Effects of Oral Antidiabetic Drugs on Changes in the Liver-to-Spleen Ratio on Computed Tomography and Inflammatory Biomarkers in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease

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ABSTRACT

Purpose: Oral antidiabetic drugs (OADs) such as pioglitazone and metformin have beneficial effects in patients with nonalcoholic steatohepatitis. We prospectively assessed the effects of OADs on nonalcoholic fatty liver disease (NAFLD) in 886 men with type 2 diabetes mellitus and in a murine model of NAFLD.

Methods: Patients were randomized to receive pioglitazone, metformin, sitagliptin, or a non-OAD (control) for 6 months. All the patients received dietary and exercise guidance once a month during this study. Changes in the liver-to-spleen ratio on computed tomography (CT) and NAFLD-related parameters were measured from baseline to the end of treatment.

Findings: The liver/spleen ratio improved significantly in the pioglitazone and metformin groups compared with the control group (both $P < 0.01$), but not in the sitagliptin group ($P = 0.73$). The mean changes from baseline were −3.464 ± 10.156%, 19.236 ± 9.896%, 4.783 ± 1.467%, and 1.328 ± 0.802% in the control, pioglitazone, metformin, and sitagliptin groups, respectively. Multivariable analysis showed that the liver/spleen ratio was strongly correlated with high-sensitivity C-reactive protein concentration in the pioglitazone group ($F = 9.973$; $P < 0.01$) and abdominal visceral fat volume in the metformin group ($F = 6.049$; $P < 0.05$).

Conclusions: Pioglitazone elicited the greatest improvements in features of NAFLD in type 2 diabetes mellitus. (Trial Registration: www.isrctn.org/, ISRCTN33414972, http://www.isrctn.org/) (*Clin Ther.* 2017;39:558–566)

Key words: OAD, NAFLD, T2DM, CT, L/S ratio.

INTRODUCTION

The high incidence of nonalcoholic fatty liver disease (NAFLD) in patients with metabolic syndrome is of great concern, particularly as metabolic syndrome also causes type 2 diabetes mellitus (T2DM) through the development of insulin resistance.[1,2] Approximately 20% of the total population of Europe and the United States have NAFLD, with 3% (~8.5 million people) having nonalcoholic steatohepatitis (NASH).[3]

Although the pathologic causes of NASH have not yet been clarified, the "2-hit" model proposed[4] is widely accepted. Peroxisome oxidation, a component of mitochondrial oxidation, generates active oxygen/free radical species during the metabolic process. Endotoxins derived from enteric bacteria induce inflammatory cytokines, which contribute to the generation of oxidative stress.[5] Levels of the oxidative stress marker thioredoxin were shown to be higher in individuals with NASH than in those with simple fatty liver. Therefore, aggressive interventions during the early stages of NAFLD may help prevent its progression.

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Diet and exercise therapy are routinely recommended for the treatment of NAFLD because they achieve meaningful reductions in waist circumference, visceral fat, and blood pressure. However, glycemic control is usually inadequate in patients with NAFLD, and further deterioration occurs with the development or progression of NAFLD, particularly in patients with T2DM. These findings suggest the need for additional therapeutic strategies in the treatment of NAFLD.

The major gluconeogenic and lipid-metabolizing enzymes in the liver are under the transcriptional control of peroxisome proliferator-activated receptor-γ (PPAR-γ) and AMP-activated protein kinase via direct and indirect pathways. Metformin, a first-line oral antidiabetic drug (OAD) used to treat T2DM, targets the AMP-activated protein kinase signaling pathway to inhibit hepatic gluconeogenesis and to enhance glucose use in muscle.[6] This pathway is also linked to PPAR-γ through PPAR receptor coactivator 1.[7,8] A second OAD, sitagliptin, has been shown to inhibit the enzyme dipeptidyl peptidase 4, thereby preventing the degradation of incretins such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide, extending their bioavailability.[9,10] In addition, sitagliptin has been reported to prevent high-fat diet–induced tissue inflammation and hepatic steatosis.[11]

Considering these preclinical and clinical features of NAFLD, we hypothesized that several OADs may be effective treatments for NAFLD. Traditionally, in addition to abdominal echo, a biopsy has been required for the definitive diagnosis of NAFLD. Fat content, however, can be more accurately determined using magnetic resonance (MR) imaging and proton MR spectroscopy. Liver fat levels, assessed by calculating liver-to-spleen (L/S) ratios on plain computed tomography (CT), have been found to significantly correlate with liver fat levels on MR imaging and proton MR spectroscopy.[12,13] CT scans are less costly, require a shorter time for imaging than MR, and can be implemented at multiple institutions. We therefore analyzed the effects of 3 OADs—pioglitazone, metformin, and sitagliptin—each with distinct mechanisms of action, in patients undergoing CT.

RESEARCH DESIGN AND METHODS

Patients

The protocol for this trial and supporting CONSORT checklist are available as supporting information (see Checklist S1 and Protocol S1). Recruitment occurred at 4 institutions (hospitals affiliated with the University of the Ryukyus, Hokubu Hospital, Eucalia Okinawa Kanna Hospital, and Chubu Tokushukai Hospital) between August 1, 2010 and December 27, 2013. This study is registered at www.isrctn.org/ (ISRCTN33414972). (We were delayed in registering this study after enrollment of participants started because we initially did not view it as a clinical trial.) We confirm that all ongoing and related trials for this drug/intervention are registered. Participants were diabetic men 40 to 70 years of age who were previously untreated for T2DM and had a body mass index (BMI) >25 kg/m^2, a weight change of <1 kg in the 3 months before enrollment, glycosylated hemoglobin (HbA_{1c}) of 6.4% to 7.9% (National Glycohemoglobin Standardization Program units) or 46 to 63 mmol/mol (International Federation of Clinical Chemistry units), and fasting plasma glucose of 126 to 261 mg/dL. The exclusion criteria included subjects who consumed >20 g alcohol daily, had an autoimmune disease, were carriers of a hepatitis virus, were at high risk of the development of metabolic disorders (eg, lactic acidosis, ketosis, precoma, or diabetic coma), had serious liver and/or renal dysfunction or severe infection, were in a perioperative period, or had a known allergy to any of the drugs used in this study. All participants provided written informed consent before enrollment, and the study protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of the Ryukyus.

Study Design and Treatments

Subjects were classified into 2 groups based on the presence or absence of NAFLD, defined by hepatic ultrasound (bright liver relative to the kidney, deep beam attenuation, and poor vascular visualization) and transaminase measurements[14] (**Figure 1**). All subjects were provided with dietary and exercise guidance once a month during the study. Blood samples were obtained to measure concentrations of aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, cholinesterase, fasting plasma glucose, fasting insulin, LDL-C, HDL-C, triglycerides, nonesterified fatty acids, high-sensitivity C-reactive protein (hsCRP), soluble tumor necrosis factor receptors (sTNFRs) 1 and 2, high-molecular weight (HMW) adiponectin, and ferritin. Plasma concentrations sTNFRs 1 and 2 (R&D Systems,