressure, lipid profiles, and albuminuria; and (4) body composition determined by dual-energy x-ray absorptiometry.

Results: At baseline, patients with diabetes had lower body mass index and percentage of body fat but higher waist-hip ratios and were more insulin resistant. Orlistat therapy reduced body weight, waist and hip circumferences, percentage of total body fat, blood pressure, fasting plasma glucose and lipid levels, albuminuria, and insulin sensitivity indices in both groups (all, $P<.05$). Despite less weight reduction, we found a greater percentage of reduction from baseline in glycosylated hemoglobin level (–11.6% vs –3.6%; $P<.001$), fasting plasma glucose level (–18.2% vs –5.0%; $P<.001$), and systolic blood pressure (–7.1% vs –3.1%; $P=.02$) in patients with diabetes. Obese subjects without diabetes had greater improvements in triglyceride levels, albuminuria, and the homeostasis model assessment (all, $P<.01$).

Conclusion: Short-term orlistat treatment without the use of a hypocaloric diet significantly improved insulin sensitivity and cardiovascular risk profiles in severely obese Chinese patients with or without type 2 diabetes.

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OBESITY IS considered by the World Health Organization to be a chronic disease and a massive public health problem.[1] The rising prevalence of childhood obesity and young-onset diabetes mellitus in Asian populations represents major health care challenges because of the frequent coexistence of multiple risk factors and their long duration of disease.[2,3] Many studies have confirmed the close associations between obesity and type 2 diabetes, hypertension, dyslipidemia, insulin resistance, and albuminuria.[4-9] The clustering of these risk factors acts synergistically to increase cardiovascular morbidity and mortality. A weight reduction of 5% to 10% has been shown to improve the cardiovascular risk profile and glycemic control.[10-15] Apart from dietary restriction and lifestyle modification, pharmacological agents are often used in weight reduction programs. Orlistat is an inhibitor of the gastrointestinal lipase that reduces the absorption of dietary fat by about 30%.[16] Previous studies have confirmed the efficacy of orlistat in weight reduction with improvement in cardiovascular risk factors among obese white subjects.[17-24] In contrast, there is a paucity of data on the efficacy of these drugs in Asian populations, despite the high prevalence of relative obesity in these countries.[25] Moreover, given the close relationships among insulin resistance, obesity, and cardiovascular risk factors, the effects of orlistat treatment on insulin sensitivity have not been fully examined. To date, most of these studies were conducted in conjunction with a closely supervised hypocaloric diet. Although several studies suggest that weight reduction in obese subjects with diabetes was less than that in subjects with glucose tolerance values within the reference range when given the same dosages

of orlistat, these studies were conducted in different clinical settings.[17,22] In this study, we compared the efficacy of 6-month orlistat treatment on weight reduction, cardiovascular risk factors, and insulin sensitivity between young obese Chinese subjects with or without type 2 diabetes in a general medical clinic setting.

METHODS

SUBJECTS

Obese subjects aged 18 to 50 years with a body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) of at least 27 were recruited from the medical outpatient clinics at the Prince of Wales Hospital, Shatin, Hong Kong. These subjects were initially referred to the hospital for weight management. Subjects with type 2 diabetes, diagnosed according to the 1985 World Health Organization criteria, were recruited from the diabetes clinic. Obese nondiabetic subjects had fasting plasma glucose levels of less than 110 mg/dL (<6.1 mmol/L) and were recruited from the endocrine clinic. Secondary causes of obesity were excluded. All of these subjects had received advice on dietary restriction and lifestyle modification but remained obese with a stable body weight (±2%) for at least 6 months before recruitment to the study. The study was approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong. All subjects gave written informed consent.

Exclusion criteria included pregnancy, lactation, childbearing potential with inadequate contraceptive measures, psychiatric or neurological disorders, alcohol or other substance abuse, a history of recurrent nephrolithiasis or symptomatic cholelithiasis, previous gastrointestinal tract surgery for weight reduction, a history or the presence of malignancy, a significant history of cardiovascular complications (eg, stroke, ischemic heart disease, and congestive heart failure), and renal impairment with a plasma creatinine level of greater than 1.7 mg/dL (>150 µmol/L).

STUDY DESIGN

We conducted an open-label, prospective cohort study. After giving written informed consent, eligible subjects underwent a comprehensive assessment including documentation of medical history, physical examination, anthropometric indices, and measurement of laboratory variables. All subjects underwent a 75-g oral glucose tolerance test (OGTT) at baseline and at 6 months on discontinuation of treatment. Plasma glucose and insulin levels were measured at 0, 15, 30, 60, and 120 minutes during the OGTT. Insulin resistance was estimated using the OGTT-derived homeostasis model assessment (HOMA-IR) derived from the following equation[26]:

$$\text{HOMA-IR} = (\text{Fasting Plasma Glucose Level} \times \text{Fasting Plasma Insulin Level})/22.5$$

The insulin sensitivity indices were determined by the OGTT-derived composite measure of whole-body insulin sensitivity (COMPOSITE-IS) derived from the following equation[27]:

$$\text{COMPOSITE-IS} = \frac{10\,000}{\sqrt{\begin{array}{l}\text{Fasting Plasma Insulin Level} \\ \times \text{ Fasting Plasma Glucose Level} \\ \times \text{ (Mean OGTT Plasma Glucose Level} \\ \times \text{ Mean OGTT Plasma Insulin Level)}\end{array}}}$$

Patients treated with insulin (n=5) were not included in the analysis of insulin concentration, insulin resistance, and sensitivity indices. Body composition was measured by means of dual-energy x-ray absorptiometry (Hologic Elite 4500A; Hologic, Inc, Bedford, Mass) at baseline and at the completion of study.

All subjects were given orlistat capsules, 120 mg 3 times daily, with appropriate instructions and warnings about adverse effects. Subjects were asked to maintain their usual diet. No specific recommendation was given regarding the type of food that subjects should consume. Lipid-soluble vitamins were not supplemented, as the study lasted only 6 months. Subjects returned to the clinic at monthly intervals after at least 8 hours of fasting and without taking their usual medications on the visit day. At each visit, body weight and waist and hip circumferences were measured with the subjects wearing light clothing and no shoes. Sitting blood pressure, after at least 5 minutes of rest, was measured by the same research nurse throughout the study using an appropriately sized cuff. The mean values of 2 readings taken 1 minute apart were used and the Korotkoff sound V was taken as the diastolic blood pressure reading. In all subjects, fasting plasma glucose concentration was measured at each visit. Levels of glycosylated hemoglobin (HbA_{1c}), fasting plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and calculated low-density lipoprotein cholesterol (LDL-C) were measured at baseline and 3-month intervals. We measured 24-hour urinary albumin excretion in duplicate at baseline, month 3, and month 6 after the exclusion of urinary tract infection.

At baseline and the end-of-study visit, quality of life was assessed by means of the Chinese version of the 36-Item Short-Form Health Survey (SF-36).[28] At each visit, all adverse events and effects and drug tolerability were recorded, and treatment compliance was confirmed by capsule counting. All subjects were instructed to continue with their usual diet and medications, with careful documentation of all changes in medications, if any.

Plasma glucose level (hexokinase method), levels of TC (enzymatic method), TG (enzymatic method without glycerol blanking), and HDL-C (dextran sulfate–magnesium chloride precipitation) were measured on a Hitachi 911 automated analyzer (Boehringer Mannheim, Mannheim, Germany) using reagent kits supplied by the manufacturer of the analyzer. The precision performance of these assays was within the manufacturer's specifications. Levels of LDL-C were calculated using the Friedewald equation.[29] Levels of HbA_{1c} were measured by means of an automatic ion-exchange chromatographic method (Bio-Rad Laboratories, Hercules, Calif) (reference range, 5.1%-6.4%). Plasma C peptide level was measured by means of radioimmunoassay (Novo Nordisk, Copenhagen, Denmark) with an intra-assay coefficient of variation of 3.4% and an interassay coefficient of variation of 9.6%. (The lowest detection limit was 0.1 nmol/L.)

STATISTICAL ANALYSIS

In a study involving obese patients with type 2 diabetes, an SEM of 0.51 kg (n=139) was associated with a mean weight loss of 6.2 kg after 1 year of treatment with orlistat.[22] Using these data, we estimated that 34 patients were required to give a 0.8 power at an α level of .05 (2-sided) to achieve a clinically relevant weight change of 3 kg after 6 months of orlistat treatment.

Statistical analysis was performed using the Statistical Program for Social Sciences (version 9.0; SPSS Inc, Chicago, Ill). Intention-to-treat analysis using the late-observation-carried-forward approach was performed. Levels of 24-hour urinary albumin excretion, plasma TG, and insulin were logarithmically transformed due to skewed distributions. All data are expressed as mean±SD or geometric mean ×/÷antilogarithm SD as appropriate. Unpaired *t* test was used for between-group comparisons of the diabetic and nondiabetic groups. We used a paired *t* test for within-patient comparisons of metabolic indices and cardiovascular risk factors between baseline and 6 months, and

Table 1. Clinical and Biochemical Characteristics of Young Chinese Obese Patients With or Without Type 2 Diabetes Before and After 6-Month Treatment With Orlistat[a]

	Diabetic (n = 33)		Nondiabetic (n = 27)	
	Baseline	6-Month	Baseline	6-Month
Anthropometry				
Weight, kg	93.2 ± 18.4	90.3 ± 18.6[b]	98.7 ± 18.8	94.0 ± 19.1[b]
Body mass index[c]	34.2 ± 4.7	33.0 ± 4.8[b]	37.2 ± 6.0[d]	35.4 ± 6.4[b]
Waist circumference, cm	105.0 ± 10.1	101.2 ± 10.9[b]	105.5 ± 13.6	100.1 ± 13.6[b]
Hip circumference, cm	110.5 ± 9.7	108.7 ± 9.3[e]	120.6 ± 11.3[f]	116.3 ± 11.8[b]
Waist-hip ratio	0.95 ± 0.06	0.93 ± 0.05[e]	0.87 ± 0.07[f]	0.86 ± 0.06[e]
DEXA-assessed body fat, %	34.5 ± 6.6	33.0 ± 6.1[b]	38.8 ± 6.0[g]	37.1 ± 6.6[b]
DEXA-assessed lean mass, %	58.7 ± 12.5	58.9 ± 13.0	57.9 ± 11.0	56.9 ± 11.1[e]
Metabolic profiles				
Fasting plasma glucose, mg/dL[h]	175 ± 70	130 ± 43[b]	97 ± 27[f]	90 ± 16
HbA_{1c}, %	8.5 ± 2.0	7.2 ± 1.3[e]	5.6 ± 0.7[f]	5.3 ± 0.5[i]
TC, mg/dL[h]	197 ± 54	174 ± 39[e]	197 ± 32	178 ± 31[e]
LDL-C, mg/dL[h]	104 ± 31	93 ± 27[e]	124 ± 32[d]	104 ± 27[b]
HDL-C, mg/dL[h]	42 ± 8	39 ± 19	46 ± 12	46 ± 12
TG, mg/dL[hj]	221×/÷204	195×/÷177	142×/÷159[d]	115×/÷150[e]
Systolic blood pressure, mm Hg	124 ± 18	115 ± 17[b]	112 ± 12[g]	108 ± 12[e]
Diastolic blood pressure, mm Hg	85 ± 13	77 ± 7[b]	80 ± 10	75 ± 12[b]
24-hour UAE, mg/d[j]	84.6×/÷6.9	69.2×/÷5.5	17.1×/÷3.8[f]	13.5×/÷3.5[i]
Fasting plasma insulin, μIU/mL[hjk]	16×/÷0.3	15×/÷0.3	15×/÷0.6	12×/÷0.3
HOMA-IR[jk]	40.7×/÷1.6	28.3×/÷2.1[e]	24.0×/÷1.9[f]	17.2×/÷2.3[e]
COMPOSITE-IS[jk]	6.9×/÷1.5	9.3×/÷1.9[e]	7.6×/÷1.8	10.7×/÷2.0[b]
Concomitant medications, No. (%)				
Oral antidiabetic drugs	27 (82)		0	
Insulin treatment	5 (15)		0	
Antihypertensive treatment(s)	16 (48)		2 (7)	
Drug(s) for lowering lipid levels	6 (18)		1 (4)[f]	

[a]Unless otherwise indicated, data are given as mean ± SD. Equations to determine the values of the insulin sensitivity index derived from the homeostasis model assessment (HOMA-IR) and a composite measure of whole-body insulin sensitivity index (COMPOSITE-IS) are given in the "Study Design" subsection of the "Methods" section. The diabetic patients consisted of 13 male and 20 female patients (mean ± SD age, 36 ± 8 years); the nondiabetic patients consisted of 7 male and 20 female patients (mean ± SD age, 32 ± 10 years). DEXA indicates dual-energy x-ray absorptiometry; HbA_{1c}, glycosylated hemoglobin level; TC, total cholesterol level; LDL-C, low-density lipoprotein cholesterol level; HDL-C, high-density lipoprotein cholesterol level; TG, triglyceride level; and UAE, urinary albumin excretion.

[b]$P<.001$ for within-group comparison between baseline and 6-month treatment values using the paired *t* test.

[c]Calculated as weight in kilograms divided by the square of height in meters.

[d]$P<.05$ for between-group comparison at baseline.

[e]$P<.02$ for within-group comparison between baseline and 6-month treatment values using the paired *t* test.

[f]$P<.001$ for between-group comparison at baseline.

[g]$P<.01$ for between-group comparison at baseline.

[h]To convert glucose to millimoles per liter, multiply by 0.0555; TC, LDL-C, and HDL-C to millimoles per liter, by 0.0259; TG to millimoles per liter, by 0.0113; and insulin to picomoles per liter, by 6.945.

[i]$P<.05$ for within-group comparison between baseline and 6-month treatment values using the paired *t* test.

[j]Expressed as geometric mean ×/÷ antilogarithm SD.

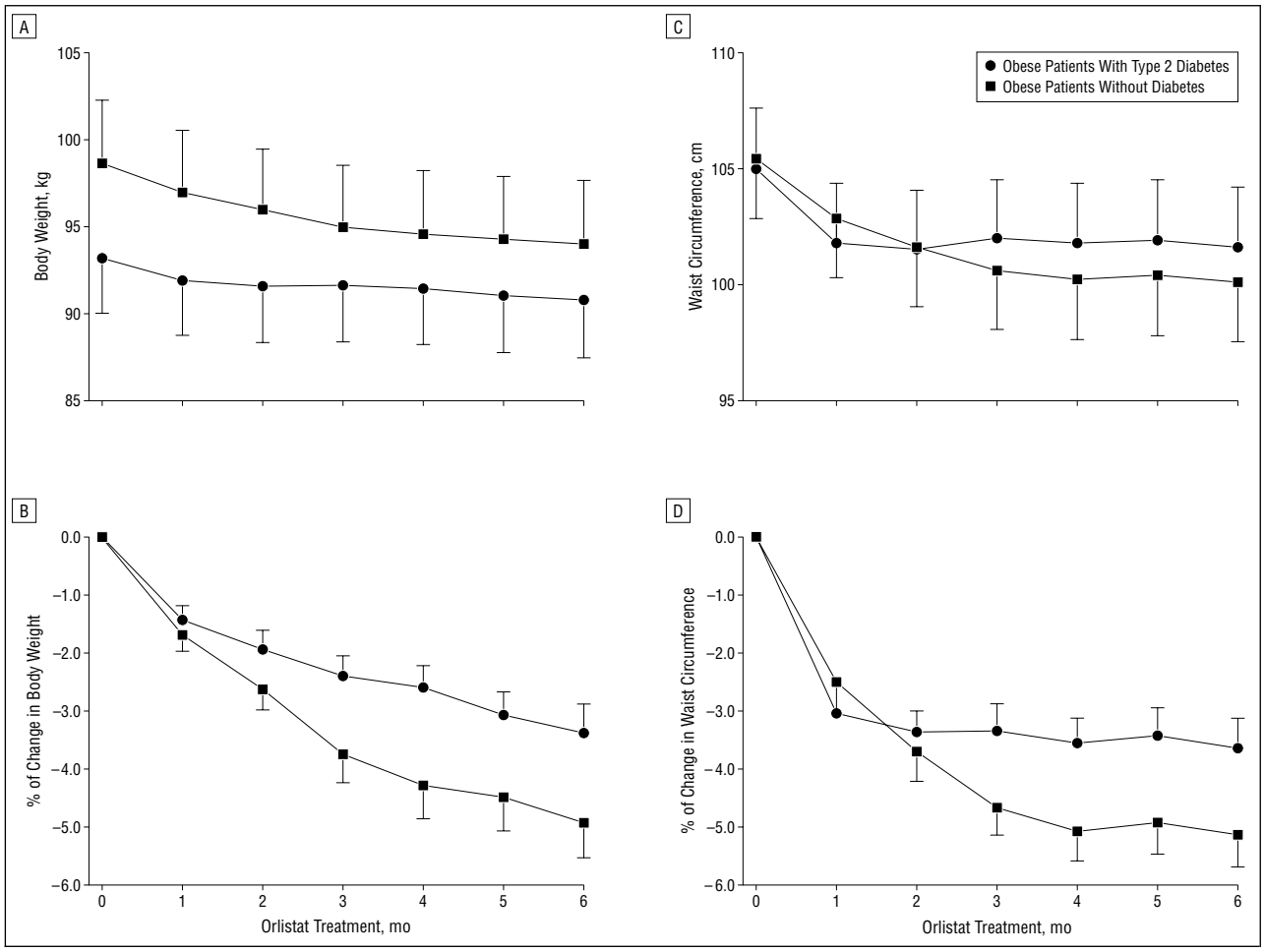
[k]Insulin-treated patients (n = 5) were not included in the analysis.

repeated-measures analysis of variance (ANOVA) to examine the effects of the presence or absence of diabetes, duration of treatment, and their interactions on these variables. We used Pearson correlation analysis to examine the relationships between percentage of changes in body weight, percentage of body fat, waist circumference, and cardiovascular risk factors. $P<.05$ (2-tailed) was considered to be significant.

RESULTS

Sixty obese patients (30 with type 2 diabetes mellitus and 30 with normal fasting plasma glucose levels) were recruited into the study. Four patients were prematurely discontinued from the study owing to pregnancy (1 patient from the diabetic group at month 5), withdrawal of consent (1 patient from the diabetic group), and nonattendance of last visit (1 patient from each group). However, their data were included using the intention-to-treat analysis. In addition, 3 subjects in the nondiabetic group were newly diagnosed as having type 2 diabetes mellitus on results of the formal 75-g OGTT and were included in the diabetic group for analysis purpose. As a consequence, 33 patients with diabetes and 27 nondiabetic patients were included in the present study.

At baseline, patients with diabetes had a lower BMI ($P=.04$), hip circumference ($P<.001$), and dual-energy x-ray absorptiometry–assessed body fat percentage ($P<.01$) but a higher waist-hip ratio (WHR; $P<.01$) than nondiabetic patients (all, $P<.05$). They also had higher plasma TG levels ($P=.02$), systolic blood pressure ($P<.001$), and urinary albumin excretion ($P<.001$) and were more insulin resistant (HOMA-IR; $P<.001$) than their nondiabetic counterparts (**Table 1**). In the dia-



Changes in body weight and waist circumference in 33 obese patients with type 2 diabetes and 27 nondiabetic obese patients during a 6-month treatment with orlistat, 120 mg 3 times daily. A, Change during the study in body weight; B, percentage of changes in body weight; C, change in waist circumference; and D, percentage of changes in waist circumference. Changes are measured from the initial baseline values. Data are given as mean±SEM.

betic group, 7 patients were on dietary restriction; 7 received metformin hydrochloride; 14 received metformin and sulfonylureas; and 5 patients received insulin therapy. Nearly 50% and 18% of the patients with diabetes received concurrent antihypertensive drugs and drugs to lower lipid levels, respectively. That was in contrast to about 7% and 4%, respectively, in the nondiabetic group. Medication therapy was not altered during the study period.

ANTHROPOMETRY

After the 6-month orlistat treatment, we found significant reductions in body weight, BMI, percentage of body fat, waist and hip circumferences, and WHR in both diabetic and nondiabetic groups (all, $P<.001$; Table 1). As depicted in the **Figure**, absolute and percentage of change in BMI and waist circumference declined gradually and significantly in both groups throughout the study. We found no difference in the mean percentage of changes in BMI and waist circumference between the 2 groups, although the reduction in WHR was greater in patients with diabetes (**Table 2**). Total body fat was reduced significantly in both groups ($P<.001$, repeated-measures ANOVA), and the percentage of reduction was greater in the nondiabetic group ($P=.02$, repeated-measures ANOVA). The reduction of lean body mass was observed only in the nondiabetic group ($P=.003$).

CARDIOVASCULAR RISK PROFILES AND INSULIN SENSITIVITY

Results of univariate analysis (Table 1) and repeated-measures ANOVA (Table 2) demonstrated significant treatment effects for orlistat in all cardiovascular risk factors except for HDL-C level in both groups. We found significant group-treatment interactions among patients with diabetes who had greater reduction from baseline in systolic blood pressure ($P=.02$), HbA_{1c} level ($P<.001$), and plasma glucose level ($P<.001$) than the nondiabetic group (repeated-measures ANOVA). Measures of insulin action, including HOMA-IR and COMPOSITE-IS, also improved with orlistat treatment in both groups ($P<.001$). The improvement in HOMA-IR was significantly greater in the nondiabetic group ($P=.002$).

CORRELATIONS

Table 3 shows the correlation matrix among various anthropometric, glycemic, lipid, blood pressure, albumin-

Table 2. Changes in Body Weight, Anthropometric Measurements, and Cardiovascular Risk Factors in Young Chinese Obese Patients With or Without Type 2 Diabetes*

	Mean % of Change		*P* Value		
	Diabetic Obese Patients	Nondiabetic Obese Patients	Interaction Effect	Treatment Effect	Group Effect
Anthropometry					
Weight, kg	−3.3	−4.9	.02	<.001	.44
Body mass index†	−3.3	−4.9	.03	<.001	.09
Waist circumference, cm	−3.6	−5.1	.04	<.001	.81
Hip circumference, cm	−1.6	−3.6	.004	<.001	.002
Waist-hip ratio	−1.9	−1.6	.52	<.001	<.001
DEXA-assessed body fat, %	−4.4	−4.8	.63	<.001	.02
DEXA-assessed lean mass, %	+0.4	−1.8	.02	.16	.65
Metabolic profiles					
Fasting blood glucose, mg/dL‡	−18.2	−5.0	.02	<.001	<.001
HBA_{1c}, %	−11.6	−3.6	.03	<.001	<.001
TC, mg/dL‡	−9.4	−9.5	.71	<.001	.74
LDL-C, mg/dL‡	−9.9	−13.5	.35	<.001	.13
HDL-C, mg/dL‡	−0.7	+0.4	.42	.27	.02
TG, mg/dL‡	−1.6	−19.7	.75	.04	.003
Sitting systolic blood pressure, mm Hg	−7.1	−3.1	.01	<.001	.02
Sitting diastolic blood pressure, mm Hg	−8.9	−7.1	.36	<.001	.06
24-hour UAE, mg/d	−3.1	−6.7	.81	.02	<.001
Fasting plasma insulin, μU/mL‡§	−4.1	−8.9	.50	.01	.21
HOMA-IR§	−11.7	−19.5	.87	<.001	.002
COMPOSITE-IS§	+56.8	+56.7	.82	<.001	.23

*Comparisons were made after the 6-month treatment with orlistat using intention-to-treat analysis and repeated-measures analysis of variance. Equations to determine the HOMA-IR and COMPOSITE-IS values are given in the "Study Design" subsection of the "Methods" section. Abbreviations are explained in the first footnote to Table 1.

†Calculated as weight in kilograms divided by the square of height in meters.

‡SI units for glucose, TC, LDL-C, HDL-C, and TG are millimoles per liter; insulin, picomoles per liter.

§Insulin-treated patients (n = 5) were not included in the analysis.

uretic, and insulin resistance/sensitivity indices represented in percentage of changes during the 6-month orlistat treatment in the whole study population. Changes in anthropometric indices, including body weight, waist circumference, and dual-energy x-ray absorptiometry–derived percentage of body fat, were associated with changes in TG, TC, and LDL-C concentrations and HOMA-IR (all, $P<.05$). Changes in HOMA-IR and COMPOSITE-IS were correlated with changes in systolic blood pressure and glycemic and lipid indices (all, $P<.05$).

QUALITY-OF-LIFE DATA

Table 4 shows the comparisons of quality-of-life scores as measured by the SF-36 between baseline and the end of the 6-month orlistat treatment. At baseline, obese patients with diabetes perceived their general health ($P=.007$) and the role-physical dimension ($P=.05$) as being worse than that of the nondiabetic group. In addition, their baseline total dimension scores on the SF-36 were lower, suggesting a poorer quality of life than that of nondiabetic patients ($P=.04$). After the 6-month orlistat treatment, we found significant improvements in the physical functioning, role-physical, and total dimension scores in the whole study group, especially in patients with diabetes (all, $P<.05$).

TOLERABILITY

Adverse events were uncommon apart from effects on the gastrointestinal tract. Most gastrointestinal tract events were of mild to moderate intensity and occurred early during treatment. No specific instruction was given on how to avoid adverse effects to the gastrointestinal tract. Most subjects reduced fatty food intake with improvements in abdominal symptoms. No subject withdrew from the study because of adverse effects to the gastrointestinal tract.

COMMENT

The primary objective of the present study was not to demonstrate the efficacy of orlistat treatment, which has been shown in many long- and short-term trials. Rather, we aimed to confirm that short-term (6-month) orlistat treatment in a general medical clinic setting without the administration of a closely supervised hypocaloric diet could also produce a meaningful weight loss among obese Chinese patients with or without diabetes. According to the Asia-Pacific Obesity Guideline, our patients had clinically severe obesity with a mean BMI value of about 35 compared with the Asian definition of 25 for obesity.[25] Despite a modest weight reduction of 3% to 5%, this was associated with disproportionate improvement in most of the cardiovascular risk factors, including insulin sensitivity and albuminuria in both groups of patients.

Most clinical trials with orlistat were conducted in specialized obesity clinics where subjects received close supervision on compliance to dietary intake, physical activity, and medication. These highly specialized clinics are not widely available in daily clinical practice. Indeed, Williamson[30] once commented that the efficacy of weight-

Table 3. Correlation Coefficient Between Percentage of Changes of Anthropometric, Glycemic, Lipid, Blood Pressure, and Insulin Sensitivity Indices*

	Body Weight	Body Fat, %†	Waist	Fasting Blood Glucose Level	HbA_{1c}	TC	LDL-C	TG	Systolic Blood Pressure	Diastolic Blood Pressure	UAE	Insulin	HOMA-R	COMPOSITE-IS
Body weight	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Body fat, %	0.58‡	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Waist	0.56‡	0.40§	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Fasting blood glucose level	NS	NS	NS	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
HbA_{1c}	NS	NS	NS	0.81‡	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
TC	0.33§	0.29‖	0.26‖	NS	0.31‖	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
LDL-C	0.33‖	0.39§	0.43§	NS	0.31‖	0.82‡	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
TG	NS	0.28‖	NS	0.33‖	0.27‖	NS	NS	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Systolic blood pressure‖	NS	NS	NS	0.26‖	NS	NS	NS	NS	. . .	. . .	. . .	. . .	. . .	. . .
Diastolic blood pressure	NS	NS	NS	NS	NS	NS	NS	NS	0.46‡	. . .	. . .	. . .	. . .	. . .
UAE	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	. . .	. . .	. . .	. . .
Insulin¶	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	. . .	. . .	. . .	. . .
HOMA-IR¶	0.30‖	NS	NS	0.48‡	0.45‡	0.30‖	NS	0.36‖	NS	NS	NS	0.70‡	. . .	. . .
COMPOSITE-IS¶	NS	NS	NS	–0.38‡	–0.21‖	NS	NS	NS	–0.33§	NS	NS	–0.72‡	–0.70‡	. . .

*The entire study population, including 30 obese patients with type 2 diabetes and 26 nondiabetic obese patients, underwent evaluation during the 6-month study. Equations to determine the HOMA-IR and COMPOSITE-IS values are given in the "Study Design" subsection of the "Methods" section. NS indicates not significant. Other abbreviations are explained in the first footnote to Table 1.

†Derived from DEXA.

‡$P<.001$ using Pearson correlation analysis.

§$P<.01$ using Pearson correlation analysis.

‖$P<.05$ using Pearson correlation analysis.

¶Insulin-treated patients with diabetes (n = 5) were not included.

Table 4. Comparisons of SF-36 Scores Between Baseline and End of 6-Month Orlistat Treatment in Obese Patients With and Without Type 2 Diabetes*

	All Patients (N = 56)		Diabetic Obese Patients (n = 30)		Nondiabetic Obese Patients (n = 26)	
SF-36 Dimension	Baseline	End of Treatment	Baseline	End of Treatment	Baseline	End of Treatment
Physical functioning	85.9 ± 13.8	89.1 ± 14.0†	83.9 ± 12.5	89.8 ± 12.7‡	88.3 ± 15.2	88.3 ± 15.7
Role-physical	62.1 ± 39.2	77.6 ± 35.3‡	53.9 ± 39.2	72.7 ± 36.7†	72.1 ± 37.6	83.7 ± 33.1
Bodily pain	69.0 ± 29.0	74.0 ± 27.0	66.8 ± 27.6	71.4 ± 24.1	71.8 ± 31.0	77.2 ± 30.4
General health	43.0 ± 24.8	47.2 ± 25.5	35.3 ± 19.9	37.8 ± 21.1	52.4 ± 27.3	58.9 ± 26.0
Vitality	53.8 ± 19.0	55.9 ± 18.1	50.9 ± 17.2	54.8 ± 17.4	57.3 ± 20.8	57.3 ± 19.1
Social functioning	86.9 ± 18.9	88.1 ± 19.9	85.2 ± 17.2	91.0 ± 15.3	88.9 ± 21.0	84.6 ± 24.3
Role-emotional	67.2 ± 38.7	71.8 ± 39.9	60.4 ± 39.2	67.7 ± 41.9	75.6 ± 37.2	76.9 ± 37.4
Mental health	71.3 ± 22.0	74.2 ± 18.9	71.5 ± 21.3	74.0 ± 16.7	71.1 ± 23.4	74.5 ± 21.6
Total score	539.1 ± 144.9	578.1 ± 140.6‡	507.9 ± 119.3	559.3 ± 118.2†	577.6 ± 163.6	601.3 ± 163.5

*Data are given as mean ± SD. SF-36 indicates the Chinese version of the 36-Item Short-Form Health Survey.

†$P<.05$ using paired *t* tests for the comparison between baseline and end-of-treatment scores.

‡$P<.02$ using paired *t* tests for the comparison between baseline and end-of-treatment scores.

reducing drugs in the absence of concomitant lifestyle modification remains unclear. In the present study, all patients had made previous attempts to lose weight by dietary restriction and other lifestyle modifications, but the weight-reducing effects were only short-lived. Before recruitment to the study, their body weights had been stable for at least 6 months. To examine the effect of orlistat on weight reduction without the confounding factor of a hypocaloric diet, subjects were asked to maintain their previously modified diet. Hence, our findings are of particular relevance to day-to-day clinical practice.

One of the unique features of this study relates to the documentation in risk profiles and responses to treatment with orlistat between obese subjects with or without diabetes studied in the same clinical setting. Most previous studies on orlistat excluded patients with diabetes. Our finding of less weight loss in the diabetic group confirms previous observation that obese patients with diabetes have greater difficulty in achieving and maintaining weight loss than matched nondiabetic overweight subjects.[31] This difference in treatment responses has been attributed to the weight-gaining effects of insulin and oral antidiabetic drugs.[32] However, despite having a lesser degree of weight reduction, patients with diabetes had similar improvements in cardiovascular risk factors such as TC, LDL-C, and TG levels; diastolic blood pressure; and insulin resistance compared with nondiabetic individuals. More important, greater reductions occurred in fasting

plasma glucose and HbA_{1c} levels and systolic blood pressure in the diabetic than in the nondiabetic group. This pattern of improvement in risk factors disproportionate to the degree of intervention is in accordance with previous studies such as the Hypertension Optimal Treatment trial,[33] Scandinavian Simvastin Survival Study,[34] and Systolic Hypertension in Europe Trial[35] in which patients with diabetes often had better clinical outcomes than their nondiabetic counterparts. Results from the present study confirm recent findings that treatment with orlistat leads to improvement in cardiovascular risk factors.[36-38] Without a placebo group, it is not certain whether orlistat has a direct effect on cardiovascular risk factors independent of weight reduction. Nevertheless, the sharp decline in the body weight and waist circumference within the first 4 weeks of treatment supports the notion that weight reduction precedes improvement in metabolic variables.

At present, experimental and clinical evidence show that obesity, in particular central adiposity, is the main culprit of insulin resistance and cardiovascular risks, due to several mechanisms, including the direct inhibitory effect of insulin by tumor necrosis factor α, secreted by the adipocytes.[39,40] Many of the cytokines and vasoactive peptides secreted by adipocytes can cause endothelial dysfunction, which in turn contributes to the development of atherosclerosis.[41] Furthermore, visceral adipocytes are metabolically more active than subcutaneous fat. They represent an efficient source of energy stores that can be rapidly mobilized with greater release of free fatty acids. The increased release of free fatty acids from adipocytes can also lead to inhibition of glucose transport and phosphorylation in skeletal muscle,[42,43] steatohepatitis, and increased gluconeogenesis,[44] all of which can worsen insulin resistance and glucose intolerance. Against this mechanistic evidence, the higher WHR, which correlated well with visceral adiposity as measured by magnetic resonance imaging, was accompanied by a more adverse cardiovascular risk profile and more insulin resistance in our diabetic patients.[45] In the present study, patients with diabetes had features of the metabolic syndrome of increased WHR, systolic blood pressure, TG levels, albuminuria, and insulin resistance. After orlistat therapy, they had greater reduction in WHR. This preferential loss of central obesity in patients with diabetes may explain their disproportionate improvements in cardiovascular risk factors.

Orlistat treatment was associated with significant improvement in the HOMA-IR and COMPOSITE-IS indices. On the basis of good correlations with the euglycemic insulin clamp, both indices were selected from the array available. The HOMA-IR is compiled from the fasting levels of glucose and insulin. It therefore reflects mainly insulin resistance in the liver during the steady state. The assumption that hepatic and peripheral (muscle) insulin sensitivities are equivalent may not be valid in all cases.[46] The use of the COMPOSITE-IS provides information on insulin sensitivity in liver and muscle. Both indices were associated with changes in body composition and cardiovascular risk factors. In this connection, the improvement in HOMA-IR was mainly due to reduction in fasting plasma glucose level in diabetic patients and in fasting insulin levels in nondiabetic subjects. These results suggest that the attenuation in insulin resistance after weight reduction might have different mechanisms in obese individuals with or without diabetes.

In the present study, weight reduction due to orlistat treatment was associated with a 3% to 7% reduction in albuminuria compared with baseline in these obese subjects. Evidence now suggests that obesity is an independent predictor for albuminuria[47-49] and that this association may be in part due to the large number of vasopeptides such as transforming growth factor β and angiotensin II secreted by the adipocytes.[41,50] Given the powerful predictive role of albuminuria on cardiorenal outcomes, the beneficial effect of weight reduction on this risk factor is particularly noteworthy.[51]

In a recent meta-analysis, modest weight reduction has been shown to improve glucose intolerance and reduce the rate of diabetes onset.[18] Given the beneficial effects of weight reduction on multiple risk factors, including insulin resistance or sensitivity, as shown in our study, treatment with orlistat may reduce the risk of progression to diabetes in high-risk obese subjects. Similarly, given the current evidence regarding the beneficial effects of reduction in blood pressure,[33] blood glucose level,[52] blood cholesterol level,[34] and albuminuria[53] on mortality and cardiovascular morbidity in diabetic subjects, our findings support a potential therapeutic role of orlistat to reduce cardiovascular risks in diabetic patients. Nevertheless, prospective randomized clinical trials with predefined end points need to be conducted to test these hypotheses.

Several limitations exist in the present study. First, it was not a placebo-controlled trial, but previous studies have already established the efficacy of orlistat on weight reduction in obese subjects. Second, an energy-reducing diet was not given in conjunction with orlistat therapy. However, our subjects failed to control their body weight with dietary restriction before entry to the present study. The continuation of their previously modified diet without particular reinforcement provides a more real-life clinical setting in our assessment of the usefulness of orlistat in a pragmatic weight management program. Finally, a heterogeneous group of obese subjects were included in the present study. Nevertheless, this scenario is again typical of general medical practice, so our findings should be generalized to most obese subjects.

CONCLUSIONS

This study confirmed the efficacy of orlistat in reducing weight among young obese Chinese patients with or without type 2 diabetes. The modest amount of weight loss achieved without the use of a hypocaloric diet was accompanied by significant improvements in metabolic control, insulin sensitivity, and cardiovascular risk factors including albuminuria. These data support the use of orlistat as an adjunct for management of obesity, with or without diabetes.

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