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Pioglitazone, but not metformin, reduces liver fat in Type-2 diabetes mellitus independent of weight changes☆

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Abstract

Background: Pioglitazone (Pio) treatment induces weight gain in Type 2 diabetes mellitus (T2DM), which could worsen hepatic lipid accumulation, and alter adiponectin and high-sensitivity C-reactive protein (hs-CRP). **Objective:** To compare changes in hepatic lipid, serum adiponectin and hs-CRP in diabetics treated with Pio (with and without weight gain) against metformin (Met) treatment, which produces weight loss. **Design:** Fifty-one men and women with T2DM, naive to thiazolidinediones, entered a 16-week, open-label, parallel arm study, where participants were randomized to one of three groups: (1) Pio plus the American Diabetes Association diet (Pio+ADA); (2) Pio plus a portion control weight loss diet (Pio+PC), or (3) metformin plus ADA diet (Met+ADA). **Methods:** Hepatic lipid was assessed with abdominal computed tomography (CT) and the serum adiponectin and hs-CRP by enzyme-linked immunosorbent assay at baseline and study end. **Results:** Forty-eight subjects completed the study. The Pio+ADA group gained (mean±S.E.M.) 2.15±1.09 kg, while Pio+PC and Met+ADA group lost −2.59±1.25 and −3.21±0.7 kg, respectively. Pio-treated groups (Pio+ADA and Pio+PC) significantly decreased hepatic fat as indicated by increased liver density on CT scan [10.1±2.4: 11.4±1.0 Hounsfield units (HU)], compared with Met+ADA group (−2.4±3.1 HU). The Pio groups demonstrated significantly increased serum adiponectin, (8.6±1.5; 7.4±1.6 μg/ml) independent of weight change, compared to Met+ADA (−0.14±0.6 μgm/ml) group which lost weight. Serum hs-CRP decreased in groups showing weight loss (Pio+PC, −3.1±1.7 mg/l; Met+ADA, −1.5±1.2 mg/l) compared to Pio+ADA (1.8±3.0 mg/l) group that gained weight. **Conclusions:** Pio treatment in T2DM significantly reduced hepatic lipid and increased adiponectin independent of weight change, while decreasing hs-CRP with weight loss.

Keywords: ALT; NAFLD; NASH; Metformin; Cardiovascular disease; Adiponectin; hs-CRP; Diabetes; Obesity, Adipose tissue

1. Background

Thiazolidinediones (TZDs) are potent agonists for the peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptor. PPAR-γ activation by pioglitazone (Pio) improves insulin sensitivity (Waugh, Keating, Plosker, Easthope, & Robinson, 2006) and attenuates inflammatory markers (Berg & Scherer, 2005; Giannini, Serio, & Galli, 2004; Granberry & Fonseca, 2005; Kostadinova, Wahli, & Michalik, 2005). Weight gain is one major drawback to treatment with TZDs (Fonseca, 2003; Gupta, Smith, Greenway, & Bray, 2009; Smith et al., 2005). Since weight gain is typically associated with an increase in insulin resistance, a decrease in anti-inflammatory markers and an increase in proinflammatory markers, it is unclear if full benefits of the TZD treatment are realized in the presence of weight gain. We have recently shown that Pio treatment, when combined with a portion-controlled diet that prevents the weight gain, not only prevented weight gain but also resulted in weight loss (Gupta et al., 2009).

Nonalcoholic fatty liver disease (NAFLD), often present with the metabolic syndrome (Hamaguchi et al., 2005), is also common in diabetes mellitus (Younossi, Gramlich, Matteoni, Boparai, & McCullough, 2004) and obesity (Boppidi & Daram, 2008). It is manifest as a simple elevation of serum

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alanine aminotransferase (ALT), triglyceride (TG) accumulation in hepatocytes (hepatic steatosis) or inflammation of hepatocytes (steatohepatitis or NASH). Nonalcoholic steatohepatitis (NASH), in a fraction of the affected individuals, leads to fibrosis and cirrhosis of the liver, hepatocellular carcinoma, and even death. Nonalcoholic fatty liver disease (NALFD) is an independent predictor for cardiovascular disease risk in metabolic syndrome (Hamaguchi et al., 2007). Despite the increasing prevalence of NAFLD and potential for adverse outcomes with NASH, interventions are limited to weight loss, exercise, and modification of associated comorbid conditions.

Weight loss reverses hepatic steatosis (Assy, Hussein, & Abassi, 2007). TZDs decrease serum ALT and modulate hepatic steatosis and steatohepatitis (Khashab & Chalasani, 2007), but it is unclear whether the treatment associated weight gain offsets these effects to some degree. Adiponectin, which is secreted by adipose cells, is reduced in metabolic syndrome, diabetes, and obesity and is increased by weight loss and TZD treatment (Nedvídková, Smitka, Kopský, & Hainer, 2005; Swarbrick & Havel, 2008). Whether this effect is modulated by the weight gain associated with TZD treatment is also unknown. In contrast, high-sensitivity C-reactive protein (hs-CRP) is increased in many disease states, including diabetes mellitus and obesity (Musunuru et al., 2008; Ridker & Morrow, 2003). In this study, we compared the changes in hepatic lipid and serum adiponectin and hs-CRP in obese Type 2 diabetics treated with Pio (with and without weight gain) against metformin (Met) treatment, which *is known to be associated with* weight loss. We report the change in the ALT, liver lipid deposition, serum adiponectin, and serum hs-CRP along with the alterations in waist circumference, systolic and diastolic blood pressure, fasting serum glucose, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs).

2. Research design and methods

2.1. Study participants

Men and women, aged 35–75 years with Type 2 diabetes mellitus (T2DM) never treated with a TZD were recruited. They each signed an informed consent approved by the institutional review board after reading it and having their questions answered. T2DM was diagnosed in one of three ways: (1) a confirmed fasting plasma glucose of >126 mg/dl on two occasions; (2) a glucose >200 mg/dl 2 h after a 75-g glucose load; or (3) on current treatment with a single oral antidiabetic drug other than a TZD. Patients could be treated with diet, Met or sulfonylureas and had to be willing to be randomized to one of the three arms of the trial. Fasting plasma glucose at entry had to be <200 mg/dl. Use of adequate contraceptive control was required for women. This could include oral contraceptives, tubal ligation, hysterectomy, or postmenopausal status, as defined by more than 6 months without a menstrual cycle and follicle stimulating hormone level of >40 mIU/ml. Patients on a stable dosage of medication for chronic medical conditions were included. Patients were excluded if they had significant renal, cardiac, liver, lung, or neurological disease; although controlled hypertension with a baseline blood pressure was less than 140/90 mmHg on medications was acceptable. Patients with prior use of one of the two available thiazolidinediones (rosiglitazone or Pio), patients receiving β-blockers, patients currently pregnant, smokers, and subjects who abused alcohol or drugs were also excluded. If liver function tests at baseline (aspartate transaminase, alanine transaminase) were greater than 2.5 times the upper limit of normal, the subjects were not enrolled. Metal objects that would interfere with the measurement of visceral fat by CT, such as implanted rods or surgical clips, prevented patients from participating. In addition, patients taking drugs known to affect energy metabolism or body weight, such as orlistat, sibutramine, ephedrine, or corticosteroids, were excluded.

2.2. Clinical protocol

A total of 51 subjects meeting all criteria were randomized into this 16-week clinical trial (ClinicalTrials.gov NCT00219440). They were randomly assigned to one of the three treatment groups: (1) A group treated with Pio plus standard dietary advice from the American Diabetes Association (Pio+ADA); (2) a group treated with Pio who received the portion-controlled weight loss diet (Pio+PC); and (3) a group treated with Met and the same dietary advice that was given to the first group (Met+ADA). Patients were started on Pio at a dose 30 mg/day or Met at a dose of 500 mg/day. The hemoglobin A1c target was <7.0%. If, after 8 weeks, the hemoglobin A1c level was >7.0% or the fasting plasma glucose level was >100 mg/dl, the dosage of Pio was increased to 45 mg/d. This occurred in only one participant. The dose of Met was increased by 500 mg every week, based upon subject tolerance. A maximum dose of 2 g/d was taken as 1000 mg twice a day. As a safety criterion, individuals with an increase in HbA1c >11% or an increase in the fasting plasma glucose >240 mg/dl were to be treated with sulfonylurea and/or insulin. No participant met this criterion. The participants were randomly assigned to the three treatment groups. Their prestudy treatment profile was as follows: 17 subjects on no medications (three, eight, and six, respectively, were randomized to Pio+ADA, Pio+PC, and Met+ADA groups), 10 subjects on sulfonylurea (three, three and four, respectively, were randomized to Pio+ADA, Pio+PC, and Met+ADA groups), and 21 subjects on Met (eight, seven, and six, respectively, were randomized to Pio+ADA, Pio+PC, and Met+ADA groups). Two subjects in the Met+ADA group, by random selection, continued to receive the same dose of Met (2 g/day) that they had been receiving prior to the study. All participants were seen in our outpatient clinic 2, 4, 8, 12, and 16 weeks after randomization. A fasting weight, pulse rate,