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The Metabolic Effects of Troglitazone in Patients with Diabetes and End-Stage Renal Disease

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Thiazolidinediones (TZD) are effective agents for the treatment of hyperglycemia, and appear ideal in diabetic patients with progressive or end-stage renal disease because of its predominant hepatic clearance. Troglitazone, the first available TZD for clinical use, was withdrawn due to safety concerns; however, studies completed with this agent can provide a better understanding of the class effect of TZDs. This study was an open-label, controlled clinical trial examining the safety and efficacy of troglitazone in type 2 diabetic patients with end-stage renal disease (ESRD). Twelve subjects were randomized to parallel study groups and treated for 6 mo with or without troglitazone at a maximum dose of 600 mg/d in addition to continuing their previous diabetes medications (insulin or sulfonylurea). The results showed no significant differences in glycemic control with or without troglitazone treatment for 6 mo. However, there was a significant reduction in insulin dosage with troglitazone treatment (22.9 ± 7.3 units/d) than without troglitazone treatment (54 ± 12.9 units/d) ($p < 0.05$), as well as the change in the insulin dosage from baseline between the two groups (troglitazone, –8.4 units vs control, +4.3 units, $p < 0.05$). Weight changes and aspartate aminotransferase levels greater than 1.5 times the upper limit of normal were not observed in participants of either treatment group. This study demonstrates that troglitazone was safe and effective for the treatment of hyperglycemia in patients requiring dialysis, and strongly supports the clinical use of currently available TZDs in diabetic patients with renal failure.

Key Words: End-stage renal disease; thiazolidinediones; reduced insulin dosage.

Introduction

Diabetes mellitus, especially type 2 diabetes, is the leading cause of end-stage renal disease (ESRD) in the US *(1)*. Management of hyperglycemia in patients with ESRD is difficult as blood sugar levels are labile and the pharmacokinetics of insulin and oral medications change under uremic conditions *(2,3)*. Poor glycemic control is associated with worsening of eye, heart, neuropathic, and foot complications *(4)*. A recent observational study has shown that at the initiation of hemodialysis, patients with diabetes and good glycemic control (HbA1c level < 7.5%) had better long-term survival than those individuals with poor glycemic control (HbA1c level ≥7.5%) *(5)*. Thus, there is a need to control hyperglycemia in patients with diabetes and renal failure to reduce worsening complications and improve survival.

Chronic renal failure affects the bioavailability of many drugs because uremia decreases GI absorption, changes first-pass hepatic metabolism, impairs protein binding especially of acidic drugs, and alters interaction with other medications *(6)*. Moreover, pharmacologic treatment of patients with dialysis-dependent renal failure must take into consideration the dialyzability of drugs, which is concentration and diffusion dependent and influenced by factors such as drug size, percentage protein binding, and the volume of distribution along with dialysis flow rate and membrane pore size *(7)*. Thiazolidinediones (TZDs) are oral antidiabetic (OAD) agents called insulin sensitizers, which are effective in the treatment of hyperglycemia in patients with type 2 diabetes *(8,9)*. These OAD agents are exclusively metabolized by the liver and appear ideal for the management of hyperglycemia in type 2 diabetic individuals with progressive or end-stage renal disease. Currently, there are two TZDs, rosiglitazone and pioglitazone, available for the treatment of hyperglycemia *(10)*. Recently, a retrospective chart review study reported the efficacy and safety of TZDs for the management of hyperglycemia in ambulatory patients with ESRD *(11)*. Measurements of rosiglitazone in patients with varying degrees of renal failure demonstrated no pharmacokinetic differences and an apparent increased clearance resulting in lower mean levels of this drug in severe renal insufficiency (CrCl<29 mL/min) *(12)*. The pharmacokinetic

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profile of rosiglitazone in patients requiring hemodialysis was not different from the profile seen in healthy volunteers *(13)*. Troglitazone, the first available TZD was withdrawn from clinical use in March 2000 due to safety concerns over idiosyncratic hepatotoxicity *(14)*. Still, studies conducted with troglitazone prior to its withdraw can assert the use of currently available TZDs in the treatment of hyperglycemia, specifically in patients with ESRD. We present data on the effectiveness of troglitazone in diabetic patients with renal failure requiring dialysis.

Results

Subjects

A total of 323 eligible subjects were identified, and 26 subjects completed the screening process that resulted in 12 subjects enrolling in the study. Six subjects were randomized to the troglitazone group and six to the control group. Three subjects in the troglitazone group failed to complete the 6-mo protocol. One subject died at wk 7 (unrelated to study drug or glycemic control) and a second subject withdrew following an unrelated serious adverse event (hip fracture) at wk 17. A third subject withdrew from the study for personal reasons (fear of liver toxicity). The other three subjects completed the 6-mo study without complications.

Five of six subjects in the control group completed the entire 6-mo study. One subject withdrew at wk 11 for personal reasons. Four subjects in the control group crossed-over to troglitazone treatment after completing the 6-mo protocol; however, none of these subjects were able to complete 6 mo of treatment. One subject withdrew after the first visit. The remaining three subjects completed wk 16, 17, and 18, respectively, before the study was abruptly terminated. The "crossover" subjects were also included as troglitazone treatment for analysis of outcomes measures. The month-six data set at the end of the control treatment period was used as the new baseline data for these four "crossover" subjects.

Baseline Characteristics

There were no significant differences in age (yr), weight (kg), and BMI (kg/m^2) among participants initially randomized to control and troglitazone groups as shown in Table 1. Additionally, baseline blood glucose values as determined by pre-prandial SMBG average for the week prior to study visit (7.84 ± 0.48 mmol/L vs 8.62 ± 0.63 mmol/L, $p = 0.37$) and HbA1c levels (6.97 ± 0.44% vs 6.59 ± 0.31%, $p = 0.48$) were not significantly different between the control and troglitazone groups. There were no significant differences in baseline analysis of liver function studies in either group (AST levels; control 15.5 ± 2.4 U/L vs troglitazone 15.4 ± 2.6 U/L, $p = 0.74$).

Four control subjects were taking insulin and the other two individuals were receiving sulfonylurea. Five of six troglitazone subjects were taking insulin, while one individual received sulfonylurea. Two of the control-crossover subjects were on insulin and two were on sulfonylurea. Thus, a total of seven individuals on insulin treatment and three individuals taking a sulfonylurea received troglitazone during the study. There was no significant difference ($p = 0.21$) in insulin requirements (i.e., total units per day) between control (48.5 ± 16.3 units) and troglitazone (31.4 ± 6.7 units) subjects at baseline. There was no significant difference in baseline total cholesterol in the control group compared to the troglitazone group (9.22 ± 1.26 mmol/L vs 9.31 ± 0.58 mmol/L, $p = 0.95$, control vs troglitazone, respectively).

Table 1
Baseline Characteristics of Diabetic Patients with ESRD

	Control subjects	Troglitazone subjects	*p*
Patients	6	6	
Male:female	2:4	2:4	
Age (yr)	52.0 ± 5.5	58.8 ± 6.2	ns
Insulin treatment	4	5	
Sulfonylurea treatment	2	1	
BMI (kg/m^2)	29.6 ± 3.2	28.9 ± 2.8	ns
SMBG (mmol/L)	7.84 ± 0.48	8.62 ± 0.63	ns
HbA1c (%)	6.97 ± 0.4	6.59 ± 0.3	ns
Insulin dose (units/d)	48.5 ± 16.3	31.4 ± 6.7	ns
BUN (mg/dL)	72.3 ± 5.8	59.3 ± 7.0	ns
Creatinine (mg/dL)	10.2 ± 1.1	8.2 ± 1.1	ns
Total cholesterol (mg/dL)	166.0 ± 22.6	167.6 ± 10.4	ns
AST (U/L)	15.2 ± 4.0	16.3 ± 2.6	ns

Efficacy of Troglitazone

Analysis of efficacy was performed comparing subjects treated with troglitazone, which included the initially randomized and the completed control group "crossover" patients, and subjects initially randomized to control treatment. Blood glucose values at month 6 (i.e., completion of the study or LOCF) were not significantly different [7.06 ± 0.94 mmol/L vs 7.19 ± 0.66 mmol/L, $p = 0.88$; control ($n = 6$) vs troglitazone ($n = 8$), respectively], with or without troglitazone treatment (Fig. 1). There was also no significant difference in HbA1c values at month 6 (6.27 ± 0.37% vs 7.13 ± 0.69%, $p = 0.32$). Furthermore, there were no significant changes in the fasting SMBG values at baseline compared to last visit in either treatment groups (control, 7.84 ± 0.48 mmol/L vs 7.06 ± 0.42 mmol/L, $p = 0.24$ or troglitazone, 8.62 ± 0.63 mmol/L vs 7.19 ± 0.66 mmol/L, $p = 0.15$). In addition, HbA1c values at baseline (month 0) and completion (at month 6 or LOCF) were not significantly different with either treatment (control, 6.97% to 6.27%, $p = 0.26$; troglitazone, 6.59% to 7.13%, $p = 0.45$).

There was a significant difference in insulin dosage at the end of the control and troglitazone treatment periods (control $n = 4$, 54 ± 12.9 units/d vs troglitazone $n = 7$, 22.9 ± 7.3 units/d, $p < 0.05$) (Fig. 2A). Two of six subjects were able to discontinue insulin treatment entirely while on troglita-

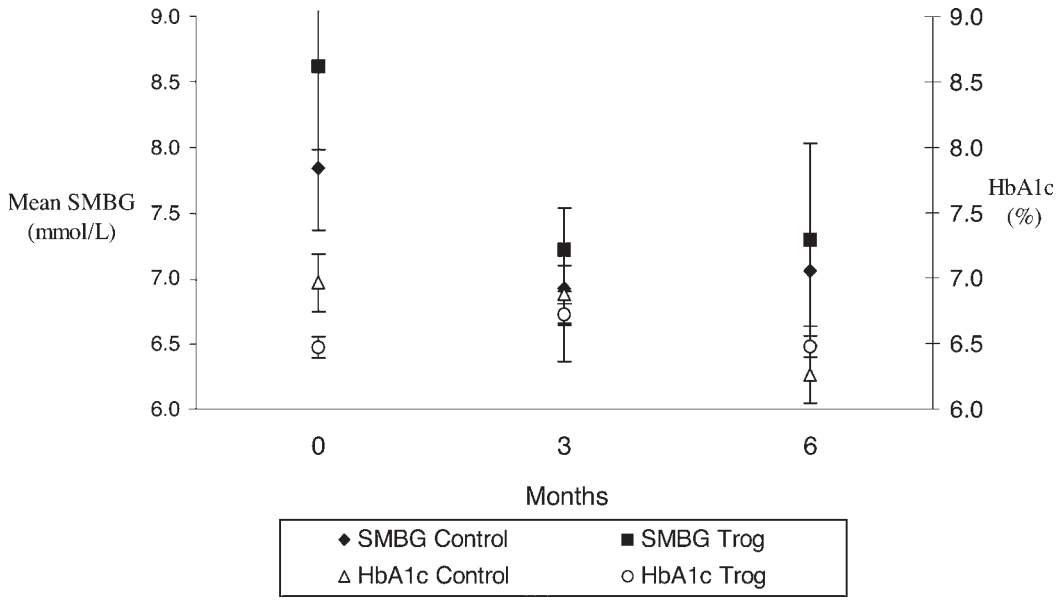

Fig. 1. The effect of troglitazone on SMBG profiles and HbA1c levels in diabetic patients with ESRD.

zone. There was a clear need for participants to increase insulin dosage to improve glycemic profiles during control treatment, and according to protocol, reduce dosage to minimize hypoglycemia on troglitazone. There were no significant changes in insulin requirements at the end of the study from baseline among subjects with troglitazone treatment, (baseline vs end of study, 31.4 ± 6.7 units/d to 22.9 ± 7.3 units/d, $p = 0.40$) or control treatment (baseline vs end of study; 48.5 ± 16.3 units/d to 54 ± 12.9 units/d, $p = 0.82$). However, the reduction in insulin dosage of 8.4 units ± 4.12 units per day with troglitazone treatment as compared to the increase in insulin dosage of 4.4 units ± 5.47 units per day during control treatment was statistically significant ($p < 0.05$) (Fig. 2B).

Safety Measurements

There was no significant change in weight (kg) at the last visit as compared to baseline with either control ($n = 6$, 76.6 ± 9.1 vs 76.6 ± 7.8, $p = 1$) or troglitazone treatment ($n = 7$, 75.3 ± 7.3 vs 83.1 ± 10.5, $p = 0.91$), and at the end of the study (control, 76.6 ± 7.8 vs troglitazone, 83.1 ± 10.5, $p = 0.97$). At no time did AST levels rise to greater than 1.5 times the upper limit of normal in participants with either treatment. There was no difference in AST levels among subjects with either treatment at the end of the study (control $n = 6$, 19.8 ± 2.6 U/L vs troglitazone $n = 8$, 15.1 ± 2.8 U/L, $p = 0.26$).

Discussion

The current management of hyperglycemia for diabetic patients with ESRD is similar to hyperglycemia treatment for the general diabetic population some 20–30 yr ago. Unfortunately, ESRD patients have reduced therapeutic options and are usually treated with insulin or a sulfonylurea (SU), and because the risk of hypoglycemia is high, there is a tendency to keep these individuals relatively hyperglycemic. The meglitinides and once a day SU called glimepiride, are primarily cleared by the liver and are used in patients with renal failure *(15)*. The use of these agents is complicated by the variable absorption rate and clearance, which causes difficulties in the timing of food resulting in labile blood sugar levels. Many patients have significant basal and post-prandial hyperglycemia that requires insulin to maintain glycemic control. Yet, these patients do not appreciate the multiple daily injections regimen and are inclined to take once daily intermediate-acting insulin to cover the daytime meals. Other oral agents such as metformin are contraindicated in patients with renal insufficiency, and α-glucosidase inhibitors, acarbose and miglitol, are not recommended for patients with renal failure because of the lack of long-term clinical trial data *(15)*. Thiazolidinediones are primarily metabolized through the hepatic cytochrome P450 system and are potentially useful in the ESRD population. Moreover, because insulin resistance is demonstrated in non-diabetic patients with ESRD, the possibility of uremic factors contributing to increased insulin resistance in type 2 diabetes supports a greater role for TZDs in the treatment of hyperglycemia *(16,17)*. Recent studies have demonstrated the efficacy and safety of rosiglitazone in the treatment of hyperglycemia in patients with diabetic nephropathy and mild to moderate renal failure *(18,19)*. Participants evaluated in these studies had CrCl between 30 and 80 mL/min, and rosiglitazone was evaluated in combination therapy with SU or insulin. Other than a retrospective chart review of treatment efficacy in the ambulatory clinical setting *(11)*, no studies have reported the treatment effect of any TZD in diabetic patients requiring dialysis.

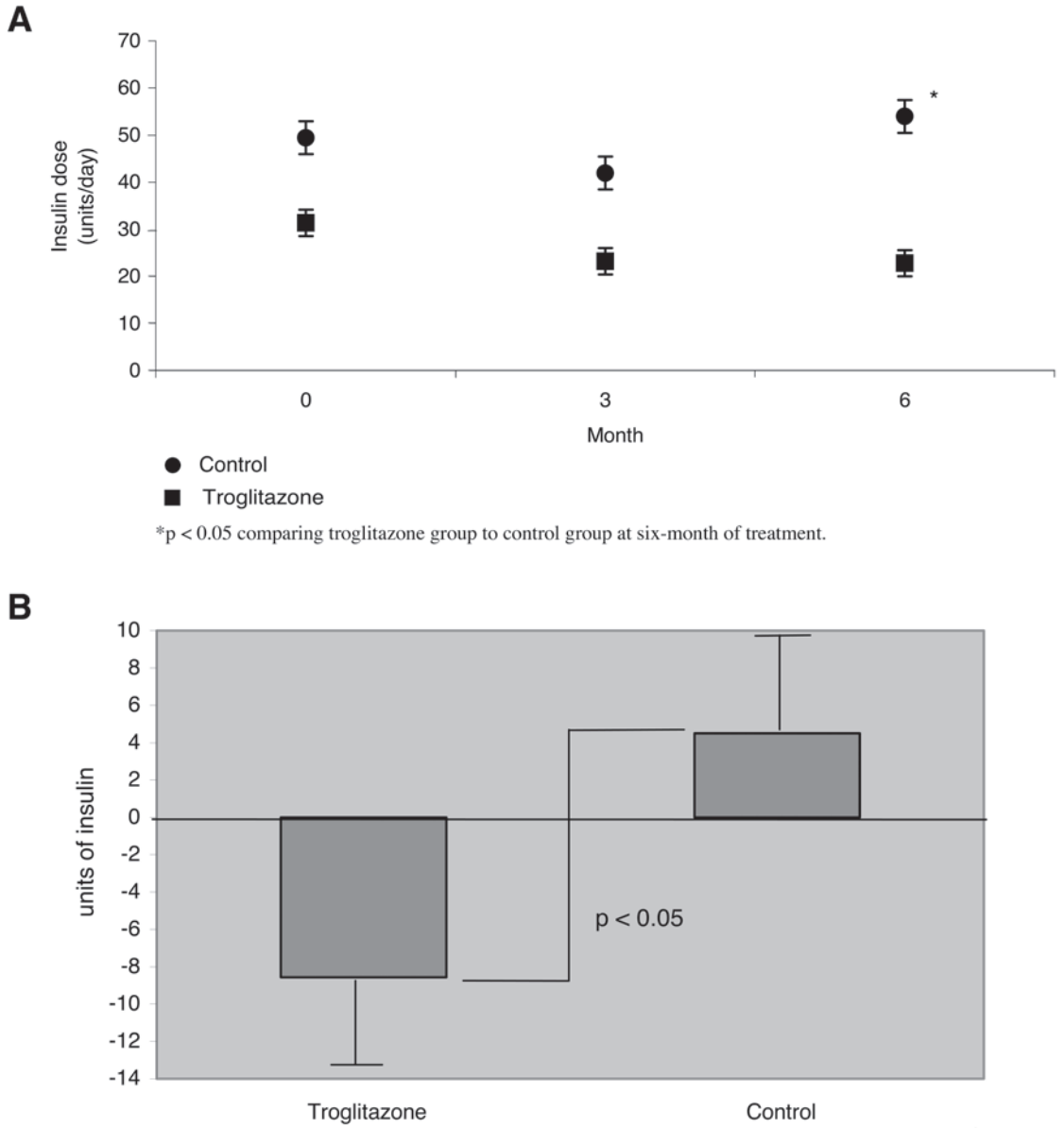

Fig. 2. (**A**) The effect of troglitazone on insulin requirement in diabetic patients with ESRD. (**B**) The change from baseline in insulin dosage in the troglitazone and control groups.

This study has demonstrated that troglitazone can be safely added to existing insulin or sulfonylurea regimens for diabetic patients undergoing dialysis. There were no significant elevations in liver function tests or weight changes, even at the highest available doses. The fasting SMBG values decreased approx 1.43 mmol/L with troglitazone treatment compared to 0.78 mmol/L without TZD treatment ($p = 0.15$); however, the HbA1c levels between the two treatment regimens were not significantly different for a number of reasons. First, the number of participants in this study was small. We found that many diabetic patients with ESRD were reluctant to take part in this clinical trial because of an already busy schedule of dialysis and other physician appointments, additional medications and monitoring, the lack of enthusiasm to "get off" insulin or lower insulin dosage, and the fear of liver toxicity. Second, insulin dosage was reduced in patients treated with troglitazone based on the frequency of hypoglycemia or achieved targeted goal of FBS < 6.67 mmol/L. Dosage reduction occurred more often based on safety consideration rather than on efficacy. Third, baseline HbA1c levels were already at the targeted goal of < 7%, and thus further reduction in HbA1c levels to achieve statistical significance would have been difficult and require more participants. Despite the similar glycemic levels with and without troglitazone therapy, there was a significant decrease in total units per day of insulin used with troglitazone treatment and two of six individuals discontinued insulin treatment altogether.

The potential use of thiazolidinediones in the management of hyperglycemia in patients with ESRD offers addi-

tional support for the medically complicated, often neglected, and poorly controlled diabetic patients. The findings of this study add to the growing body of evidence that support the use of TZDs in patients with mild to moderate renal insufficiency. Despite the withdraw of troglitazone from clinical use in the United States, the findings of this study may also apply to the potential use of currently available agents. Rosiglitazone and pioglitazone are hepatically cleared albeit by a different cytochrome P450 enzyme (CYP3A28) pathway and have shown minimal hepatotoxicity (CYP3A4) *(20,21)*. The usefulness of these two agents in the treatment of hyperglycemia in diabetic patients with ESRD has not been clearly demonstrated. Thus, a large long-term study with either rosiglitazone or pioglitazone in diabetic patients with renal failure is needed.

Methods

Study Design

The study was an open-label, controlled clinical trial examining the anti-hyperglycemic effect of troglitazone in type 2 diabetic patients with ESRD. The participants were randomized to parallel study groups and treated for 6 mo. Subjects in the troglitazone group were started on 200 mg/d and titrated to a maximum dose 600 mg/d in addition to continuing previous diabetes medications (insulin or sulfonylurea). Subjects without troglitazone (control) continued to receive their current diabetes medication regimen (insulin or sulfonylurea). These control subjects were eligible to "cross-over" into the troglitazone treatment group after completing 6 mo of the protocol. Eligible participants were men and women aged 18 or older with physician-diagnosed diabetes mellitus type 2 and ESRD treated with either hemodialysis or peritoneal dialysis. Subjects must have been treated with insulin or a sulfonylurea or if not taking insulin, had HbA1c > 7%. Subjects with known liver disease or cirrhosis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal, congestive heart failure (CHF) or cardiomyopathy, or sensitivity to troglitazone or components of troglitazone were excluded. The Committee on Human Studies of the University of Hawaii and the Institutional Review Board of Saint Francis Medical Center approved the study protocol and informed consent document. Informed consent was obtained from all subjects prior to participation in the study.

Protocol

Eligible subjects were randomized to either with troglitazone or without troglitazone (control) group using a table of random numbers assigned by an independent investigator *(22)*. Subjects were seen at 4-wk intervals for 6 mo. Clinical efficacy measurements included assessment of HbA1c, two to four times per day self-monitoring of blood glucose (SMBG) profiles, insulin or oral medication dosage requirements, and anthropometric measurements (i.e., height, weight, BP, HR, and BMI). All subjects had glycemic treatment regimens optimized using SMBG values. The goals for blood glucose control were in accordance with American Diabetes Association guidelines with a fasting value < 6.67 mmol/L and HbA1c level < 7%. Adjustment of insulin or oral hypo-glycemic agents was made based on patient's submitted SMBG records every 2 wk. Clinical safety measurements included a complete medical history, physical examination, biochemical safety profiles as determined by general chemistry analysis (i.e., hepatic profile, total blood count, and electrolytes), evaluation for exclusion criteria, thyroid test, EKG, and diabetes education and counseling.

Biochemical and Statistical Analysis

All blood samples for clinical efficacy and safety measures were performed in a single assay in the local clinical laboratory using Hitachi 747 Autoanalyzer (Boehringer-Mannheim).

Data analysis was performed comparing subjects treated with troglitazone, which included the initially randomized and completed control crossed-over patients and subjects with control treatment. The outcomes of HbA1c levels, blood glucose profiles (blood glucose values were averaged for the week prior to study visit), insulin and sulfonylurea dosage, and safety measures were evaluated. The last study site visit was considered the final visit and included as the 6-mo data for analysis even if this visit was not at the 6-mo mark (Last Observation Carried Forward, LOCF). Significance of the findings between the two groups was determined by Student's "*t*" test.

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