Efficacy of Troglitazone on Body Fat Distribution in Type 2 Diabetes

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OBJECTIVE — The insulin-sensitizing action of troglitazone may be mediated through the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) and the promotion of preadipocyte differentiation in adipose tissue on which troglitazone has depot-specific effects. We investigated the relationship between efficacy of the drug and body fat distribution. Changes in body fat distribution were also investigated by long-term administration of the drug.

RESEARCH DESIGN AND METHODS — Troglitazone was given at a dose of 400 mg/day to 20 patients with type 2 diabetes whose diet and sulfonylurea therapy produced unsatisfactory glycemic control (HbA_{1c} >7.8%) and whose insulin secretory capacity was found to be preserved (postprandial C-peptide >3 ng/ml). HbA_{1c} values, serum lipid levels, and body weight were measured monthly. Body fat distribution was evaluated in subcutaneous (SC) and visceral fat using a computed tomography scan at umbilical levels before and after troglitazone therapy.

RESULTS — During the 1-year troglitazone treatment, HbA_{1c} was significantly decreased (from 9.2 ± 0.2 to 7.1 ± 0.2%, $P < 0.01$), showing lowest values at 4–6 months, whereas body weight was significantly increased (BMI 24.6 ± 0.6 to 25.7 ± 0.6 kg/m^2, $P < 0.01$). Reduction of HbA_{1c} (ΔHbA_{1c}) from the baseline value during treatment was significantly greater in obese patients (BMI >26 kg/m^2) than in nonobese patients (−3.2 ± 0.4 vs. −2.1 ± 0.3%, $P < 0.05$) and was more significant in women than in men (−3.2 ± 0.2 vs. −1.4 ± 0.2%, $P < 0.01$). The level of ΔHbA_{1c} during treatment showed a significant negative correlation with SC fat area (r = −0.742, $P < 0.01$) but not with visceral fat area. Weight gain during troglitazone treatment resulted in increased accumulation of SC fat without a change in visceral fat area and, consequently, in a significant decrease in the visceral-to-SC fat ratio.

CONCLUSIONS — Predominant accumulation of SC fat for the visceral fat tissue was an important predictor of the efficacy of troglitazone therapy in patients with type 2 diabetes. Greater efficacy of troglitazone was observed in women who were characterized by more accumulation of SC adipose tissue than men. Long-term administration of the drug resulted in weight gain with increased accumulation of SC adipose tissue, probably because of the activation of PPAR-γ in the region.

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Troglitazone, a thiazolidinedione derivative, is a member of a new class of orally active drugs that enhance insulin action. In animal models of insulin resistance, spontaneously obese diabetic animals (1,2), and patients with type 2 diabetes (3–11), thiazolidinedione was effective for abnormal glucose and lipid metabolism associated with insulin resistance through the reduction of peripheral insulin resistance.

Thiazolidinediones have a high affinity for the ligands of peroxisomal proliferator-activated receptor-γ (PPAR-γ), which is highly expressed in adipose tissue and plays an important role in the differentiation of adipocytes (12). Activation of PPAR-γ and promotion of preadipocyte differentiation by thiazolidinediones has also been closely associated with antihyperglycemic potency (13,14). Thiazolidinediones have a site-specific effect on differentiation of human preadipocytes; this effect is markedly enhanced in subcutaneous (SC) fat, although preadipocytes from visceral fat were found to be refractory to the drug (15). In light of the depot-specific effects of troglitazone, we investigated the relationship between its efficacy and body fat distribution. The distribution of fat is known to be of greater relevance than the degree of obesity. Visceral fat accumulation is closely associated with the insulin-resistance syndrome, including glucose tolerance, hyperlipidemia, hypertension, and cardiovascular disease (16). Despite the primary action of troglitazone on adipogenesis, most clinical studies of this drug consisted of only 3–4 months of evaluation (3–5). In this study, we investigated whether long-term administration of this drug affects body fat distribution in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A total of 20 randomly selected outpatients with type 2 diabetes, who were treated at the Nagasaki University School of Medicine and could not achieve optimal control (HbA_{1c} >7.8%) on a submaximal dose of sulfonylurea (glibenclamide 5–10 mg/day, gliclazide 80–160 mg/day) and in whom the insulin secretory capacity (postprandial C-peptide >3 ng/ml) was preserved, were enrolled in this study. Clinical characteristics of the patients are shown in Table 1. Those patients who chronically used insulin, had experienced a recent body weight change, and had a history of ketoacidosis, heart disease, renal disease, and/or liver disease were excluded. In accordance with the recommendation of the Japan Diabetes Society, all patients were instructed not to

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Abbreviations: CT, computed tomography; PPAR-γ, peroxisome proliferator-activated receptor-γ; SC, subcutaneous; TNF-α, tumor necrosis factor-α.

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

Table 1—*Clinical characteristics of the study patients*

Age (years)	63.5 ± 2.0
Sex (M/F)	7/13
BMI (kg/m^2)	24.7 ± 0.6
Duration of diabetes (years)	12.1 ± 2.1

Data are means ± SEM, unless otherwise indicated.

change their diet or exercise regimen over the entire course of the study.

Patients were administered 400 mg/day troglitazone in combination with sulfonylurea for 12 months. Markers of glycemic control, including blood glucose levels and HbA_{1c} levels, were used as primary efficacy parameters. Body weight and blood pressure were recorded monthly throughout the study. A blood sample was taken monthly for liver function tests, full blood counts, and renal function tests that included measurement of urea and creatinine. To evaluate the efficacy of troglitazone, reduction of HbA_{1c} (ΔHbA_{1c}) (i.e., the difference between the mean HbA_{1c} value for 3 months before the treatment and the lowest value of HbA_{1c} during the treatment) was calculated. Blood glucose levels were measured by glucose oxidase methods. HbA_{1c} was measured by high-performance liquid chromatography. Serum C-peptide was measured by radioimmunoassay.

Computed tomography (CT) was applied to evaluate areas of SC and visceral fat before and after troglitazone therapy. The CT scan was performed at the umbilical level with the subject resting in the supine position (Fig. 1*A*). The total area of the cross-sectional fat region (i.e., including both SC and visceral fat) at the umbilical level was traced inside the skin to calculate the total number of pixel showing CT values between −50 and −150 Hounsfield units (Fig. 1*B*). The visceral fat area was traced manually along the inside of the abdominal wall, and the number of pixels showing the same range of CT values was calculated for this region (Fig. 1*C*). Then, the ratio of the visceral to the SC fat area was calculated as follows: (visceral fat area)/(total fat area − visceral fat area) × 100 (%).

Statistical analysis

Values were expressed as means ± SEM. Statistical analyses were performed by 2-tailed Student's *t* test for paired data and Wilcoxon's rank-sum test for nonparametric analysis of unpaired data. A value of $P < 0.05$ was considered significant.

RESULTS — Figure 2 shows the mean HbA_{1c} value during the treatment. HbA_{1c} levels were stable before troglitazone treatment and began to decrease after treatment. The decline in HbA_{1c} values was significant at 1 month, and the level continued to decrease throughout the first half of treatment, showing the lowest values at 4–6 months (Fig. 2). Body weight increased, and the maximal increase was observed at 6–12 months after the therapy (59.8 ± 1.8 vs. 62.5 ± 1.8 kg, $P < 0.01$). The levels of total cholesterol and HDL cholesterol did not change significantly. The levels of triglyceride were significantly decreased (Table 2).

To evaluate the blood glucose–lowering effect of troglitazone, the ΔHbA_{1c} was calculated for each patient. ΔHbA_{1c} was greater in obese subjects than in nonobese subjects (−3.19 ± 0.42 vs. −2.12 ± 0.26%, $P < 0.05$) (Fig. 3). However, no statistically significant correlation was observed between ΔHbA_{1c} and BMI ($r = -0.326$, $P = 0.160$). ΔHbA_{1c} was significantly greater in women than in men (−3.2 ± 0.2 vs. −1.4 ± 0.2% $P < 0.01$).

We examined the relationship between the efficacy of troglitazone and the change

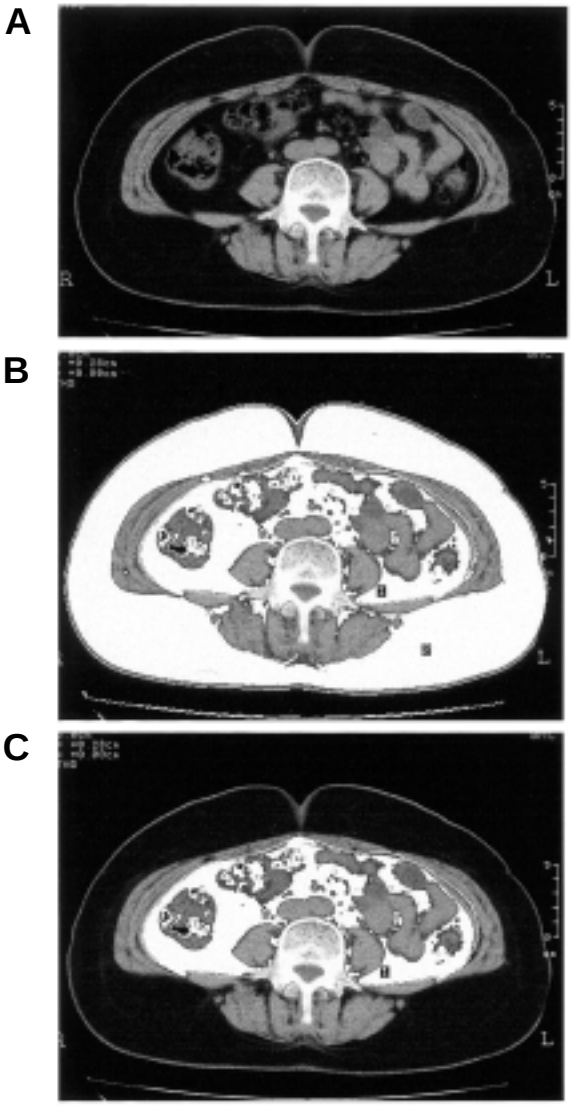

Figure 1—*Area defined to calculate the total and visceral fat. Cross-sectional CT scans at the umbilical level in the supine position (*A*), total area of fat region including both SC and visceral fat (*B*), and the visceral fat area (*C*) are shown.*

of body fat distribution (Fig. 4). The level of ΔHbA_{1c} during treatment was significantly negatively correlated with SC fat area ($r = -0.742$, $P < 0.001$) (Fig. 4*A*) but not with visceral fat area ($r = -0.06$, $P = 0.786$) (Fig. 4*B*). We also observed significant weight gain during treatment with troglitazone. Changes in body fat distribution were examined before and after treatment (Fig. 5). Troglitazone treatment resulted in significant increase of accumulation of SC fat (217.6 ± 18.5 vs. 188.0 ± 15.6 cm^2, $P < 0.01$), no change in visceral fat area (125 ± 13.2 vs. 121.0 ± 11.1 cm^2, $P = 0.492$), and, consequently, significant decrease in the visceral-to-SC fat ratio (0.64 ± 0.07 vs. 0.72 ± 0.09, $P < 0.05$).

CONCLUSIONS — Clinical studies on the effects of troglitazone have, for the most part, been conducted using obese patients (BMI >27 kg/m^2) with type 2 diabetes (3,4,6–9). The index of insulin resistance that considers the degree of obesity and/or fasting C-peptide levels has been reported to be a good predictor of blood glucose–lowering effects by troglitazone (3,5,8). Iwamoto et al. (5) reported that 46% of 126 diabetic patients who received troglitazone were responders (HbA_{1c} reduction >1%) and the remaining 54% were nonresponders (HbA_{1c} reduction <1%). In the responder group, BMI was significantly higher than that in the nonresponder group (BMI 25.0 ± 3.3 vs. 23.4 ± 3.4 kg/m^2, $P < 0.01$) (5). Maggs et al. (8) reported that the fasting C-peptide level was a positive indicator of a good glucose-lowering effect in type 2 diabetic patients. Suter et al. (3) reported the efficacy of troglitazone in 11 obese patients with type 2 diabetes. The majority of obese patients (72%) were responders, and patients in the nonresponder group (28%) showed the lowest insulin secretory profiles (3). Our results showed that reduction of HbA_{1c} by troglitazone was significantly greater in obese patients (BMI >26 kg/m^2) than in nonobese patients with type 2 diabetes (Fig. 3), confirming the findings in previous reports.

In the present study, we examined the relationship between the efficacy of troglitazone treatment and body fat distribution in patients with type 2 diabetes whose insulin secretory capacity was preserved (postprandial C-peptide >3 ng/ml).

We found that reduction of HbA_{1c} during the troglitazone treatment closely correlated with the increase of the SC adipose tissue area (Fig. 4). We found that adiposity

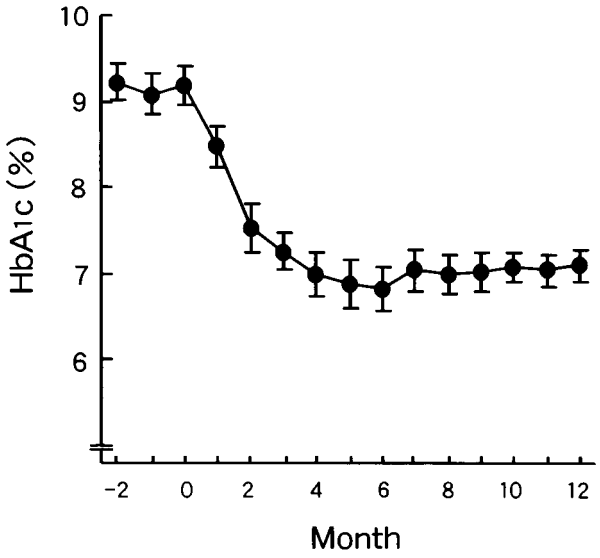

Figure 2—*Mean HbA_{1c} values in patients with type 2 diabetes during the baseline periods and during treatment with troglitazone.*

Table 2—*Mean changes of HbA_{1c}, lipids, and body fat distribution before and after 12 months of treatment*

	Before	After
BMI (kg/m^2)	24.6 ± 0.6	25.7 ± 0.6*
HbA_{1c} (%)	9.2 ± 0.2	7.1 ± 0.2*
Serum lipids		
Total cholesterol (mg/dl)	209.4 ± 7.4	209.9 ± 6.5
Triglyceride (mg/dl)	129.0 ± 10.9	113.2 ± 11.4†
HDL cholesterol (mg/dl)	58.8 ± 3.1	58.7 ± 3.1
Body fat distribution		
Visceral fat (cm^2)	121.0 ± 11.1	125.3 ± 13.2
Subcutaneous fat (cm^2)	188.0 ± 15.6	217.6 ± 18.5*
Visceral-to-SC fat ratio	0.72 ± 0.09	0.64 ± 0.07†

Data are means ± SEM. *$P < 0.001$ vs. before treatment; †$P < 0.05$ vs. before treatment.

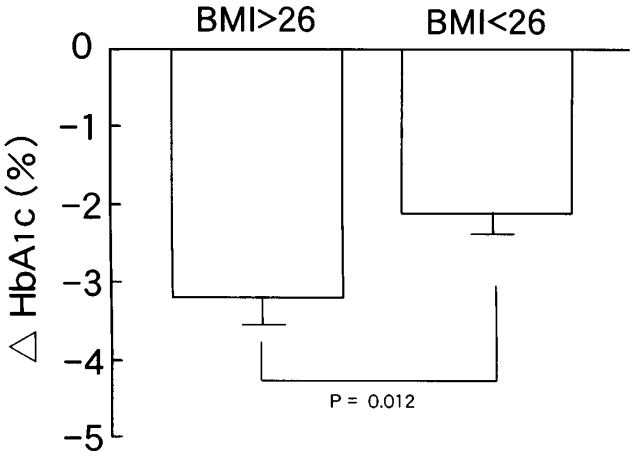

Figure 3—*Comparison of decrease of HbA_{1c} in obese (BMI >26 kg/m^2) and nonobese (BMI <26 kg/m^2) diabetic patients during treatment with troglitazone.*

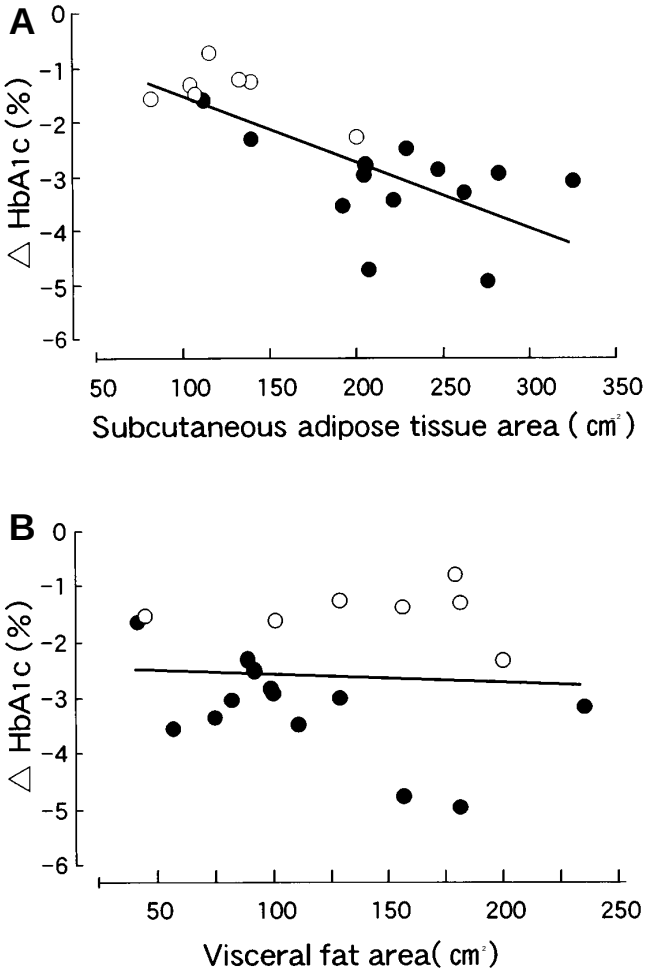

Figure 4—*Relationship between ΔHbA_{1c} during the treatment with troglitazone and body fat distribution during the baseline periods.* A*: SC fat area (*r = *−0.742,* P = *0.0002).* B*: Visceral fat areas (*r = *−0.06,* P = *0.786).* ●*, Women;* ○*, men.*

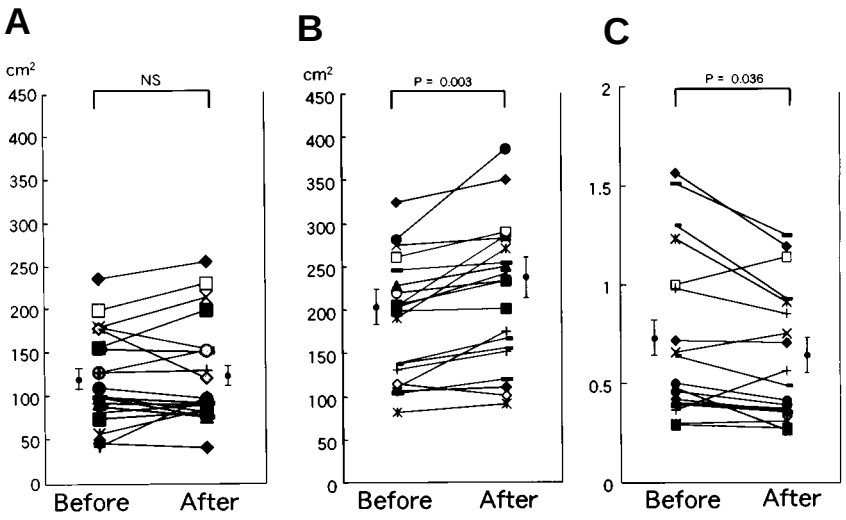

Figure 5—*Changes of body fat distribution in each patient before and after treatment with troglitazone.* A*: Visceral fat.* B*: SC fat.* C*: Visceral-to-SC fat ratio. Bars represent means ± SEM.*

characterized by a predominant accumulation of SC fat tissue for the visceral fat was an important predictor of the efficacy of troglitazone. Women are known to have preponderant accumulation of SC adipose tissue, showing lower visceral-to-SC fat ratios than men at the same BMI (17). In our results, efficacy of troglitazone was greater in women than in men, which confirmed a previous report (18). Our findings may explain the reason why clinical efficacy of troglitazone was greater in women than in men.

Thiazolidinedione binds to and stimulates transcriptional activity in the nuclear hormone receptor PRAR-γ, which is highly expressed in human adipose tissue (12). A close relationship between antidiabetic action and the potency of troglitazone to stimulate PPAR-γ has been shown to exist (13,14). Activation of PPAR-γ in adipose tissue induced by the drug stimulates preadipocyte differentiation (12) and may affect the size of adipocytes, which are associated with insulin resistance. In obese Zucker rats, troglitazone administration resulted in an increased number of small adipocytes and a decreased number of large adipocytes, the latter of which was associated with the reduction of tumor necrosis factor-α (TNF-α) and leptin (19). TNF-α has been postulated as an important cause of insulin resistance in obesity. Troglitazone has a depot-specific effect on human preadipocyte differentiation (15). PPAR-γ is more highly expressed in human SC adipose tissue than in visceral fat tissue (20). Troglitazone promoted the differentiation of human preadipocytes from SC adipose tissue, although preadipocytes from visceral fat tissue were refractory to the drug (15). We can tentatively speculate that the action of troglitazone is more pronounced on SC adipose tissue than on visceral fat tissue, involves the activation PPAR-γ, promotes preadipocyte differentiation, and increases the number of small adipocytes. By virtue of these characteristics, troglitazone leads to amelioration of insulin resistance. The ability of the drug to differentiate preadipocytes would also be expected to induce lipogenesis and fat cell proliferation, which leads to weight gain. We observed significant weight gain in patients who underwent long-term administration of troglitazone, although we cannot completely exclude the fact that some of the weight gain might have been because of water retention. Because most clinical studies on treatment with troglitazone have been conducted over a relatively short term (3–4 months), significant weight

gain has not been reported (3,4,9,11). On the other hand, weight gain has been reported for relatively long-term (6–12 months) administration of the drug (7,10). Based on previous reports on body fat distribution by short-term (3 months) treatment with troglitazone, a significant increase in visceral fat and SC fat in response to such treatment has not been reported (9,11). We confirmed that in patients who underwent long-term (12 months) administration of troglitazone, significant increases in visceral fat were not observed, even when weight gain occurred (Fig. 5). This finding may be because of the relatively beneficial effects of troglitazone, considering that weight gain by the improvement of glycemic control by sulfonylurea therapy is often associated with visceral fat accumulation (22). However, troglitazone caused a significant increase in SC adipose tissue and body weight (Fig. 5). Because of the possibility of the action of thiazolidinedione on adipogenesis and its modulations of the appetite center (21,23), careful management of weight gain should be required for patients undergoing long-term treatment with thiazolidinedione, which is frequently prescribed for obese type 2 diabetic patients. It should also be emphasized that in the treatment of obese type 2 diabetic patients, weight reduction by diet therapy is the first step for improving insulin resistance.

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