Effects of Pioglitazone Versus Diet and Exercise on Metabolic Health and Fat Distribution in Upper Body Obesity

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OBJECTIVE — Insulin resistance is associated with visceral adiposity, and interventions that reduce this depot, e.g., diet and exercise, improve insulin resistance. Thiazolidinediones (TZDs) also improve insulin action but paradoxically increase total fat mass, perhaps through remodeling (recruitment of smaller fat cells) and redistribution of adipose tissue. We assessed the effects of pioglitazone versus diet and exercise on fat distribution and the relationship between fat distribution and insulin sensitivity in upper body obesity.

RESEARCH DESIGN AND METHODS — Thirty-nine upper body obese, insulin-resistant, nondiabetic men and premenopausal women were randomly assigned to receive either 30 mg/day pioglitazone or a diet and exercise program for 20 weeks. Before and after the intervention, insulin sensitivity, body composition, body fat distribution (waist-to-hip ratio [WHR], computed tomography abdomen, and dual-energy X-ray absorptiometry), and abdominal and femoral fat cell size were assessed.

RESULTS — Diet and exercise resulted in an 11.8 ± 1.1 kg weight loss. Both diet and exercise and pioglitazone improved insulin sensitivity, but only the former was associated with loss of intra-abdominal fat. Pioglitazone increased total body fat, which preferentially accumulated in the lower body depot in both men and women. WHRs decreased in both groups. Abdominal fat cell size decreased ($P = 0.06$) after diet and exercise. No statistically significant changes in fat cell size were observed in pioglitazone-treated volunteers.

CONCLUSIONS — In nondiabetic upper body obese subjects, increasing insulin sensitivity via diet and exercise accompanies reductions in visceral fat. Pioglitazone treatment also improves insulin sensitivity and lowers WHR, but this is due to a selective increase in lower body fat. This confirms a site-specific responsiveness of adipose tissue to TZD and suggests that improvements in insulin sensitivity by pioglitazone are achieved independent of changes in intra-abdominal fat.

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B ody fat distribution is an important variable in the relationship between overweight and insulin resistance. Intra-abdominal or visceral fat accumulation is more strongly associated with insulin resistance, and insulin resistance can be improved by decreasing this fat depot via diet, exercise, or surgery (1,2). Thiazolidinediones (TZDs) are also known to improve insulin sensitivity despite paradoxically increasing total fat mass (3–5). It has been suggested that redistribution of body fat may contribute to their insulin-sensitizing qualities. Indeed, regional variability in TZD responsiveness has been demonstrated; preadipocytes from subcutaneous fat differentiate more in response to TZD in vitro than visceral adipose tissue (6). If the same phenomenon occurs in vivo, one would expect selective adipocyte proliferation and thus body fat redistribution.

However, studies of animals and diabetic humans have reported increasing, decreasing, and unchanged visceral and subcutaneous fat depots after TZD administration despite improved insulin sensitivity (3–5,7,8). This suggests that TZD effects on visceral adiposity, if present in vivo, might not contribute to their insulin sensitization.

We assessed the effects of pioglitazone on fat distribution, fat cell size, and the relationship between fat distribution and insulin sensitivity in upper body obesity, a known insulin-resistant state. Comparison of the effects of pioglitazone with diet and exercise, a standard intervention to improve insulin sensitivity, was performed to place the results in context.

RESEARCH DESIGN AND METHODS

— Written informed consent was obtained from 68 healthy upper body obese men and premenopausal women. Subjects were nondiabetic, sedentary, and weight stable up to at least 6 months before entering the research program. Inclusion criteria consisted of a BMI of 28–36 kg/m^2 and one of the following three items: *1)* waist-to-hip ratio (WHR) >0.85 (women) or >0.95 (men); *2)* computed tomography (CT)-measured visceral fat area >120 cm^2 (women) or >180 cm^2 (men); or *3)* a ratio of visceral to total fat >0.30 (women) or >0.40 (men). If WHR exceeded 0.80 (women) or 0.90 (men), and fasting glucose was between 100–126 mg/dl, volunteers were included regardless of the CT results. Exclusion criteria were a history of coronary heart disease, atherosclerosis, known systemic illness, renal or liver failure, clinically diagnosed type 2 diabetes, hyper-

tension requiring medication that could not be safely stopped 2 weeks before the study, smoking, pregnancy, and breast-feeding. Thirteen volunteers were excluded on the basis of screening laboratory results, 10 volunteers withdrew before starting the program and 6 dropped out for a variety of reasons. One volunteer was excluded for noncompliance with the diet and exercise program.

Study protocol

The remaining 39 volunteers underwent blood testing (complete blood count, chemistry panel, and lipid profile), an insulin-modified intravenous glucose tolerance test, CT measures of visceral fat area (L_{2-3} level) (9), and dual-energy X-ray absorptiometry (DEXA) (DPX-IQ; Lunar Radiation, Madison, WI) for body composition assessment before and after the intervention. Adipose tissue biopsies were taken from femoral and abdominal subcutaneous areas. Oxygen consumption ($\dot{V}_{O_{2peak}}$) and maximum heart rate were determined by a graded exercise test performed on a Quinton (Seattle, WA) motor-driven treadmill using a modified Bruce protocol (10). Heart rate and rhythms were monitored continuously via a 10-lead electrocardiogram. The difference between resting and maximal heart rate defined the heart rate reserve, which was used to determine exercise intensity goals for those in the diet and exercise program (see below).

After the baseline measurements, the volunteers were randomized to receive 30 mg pioglitazone daily or a diet and exercise program for 18–20 weeks. The pioglitazone treated volunteers were monitored every 4 weeks for weight, liver function tests, and pill counts. Diet and exercise volunteers were instructed in a 500-kcal deficit diet and in an exercise program starting with 15 min of aerobic exercise three times per week at 50% of each individual's heart rate reserve. This was gradually increased to 45 min aerobic exercise four times a week at 60–70% of heart rate reserve. In addition, the diet and exercise group participated in a behavior modification (modified LEARN) program biweekly and worked with a general clinical research center dietitian every 4 weeks. After 18–20 weeks, all tests and biopsies were repeated.
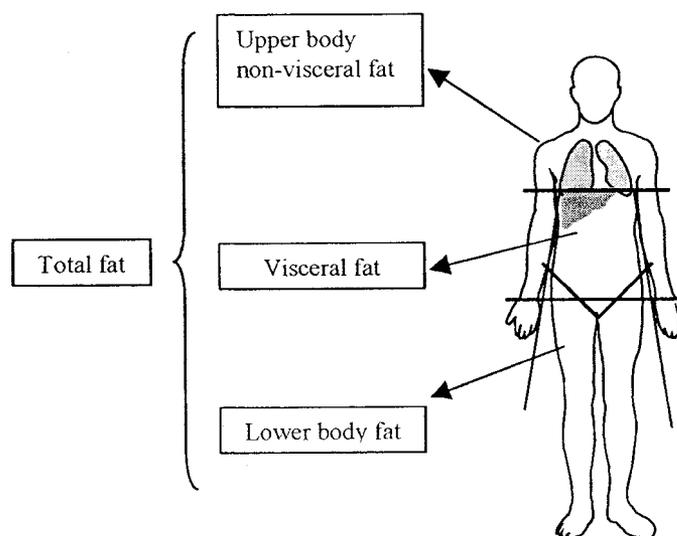

Figure 1—*Determination of fat compartments using DEXA and computed tomography. Lower body fat is considered fat caudal to the inguinal ligaments; upper body fat is equal to total fat minus lower body fat. To estimate visceral fat mass, the DEXA and CT data are both used. Horizontal lines are used at the level of the symphysis pubis and the diaphragm on the DEXA image to encompass abdominal fat. Arms are positioned during the scan to allow diagonal lines to be placed to separate them from the abdomen. The ratio of visceral-to-total abdominal fat from CT is multiplied by abdominal fat from DEXA to estimate visceral fat. Upper body fat minus visceral fat is upper body nonvisceral fat.*

Assessment of fat compartment volume

The CT images were analyzed to distinguish compartmental fat volumes, as previously described (9). Results were combined with data from DEXA (9) to calculate the following fat compartments: total body fat, lower body fat, upper body nonvisceral fat, and visceral (intraabdominal) fat (Fig. 1).

Fat biopsies and fat cell size

Subcutaneous fat was aspirated from femoral and abdominal depots under sterile conditions using local anesthesia. Fat was immediately rinsed with saline and digested in a HEPES/collagenase solution (37°C; Sigma Type II C-6885). Adipocytes were isolated (centrifuge) and stained with methylene blue to visualize the nuclei. Digital photographs were taken at 10× magnification , after which the diameters of ≥150 cells per site were measured using National Institutes of Health Image Analysis software for PCs from Scion (Frederick, MD). Histograms were graphically and numerically displayed. Cell volumes were calculated using the Goldrick formula (11). Adipocellular lipid content was calculated as fat cell volume times 0.95.

Assays

The following assays were used: glucose: Hitachi 912 Chemistry Analyzer using the hexokinase reagent (Boehringer Mannheim, Indianapolis, IN) or the Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA); insulin: chemiluminiscence method with Access Ultrasensitive Immunoenzymatic Assay system (Beckman, Chaska, MN); C-peptide: direct, double antibody sequential radioimmunoassay (Linco Research, St. Louis, MO); triglycerides: Hitachi 912 chemistry analyzer using Technicon triglyceride reagent (Bayer, Tarrytown, NY).

Intravenous glucose tolerance test. An intravenous injection of 0.33 g/kg dextrose (D_{50}) at time (t) = 0 min was followed by 0.02 units/kg insulin at t = 20 min. Blood samples for plasma glucose (Beckman Glucose Analyzer) and insulin concentrations were taken at t = 0, 2, 4, 8, 10, 18, 24, 32, 40, 60, 70, 120, and 180 min. Data were analyzed using Bergman's minimal model (12,13).

Statistical analysis

Values are expressed as means ± SE. Statistical comparisons of the two groups (pioglitazone versus diet and exercise) and the responses of the groups to the

Table 1—*Demographic and body composition before and after intervention*

	Diet/exercise		Pioglitazone		
	Pre	Post	Pre	Post	P-Δ
Age (years)	41 ± 2	—	36 ± 2	—	—
Weight (kg)	97.5 ± 3.3	85.8 ± 3.1*	98.2 ± 2.7	100.9 ± 3.0†	0.0001
BMI (kg/m²)	32.1 ± 0.7	27.7 ± 0.8*	33.4 ± 0.6	34.0 ± 0.7‡	0.0001
Waist circumference (cm)	105 ± 2	95 ± 2*	107 ± 2	107 ± 2	0.0001
Hip circumference (cm)	111 ± 1	105 ± 2*	115 ± 1	119 ± 2*	0.0001
WHR	0.95 ± 0.02	0.90 ± 0.01*	0.94 ± 0.01	0.90 ± 0.01*	0.42
Body fat (%)	40 ± 1.4	32 ± 1.8*	41 ± 1.4	41 ± 1.5	0.0001
Body fat (kg)	35.8 ± 1.5	26.5 ± 1.9*	38.0 ± 1.5	39.3 ± 1.7†	0.0001
FFM (kg)	59.0 ± 2.5	58.5 ± 2.4	58.0 ± 2.2	59.1 ± 2.2	0.07

Data are means ± SE. Baseline values are not significantly different between diet and exercise and pioglitazone groups. *$P < 0.001$; †$P < 0.01$; and ‡$P < 0.05$ before versus after the intervention. P-Δ signifies the difference between the effect of the two interventions.

interventions were done using repeated-measures ANOVA, followed by t tests (paired or nonpaired) if needed. P values <0.05 were considered statistically significant.

RESULTS

Subject characteristics
Nineteen volunteers (10 men and 9 women) completed the diet and exercise intervention and 20 volunteers (10 men and 10 women) completed the pioglitazone intervention. The two groups were well matched for age, BMI, WHR, insulin sensitivity parameters, and body composition (Tables 1–3). The preintervention fasting plasma insulin concentrations were greater ($P < 0.05$) in the pioglitazone than in the diet and exercise group, and the subcutaneous fat area by CT was greater ($P < 0.05$) in the pioglitazone group.

Relationship between body composition and metabolic variables
At baseline, fasting plasma insulin concentrations correlated with weight ($r = 0.37$, $P < 0.05$), waist circumference (0.35, $P < 0.05$), and WHR (0.37, $P < 0.05$). C-peptide was significantly correlated with these parameters as well as with BMI (0.33, $P < 0.05$) and visceral fat area (0.33, $P < 0.05$). At baseline, insulin sensitivity index (S_i) correlated positively with HDL but negatively with WHR (-0.36, $P < 0.05$) and total abdominal fat area by CT (-0.36, $P < 0.05$).

Body composition changes in response to intervention
The diet and exercise program induced a weight loss of 11.8 ± 1.1 kg (9.5 ± 1.0 for women, 13.9 ± 1.5 for men) by loss of fat, not fat-free mass (FFM). Because adipose tissue mass is 85% lipid and 15% water (14), and because DEXA measurement of FFM includes this adipose tissue water, the loss of adipose without loss of FFM suggests favorable changes in muscle mass. Proportionately more abdominal than femoral and more visceral than subcutaneous abdominal fat was lost, as evidenced by the changes in WHR, the ratio of visceral fat to subcutaneous abdominal fat area, and the various fat compartments measured by DEXA (Tables 1 and 3). Fat cell lipid content decreased in the abdominal ($P = 0.06$) but not the femoral depot ($P = 0.33$) with diet and exercise.

In the pioglitazone group, the average weight gain of 2.7 ± 0.7 kg was attributed to an increase in fat (1.3 kg), predominantly in the leg depot, and to increased FFM (1.1 kg, $P = 0.07$). There was no change in abdominal fat compartments (visceral or upper body nonvisceral). Consistent with the DEXA and CT data, WHR decreased due to increased hip, but not waist, circumference. The average adipocyte lipid content after the pioglitazone treatment was less in both the femoral and abdominal sites but the difference from baseline was not statistically significant (decrease by 0.09 μg lipid/cell in femoral, $P = 0.15$; decrease by 0.06 μg lipid/cell in abdominal, $P = 0.23$).

Metabolic response to intervention
The increase in S_i was greater in the diet and exercise than in the pioglitazone group, although the difference between the two treatments was not statistically significant ($P = 0.15$). Decreases in fast-ing plasma glucose and C-peptide concentrations were similar in both groups. The changes in serum lipid concentrations were more marked in the diet and exercise group; the only significant between-group difference, however, was for serum total cholesterol (Table 2). The greater decrease in insulin in the pioglitazone group is confounded by higher baseline concentrations. In the diet and exercise group, blood pressure decreased from 128 ± 4/82 ± 2 to 122 ± 3/76 ± 2 ($P < 0.0001$ for systolic and $P = 0.07$ for diastolic), and in the pioglitazone group, blood pressure decreased from 129 ± 4/80 ± 3 to 127 ± 3/75 ± 2 ($P < 0.05$ for diastolic only). Overnight postabsorptive plasma free fatty acid concentrations were not different between the two groups before or after treatment.

Relationship between change in body composition and change in metabolic variables
Changes in S_i were not significantly correlated with changes in body composition in either group (results not shown). In addition, changes in glucose, C-peptide, or S_i did not correlate with changes in femoral or abdominal fat cell size in either group.

CONCLUSIONS — We compared the effects of two insulin-sensitizing regimens, pioglitazone versus diet and exercise, on body composition, body fat distribution, and insulin sensitivity. Nondiabetic upper body obese adults were studied because of the high prevalence of insulin resistance in this population. The anticipated improvement in S_i occurred with each treatment, and the change in body fat compartments in response to diet

Table 2—*Effects of diet/exercise and pioglitazone on insulin sensitivity and lipids*

	Diet/exercise		Pioglitazone		
	Pre	Post	Pre	Post	P-Δ
Fasting glucose (mg/dl)	96 ± 2	91 ± 2*	97 ± 2	92 ± 2†	0.69
Fasting insulin (μU/ml)	8 ± 1	5 ± 1*	11 ± 1	7 ± 1*	0.06
Fasting C-peptide (nmol/l)	0.60 ± 0.04	0.45 ± 0.03*	0.68 ± 0.04	0.50 ± 0.03*	0.61
Serum triglyceride (mg/dl)	162 ± 31	102 ± 12†	171 ± 16	156 ± 16	0.26
HDL cholesterol (mg/dl)	39 ± 2	38 ± 2	34 ± 2	35 ± 2	0.08
Total cholesterol (mg/dl)	201 ± 18	159 ± 7‡	195 ± 7	190 ± 7	0.01
S_i (mU/l)$^{-1} \cdot$ min^{-1}	5.31 ± 0.97	10.34 ± 1.88*	4.23 ± 0.61	6.60 ± 1.09†	0.15

Baseline values are not significantly different between diet and exercise and pioglitazone except in fasting insulin, which were higher in the pioglitazone group than in the diet and exercise group ($P = 0.04$). *$P < 0.001$; †$P < 0.01$; and ‡$P < 0.05$ before versus after the intervention. P-Δ signifies the difference between the effect of the two interventions.

and exercise was consistent with previous reports. We unexpectedly found that pioglitazone resulted in the preferential accumulation of lower body fat rather than loss of visceral fat. Thus, both diet and exercise and pioglitazone resulted in a reduced WHR but the mechanism was quite different. The shift toward a lower body fat distribution by pioglitazone via gain of leg fat, not loss of visceral fat, is consistent with adipose depot–specific responses, but not of the type previously reported.

The lack of change in intra-abdominal adipose tissue area with pioglitazone is consistent with some, but not all, previous findings. Four reports described no change (4,5,7,15) and three a decrease (3,7,16). Most (4,5,7,15,16), but not all (4), reported a decrease in the visceral-to-subcutaneous abdominal fat ratio. However, the investigators reporting reductions in visceral fat combined TZDs with energy-restricted diets (7,16) or other medication (3), which may have modulated the TZD effects. These investigators studied the effects of TZDs in type 2 diabetic adults, a different study population from our insulin-resistant nondiabetic volunteers. Although it is possible that the response to TZDs is different between diabetic and nondiabetic humans, we note that a trend toward decreasing WHR despite an increasing waist diameter was noted in adults with type 2 diabetes (3), suggesting that our finding is not entirely unique to nondiabetic volunteers.

Pioglitazone increased leg fat without influencing upper body fat mass. The trend toward smaller femoral fat cell size in the pioglitazone group in the face of increased leg fat mass suggests adipocyte proliferation rather than hypertrophy was responsible for the leg fat gain. This would be consistent with the peroxisome proliferator–activated receptor-γ agonist effects of pioglitazone on preadipocytes. If the improvements in insulin sensitivity we observed are related to changes in adipose tissue metabolism, these data suggest an independent role for the relative amount of lower body fat. Alternatively, pioglitazone may improve S_i and increase lower body fat independently.

A number of investigators have examined the site-specific actions of TZD on adipose tissue remodeling. In vitro responsiveness of abdominal subcutaneous, but not omental human preadipocytes to TZD, has been reported (6). In vivo, ovarian adipose tissue was more sensitive to TZD than retroperitoneal or subcutaneous abdominal fat Zucker rats (8). Although not specifically supportive

Table 3—*Effects of diet/exercise and pioglitazone on fat distribution and fat cell size*

	Diet/exercise		Pioglitazone		
	Pre	Post	Pre	Post	P-Δ
CT abdomen					
SC fat (cm^2)	259 ± 15	196 ± 18*	317† ± 18	328 ± 23	0.04
Visceral (cm^2)	203 ± 29	123 ± 22*	154 ± 15	154 ± 17	0.0001
Visceral/SC	0.80 ± 0.11	0.66 ± 0.11*	0.50† ± 0.05	0.48 ± 0.05	0.007
DEXA fat (kg)					
Total body	35.8 ± 1.5	26.5 ± 1.9*	38.0 ± 1.5	39.3 ± 1.7‡	0.0001
Leg	11.7 ± 0.8	8.7 ± 0.8*	13.8 ± 0.8	14.8 ± 0.9*	0.0001
CT + DEXA fat (kg)					
UBNV	18.3 ± 0.7	14.5 ± 1.0*	19.8 ± 0.9	20.2 ± 0.8	0.0001
Visceral	5.8 ± 0.6	3.3 ± 0.5*	4.4 ± 0.4	4.3 ± 0.4	0.0001
Fat cell size (μg lipid/cell)					
Abdominal	0.84 ± 0.19	0.68 ± 0.16	0.81 ± 0.18	0.75 ± 0.17	0.52
Femoral	0.85 ± 0.19	0.79 ± 0.18	0.85 ± 0.19	0.76 ± 0.17	0.60

Data are means ± SE. Baseline values are not significantly different between diet and exercise and pioglitazone except as noted. *$P < 0.001$ before versus after the intervention; †$P < 0.05$ diet and exercise versus piolitazone at baseline; and ‡$P < 0.01$ before versus after the intervention; P-Δ signifies the difference between the effect of the two interventions. SC, subcutaneous; UBNV, upper body nonvisceral.

of our observations regarding leg fat, both findings suggest a regional difference in TZD sensitivity.

As expected, S_i correlated with WHR and total abdominal fat at baseline. This was expected given the known association between insulin resistance and visceral fat accumulation (17). The relative weakness of the correlation coefficients between S_i and anthropometric/body composition parameters in our population are likely due to the selection of the participants; the narrow range of S_i and body fat/fat distribution variables reduced the strength of the associations. Given the weak correlation coefficients between S_i and body composition at baseline, it is not surprising that changes in S_i were not significantly correlated with changes in the parameters we assessed with regards to adipose tissue mass, distribution, or cellularity. The relatively small interindividual variation in fat and visceral fat loss in the diet and exercise group, combined with inherent individual differences in the S_i response to weight loss, may limit the ability to detect a correlation between fat loss and improvement in S_i. Alternatively, improvements in S_i from 5 months of exercise and energy restriction may be independent of and greater than the effects of regional fat loss, such that the underlying relationship is undetectable. It is also possible that the precision of measurement of insulin action with the intravenous glucose tolerance test is insufficient for detecting a relationship despite the relatively accurate measures of fatness.

In conclusion, weight loss via diet and exercise and pioglitazone improve insulin sensitivity and shift adipose tissue toward a lower body fat distribution in upper body obese nondiabetic adults. Pioglitazone selectively increased lower body fat, apparently via adipocyte proliferation, whereas preferential loss of visceral/upper body subcutaneous fat occurred with diet and exercise. Understanding the depot specific action of TZD may help define the insulin-sensitizing properties of this class of compounds.

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