

# Effects of a Thiazolidinedione Compound on Body Fat and Fat Distribution of Patients With Type 2 Diabetes

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**OBJECTIVE** — To examine the effects of a thiazolidinedione (600 mg troglitazone) insulin-sensitizing treatment on total body fat measured by underwater weighing, on intra- and extra-abdominal fat mass using magnetic resonance imaging (MRI), and on anthropometric measures.

**RESEARCH DESIGN AND METHODS** — Type 2 diabetic outpatients were studied in a double-blind randomized trial carried out at Glasgow Royal Infirmary, Scotland.

**RESULTS** — Groups who received troglitazone (8 men, 3 women) and placebo (8 men, 2 women) were well matched for age, BMI, total body fat percentage by underwater weighing, and intra-abdominal fat (kilograms) by MRI. After 12 weeks, body weight changes in the troglitazone group (mean +0.66 kg [95% CI -0.71 to 2.04],  $P = 0.31$ ) and the placebo group (mean +0.25 kg [-0.64 to 1.13],  $P = 0.55$ ) were not statistically different. Changes in total body fat with troglitazone (mean +1.02% body wt [-1.13 to 3.17],  $P = 0.32$ ) and placebo (mean -0.54% body wt [-1.68 to 0.59],  $P = 0.31$ ) were not significantly different. There was, however, a decrease in intra-abdominal fat mass in the troglitazone-treated group (mean -0.47 kg [-0.79 to -0.13],  $P = 0.01$ ), and this was significantly different ( $P = 0.03$ ) from placebo treatment (mean -0.41 kg [-0.77 to -0.05]).

**CONCLUSIONS** — Treatment with the thiazolidinedione troglitazone in human patients with type 2 diabetes decreases intra-abdominal fat mass but does not affect total body fat or weight. This potentially valuable effect points to a differential action on insulin sensitivity in different adipose tissue depots.

*Diabetes Care* 22:288–293, 1999

Thiazolidinedione compounds enhance the effect of insulin on peripheral tissues and the liver, thus improving hyperglycemia and hyperinsulinemia and decreasing LDLs and triglycerides while increasing HDLs in subjects with type 2 diabetes (1). The mechanism of action of thiazolidinediones has not yet been fully elucidated; however, they appear to work by either mimicking or enhancing insulin action without affecting  $\beta$ -cell insulin secretion (2). The end result is to improve

insulin-mediated glucose disposal and reduce hepatic glucose output, possibly through an increase in clearance of circulating free fatty acids (1,3). It is speculated that troglitazone may interact with a family of nuclear receptors, including the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), which is expressed mainly in adipose tissue (4). The actions would thus be expected to induce lipogenesis and fat cell proliferation, but such effects have not been reported in humans. An increase in

body fat, particularly intra-abdominal fat mass could have adverse health consequences, since increased intra-abdominal fatness is associated with the metabolic syndrome, including hyperlipidemia, hypertension, and type 2 diabetes. The present study investigated the effects of a thiazolidinedione troglitazone treatment on direct measurements of total body fat by underwater weighing and abdominal fat distribution by magnetic resonance imaging (MRI) in patients with type 2 diabetes in a 12-week double-blind randomized study.

## RESEARCH DESIGN AND METHODS

### Subjects and study design

There were 16 male (aged 44–66 years) and 5 female (aged 49–74 years) patients with type 2 diabetes who were recruited from the Diabetes Centre, Glasgow Royal Infirmary. Subject selection was based on BMI of 40 kg/m<sup>2</sup>, which is below the upper limit for MRI, and fasting blood glucose between 8 and 16 mmol/l at the prestudy screen. Subjects were aged over 40 years and treated by diet alone or diet and sulphonylurea drugs. There was no alteration to subjects' diets or exercise regimens, and no other active diseases were present.

Ethical approval was obtained from both the Glasgow Royal Infirmary Joint Ethics Committee and the Health Care International Joint Ethical Committee.

### Clinical measurements

Subjects attended the clinic in the morning for a fasting blood sample for analysis of biochemical factors, including blood glucose, HbA<sub>1c</sub>, serum lipids (total cholesterol, LDL, HDL, and triglycerides), heart rate, blood pressure (lying down and at rest), and electrocardiogram.

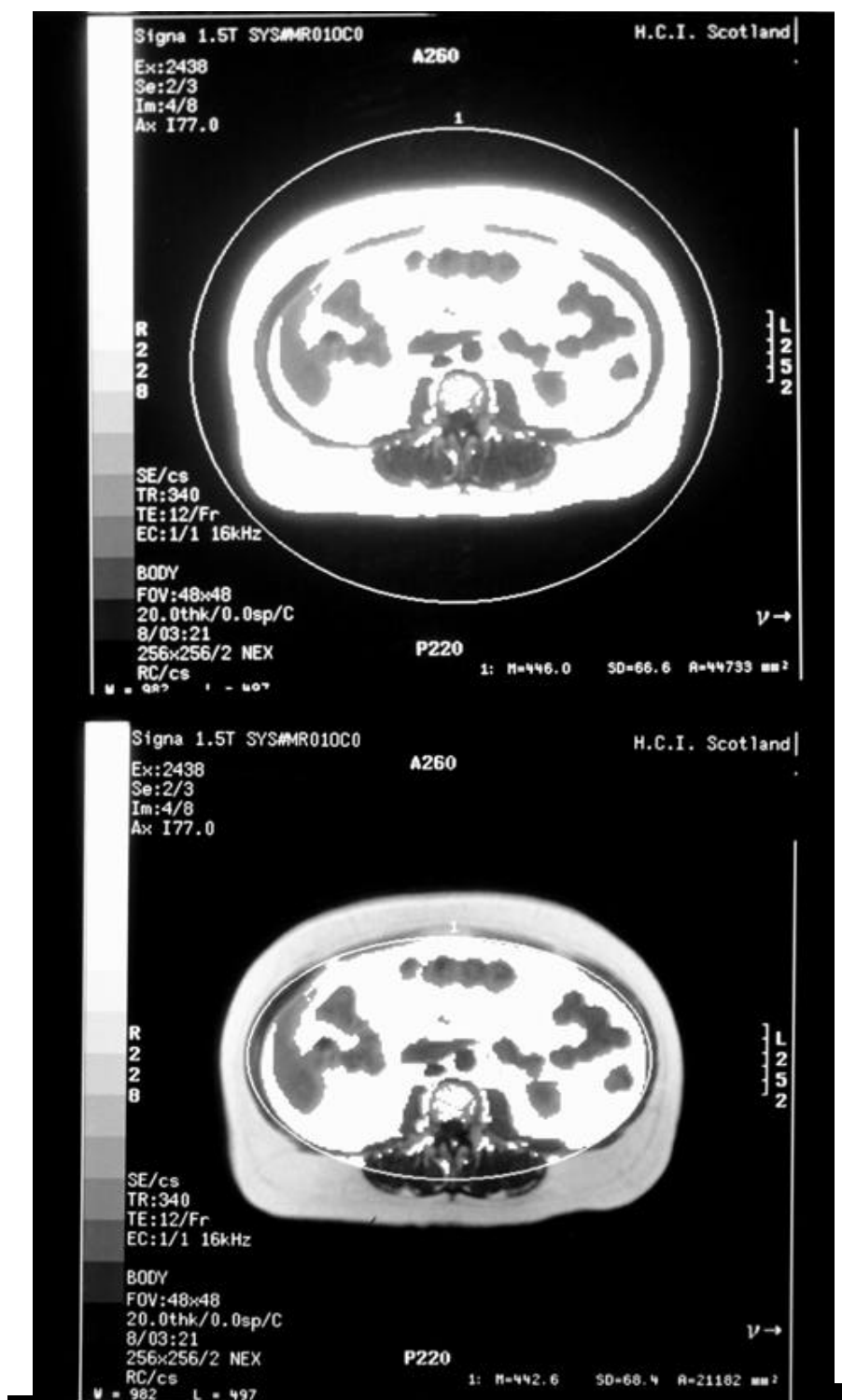
### Anthropometry

Subjects were measured in light clothes and with an empty bladder, using calibrated scales and stadiometer. Body weight was measured to the nearest 0.1 kg and height to the nearest millimeter. Waist circumference was measured midway between the

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**Abbreviations:** MRI, magnetic resonance imaging; PPAR- $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ . A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



**Figure 1**—Transverse cross-sectional area of MRI for measuring total abdominal fat (upper panel) and intra-abdominal fat (lower panel) in a female type 2 diabetic patient. Fat contents are highlighted within the ovoid line.

iliac crest and the lowest rib margin, hip circumference at the level of the great trochanters (5). BMI was calculated as weight in kilograms divided by height squared (meters squared).

#### Total body fat by underwater weighing

The mean of four measurements of body density with an empty bladder was taken with four simultaneous breath nitrogen

dilution measurements to correct for residual lung volume. Mean body fat was calculated from the body density measurements. A full description of total body fat estimation from underwater weighing has been previously published (6).

#### Abdominal fat measured by MRI

The tissues of the abdomen were scanned using MRI (General Electric Corporation, Milwaukee, WI) with a magnetic field strength of 1.5 Tesla. Ordinary spin echo sequences were used with repetition time of 350 ms and echo time of 12 ms. Subjects had an empty bladder and were fasting.

**Abdominal fat imaging.** Four sagittal images of the trunk were scanned to find the vertebral column. To obtain reproducible imaging volumes, the volume of the abdomen was taken to extend from the bottom of the inferior plate of the L1 vertebra to the bottom of inferior plate of the L5 (Fig. 1). Data were collected from as many 20-mm-thick sections (Fig. 1) as could completely fit within that interval. This imaging volume approximately corresponds closely to the levels from the xiphisternum to the anterior iliac crest in our previous MRI studies (7) but was more reproducible.

**Calibrations of lipid and water.** A lump of lard (lipid) was placed next to a container of water in the MRI scanner to simulate lipid in adipose tissue and lean tissue in vivo. The scan was analyzed to obtain the threshold value at which only the fat in the lard could be imaged (while the imaging of water just disappears). Pilot tests determined that the threshold value should be set at 300 (arbitrary units) for every subject for subsequent calculations.

**Calculations of intra-abdominal and extra-abdominal adipose tissue and fat volumes.** After setting an appropriate threshold value (300–3000 window level) that separates fat (lipid) from lean tissues (water), the volume of intra-abdominal and extra-abdominal adipose tissue was calculated.

The number of pixels for total abdominal adipose tissue was obtained from the region of interest by encircling the whole abdomen contents with an ovoid line (Fig. 1). To obtain the number of pixels for total intra-abdominal adipose tissue, the ovoid line was then reduced to encircle the intra-abdominal contents at the position of the fascial plane, to separate intra-abdominal from extra-abdominal adipose tissue (Fig. 1). Total volume of abdominal adipose tis-

**Table 1—Baseline characteristics of 11 subjects (8 men, 3 women) who were treated with troglitazone and 10 subjects (8 men, 2 women) on placebo for 12 weeks**

	Troglitazone	Placebo	P
Age (years)	58.0 ± 8.6 (44.1–68.7)	58.6 ± 7.50 (48.4–74.1)	0.78
Weight (kg)	78.9 ± 11.2 (61.7–102.0)	82.1 ± 12.2 (61.8–107.2)	0.88
Height (m)	1.66 ± 0.09 (1.49–1.78)	1.69 ± 0.09 (1.59–1.85)	0.54
BMI (kg/m <sup>2</sup> )	28.7 ± 3.9 (22.9–37.1)	28.6 ± 3.76 (24.0–35.6)	0.71
Waist circumference (cm)	100.1 ± 10.3 (82.1–122.5)	102.7 ± 9.1 (90.6–116.5)	0.79
Waist-to-hip ratio	1.03 ± 0.12 (0.90–1.36)	1.02 ± 0.06 (0.93–1.12)	0.82
Total body fat (% body wt)	34.5 ± 7.1 (25.6–45.1)	33.4 ± 9.2 (23.2–54.4)	0.89
Total body fat (kg)	27.4 ± 7.3 (15.8–38.1)	28.6 ± 10.2 (19.4–48.7)	0.78
Extra-abdominal fat (kg)	2.11 ± 1.0 (1.00–4.10)	2.00 ± 0.91 (1.00–4.09)	0.50
Intra-abdominal fat (kg)	2.36 ± 0.51 (1.71–3.01)	2.41 ± 0.60 (1.64–3.44)	0.82
Blood glucose (U/l)	10.6 ± 2.79 (6.30–15.5)	11.5 ± 2.67 (7.20–15.60)	0.45
HbA <sub>1c</sub> (%)	7.51 ± 1.38 (4.70–9.50)	8.38 ± 1.52 (6.90–12.10)	0.20
γ-Glutamyltransferase (U/l)	57.1 ± 31.6 (22.0–115.0)	58.70 ± 53.3 (12.0–185.0)	0.93
Aspartate aminotransferase (U/l)	16.6 ± 3.20 (12.0–23.0)	18.20 ± 8.10 (7.0–38.0)	0.60
Alanine aminotransferase (U/l)	21.5 ± 6.8 (12.0–33.0)	23.4 ± 7.43 (13.0–31.0)	0.60
Alkaline phosphatase (U/l)	181.8 ± 39.83 (125–230)	185.0 ± 49.0 (110–285)	0.90

Data are means ± SD (range). Extra-abdominal fat was measured from the bottom of L1 to the bottom of L5 vertebrae. P values are from independent t tests for the differences in baseline characteristics between groups.

sue (in millimeters cubed) was obtained by summing the adipose tissue areas in eight (or nine in eight men) continuous transverse scans, obtained in each subject from the bottom of L1 to the bottom of L5 vertebrae and multiplied by 20 mm (slice thickness). A factor of 10<sup>-6</sup> was used to convert millimeters cubed to liters of adipose tissue volume and then to mass of fat (kilograms), assuming that adipose tissue contains 80% fat, 2% protein, and 18% water (with negligible minerals) (8), with corresponding

densities of 0.900, 1.34, and 0.993 kg/l (9), giving an average adipose tissue density of 0.9255 kg/l. The difference between the total volumes of abdominal fat and intra-abdominal fat provides the total volume of extra-abdominal fat.

The coefficient of variation using this method for repeated estimation of total intra-abdominal fat in the MRI images was 0.9% (10), which improved on the previous “hand drawn” method from the earlier MRI study of abdominal adipose tissue (7).

Subjects were allocated randomly to receive either troglitazone in three tablets of 200 mg daily or matching placebo. Randomization was carried out in accordance with the code generated by Medical Data Sciences Clinical Pharmacology.

**Statistics**

After visual inspection of the data to check for normal distribution, paired t tests were used to compare the changes in measures of body composition within each treatment group.

Independent t tests were used to compare the differences in the changes of measurements between troglitazone-treated and placebo-treated groups. A power calculation was used to determine the sample size required to show a 0.05 kg/l difference in body density between placebo and troglitazone treatment over 12 weeks. Power was calculated at 90% with a significance level of 5%. An estimate of intersubject SD of 0.02 kg/l was assumed.

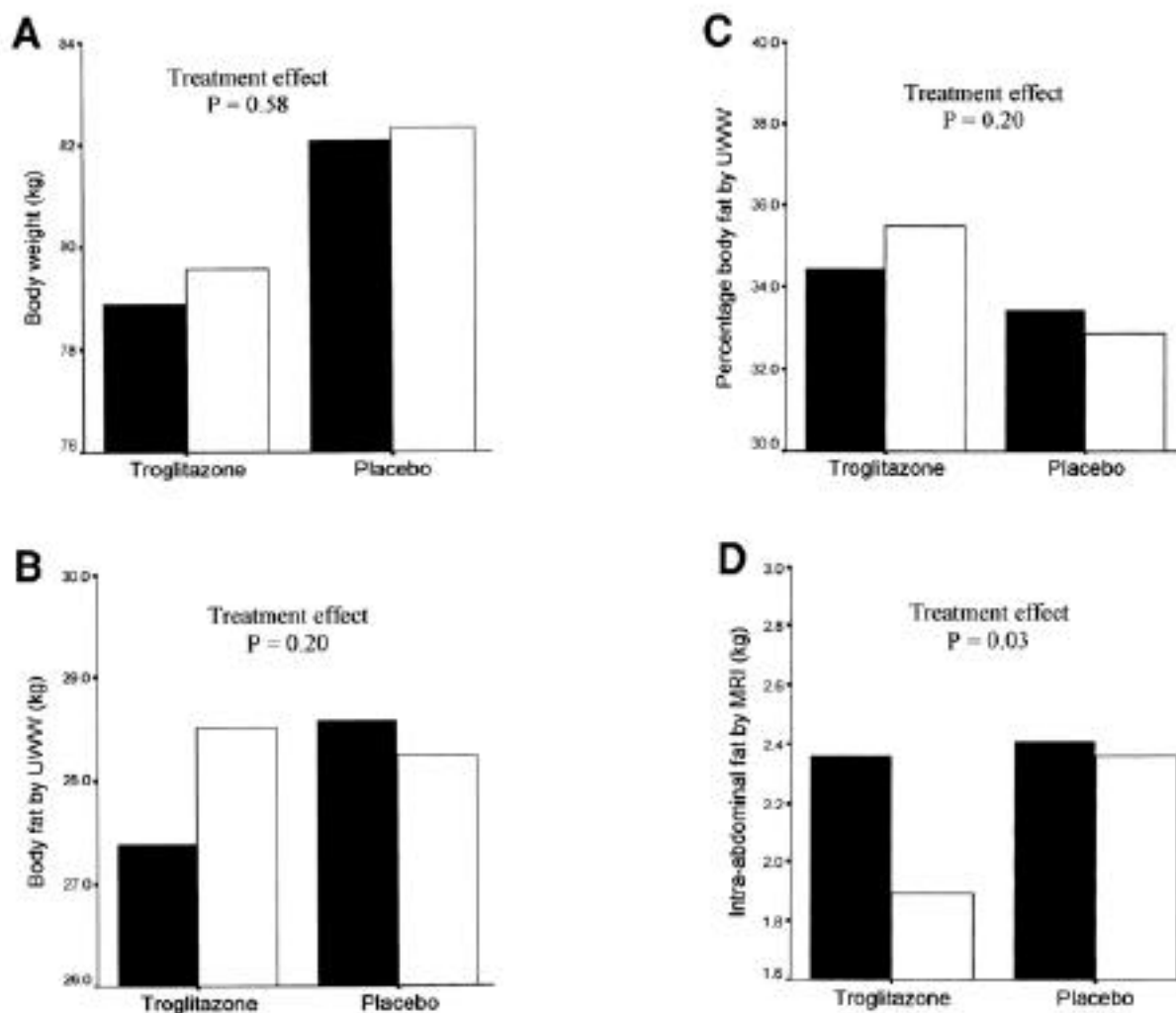
**RESULTS** — Treatment groups were well matched for age, BMI, percentage body fat by underwater weighing, and intra-abdominal fat by MRI. Table 1 shows the baseline characteristics and biochemical measures for subjects. There were no significant differences in anthropometric measurements between the troglitazone-treated and the placebo-treated groups at baseline.

Table 2 and Fig. 2 show the changes in body composition between treatment

**Table 2—Changes in body composition (end point minus baseline values)**

	Troglitazone	Placebo	Differences (treated – placebo)	P
Weight (kg)	0.66 (–0.71 to 2.04)	0.25 (–0.64 to 1.13)	0.42 (–1.15 to 1.98)	0.58
BMI (kg/m <sup>2</sup> )	0.25 (–0.25 to 0.75)	0.09 (–0.23 to 0.40)	0.16 (–0.40 to 0.73)	0.55
Waist circumference (cm)	2.11 (0.50 to 3.73)	–0.05 (–3.72 to 3.81)	2.16 (–1.5 to 5.84)	0.23
Waist-to-hip ratio	–0.08 (–0.20 to 0.04)	–0.03 (–0.08 to 0.02)	–0.06 (–0.18 to 0.07)	0.37
Total body fat (% body wt)	1.02 (–1.13 to 3.17)	–0.54 (–1.68 to 0.60)	1.56 (–0.88 to 3.99)	0.20
Total body fat (kg)	1.11 (–0.94 to 3.16)	–0.35 (–1.28 to 0.58)	1.46 (–0.82 to 3.73)	0.20
Extra-abdominal fat (kg)	–0.08 (–0.33 to 0.16)	–0.09 (–0.24 to 0.06)	0.01 (–0.28 to 0.26)	0.94
Intra-abdominal fat (kg)	–0.47 (–0.79 to –0.13)	–0.06 (–0.22 to 0.10)	–0.41 (–0.77 to –0.05)	0.03
Blood glucose (U/l)	–0.88 (–3.56 to 1.80)	0.28 (–1.61 to 2.17)	–1.16 (–4.28 to 1.96)	0.45
HbA <sub>1c</sub> (%)	–0.84 (–1.41 to –2.83)	0.29 (–0.69 to 1.26)	–1.09 (–2.09 to –0.17)	0.02
γ-Glutamyltransferase (U/l)	–32.3 (–53.2 to –11.4)	21.0 (–27.4 to 69.4)	–53.3 (–100.6 to –6.0)	0.03
Aspartate aminotransferase (U/l)	–0.09 (–2.82 to 2.64)	–3.67 (–10.01 to 2.67)	3.58 (–2.35 to 9.50)	0.22
Alanine aminotransferase (U/l)	–0.27 (–5.52 to 4.98)	2.67 (–2.80 to 8.13)	–2.94 (–10.03 to 4.15)	0.40
Alkaline phosphatase (U/l)	–36.8 (–51.8 to –21.9)	7.2 (–4.0 to 18.4)	–44.0 (–62.2 to –25.9)	<0.01

Data are means (95% CI). Values for troglitazone and placebo are from paired t test for the differences between baseline and 12 week follow-up data, and values for differences are from independent t tests for the differences of changes in measures of adiposity between treatment groups.



**Figure 2**—A: Body weight at baseline and at 12 weeks in troglitazone- and placebo-treated groups. B: Total body fat mass measured by underwater weighing (UWW) (in kilograms) at baseline and at 12 weeks in troglitazone- and placebo-treated groups. C: Percentage body fat by underwater weighing at baseline and at 12 weeks in troglitazone- and placebo-treated groups. D: Intra-abdominal fat by MRI at baseline and at 12 weeks in troglitazone- and placebo-treated groups. ■, week 0; □, week 12.

groups. There was some suggestion of a tendency (not significant) for weight, total body fat, and BMI to gain in subjects who were treated with troglitazone, but the data did not indicate any difference from placebo at the  $P = 0.05$  level. There were small increases in waist circumference with troglitazone, but these were not significantly different from placebo. A significant decrease in intra-abdominal fat was seen in subjects treated with troglitazone over 12 weeks, and this was significantly different from that seen with placebo treatment, where there was no change.

**CONCLUSIONS** — Obesity and raised intra-abdominal fat are characteristic of type 2 diabetes and the prediabetic state

and can be related to many of the metabolic abnormalities linked to diabetic complications and ill health, including hyperlipidemia and hypertension. The present study was not itself designed to have the power to evaluate the effect of a thiazolidinedione on metabolic variables, which has been demonstrated elsewhere (1), or its effect on intra-abdominal fat. However, it is now well established that intra-abdominal fat is associated with a variety of metabolic disorders, including hyperlipidemia, hypertension, and diabetes (11), and that a decrease in intra-abdominal fat leads to decreases in plasma triglycerides, glucose, and insulin and increases HDLs (12).

In vitro and animal studies indicate that thiazolidinediones work by either mimicking

or enhancing insulin action at both receptor and postreceptor levels, and in both peripheral and hepatic tissues, without any effects on  $\beta$ -cell insulin secretion (2). The end result is the improvement of insulin-mediated glucose disposal and the reduction of hepatic glucose output, possibly involving the reduced plasma triglyceride and increased clearance of circulating free fatty acids (1,3). It has been shown that troglitazone treatment for 12 weeks improves glycemic response in patients with impaired glucose tolerance, while plasma insulin falls in both fasting and postprandial states (13). The action of thiazolidinediones are, therefore, in contrast with the effects of sulphonylurea hypoglycemic drugs, which increase plasma insulin levels in type 2 diabetic subjects (14). Thiazolo-

lidinediones are known to increase insulin sensitivity, reduce cholesterol and triglycerides, and increase HDL cholesterol (15). These changes would not be expected if a global effect on insulin sensitivity were to increase body fat, and particularly intra-abdominal fat. The present study indicates more subtle or tissue-specific actions.

Increased insulin, or increased insulin sensitivity, enhances lipogenesis and causes weight gain in patients on insulin or sulphonylurea treatment. The gain in total body fat observed with troglitazone in animal studies may be due to activation by thiazolidinediones of the ligand-sensitive transcription factor PPAR- $\gamma$ . Activation of these receptors promotes adipocyte differentiation and regulation of a number of gene encoding proteins that regulate lipid metabolism, suggesting that PPAR- $\gamma$  may play a role in the adipogenic signaling cascade and in lipid metabolism. These mechanisms would increase fat deposition in adipose tissue as a consequence of increased insulin sensitivity. However, recent findings by Lefebvre et al. (16) suggest that obese individuals have increased PPAR- $\gamma$  expression in subcutaneous adipose tissue rather than in intra-abdominal sites. The data from the present study on total body fat, and on extra-abdominal fat in the lumbar region, although not significantly different from data with placebo, would be consistent with minor increases in body weight and subcutaneous fat on troglitazone in humans. With a view toward use for the treatment of type 2 diabetes or glucose intolerance, the present study set power (90% at  $P \leq 0.05$ ) to exclude an effect of 1.4% on percentage body fat, which equated to an  $\sim 1$  kg effect on body weight in 12 weeks. The results, in fact, showed upper 95% limits of 2 kg of body weight or 3 kg of total body fat.

The results thus indicate that any effect on total body fat or weight is likely to be small and to be outweighed in terms of metabolic consequences by the 15% reduction in intra-abdominal fat and significant improvements in alkaline phosphatase and  $\gamma$ -glutamyl transferase. The significant reduction in intra-abdominal fat after treatment with troglitazone is a favorable result, in keeping with the known metabolic improvements. Why intra-abdominal fat mass falls while total body fat is maintained cannot be answered directly by this present study, but the results suggest that the effect of thiazolidinediones on insulin sensitivity through its action on PPAR- $\gamma$  or other

mechanisms is less marked in the intra-abdominal fat than in other insulin-sensitive tissues. Subcutaneous preadipocytes are more sensitive to the differentiating effect of thiazolidinediones to promote PPAR- $\gamma$  than intra-abdominal cells (17), which originate as brown adipose tissue (18); therefore, insulin sensitivity increases more in subcutaneous than in intra-abdominal adipose tissue. In animal studies, thiazolidinediones stimulate uncoupling protein in brown adipose tissue, leading to thermogenesis and local lipolysis with a reduction in fat content (19). The improvement in liver function tests in the present study provides some supportive evidence for a localized action on body fat, since it would be in keeping with a reduction in hepatic steatosis in these patients, but the liver was not imaged in the present study. This hypothesis is new, and is not supported directly by other published data, and thus must be regarded as speculative. The abnormalities of liver function reported in  $\sim 2\%$  of patients (20) were not observed in the present study.

In conclusion, the thiazolidinedione troglitazone has no clinically important net effect over 12 weeks on weight or total body fat in type 2 diabetic patients. There is some suggestion that total body fat may be very slightly increased, but this is offset by a significant reduction in intra-abdominal fat mass and improvement in liver function tests, in keeping with known improvements in metabolic risk factors. This effect points to a differential action on insulin sensitivity in different adipose tissue depots in humans.

**Acknowledgments** — This study was funded by Glaxo Wellcome Research and Development, Greenford, Middlesex, U.K. The Department of Human Nutrition was supported by a grant from Rank Prize Funds and the Rank Foundation.

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