Effects of Troglitazone on Fat Distribution in the Treatment of Male Type 2 Diabetes

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We investigated the efficacy of additional administration of 400 mg troglitazone (+T), which became available as a treatment for type 2 diabetes following the demonstration of its ability to reduce insulin resistance, in combination with diet (D + T) or sulfonylurea (S + T) therapy. Body fat area as determined by computed tomographic (CT) scanning at the umbilical level, as well as several clinical and biochemical parameters of glycemic control and lipid metabolism, were compared before and after 3 months of additional treatment with troglitazone. The body mass index (BMI) tended to increase in both groups (22.7 ± 0.6 *v* 23.2 ± 0.6 kg/m^2 in D + T, nonsignificant [NS]; 22.2 ± 0.5 *v* 22.3± 0.5 kg/m^2 in S + T, NS), while it tended to decrease in the control group (only diet therapy, 23.6 ± 0.6 *v* 23.1 ± 0.8 kg/m^2, NS). Mean blood pressure ([BP] 96 ± 3 *v* 89 ± 4 mm Hg, $P < .05$) decreased significantly in the D + T group. Changes in the glycemic and lipid profile and leptin did not reach statistical significance. The D + T group showed a significant decline in immunoreactive insulin ([IRI] 12.4 ± 1.2 *v* 8.0 ± 1.0 μU/mL, $P < .05$), reflecting markedly reduced insulin resistance, as well as a significant increase in plasma insulin-like growth factor-1 ([IGF-1] 175.7 ± 14.2 *v* 189.8 ± 12.6 ng/mL, $P < .05$). A slight weight gain was associated with a tendency for subcutaneous fat to increase, while visceral fat decreased in both troglitazone-treated groups. The decrease in the visceral to subcutaneous fat ratio (V/S ratio) was statistically significant in the D + T group (1.09 ± 0.11 *v* 0.94 ± 0.09, $P < .05$), while the V/S ratio in the control group did not change. A notable finding of this study is the difference in the response to troglitazone between subcutaneous and visceral adipose tissue. It is suggested that troglitazone may exert beneficial effects by reducing visceral fat.

THE THREE MOST IMPORTANT pathophysiological mechanisms underlying type 2 diabetes (non–insulin-dependent diabetes mellitus) are impaired insulin secretion, increased glucose production by the liver, and insulin resistance in target tissues.[1] The latter metabolic abnormality has been shown in both animal studies and clinical trials to be ameliorated by a novel class of medications termed thiazolidinediones.[2-5] Troglitazone, a newly approved member of this class of antidiabetic agents, has been shown to decrease plasma glucose in diabetic and obese insulin-resistant rodent models and in patients with type 2 diabetes.[6-9] Troglitazone improves glucose tolerance without stimulating insulin secretion.[7] However, despite intensive studies, the detailed mechanisms by which troglitazone enhances the action of insulin, ie, a reduction of insulin resistance in the liver and peripheral target tissues, remain unknown.

It is well recognized that the accumulation of visceral fat is associated with insulin resistance and the development of macrovascular disease.[10-13] The reduction of insulin resistance is regarded as very important for the prevention of macrovascular disease.

An in vitro study using the 3T3-L1 adipocyte cell line demonstrated that thiazolidinedione enhances the action of insulin- or insulin-like growth factor-1 (IGF-1)-mediated differentiation of these cells into mature adipocytes.[14] In light of the possible interaction of thiazolidinediones with adipose tissue, suggesting an indirect effect of these agents on insulin target tissues, we evaluated the changes in fat distribution by computed tomographic (CT) scanning at the umbilical level in subjects during a 3-month clinical trial of troglitazone in addition to other treatments for type 2 diabetes. In addition, we examined several parameters of glycemic control and lipid metabolism, including leptin and IGF-1.

SUBJECTS AND METHODS

Subjects and Protocol

Forty-eight type 2 diabetic male patients evaluated at the outpatient diabetic clinic of Keio University Hospital in Tokyo were enrolled in the study. The patients were divided into three groups. The first group contained 18 patients who were treated with diet therapy only until the start of this study and were additionally administered troglitazone (CS-045; Sankyo Pharmaceutical, Tokyo, Japan) for 3 months (D + T group). The second group contained 15 patients who were receiving a sulfonylurea (glibenclamide 1.25 to 5.0 mg/d, Yamanouchi, Tokyo, Japan; or gliclazide 40 to 80 mg/d, Dainippon, Tokyo, Japan) and were additionally administered troglitazone for 3 months (S + T group). Patients with low levels of insulin secretion (fasting serum immunoreactive insulin [IRI] < 6 to 7 μU/mL) were administered glibenclamide 2.5 or 5.0 mg/d or gliclazide 80 mg/d, and other patients were administered glibenclamide 1.25 mg/d or gliclazide 40 mg/d. Patients with signs of atherosclerosis such as a carotid atheromatous plaque or an abnormal electrocardiogram were administered gliclazide, which has an antiplatelet effect. The dose of sulfonylurea for each patient was unchanged during the study period. These 33 patients received a 200 mg tablet of troglitazone twice per day, the first dose after breakfast and the second after dinner. The tablets were counted every 2 weeks, and compliance in these patients was 100% during 3 months. The third group contained the other 15 patients who were treated with diet therapy only and continued diet therapy as control subjects (control group). All 48 subjects received dietary instructions for using a meal-exchange plan by nutritionists. The ideal dietary caloric intake for each patient was calculated as the ideal body weight (kilograms) × 25 kcal/kg. It was confirmed by questionnaire that the physical activity level was almost constant in each subject throughout the study period.

The age distribution and body mass index (BMI) of the three groups

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Submitted September 5, 1998; accepted March 1, 1999.

Presented at the 18th Annual Meeting of the Japanese Society for the Study of Obesity, October 30-31, 1997, Tokyo, Japan.

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0026-0495/99/4809-0005$10.00/0

Table 1. Baseline Characteristics of Patients With Type 2 Diabetes (male subjects only)

Characteristic	D + T	S + T	Diet Only (control)
No. of subjects	18	15	15
Age (yr)	53.5 ± 2.6	57.1 ± 3.3	50.9 ± 3.6
BMI	22.7 ± 0.6	22.2 ± 0.5	23.6 ± 0.6
Weight (kg)	63.0 ± 1.6	61.8 ± 1.6	67.3 ± 2 1
FPG (mg/dL)	176 ± 9	190 ± 13	146 ± 16
HbA_{1c} (%)	8.3 ± 0.4	8.9 ± 0.2	8.1 ± 0.4

NOTE. Values are the mean ± SEM.

at the start of the study are listed in Table 1. There were no significant differences in any of these parameters between the three groups The body weight, mean blood pressure (BP), distribution of subcutaneous and visceral fat, serum lipid profile, and several parameters reflecting additional treatment efficacy were determined before and after 3 months of troglitazone treatment.

Measurements

BP was determined in the sitting position after a 10-minute rest. Blood samples were drawn from each subject before breakfast in the early morning, after overnight bed rest. Fasting plasma glucose (FPG) was determined by the glucose oxidase method Hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatography (Toso, Tokyo, Japan). Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured enzymatically by an autoanalyzer (Hitachi, Tokyo, Japan) IGF-1 was determined by immunoradiometric assay. Plasma insulin (IRI) and leptin levels were measured by radioimmunoassay (Shionogi, Tokyo, Japan; and Linco Research, St. Charles, MO) as described previously.[15] It was not possible to measure the leptin level in the control group.

Subcutaneous and visceral fat distribution was determined by measuring a −150 Hounsfield unit (HF) to −50 HF area using a modification of the method of CT scanning at the umbilical level of Tokunaga et al.[16] CT images were obtained both before and after 3 months of treatment in 10 patients in the D + T group, and seven patients in the S + T group, and all 15 patients in the control group. In eight patients in the D + T group and eight in the S + T group, it was not possible to obtain CT images after 3 months. The visceral to subcutaneous fat ratio (V/S ratio) was also calculated for each group.

All subjects provided informed consent to participate in the study. The design and aims of the clinical trial were approved by the Medical Ethics Committee of Keio University Hospital.

Statistical Analysis

All results are presented as the mean ± SEM. Differences between groups and before versus after additional treatment were analyzed using a paired t test. A P value less than .05 was considered statistically significant.

RESULTS

Both additional troglitazone treatment groups showed a mild but nonsignificant (NS) increase in BMI, while the control group showed a decrease. Mean BP decreased significantly in the D + T group ($P < .05$) (Fig 1).

FPG and HbA_{1c} tended to decrease in each group, but the changes did not reach statistical significance. There were no significant changes in TC, HDL-C, and TG in each group (Table 2). A statistically significant decrease in IRI was found in the D + T group ($P < .05$), whereas the decrease in the S + T group did not reach statistical significance (Fig 2). There was no statistically significant correlation between BP and IRI in these subjects. Serum IGF-1 significantly increased after treatment in the D + T group ($P < .05$) (Fig 3).

The results concerning changes in fat distribution are shown in Table 3. Visceral fat tended to decrease in each group, while subcutaneous fat tended to increase in both troglitazone-treated groups and tended to decrease in the control group. Consequently, the V/S ratio decreased, but the only statistically significant difference was found in the D + T group ($P < .05$) (Fig 4).

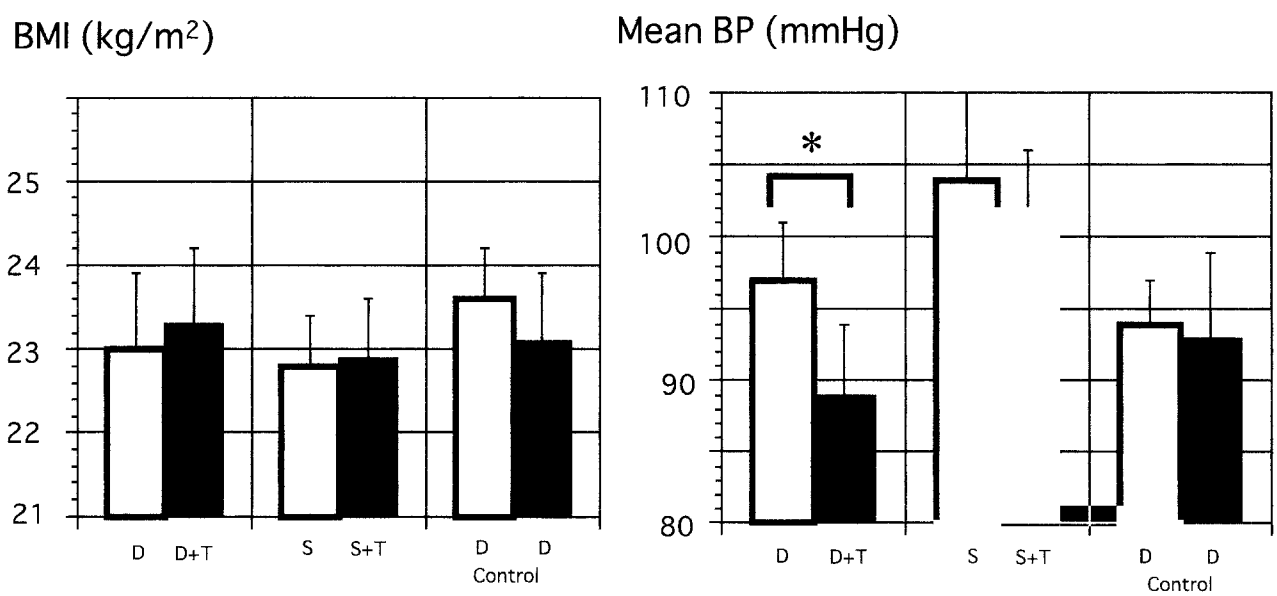


Fig 1. Effects of additional treatment with troglitazone (+T) on BMI and mean BP. Values are the mean ± SEM. *$P < .05$. (□) Before addition of troglitazone; (■) after 3 months of troglitazone. The control group received no medication: (□) before and (■) after 3 months. D, diet; S, sulfonylurea.

Table 2. Effects of 3-Month Additional Treatment With Troglitazone on Glycemic and Lipid Parameters (male subjects only)

Group	Parameter	Before	After 3 Months
D + T (n = 18)	FPG (mg/dL)	176 ± 7	160 ± 14
	HbA_{1c} (%)	8.3 ± 0.4	7.9 ± 0.3
	TC (mg/dL)	204.8 ± 9.9	216.0 ± 9.0
	HDL-C (mg/dL)	54 ± 3	53 ± 4
	TG (mg/dL)	142 ± 20	133 ± 18
	Leptin (ng/mL)	3.9 ± 0.9	4.2 ± 1.0
S + T (n = 15)	FPG (mg/dL)	190 ± 13	179 ± 12
	HbA_{1c} (%)	8.9 ± 0.2	8.8 ± 0.3
	TC (mg/dL)	205.2 ± 9.2	221.0 ± 9.0
	HDL-C (mg/dL)	47 ± 2	50 ± 3
	TG (mg/dL)	161 ± 19	142 ± 20
	Leptin (ng/mL)	3.1 ± 0.3	3.7 ± 0.6
Diet only (control, n = 15)	FPG (mg/dL)	146 ± 16	142 ± 11
	HbA_{1c} (%)	8.1 ± 0.4	7.9 ± 0.2
	TC (mg/dL)	208.4 ± 17.0	198.0 ± 12.0
	HDL-C (mg/dL)	58 ± 8	57 ± 6
	TG (mg/dL)	164 ± 52	128 ± 17

NOTE. Values are the mean ± SEM. None of the changes in the parameters reached statistical significance.

None of the patients experienced adverse events such as liver dysfunction or leg edema and all participants completed the clinical trial. Hepatic enzyme levels were measured every 4 to 8 weeks, and no significant elevations were detected in any of the study participants.

DISCUSSION

Troglitazone is a novel oral antidiabetic agent that has been shown to have a hypoglycemic action both in rodent models[2,6] and in human studies.[7,8] An enhanced insulin sensitivity, ie, reduced resistance of target tissues to the effects of insulin, is considered responsible for its hypoglycemic action, because long-term troglitazone treatment was shown to increase the insulin receptor number and to ameliorate certain postbinding defects in target tissues.[2] More recently, troglitazone was demonstrated to decrease hepatic gluconeogenesis.[8] However, despite extensive research on troglitazone and other thiazolidinediones, the biochemical mechanisms by which these agents improve insulin resistance and decrease lipids and BP have yet to be elucidated.

Our present results reconfirm the BP-lowering effect of troglitazone.[17-19] In our study, glycemic control was not significantly improved by additional troglitazone treatment for 3 months. However, while some subjects showed improved

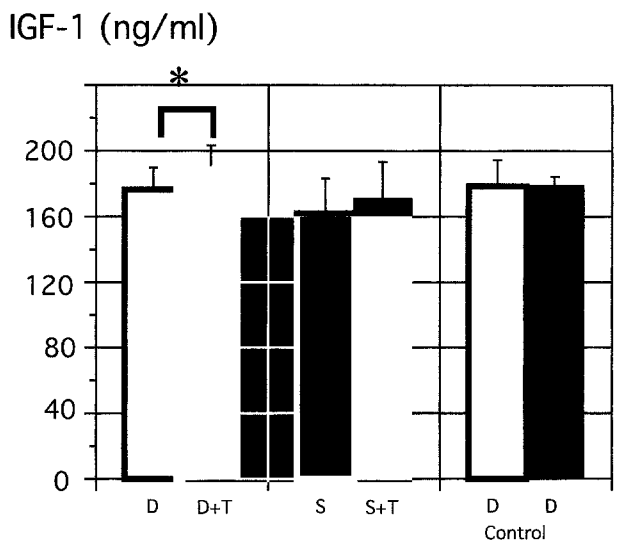
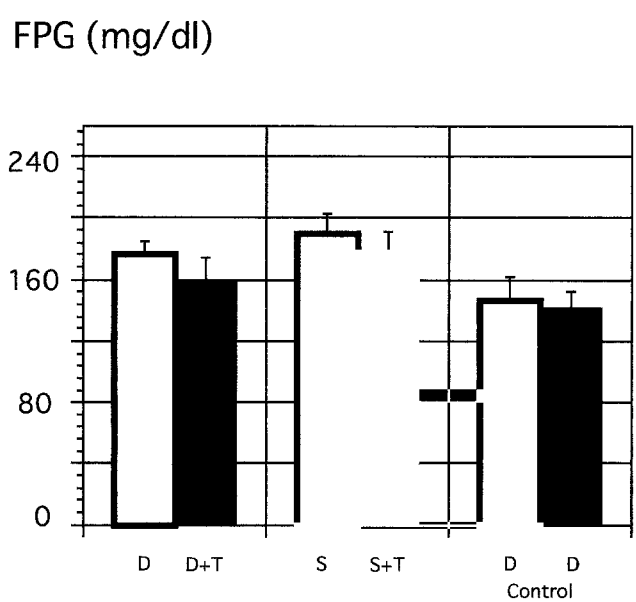


Fig 3. Effect of additional treatment with troglitazone (+T) on IGF-1. Values are the mean ± SEM. *$P < .05$. (□) Before addition of troglitazone; (■) after 3 months of troglitazone. The control group received no medication: (□) before and (■) after 3 months. D, diet; S, sulfonylurea.



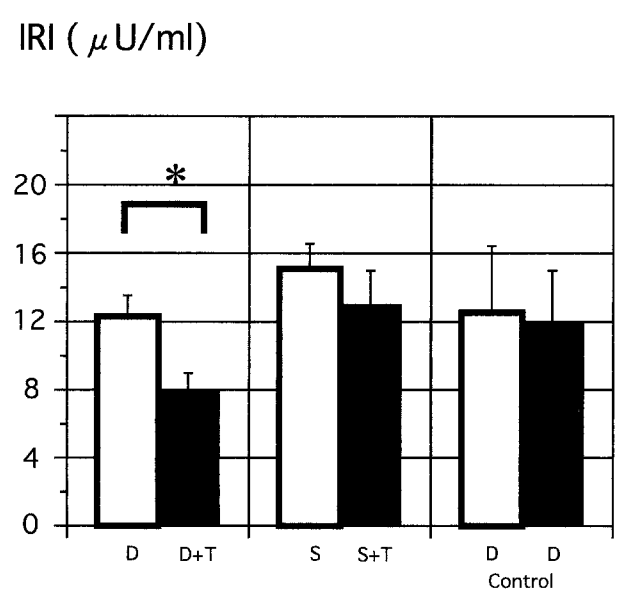


Fig 2. Effects of additional treatment with troglitazone (+T) on FPG and IRI. Values are the mean ± SEM. *$P < .05$. (□) Before addition of troglitazone; (■) after 3 months of troglitazone. The control group received no medication: (□) before and (■) after 3 months. D, diet; S, sulfonylurea.

Table 3. Effects of 3-Month Additional Treatment With Troglitazone on Fat Distribution Evaluated by CT Scanning at the Umbilical Level (male subjects only)

Group	Parameter	Before	After 3 Months
D + T (n = 10)	V fat (cm^2)	132.8 ± 21.3	122.6 ± 22.1
	S fat (cm^2)	121.1 ± 13.5	126 0 ± 17.4
	V/S ratio	1.09 ± 0.11	0.94 ± 0.09*
S + T (n = 7)	V fat (cm^2)	139.7 ± 12.0	132.6 ± 11.6
	S fat (cm^2)	108.9 ± 13.1	118.8 ± 17.0
	V/S ratio	1.44 ± 0.28	1.33 ± 0.27
Diet only (control, n = 15)	V fat (cm^2)	89.2 ± 12.4	83.4 ± 13.0
	S fat (cm^2)	99.9 ± 14.7	97.3 ± 15.7
	V/S ratio	0.94 ± 0.08	0.91 ± 0.01

NOTE. Values are the mean ± SEM.
*$P < .05$.

glycemic control within 1 month, other subjects showed improvement only after 3 months, indicating an interesting variation in the time course (data not shown). Therefore, we consider that a period of 3 months may be too short to assess additional treatment with troglitazone for glycemic control. The observation that IRI decreased in both troglitazone-treated groups, and significantly in the D + T group, supports the widely held view that insulin secretion does not increase in response to troglitazone administration.

A notable finding of this clinical study is the suggestion of differences in the response to troglitazone between subcutaneous and visceral adipose tissue. The tendency for subcutaneous fat to increase while visceral fat decreased, producing a significant decrease in the V/S ratio in the D + T group, points to a link between lipid metabolism and enhanced insulin sensitivity. It is suggested that many factors, genetics, aging, hormones, diet, exercise, stress, etc., may affect fat distribution in humans.[20-28] Above all, there is speculation that hyperinsulinemia, resulting from a hypersensitive hypothalamic-pituitary-adrenal axis state due to stress, promotes lipid accumulation in visceral adipose tissue.[20-24] Visceral adipose tissue has higher metabolic activity, as well as higher lipolytic activity, compared with subcutaneous adipose tissue.[27-31] The amount of adipose tissue may change within 3 months.[32-35] In our study, the decrease of serum insulin by troglitazone treatment might be related to the decrease of visceral adipose tissue. Differences in insulin action and in gene expression between subcutaneous and visceral adipose tissue have been shown by in vitro studies.[36,37] Our data demonstrate for the first time that troglitazone treatment may cause a change in fat distribution in vivo.

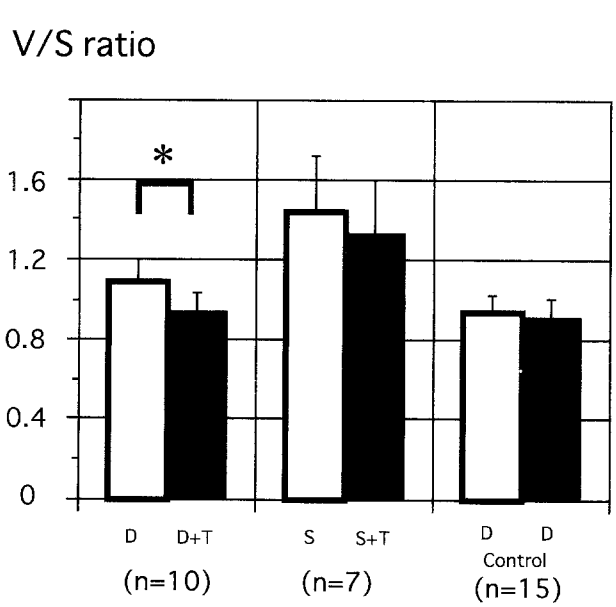


Fig 4. Effect of additional treatment with troglitazone (+T) on V/S ratio. Values are the mean ± SEM. *$P < .05$. (□) Before addition of troglitazone; (■) after 3 months of troglitazone. The control group received no medication: (□) before and (■) after 3 months. D, diet; S, sulfonylurea.

In this study, the decrease in the V/S ratio was not correlated with the decrease in mean BP, FPG, or IRI. However, because it is recognized that the accumulation of visceral fat is linked with increases in BP, FPG, and IRI and the development of macrovascular disease,[10-13] further studies are needed with a greater number of subjects (including females) and a longer duration.

Pioglitazone, another thiazolidinedione, was shown to enhance the effects of insulin and IGF-1 on the differentiation of an established adipocyte cell line, 3T3-L1.[14] Our findings of increased IGF-1 levels in both treatment groups, with a statistically significant increment in the D + T group, support the proposition that IGF-1 may be related to the differentiation of adipose tissue.[24,38]

There was no significant change in the leptin level. With in vitro studies, troglitazone caused adipose tissue to produce less leptin.[39,40] However, our results support the possibility that there may be no direct relationship between troglitazone and serum leptin in vivo.[39]

Overall, a greater improvement in metabolic parameters was observed in the D + T group versus the S + T group. We speculate that this derives from the fact that patients who need sulfonylureas may have less total body fat because of insufficient basal and postprandial insulin secretion. Troglitazone is regarded to exert its action on adipocytes, and thus subjects with less fat are less sensitive to the effects of this agent. Regarding concomitant therapy, the efficacy of troglitazone in combination with insulin was reported.[41] The possible additive, or even synergistic, effects of the other treatments used in this study must be evaluated in future clinical trials with a larger number of subjects. Given the markedly different mechanisms of action of thiazolidinediones, α-glucosidase inhibitors, and classic sulfonylureas, these agents may be suitable for different diabetic subgroups. This possibility also requires further study.

Peroxisome proliferator–activated receptor-gamma (PPARγ), which is present in the nuclear protein of adipocytes, is a major factor involved in decreasing tumor necrosis factor-alpha and fatty acid levels.[42,43] There is evidence from a murine model that thiazolidinediones act on PPARγ, although the mechanism has not been elucidated.[43,44]

In conclusion, we have evaluated the clinical additional effects of troglitazone in combination with diet or sulfonylurea treatment on fat distribution in patients with type 2 diabetes mellitus. Our data support previous findings of the blood glucose–lowering action of this agent, with a decrease in the insulin level. It is also suggested that troglitazone treatment for 3 months may cause a change in fat distribution.

ACKNOWLEDGMENT

We thank Dr Wendy Gray for editing the manuscript.

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