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ORIGINAL ARTICLE

# Safety and Effectiveness of Rosiglitazone in Type 2 Diabetes Patients with Nonalcoholic Fatty Liver Disease

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**Background/Purpose:** Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease ranging in severity from steatosis to cirrhosis. Type 2 diabetes mellitus is a cause of primary NAFLD. Thiazolidinediones have been shown to enhance insulin sensitivity, improve glycemic control in type 2 diabetes patients and to improve the histologic markers of nonalcoholic steatohepatitis. This study aims to determine the safety and effectiveness of rosiglitazone in inadequately controlled type 2 diabetes patients with NAFLD.

**Methods:** Taiwanese type 2 diabetes patients with inadequate control on insulin secretagogues and metformin, with no history of significant alcohol ingestion, with mildly elevated serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and a diagnosis of fatty liver determined by ultrasonography were enrolled. Patients were treated for 24 weeks with rosiglitazone, 4–8 mg daily. Primary endpoints were change in AST and ALT levels from baseline and reduction in A1C < 6.5%.

**Results:** Out of a total of 68 patients, 60 (88.2%) completed the study treatment without serious adverse events. Treatment in two (2.9%) patients was discontinued due to elevated AST or ALT levels to more than three times the upper limit of normal, and noncompliance or loss of follow-up in six (8.8%) patients. Of the 60 patients who completed the study treatment, mean fasting plasma glucose, A1C, fasting plasma insulin, mean ALT and homeostasis model assessment for insulin resistance were all significantly reduced. Normal AST and ALT levels were achieved and maintained for at least three consecutive measurements and through to the end of the study period in 20 (33.3%) patients. Weight increased by a mean of $2.6 \pm 2.4$ kg ($p < 0.001$).

**Conclusion:** Rosiglitazone was reasonably well tolerated in patients with inadequately controlled type 2 diabetes and NAFLD. One-third of patients showed improved liver function after treatment. [*J Formos Med Assoc* 2006;105(9):743–752]

**Key Words:** nonalcoholic fatty liver disease, rosiglitazone, thiazolidinediones, type 2 diabetes

Nonalcoholic fatty liver disease (NAFLD) is a common, but often subtle, chronic liver disease that ranges from steatosis alone to steatosis with inflammation, necrosis, fibrosis or cirrhosis.[1] Recent data indicate that NAFLD represents not only the most common form of all liver disorders, but also the most frequent cause of chronic liver disease.[2] NAFLD is characterized by asymptomatic, mildly elevated serum aminotransferase levels in the absence of significant alcohol intake or other chronic liver diseases.[2] Primary NAFLD is caused by conditions associated with insulin resistance syndrome such as type 2 diabetes, obesity and hyperlipidemia.[2–5] A more severe type of NAFLD,



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**Received:** October 18, 2005
**Revised:** November 4, 2005
**Accepted:** March 7, 2006

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nonalcoholic steatohepatitis (NASH), can lead to progressive fibrosis and eventually cirrhosis.[1] As there is no therapy that has been demonstrated to be effective for NAFLD, the focus of management is to modify potential risk factors such as obesity, hyperlipidemia and poor diabetic control.[2,6]

The thiazolidinediones (TZDs) have been shown to enhance insulin sensitivity in peripheral organs and in the liver, thereby resulting in improved glycemic control in patients with type 2 diabetes.[7–13] Additionally, treatment of NASH with rosiglitazone has improved insulin sensitivity and the histologic markers of NASH.[14] Rosiglitazone may also directly favourably influence necroinflammatory changes and fibrogenesis, resulting in downregulation of the inflammatory cascade and fibrosis.[14] These benefits, therefore, raise the potential of successfully treating type 2 diabetes patients who have NAFLD with TZDs.

Troglitazone, the first TZD, was found to improve hepatic histology in patients with NASH,[15] but the side effect of hepatotoxicity led to its subsequent withdrawal from the market. The two newer TZDs, rosiglitazone and pioglitazone, have not demonstrated the high incidence of hepatotoxicity seen with troglitazone.[16] With accumulating exposure to rosiglitazone and pioglitazone in clinical trials and in postmarketing experience, there continues to be little evidence of drug-induced hepatotoxicity.[17,18] These newer TZDs have also been reported to improve the biochemical and histologic features of NASH and support the role of insulin resistance in the pathogenesis of this disease.[14,19] However, since the subjects in these studies were mostly nondiabetic patients and since the study populations were small, the efficacy and safety of TZDs in poorly controlled diabetes patients with NAFLD remain unclear.

To our knowledge, the safety of rosiglitazone and its effects on glucose and liver function in poorly controlled type 2 diabetes with NAFLD have not been previously evaluated. The primary aim of this study was to determine the safety of rosiglitazone use in inadequately controlled type 2 diabetes patients who have NAFLD and who were already being treated with a tolerable maximal dose of insulin secretagogues and metformin. The secondary aim of this study was to evaluate the glycemic and other nonglycemic metabolic effects, including changes in liver function, in these patients.

## Methods

### *Patient selection*

This study was conducted at Mackay Memorial Hospital in Taipei, Taiwan, between February 1, 2003 and June 30, 2004. Sixty-eight Taiwanese patients with inadequately controlled type 2 diabetes who were on a tolerable maximum stable regimen of insulin secretagogues (glibenclamide 20 mg/day, gliclazide 320 mg/day, glimepiride 6–8 mg/day or repaglinide ≥ 6 mg/day) and metformin (≥ 1500 mg/day) for at least 3 months before the study period were enrolled.

Other inclusion criteria were age 18 years or older; glycosylated hemoglobin (A1C) ≥ 7.0%; no history of alcohol intake or absence of significant alcohol ingestion (< 70 g/week); mildly elevated levels (up to 2.5 times the upper limit of the normal range [ULN]) of serum aspartate aminotransferase (AST) (36–88 U/L; reference range, 5–35 U/L) and/or of alanine aminotransferase (ALT) (31–75 U/L; reference range, 5–30 U/L) recorded at least three times within 1 year before the study, with ALT levels higher than AST levels; negative diagnostic tests for viral hepatitis B and C, and a body mass index (BMI) < 40 kg/m$^2$.

Fatty liver was determined by abdominal ultrasonography, which presented as diffusely increased brightness and echogenicity.

Exclusion criteria included the following: current or previous treatment with rosiglitazone or with other TZDs; pregnancy; lactation; clinical evidence of active liver disease; normal or > 2.5 times the ULN levels of AST and/or of ALT; secondary causes of fatty liver, such as gastrointestinal bypass surgery or medications that induce steatosis; more than one episode of hypoglycemic unawareness; clinically significant heart failure (NYHA Fc ≥ III) and peripheral edema.

Throughout the course of this study, patients were instructed to continue with the same lifestyle, including diet and exercise, that they had maintained before study entry. Patients were allowed to continue using antihypertensive and lipid-lowering agents if they had been taking a stable dose for at least 8 weeks before study entry. During the entire study, the study protocol required that patients maintain their respective doses of these agents at the same levels as before study entry.

### *Study design*

This prospective, open-labeled study consisted of a 4-week screening period followed by a treatment with rosiglitazone period that lasted at least 24 weeks. Enrolled patients underwent a comprehensive medical history and physical examination. All patients gave written informed consent for study participation.

Laboratory measurements included A1C, fasting plasma glucose (FPG), AST and ALT at baseline and after 4, 8, 12, 16 and 24 weeks of treatment; and fasting plasma insulin, total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C) at baseline and after 24 weeks of treatment. Dyslipidemia was defined as TC $\geq$ 200 mg/dL and/or TG $\geq$ 200 mg/dL.

Postprandial glucose and insulin levels were measured at baseline and after 24 weeks of treatment. Body composition analysis was performed at baseline and after 24 weeks of treatment. Body weight was measured to the nearest 0.1 kg at baseline and at 4-week intervals. All patients were started on a 4 mg daily dose of rosiglitazone and were titrated up to 8 mg/day at 4-week intervals if their A1C levels remained $\geq$ 6.5%. The study protocol required no dose adjustments to be made of other oral hypoglycemic, antihypertensive and/or lipid-lowering agents during rosiglitazone treatment.

The response group was defined as patients who achieved normal AST and ALT levels and, on follow-up, continued to maintain normal AST and ALT levels on at least three consecutive assessments and through to the end of the study period.

Safety parameters were assessed during each clinic visit. During therapy, any patient who developed AST and/or ALT $\geq 3 \times$ ULN, significant weight gain that was unacceptable to the patient, serious adverse effects, including heart or hepatic failure, or any episode of severe hypoglycemia, was withdrawn from the study. Severe hypoglycemia was defined as hypoglycemia requiring hospitalization or the assistance of another person to treat and/or blood glucose $<$ 50 mg/dL. Follow-up abdominal sonography was performed after 6 months of rosiglitazone use.

### *Measurements*

Plasma glucose level was determined by the hexokinase enzymatic method, insulin level by the Coat-A-Count radioimmunoassay procedure (Diagnostic Products Corporation, LA, USA) and A1C by the high-performance boronate affinity liquid chromatography method (Primus CLC385$^{TM}$ System, MO, USA) with a normal range of 4.5–5.7%. AST and ALT were determined by the tris buffer without pyridoxal-5-phosphate method. The peroxidase method was used for TC determination, lipase method for TG, and direct immunoinhibition method for HDL-C. LDL-C was measured by the Triblock copolymer and a-cyclodextrin sulfate method and the enzymatic colorimetric method (both using the Hitachi 747 automatic analyzer, Tokyo, Japan). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated from fasting plasma insulin and FPG measurements, according to the formula: HOMA-IR = fasting plasma insulin ($\mu$U/mL) $\times$ fasting plasma glucose (mmol/L)/22.5.[20]

Blood pressure was measured before commencement of and 6 months after starting rosiglitazone treatment. Waist circumference (WC) was measured midway between the iliac crest and the lowest rib at the end of expiration. Body composition was measured using an eight-point tactile electrode, multifrequency segmental bioelectric impedance analyzer (InBody 3.0, Biospace Co., Ltd, Seoul, Korea) after 8 hours of

fasting, in accordance with the manufacturer's instructions. Measurements were taken at baseline and after 24 weeks of treatment.

### *Statistical analysis*

Descriptive statistics were used to summarize demographic and biochemical characteristics at baseline and after 24 weeks of rosiglitazone treatment. Paired Student's *t* test was used to compare changes in parameters at baseline and after treatment. One-way analysis of variance (ANOVA), $\chi^2$ and Fisher's exact tests were used to assess A1C change with time and change in percentage of cases with normalized AST and ALT with time. Stepwise regression analysis was performed using SPSS version 11 (SPSS Inc, Chicago, IL, USA) to evaluate the relationship between ALT and A1C, HOMA-IR, body weight and fat mass. Simple linear correlation was used to evaluate the relationship between change in weight and A1C, weight and fat mass, A1C and ALT, and HOMA-IR and ALT. A $p$ value $< 0.05$ was considered statistically significant.

## Results

Of the 68 patients, 60 (88.2%) completed the study treatment while eight (11.8%) discontinued treatment. Reasons for withdrawal and discontinuation of treatment were as follows: elevated AST or ALT levels $\geq 3 \times$ ULN in two patients (at 84 and 196 days, respectively), with peak AST and ALT values of 106 and 98 for AST, and 65 and 52 for ALT, respectively; noncompliance or loss of follow-up in six patients (at 28, 49, 69, 127, 151 and 163 days, respectively). Of the six patients with noncompliance or loss of follow-up, four did not return to the outpatient clinic for various periods of time during the severe acute respiratory syndrome outbreak in Taiwan. There was loss of follow-up in the other two patients. These six patients were excluded from the analyses. At the end of the study, the mean dose of rosiglitazone in the remaining patients was 7.7 mg/day and 58 (92%) were taking 8 mg/day.

The clinical and biochemical characteristics of the patients at baseline and after 24 weeks of rosiglitazone treatment are shown in the Table. Rosiglitazone treatment decreased mean FPG by $45 \pm 45$ mg/dL ($p < 0.001$), A1C by $1.4 \pm 1.1\%$ ($p < 0.001$), fasting plasma insulin by $4.2 \pm 7.2$ μU/mL ($p < 0.001$), 2-hour postprandial glucose by $51 \pm 95$ mg/dL ($p < 0.001$) and HOMA-IR by $2.88 \pm 3.65$ ($p < 0.001$).

Mean A1C reduced significantly from a baseline of $8.4 \pm 1.3\%$ to $< 7.0\%$ in 60% (36/60) and $< 6.5\%$ in 30% (18/60) of the patients. Mean ALT decreased significantly from $47 \pm 13$ U/L to $35 \pm 17$ U/L ($p < 0.001$), and AST decreased from $32 \pm 10$ U/L to $30 \pm 12$ U/L, although this change was not significant ($p = 0.333$). Mean TC, LDL-C and HDL-C all increased significantly (9.2%, 15.9% and 6.0%, respectively, $p < 0.005$), while TG decreased by 10.9%, although this reduction was not significant ($p = 0.195$). Mean diastolic blood pressure showed significant reduction at the end of the treatment period from $80 \pm 10$ mmHg to $76 \pm 9$ mmHg ($p = 0.003$), while mean systolic blood pressure showed no significant change.

Weight increased in 88.3% (53/60) of patients over the treatment period. Mean weight increased by $2.6 \pm 2.4$ kg ($p < 0.001$). Although the incidence of mild to moderate clinical edema was 20.0% (12/60), it was not severe enough to require discontinuation of treatment in any patient. There was a significant increase in mean fat mass ($2.0 \pm 3.0$ kg, $p < 0.001$), percentage of body fat ($1.7 \pm 3.6\%$, $p < 0.001$) and BMI ($1.1 \pm 1.1$ kg/m$^2$, $p < 0.001$). However, the weight of total body water did not change significantly. Mean WC decreased by 2.0 cm ($p < 0.05$), while mean waist/hip ratio (WHR) reduced by $0.06 \pm 0.08$ ($p < 0.001$).

The mean level of A1C with time and the percentage of patients with normalization of liver function in the response group with time are shown in Figure 1. Mean A1C decreased rapidly during the first 8 weeks of treatment, from 8.4% to 7.4% ($p < 0.001$), with a slower but continued decrease to 7.0% by the end of the study period. Before the addition of rosiglitazone, 63.3% (38/60) of patients had dyslipidemia,

**Table.** Biochemical and clinical characteristics of the patients at baseline and after 24 weeks of rosiglitazone treatment ($n=60$)*

| | Baseline | 24 wk | Mean change | $p^{\dagger}$ |
|---|---|---|---|---|
| Age (yr) | 56.9±8.6 | | | |
| Sex (M/F) | 27/33 | | | |
| A1C (%) | 8.4±1.3 | 7.0±1.0 | −1.4±1.1 | <0.001 |
| SBP (mmHg) | 134±13 | 133±11 | −1.8±13.8 | 0.308 |
| DBP (mmHg) | 80±10 | 76±9.0 | −3.8±9.0 | 0.003 |
| Fasting glucose (mg/dL) | 187±50 | 142±35 | −45±45 | <0.001 |
| Fasting Insulin (μU/mL) | 12.8±7.0 | 8.6±5.5 | −4.2±7.2 | <0.001 |
| HOMA-IR | 5.88±3.79 | 3.01±1.96 | −2.88±3.65 | <0.001 |
| 2-hr glucose (mg/dL) | 330±90 | 279±66 | −51±95 | <0.001 |
| 2-hr insulin (μU/mL) | 32.9±15.4 | 32.3±22.0 | −0.6±18.1 | 0.811 |
| AST (U/L) | 32±10 | 30±12 | −2.0±13 | 0.333 |
| ALT (U/L) | 47±13 | 35±17 | −12±16 | <0.001 |
| Total cholesterol (mg/dL) | 188±25 | 205±37 | 17±31 | <0.001 |
| HDL-C (mg/dL) | 42.5±8.0 | 45±8.7 | 2.5±6.6 | 0.005 |
| LDL-C (mg/dL) | 119±27 | 138±36 | 19±28 | <0.001 |
| Triglyceride (mg/dL) | 231±143 | 206±141 | −25±149 | 0.195 |
| Body weight (kg) | 71.3±13.1 | 73.9±13.8 | 2.6±2.4 | <0.001 |
| BMI (kg/m$^2$) | 27.8±3.6 | 28.8±4.0 | 1.1±1.1 | <0.001 |
| Body water weight (kg) | 33.9±7.0 | 34.2±6.9 | 0.3±2.0 | 0.306 |
| Fat mass (kg) | 22.3±6.3 | 24.3±7.5 | 2.0±3.0 | <0.001 |
| Body fat (%) | 31.1±5.9 | 32.8±6.9 | 1.7±3.6 | <0.001 |
| Waist circumference (cm) | 94.2±9.7 | 92.2±10.3 | −2.0±7.1 | 0.036 |
| WHR | 0.97±0.07 | 0.91±0.07 | −0.06±0.08 | <0.001 |

**Data are presented as mean±standard deviation; †paired Student's t tests. A1C = glycosylated hemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure; HOMA-IR = homeostasis model assessment for insulin resistance; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HDL-C = HDL-cholesterol; LDL-C = LDL-cholesterol; BMI = body mass index; WHR = waist/hip ratio.*

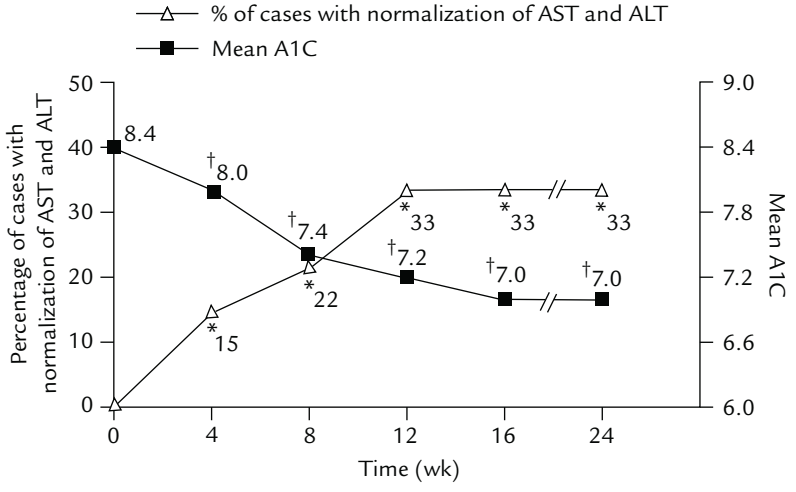


**Figure 1.** Percentage of cases with normalization of liver function and mean A1C with time in the study group ($n=60$). One-way analysis of variance was used for mean A1C with time and $\chi^2$ test was used for the percentage of cases with normalization of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with time. *$p<0.01$; †$p<0.001$.

while 70.0% (42/60) had dyslipidemia at the end of the study ($p=0.44$). In the response group, normalization of liver function was first noted as early as the 4$^{th}$ week after starting rosiglitazone in 15% (9/60) of patients. This incidence increased to 22% (13/60) by the 8$^{th}$ week and to 33.3% (20/60) by the 12$^{th}$ week. There was no significant difference in metabolic

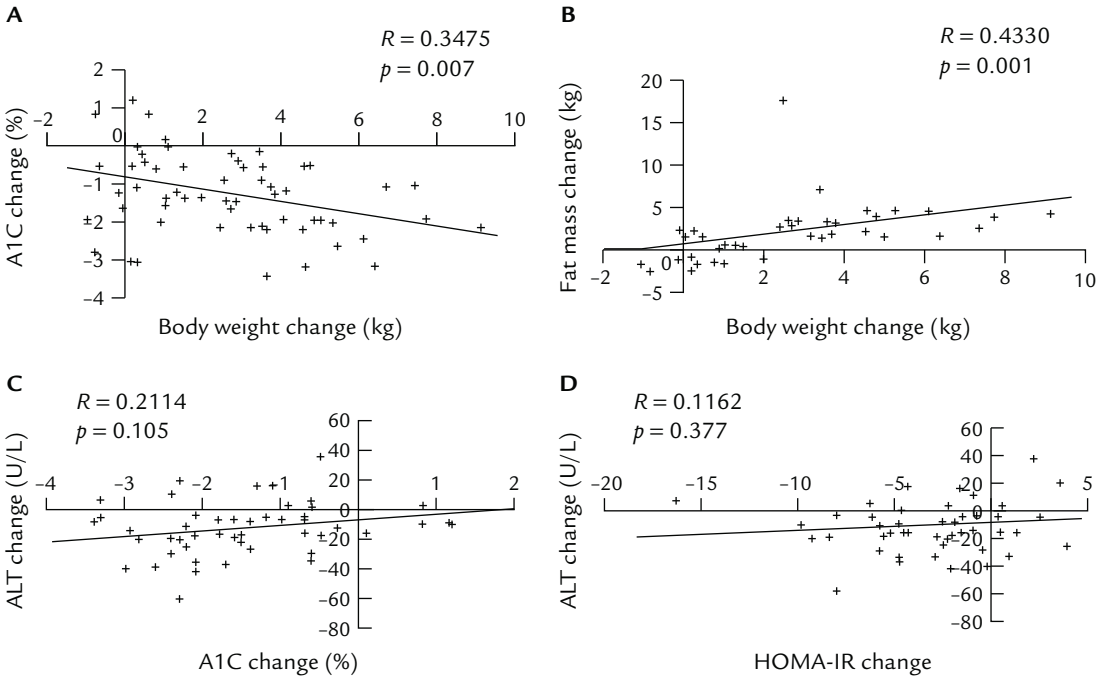


**Figure 2.** Linear correlations between: (A) change in weight and A1C; (B) change in weight and fat mass; (C) change in A1C and ALT; (D) change in HOMA-IR and ALT.

parameters such as FPG, 2-hour postprandial glucose, A1C, HOMA-IR, TC, TG, HDL-C, LDL-C, ALT and AST at baseline between the response and nonresponse groups.

Stepwise regression analysis showed no significant correlation between ALT and A1C, ALT and HOMA-IR, ALT and body weight as well as ALT and fat mass. Linear regression analysis showed significant correlations between change in weight and A1C ($p = 0.007$), and change in weight and fat mass ($p = 0.001$) (Figure 2). Follow-up abdominal sonography after rosiglitazone treatment did not show significant change in the fatty liver status in either the response or nonresponse group.

Of the initial 68 patients, only two patients (2.9%) withdrew due to elevated AST or ALT $\geq 3 \times$ ULN. In one of the two patients who withdrew due to elevated liver transaminase levels, follow-up after discontinuation of rosiglitazone showed AST and ALT levels had reduced to $< 3 \times$ ULN. In the other patient, AST and ALT levels fluctuated after stopping rosiglitazone but remained $> 3 \times$ ULN. Both patients were otherwise stable. No patient developed episodes of hypoglycemia, heart failure, weight gain or other side effects severe enough to necessitate withdrawal from the treatment protocol.

## Discussion

Of the initial 68 patients, 88.2% completed the entire 24-week course of rosiglitazone treatment and only two patients withdrew from the study due to elevated AST or ALT $\geq 3 \times$ ULN. Excluding the six patients with loss of follow-up or noncompliance, 96.8% (60/62) of patients completed the treatment course. There were no serious adverse events, although mean body weight significantly increased. These results suggest that rosiglitazone is safe for use in inadequately controlled type 2 diabetes patients with NAFLD and mildly elevated liver enzymes.

In this study, the addition of rosiglitazone to an established regimen of insulin secretagogues and metformin was effective in further lowering A1C and FPG in patients with inadequately controlled type 2 diabetes. The addition of rosiglitazone resulted in a further reduction of mean A1C by 1.4% ($p < 0.001$), with a decrease in HOMA-IR

by 2.88 (49.0%, $p < 0.001$) (Table), which was greater than the 18.6% to about 43% decrease reported in previous studies.[7,8,21] At the end of the 24-week treatment period, the response group comprised 33.3% of patients. Normalization of liver function was first noted in 15% of the patients as early as 1 month after starting treatment.

The pathogenesis of NAFLD has not been clearly established. The prevailing theory is the "two hits" hypothesis proposed by Day and James in 1998.[22] The first "hit" is attributed to the accumulation of fat within the liver, while the second "hit" is attributed to oxidative stress, which can initiate fibrosis via proinflammatory cytokines. Several studies have demonstrated that insulin resistance is associated with NAFLD,[3–5] and the severity of insulin resistance tends to increase with the stage of NAFLD.[23]

Improvement in liver function was found in previous trials of pioglitazone treatment in patients with type 2 diabetes.[24,25] In addition, the incidence of elevated AST or ALT $\geq 3 \times$ ULN was low (0–2.4%) in previous trials of TZD monotherapy or combined therapy,[7,8,21,24–29] as in this study (3.2%).

TZDs have been reported to improve the biochemical and histologic features of NASH in nondiabetic patients.[14,15,19] In a prospective pilot study, 18 nondiabetic patients with biopsy-proven NASH were treated with pioglitazone for 48 weeks. By the end of the 48 weeks, serum ALT had decreased to normal in 72% of patients. Hepatic fat content and size as determined by magnetic resonance imaging (MRI) were also decreased. Using strict criteria, histologic improvement occurred in two-thirds of patients. There was a strong positive correlation between changes in fat in the liver, as determined by MRI, and degree of steatosis, as determined by liver biopsy.[19] In another study, adults with biopsy-proven NASH were treated with rosiglitazone for 48 weeks. The 25 patients who completed the treatment had significantly improved insulin sensitivity and mean serum ALT levels (104 IU/L initially, 42 IU/L at the end of treatment). The mean global necroinflammatory score significantly improved with treatment, and the biopsies of 10 patients (45%) no longer met the reported criteria for NASH after treatment.[14] These results indicate that treatment with TZD can lead to improvement in the biochemical and histologic features of NASH and support the role of insulin resistance in the pathogenesis of this disease.[14,19] For patients with inadequately controlled type 2 diabetes and NAFLD with mildly abnormal liver function, the results of this study suggest that a trial of rosiglitazone can improve liver function within 3 months in one-third of patients. These patients require long-term follow-up to monitor blood glucose control, liver function, NAFLD change and insulin sensitivity.

The present study suggests that rosiglitazone is safe and has beneficial effects on liver function in poorly controlled type 2 diabetes patients with NAFLD. Improved liver function may result from several factors. First, TZDs improve insulin resistance by increasing insulin sensitivity in peripheral organs and in the liver.[7–13] Second, TZDs improve several components of the metabolic syndrome that could beneficially affect endothelial function, including reduction in circulating concentration of free fatty acids and improvement of lipid profile.[7–9,12,13] Third, TZDs have important anti-inflammatory effects that involve decreasing adipocytokine levels (e.g. TNF-α, PAI-1),[10–13,30–32] which are reflected by reduced high-sensitivity C-reactive protein levels, increasing adiponectin levels and attenuating monocyte chemoattractant protein-1.[33] TZDs have been shown to decrease inflammatory markers much earlier than a fall in either insulin or glucose concentrations in diabetes.[34] Our study confirmed this finding, with a fairly rapid initial improvement in liver function observed much earlier than a fall in glucose concentration. Decrease in A1C was not associated with a change in ALT, and no association was found between change in HOMA-IR and ALT as shown in Figure 2. These findings suggest that rosiglitazone may have effects beyond glucose lowering, such as anti-inflammatory effects, which are responsible for improvement of liver function. There was no significant change

in fatty liver after rosiglitazone use, as determined by abdominal sonography in either responders or nonresponders. This could be due to the relatively short duration of treatment, with biochemical changes preceding imaging alterations. The lack of significant correlation between A1C or HOMA-IR and ALT may have been due to the small decrease in ALT and/or the relatively short treatment period.

The mean body weight increase of 2.6 kg over the 24-week treatment period was mainly attributed to increased mean fat mass (2.0 kg). The incidence of peripheral edema was 20.0%, which is higher than was reported with TZD monotherapy or therapy with sulfonylureas and/or metformin (4.1–12.4%).[7,8,21,24–28] However, both WC and WHR significantly decreased after rosiglitazone use (Table), which indicates a more peripheral redistribution of fat. Previous reports also indicated that the weight gained during the use of these drugs tends to be peripheral fat rather than visceral fat and, therefore, may not be associated with increased risks linked to the metabolic syndrome.[10–13]

Similar to the findings in other studies, rosiglitazone treatment resulted in an increase in mean TC, LDL-C and HDL-C.[7,8,21] There was a decrease in TG in this study, although the change was not significant. Mean diastolic blood pressure decreased significantly after rosiglitazone use. Insulin resistance and hyperinsulinemia have been shown to be causally related to hypertension through direct effects on vascular tone, stimulation of the adrenergic nervous system and antinatriuresis.[35] In this study, HOMA-IR improved after rosiglitazone use and the reduction in diastolic pressure could be due to the improved insulin sensitivity. Diagnosis of NAFLD is based on noninvasive and invasive tests, with liver biopsy being the most definitive modality. The major limitation of this study was the lack of confirmative NAFLD by liver biopsy, although this confirmation would not be practical in most clinical settings. In clinical practice, steatosis is commonly detected by noninvasive imaging with ultrasonography, computed axial tomography (CT) and MRI. Among these imaging methods, sonography is the least expensive and MRI is the most expensive. When CT is used in the diagnosis of NAFLD, diagnostic accuracy is time-dependent and protocol-specific, and there is considerable individual variability as well as intraindividual variability during multiple examinations in the absolute liver attenuation numbers.[36] Arguments against liver biopsy include the generally good prognosis of most patients with NAFLD, the lack of an established effective therapy, and the risks and costs associated with biopsy. In clinical practice, the diagnosis of NAFLD is based on ultrasonographic evidence of "bright liver" and reduced posterior attenuation in subjects with no or moderate alcohol consumption.[37] Selecting imaging studies over liver biopsy has the advantage of avoiding the risks associated with an invasive procedure. Ultrasonography defines increased echogenicity in NAFLD and is thought to be a reasonably sensitive study.[38]

The treatment duration of 24 weeks in this study is relatively short. Further long-term studies, which combine the assessment of inflammatory markers with CT, MRI or liver biopsy, are needed to determine whether improvements in liver function are due to improvement in fatty liver, and to what extent they can be sustained over a prolonged period.

In conclusion, this study found that rosiglitazone was reasonably well tolerated, reduced FPG, postprandial glucose and A1C levels, and improved insulin sensitivity in patients with inadequately controlled type 2 diabetes complicated by NAFLD and mildly elevated transaminase levels. One-third of patients also showed improved liver function. The findings of this study suggest that rosiglitazone treatment may be appropriate in carefully selected patients with monthly monitoring of liver function.

## Acknowledgments

We thank Mr Wang-Chang Lee for his assistance with the statistical analyses in this study.

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