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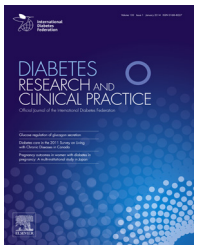

Effect of sitagliptin on intrahepatic lipid content and body fat in patients with type 2 diabetes

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ABSTRACT

Aims: To evaluate the effect of the DPP-4 inhibitor sitagliptin on intrahepatic lipid (IHL) content and body fat in overweight Japanese patients with type 2 diabetes.

Methods: A prospective, 24-week, single-center, open-label comparative study enrolled 20 Japanese patients with type 2 diabetes (male: 11, female: 9) with a BMI $\geq$ 25 kg/m^2 or fatty liver. Subjects were randomly assigned to receive treatment with sitagliptin (25 mg titrated up to 50 mg: S) or glimepiride (0.5 mg titrated up to 1 mg: G). After starting each treatment, IHL and total fat mass were evaluated by ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) and dual energy X-ray absorptiometry (DEXA), respectively at baseline and at 12 weeks and 24 weeks.

Results: After 24 weeks, HbA1c levels showed a similar significant decrease in both groups from 7.2 (7.0, 7.5) to 6.6 (6.4, 6.8)%, (54 (53, 56) to 48(47, 49) mmol/mol) with S and 7.3(6.8, 7.4) to 6.6 (6.3, 6.7)%, (55 (51, 56) to 48 (46, 49) mmol/mol) with G, median (interquartile range), $p < 0.05$ vs. baseline, with no significant differences between the two groups. The IHL and total body fat mass were decreased in S group from 24.5(18.9, 36.6) to 20.5 (14.6, 28.5)% ($p = 0.009$) and 22.5 (20.6, 33.7) to 21.6 (19.7, 32.4)kg ($p = 0.028$), respectively, but not in G group.

Conclusions: Our findings indicate that sitagliptin and glimepiride achieved similar glycemic control, but only sitagliptin reduced IHL and total body fat (UMIN: 000013356).

1. Introduction

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a position statement on type 2 diabetes mellitus (T2DM) that stresses the importance of a patient-centered approach [1,2]. In this statement, metformin (MET) is recommended as initial drug therapy to be provided simultaneously with or soon after commencing lifestyle modification because of its high efficacy

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for reducing HbA1c, low cost, low risk of hypoglycemia, and neutral effect on body weight (or weight loss). If the target HbA1c is not achieved, the second and third agents to be combined with MET are selected from among five drug classes: sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4I), glucagon-like peptide-1 (GLP-1) agonists, or basal insulin. The unique and important point of the statement is comparison of the characteristics of these five drug classes to allow selection of suitable therapy for each patient.

In the statement, DPP-4I are characterized as showing intermediate efficacy for HbA1c reduction, with a low risk of hypoglycemia, neutral effect on body weight, and few major side effects. DPP-4I increase the plasma concentration of active GLP-1, which increases insulin secretion in a glucose-dependent manner and simultaneously suppresses the secretion of glucagon. Thus, DPP-4I reduce fasting and postprandial plasma glucose levels with a relatively low risk of hypoglycemia [4,5]. A recent study showed that HbA1c reduction by DPP-4I is greater in Asian patients than Caucasians [3], so these agents are widely used for Japanese patients.

The GLP-1 receptor (GLP-1R) has been detected on human hepatocytes and adipocytes [6], and a GLP-1 analog (exendin-4) has been demonstrated to attenuate triglyceride synthesis by primary cultured human hepatocyte [7]. Furthermore, another GLP-1 agonist (liraglutide) achieved 42% reduction of the intrahepatic lipid (IHL) content and 11% reduction of the visceral fat volume in obese patients with T2DM after 6 months of treatment [8]. However, the plasma concentration of active GLP-1 is much lower during DPP4-I treatment compared with the levels during treatment with these GLP-1 agonists [9,10]. According to the ADA/EASD statement, the effect of DPP4-I on body weight is neutral, but not marked [1,2]. The effects of DPP-4I on body weight and hepatic fat accumulation have not been fully evaluated in patients with diabetes, although animal experiments have shown attenuation of hepatic steatosis by DPP-4I administration [11,12].

Therefore, the aim of the present study was to investigate the effects of sitagliptin, one of the DPP-4I, on IHL and body fat compared with low-dose SU therapy using glimepiride in Japanese patients with type 2 diabetes with a BMI $\geq$ 25 kg/m^2 or fatty liver on abdominal ultrasonography.

2. Materials and methods

2.1. Subjects

The subjects were 20 Japanese patients with T2DM (11 men and 9 women aged 58.5 (40.0, 77.0) years, median (interquartile range (IQR)) with a BMI $\geq$ 25 kg/m^2 or fatty liver detected by ultrasonography. The ultrasonography was carried out by using convex-array probe (3.5 MHz) for assessing the liver, and after a fasting period of 12 h. Diagnosis of fatty liver was attempted based on the difference between the echo intensities of the liver and kidney [13]. They were recruited from the outpatient clinic of St. Marianna University Hospital (Kawasaki, Japan) with following inclusion criteria: (1) stable, but inadequate, glycemic control (9.4% (79 mmol/mol) > HbA1c > 7.4% (57 mmol/mol)) and (2) drug-naïve or MET monotherapy. The exclusion criteria were pregnancy, severe illness, anemia, renal failure (serum creatinine $\geq$ 2.0 mg/dL) and/or overt proteinuria, chronic liver disease, thyroid disease, malignancy, severe hypoglycemia requiring assistance within the previous 6 months, and use of medications that could affect glycemic control (including systemic glucocorticoids).

2.2. Study design

Diet and exercise therapy were given at diagnosis and the patient education staff encouraged their continuation throughout the study period. All the patients were instructed by a doctor to consume a balanced diet (25 kcal/kg of ideal body weight) with about 60% of energy intake as carbohydrate, about 25% as fat, and about 15% as protein. The patients were also advised to perform one or two sessions of walking exercise (20–30 min each) on 3–5 day per week. All patients visited the outpatient clinic of our hospital every month, and were encouraged by their doctors to continue calorie restriction and exercise. Alcohol consumption was restricted to less than 20 g/day. All patients gave written informed consent, and the study was approved by the Ethics Committee of St. Marianna University School of Medicine. Patients were randomly assigned to treatment with sitagliptin (S group, n = 10) or glimepiride (G group, n = 10).

Administration of sitagliptin and glimepiride was respectively started at 25 mg/day and 0.5 mg/day after breakfast. These doses could be increased to 50 mg/day and 1.0 mg/day, respectively, in order to achieve a fasting plasma glucose (FPG) < 130 mg/dl and HbA1c < 7.0% (53 mmol/mol) up to 24 weeks. We started from half the dose of each in reference to effects of sitagliptin [14] and glimepiride [15] on blood glucose levels. Fasting blood samples were obtained at baseline, as well as at 12 weeks and 24 weeks after starting treatment.

2.3. Data collection

The following parameters were investigated: glucose, lipids [HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG), and free fatty acids (FFA)], HbA1c, glycated albumin (GA), high molecular weight adiponectin (HMW-Ad), leptin, and highly sensitive C-reactive protein (hsCRP). TG, HDL-C, LDL-C, FFA and glucose were measured by standard methods. HbA1c was measured by the latex cohesion method (Determiner HbA1c, Kyowa Medex, Tokyo, Japan). GA was determined by an enzymatic method with an albumin-specific protease, ketoamine oxidase, and an albumin assay reagent (Lucica GA-L, Asahi Kasei Pharma, Tokyo, Japan). Leptin was measured by a radioimmunoassay (LSI Medience Corporation, Tokyo, Japan). HMW-Ad was quantitated by a sandwich enzyme-linked immunosorbent assay that used two anti-human adiponectin monoclonal antibodies (Sekisui Medical Co., Ltd., Japan). Serum hsCRP was measured by latex agglutination turbidimetry (Siemens Healthcare Diagnostics, Japan).

To evaluate the liver fat content and the total body fat mass, ^{1}H-MRS and dual energy X-ray absorptiometry (DEXA) were performed at baseline, 12 weeks, and 24 weeks.