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Improvement of liver function parameters in patients with type 2 diabetes treated with thiazolidinediones

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Abstract

To increase our understanding of the effect of thiazolidinediones, a new class of antidiabetic drugs, on liver function as well as glycemic control, we investigated liver function before, during, and after treatment with troglitazone and pioglitazone.

A total of 32 patients with type 2 diabetes were studied. Glycemic control and liver function were measured before, during, and after 4 to 12 weeks of treatment with troglitazone or pioglitazone. Glycemic control was assessed by fasting levels of plasma glucose, hemoglobin A_{1c}, and serum insulin, and liver function was assessed by asparatate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (γ-GTP). Homeostasis model assessment for insulin resistance was used as an index of insulin resistance.

During treatment with troglitazone, fasting plasma glucose and hemoglobin A_{1c} levels and homeostasis model assessment for insulin resistance were significantly decreased. Serum AST, ALT, and γ-GTP levels were significantly decreased during treatment (AST, −17.4%; ALT, −27.2%; γ-GTP, −47.9%) and returned to pretreatment levels after 4 weeks of withdrawal of the drug. A similar tendency was observed during treatment with pioglitazone (AST, −4.7%; ALT, −16.4%; γ-GTP, −30.8%).

These data suggest that, in contrast to the deterioration of liver function reported in a small subset of patients treated with troglitazone, treatment with thiazolidinediones was associated with a decrease in serum transaminases in most patients. The improvement in liver function parameters known to be associated with fatty liver in the present study, together with an improvement in fatty liver reported for another class of insulin sensitizers, biguanides, suggests that thiazolidinediones may have a beneficial effect on fatty liver.

1. Introduction

Thiazolidinediones have been used clinically as insulin sensitizers for the treatment of patients with type 2 diabetes mellitus, particularly those with insulin resistance [1]. To date, 2 drugs, troglitazone and pioglitazone [2,3], have been available for clinical use in Japan. Severe deterioration of liver function, however, has been reported in a small subset of patients receiving one of these drugs, troglitazone [4-7]. Because a large number of patients with type 2 diabetes have been treated and are still under treatment with these drugs because of their beneficial effect on glycemic control and insulin sensitivity, it is important to accumulate information on the effect of these drugs on liver function as well as glycemic control. Although there have been extensive reports on patients who showed deterioration of liver function after treatment with these drugs, the liver function in most patients without significant deterioration of liver function is largely unknown. The beneficial effect of thiazolidinediones on insulin sensitivity and on glucose and lipid metabolism suggests a beneficial effect of this kind of drug on metabolism in the liver, particularly fatty liver, as was reported for biguanides [8], another class of insulin sensitizer. Improvement of liver metabolism in turn may be reflected by an improvement in liver function parameters, as reported for biguanides [8]. We therefore investigated changes in liver function as well as glycemic control during treatment with troglitazone and pioglitazone.

During the course of the study, one of the drugs, troglitazone, was withdrawn from the Japanese market

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Table 1
Clinical characteristics of patients before treatment with troglitazone

	Male	Female	Total
n	22	10	32
BW (kg)	69.2 ± 7.0	65.1 ± 6.4	67.7 ± 6.9
FPG (mg/dL)	162.8 ± 50.4	172.3 ± 30.8	166.0 ± 44.4
HbA1c (%)	7.0 ± 2.1	8.8 ± 1.0	7.6 ± 2.0
IRI (μL/mL)	7.9 ± 3.8	9.3 ± 4.4	8.4 ± 4.0
T-chol (mg/dL)	205.1 ± 48.2	212.8 ± 27.4	207.6 ± 42.0
HDL-C (mg/dL)	45.6 ± 8.0	49.1 ± 6.5	46.9 ± 7.6
TG (mg/dL)	248.1 ± 222.5	124.9 ± 25.9	205.4 ± 174.7
AST (IU/L)	24.0 ± 11.0	18.8 ± 8.3	21.9 ± 10.1
ALT (IU/L)	28.3 ± 10.9	22.9 ± 11.7	26.1 ± 11.3
γ-GTP (IU/L)	37.9 ± 18.6	23.9 ± 14.4	31.3 ± 17.8
ALP (IU/L)	187.3 ± 108.7	164.0 ± 62.2	181.5 ± 95.5
ChE (IU/L)	2696.3 ± 2019.2	2368.8 ± 2334.8	2509.1 ± 2028.7

Data are mean ± SD. BW indicates body weight; ChE = choline esterase.

because of the side effect of severe liver dysfunction in some cases [4-7]. This gave us the opportunity to investigate the changes in liver function after, as well as during, treatment in all cases treated with troglitazone. Furthermore, most cases successfully treated with troglitazone were switched to another drug, pioglitazone, after a washout period of at least 4 weeks, which made it possible to compare the effect of the 2 different drugs on glycemic control as well as liver function. The data from the current study indicated that, in contrast to a subset of patients with deterioration in liver function during treatment with troglitazone, most patients showed slight, but significant improvement of liver function as assessed by a decrease in serum levels of transaminases, which returned to pretreatment levels after withdrawal of the drug.

2. Materials and methods

2.1. Subjects

A total of 32 outpatients with type 2 diabetes mellitus attending outpatient clinics at Osaka University Medical Hospital and its affiliated hospitals were studied. None of the patients were positive for hepatitis B or C virus, and all the patients showed normal liver function test results.

2.2. Methods

As metabolic parameters, body weight, fasting levels of plasma glucose (FPG), serum insulin (IRI), hemoglobin A_{1c} (HbA1c), total cholesterol (T-chol), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured. Homeostasis model assessment for insulin resistance (HOMA-R) was calculated from FPG and fasting IRI to estimate the degree of insulin resistance [9]. As liver function parameters, asparatate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (γ-GTP) were measured before and at least 4 weeks (range, 4-12 weeks) after the start of administration of troglitazone (400 mg/d) or pioglitazone (15-30 mg/d). In addition, these parameters were measured after withdrawal of the drug in all cases treated with troglitazone.

2.3. Data analysis

Data are shown as mean ± SEM unless otherwise stated. Changes during treatment were analyzed by paired *t* test using the Stat View ver 4.0 statistical package (SAS Institute, Inc, Cary, NC).

3. Results

The subjects were 32 outpatients who were all Japanese. Their clinical characteristics are summarized in Table 1.

After administration of troglitazone, there was a significant decrease in the mean level of FPG, HbA1c, and HOMA-R scale (Table 2). No significant change was observed in body weight during treatment (Table 2).

Regarding liver function, AST, ALT, and γ-GTP levels significantly decreased during treatment (from 21.9 ± 10.1 to 18.1 ± 6.6, $P < .05$; from 26.1 ± 11.3 to 19.0 ± 9.6, $P < .001$; and from 31.3 ± 17.8 to 16.3 ± 7.5 IU/L, $P < .005$, respectively) (Fig. 1, Table 2) and returned to pretreatment levels after withdrawal of the drug (Fig. 1).

In patients who were treated with troglitazone and then switched to pioglitazone because of withdrawal of the former drug, liver function parameters decreased during treatment with troglitazone, returned to the pretreatment levels after withdrawal of the drug, and again decreased when treated with pioglitazone after a washout period of at least 4 weeks (Fig. 2).

In addition to the patients who had been treated with troglitazone and then switched to pioglitazone, 7 patients were newly started on pioglitazone without prior treatment with troglitazone. In these 12 patients treated with pioglitazone, γ-GTP and ALT levels significantly decreased during treatment (from 40.2 ± 31.1 to 27.8 ± 20.7, $P = .006$, and from 23.8 ± 12.3 to 19.9 ± 9.8 IU/L, $P = .013$, respectively) (Table 3). There was no significant difference in the decrease in transaminases between patients treated

Table 2
Metabolic and liver function parameters before and during treatment with troglitazone

	Before	During	*P*
BW (kg)	67.8 ± 6.9	68.6 ± 6.8	NS
FPG (mg/dL)	166.0 ± 44.4	137.3 ± 32.5	<.005
HbA1c (%)	7.6 ± 2.0	6.7 ± 1.7	<.005
IRI (μL/mL)	8.4 ± 4.0	5.8 ± 2.6	<.05
HOMA-R	3.4 ± 1.5	2.1 ± 1.2	<.05
T-chol (mg/dL)	207.6 ± 42.0	202.0 ± 33.4	NS
HDL-C (mg/dL)	46.9 ± 7.6	51.3 ± 11.0	<.005
TG (mg/dL)	205.4 ± 188.3	119.1 ± 67.7	<.05
AST (IU/L)	21.9 ± 10.1	18.1 ± 6.6	<.05
ALT (IU/L)	26.1 ± 11.3	19.0 ± 9.6	<.001
γ-GTP (IU/L)	31.3 ± 17.8	16.3 ± 7.5	<.005
ALP (IU/L)	181.5 ± 95.5	143.9 ± 66.6	NS

Data are mean ± SD; NS indicates not significant ($P > .05$).

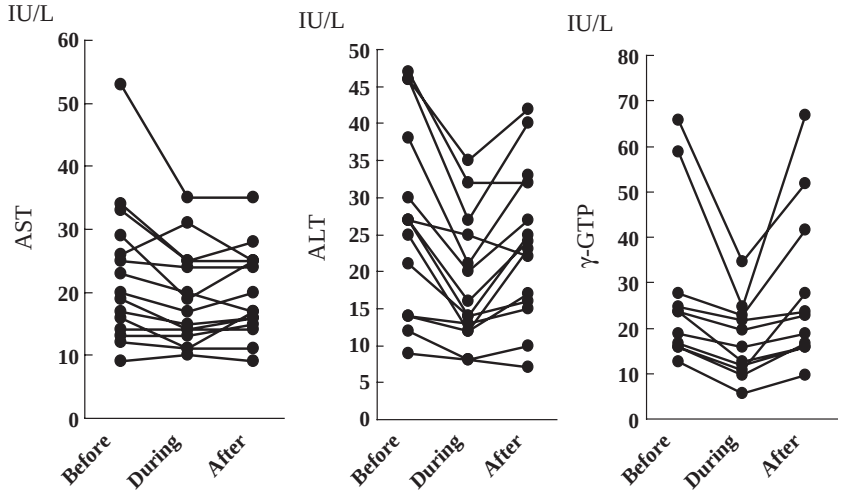

Fig. 1. AST, ALT, and γ-GTP levels before, during, and after treatment with troglitazone in patients with type 2 diabetes mellitus.

with troglitazone and those treated with pioglitazone without prior treatment with troglitazone.

4. Discussion

Insulin resistance is an important characteristic of type 2 diabetes mellitus as well as hypertension and dyslipidemia, leading to atherosclerosis and ischemic heart disease. Treatment of insulin resistance is therefore important not only for improvement of glycemic control, but also for prevention of these diseases.

Thiazolidinediones have recently been introduced as a new class of antidiabetic drugs, which improve glycemic control by improving insulin sensitivity. Two drugs, troglitazone and pioglitazone, have been available for clinical use in Japan [2,3]. Severe deterioration of liver function, however, has been reported in a small subset of patients receiving troglitazone [4-7], leading to subsequent removal of this drug from the market in several countries including Japan. Because of the large number of patients with insulin resistance and the beneficial effect of thiazolidinediones on glycemic control and insulin sensitivity in these patients, a large number of patients with type 2 diabetes worldwide are still under treatment with these drugs. Information on the effect of these drugs on liver function as well as glycemic control should therefore be accumulated for the safe and better use of this kind of drug. In the present study, we studied changes in liver function as well as glycemic control during treatment with troglitazone and pioglitazone.

Both drugs improved glycemic control and insulin sensitivity as assessed by HOMA-R, indicating that the drugs were effective in improving insulin sensitivity and glycemic control in the patients studied. As for liver function, AST, ALT, and γ-GTP did not increase, but significantly decreased during treatment with the drugs. Moreover, the levels returned to pretreatment levels after withdrawal of troglitazone, indicating that changes in liver function paralleled the administration of troglitazone. A similar tendency was also observed for pioglitazone, suggesting that the effect is not specific for troglitazone,

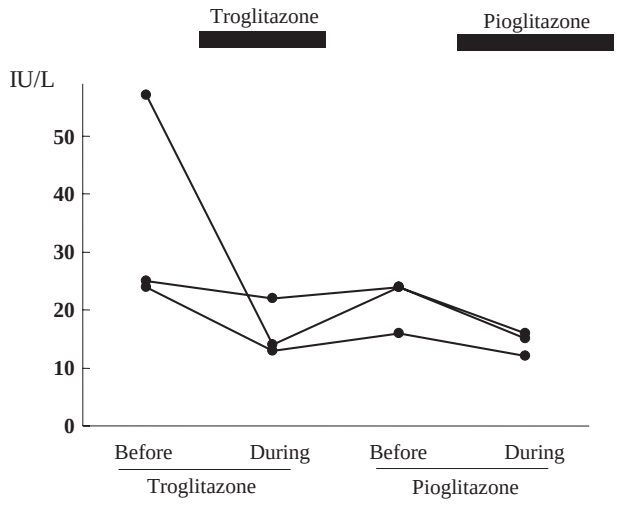

Fig. 2. γ-GTP level before, during, and after treatment with troglitazone and pioglitazone in patients with type 2 diabetes mellitus.

Table 3
Metabolic and liver function parameters before and during treatment with pioglitazone

	Before	During	P
BW (kg)	21.5 ± 33.7	21.8 ± 34.1	NS
FPG (mg/dL)	195.5 ± 56.8	143.1 ± 34.2	<.01
HbA1c (%)	8.1 ± 2.6	6.6 ± 3.1	NS
IRI (μL/mL)	8.5 ± 5.6	7.3 ± 2.5	NS
HOMA-R	3.8 ± 2.7	2.7 ± 1.5	NS
T-chol (mg/dL)	192.0 ± 22.9	208.3 ± 27.8	NS
HDL-C (mg/dL)	48.6 ± 13.2	54.2 ± 14.0	<.05
TG (mg/dL)	155.2 ± 87.6	159.3 ± 153.9	NS
AST (IU/L)	17.0 ± 5.4	16.2 ± 4.0	NS
ALT (IU/L)	23.8 ± 12.3	19.9 ± 9.8	<.05
γ-GTP (IU/L)	40.2 ± 31.1	27.8 ± 20.7	<.01
ALP (IU/L)	127.9 ± 30.0	116.8 ± 41.6	NS

Data are mean ± SD; NS indicates not significant ($P > .05$).

but is a common characteristic of the thiazolidinediones. To confirm the improvement of liver function parameters during treatment with thiazolidinediones in a much larger number of subjects, we searched for data on liver function during clinical trials of troglitazone and pioglitazone. Consistent with the present study, significant decreases in ALT and γ-GTP were observed during clinical trials of both drugs [10-12].

Insulin resistance has been reported to be closely related to fatty liver [13-16]. The improvement of liver function during treatment with thiazolidinediones, which have an insulin-sensitizing effect, in the present study may therefore have been due to improvement of fatty liver. In fact, improvement of fatty liver by troglitazone has recently been reported in patients with type 2 diabetes treated with a sulfonylurea [17]. More recently, pioglitazone treatment in patients with type 2 diabetes has been reported to decrease hepatic fat content by 47% [18]. In addition, in vitro studies showed that troglitazone inhibited TG synthesis in isolated hepatocytes [19]. A decrease in γ-GTP level associated with a decrease in intra-abdominal fat mass was reported in patients treated with troglitazone [20]. Taken together, these data suggest that the decrease in ALT and γ-GTP levels in patients treated with thiazolidinediones may reflect the improvement of fatty liver. Further studies on both the morphology and function of the liver in animal models of fatty liver as well as in a large number of subjects with fatty liver are necessary to clarify whether the improvement of liver function observed in the present study was due to the effect of thiazolidinediones on fatty liver, and if so, whether this effect is beneficial to the long-term prognosis of patients.

In conclusion, troglitazone and pioglitazone contributed to the improvement of insulin resistance and glycemic control in patients with type 2 diabetes. In addition, treatment with these drugs was associated with a decrease in serum ALT and γ-GTP, which may reflect the improvement of fatty liver. Because this study was a retrospective study, prospective studies with a controlled design are necessary to confirm the observation in this study. Further studies on both the morphology and function of the liver are necessary to clarify whether the decrease in liver function parameters in the present study as well as in previous studies is beneficial.

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