Case Reports in Gastroenterology

Case Rep Gastroenterol 2012;6:538–544
DOI: 10.1159/000341510

Published online: August 9, 2012

ISSN 1662–0631
www.karger.com/crg

Dipeptidyl Peptidase IV Inhibitor Improves Insulin Resistance and Steatosis in a Refractory Nonalcoholic Fatty Liver Disease Patient: A Case Report

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Key Words
Dipeptidyl peptidase IV · Incretin · Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Glucose intolerance · Diabetes

Abstract
A 67-year-old Asian woman was referred to Kurume University Hospital due to abnormal liver function tests. She was diagnosed with nonalcoholic fatty liver disease (NAFLD). NAFLD was treated by diet therapy with medication of metformin and pioglitazone; however, NAFLD did not improve. Subsequently, the patient was administered sitagliptin. Although her energy intake and physical activity did not change, her hemoglobin A1c level was decreased from 7.8 to 6.4% 3 months after treatment. Moreover, her serum insulin level and homeostasis model assessment-insulin resistance value were also improved, as was the severity of hepatic steatosis. These findings indicate that sitagliptin may improve insulin resistance and steatosis in patients with refractory NAFLD.

Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is rapidly increasing worldwide [1]. Over 5% of NAFLD patients develop advanced liver cirrhosis [2]. NAFLD patients also present with complicating hepatocellular carcinoma [3, 4] and

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www.karger.com/crg

extrahepatic malignancies [5] and show a poor prognosis compared to the general population [6]. Therefore, NAFLD is recognized as an important therapeutic target [4, 7].

NAFLD is frequently accompanied by insulin resistance/type 2 diabetes mellitus. Insulin-sensitizing agents have recently been reported to have a beneficial effect on NAFLD. Metformin, an insulin sensitizer, increases hepatic lipid and glucose catabolism, resulting in improved insulin resistance and hepatic steatosis in patients with NAFLD [8–10]. Pioglitazone, another insulin-sensitizing agent that modulates peroxisome proliferator-activated receptor-γ (PPARγ), reduces hepatic steatosis by enhancing fatty acid oxidation and by inhibiting hepatic fatty acid synthesis in patients with NAFLD [11, 12]. However, use of these agents alone is are not always sufficient in the treatment of NAFLD [13, 14]; as such, use of additional agents is required for patients with refractory NAFLD.

Sitagliptin is an inhibitor of dipeptidyl peptidase IV (DPP-4) and enhances the effect of glucagon-like peptide-1 (GLP-1) [15, 16]. GLP-1, a gut hormone, is known to regulate glucose metabolism by activating the GLP-1 receptor expressed in various tissues including the brain, pancreas and muscles [17–22]. Recently, Gupta et al. [23] demonstrated that the GLP-1 receptor exists in hepatocytes. In fact, GLP-1 reduced hepatic steatosis in ob/ob mice by improving insulin sensitivity [24]. Since sitagliptin up-regulates GLP-1 activity, the agent may be a potential therapeutic option for patients with NAFLD. Here we report a case of refractory NAFLD who was improved by sitagliptin treatment.

Case Report

A 67-year-old Asian woman was referred to the Digestive Disease Center, Kurume University Hospital due to abnormal liver function tests. The patient had been diagnosed with type 2 diabetes mellitus at 57 years of age. Biochemical tests showed elevated serum levels of aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase (**table 1**). Hepatitis viral makers including hepatitis B surface antigen, hepatitis B core antibody and antibody to hepatitis C virus were negative. Biochemical tests also showed no evidence of autoimmune chronic liver disease or genetic liver diseases such as Wilson disease or hemochromatosis (table 1).

Ultrasonography revealed a bright liver with deep attenuation and liver-kidney contrast, suggestive of sever fatty liver. The patient had no history of alcohol intake. Her average energy intake was 35 kcal/day/kg ideal body weight and fat intake was 25%. Her body mass index was 37.5 and her lifestyle was hypokinetic. In addition, she had an increased serum ferritin level and an increased homeostasis model assessment-insulin resistance (HOMA-IR) score, an index for insulin resistance (table 1). The patient was diagnosed with NAFLD.

Since the patient suffered from lumbago and leg pain, she could not perform exercise therapy. Thus, the NAFLD was managed by diet education. She understood the importance of diet therapy and reduced her energy and fat intake, however, her HOMA-IR score and hepatic steatosis severity did not improve (**fig. 1**). To improve her insulin resistance, she was prescribed metformin 750 mg/day. Despite the use of this anti-diabetic agent, HOMA-IR score and hepatic steatosis severity did not improve (fig. 1, **fig. 2**). Consequently, pioglitazone 15 mg/day was administered. Although her HOMA-IR score finally decreased, she experienced leg edema and a pericardial effusion (fig. 1, fig. 2). Pioglitazone was then withdrawn and her HOMA-IR score subsequently increased (fig. 1).

The patient was then administered sitagliptin 50 mg/day. Despite no change in her energy intake or physical activity, her hemoglobin A1c level decreased from 7.8 to 6.6% 4 months after treatment. Moreover, serum insulin level and HOMA-IR score also improved (fig. 1). In addition, the severity of

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fatty accumulation in the liver decreased (fig. 2) and serum alanine aminotransferase level decreased to 35 IU/dl. These findings indicated that sitagliptin improved insulin resistance and steatosis in a patient with refractory NAFLD.

Discussion

Here we presented a case of refractory NAFLD treated by sitagliptin, a DPP-4 inhibitor. Although the patient had been treated with other anti-diabetic agents, both insulin resistance and steatosis severity were improved after sitagliptin treatment, suggesting efficacy of the DPP-4 inhibitor for patients with refractory NAFLD.

Chronic caloric overconsumption is a major causative factor of NAFLD [25]. In fact, the patient's energy intake was high and, therefore, diet therapy was implemented. She understood the importance of diet therapy and reduced her energy intake; however, HOMA-IR value and steatosis severity did not improve. One possible reason is that exercise therapy, a first-line therapy for NAFLD [26, 27], was difficult to perform for this patient because of lumbago and leg pain. In addition to hypoactivity, an unknown metabolic abnormality may exist in this case, because the patient's HOMA-IR value and serum free fatty acid level were extremely high compared to the reference values.

Since previous studies have shown that metformin is effective in patients with NAFLD, we administered that medication first. However, in this case the severity of insulin resistance and hepatic steatosis did not decrease with metformin treatment. Lavine et al. [13] reported similar results, namely that metformin treatment did not improve hepatic steatosis in patients with NAFLD. Thus the effectiveness of metformin on NAFLD remains controversial, possibly because NAFLD has various etiologies, including overnutrition, drugs and genetic diseases.

We added pioglitazone to the patient's medication regimen. Addition of this drug decreased the patient's HOMA-IR value from 7.5 to 7.0%, however it was discontinued due to the development of leg edema and pericardial effusion. Plasma volume expansion is a major adverse effect of PPARγ agonists such as pioglitazone [28], which stimulate epithelial sodium channel (ENaC)-mediated renal salt absorption in the renal collecting duct. In addition, PPARγ agonists decrease Na^+ transport via the ENaC, leading to increases in systemic blood volume [29–31]. In fact, post marketing surveillance of pioglitazone showed that edema develops in 12.3% of all pioglitazone-treated diabetic patients [32]. Thus, pioglitazone may not always be appropriate for patients with NAFLD due to this adverse effect.

In our case, use of sitagliptin, a DPP-4 inhibitor, improved both the patient's insulin resistance and her hepatic steatosis severity. Although the mechanisms for this were not clear, sitagliptin is known to improve glucose intolerance and hepatic steatosis in vivo [24, 33, 34]. GLP-1 agonists were reported to improve insulin resistance and hepatic steatosis in an animal model of NAFLD [24], and the use of a GLP-1 analog was also reported to improve hepatic steatosis in a patient with NAFLD [35]. Moreover, Gupta et al. [23] recently demonstrated that the the GLP-1 receptor is located in hepatocytes, and we also revealed that a GLP-1 analog directly increased glucose uptake in human hepatocytes through activation of the adenosine monophosphate kinase signaling pathways. Taken together, we hypothesized that sitagliptin improved insulin resistance and steatosis in this case.

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In conclusion, we were the first to demonstrate that a DPP-4 inhibitor improved insulin resistance and steatosis in a patient with refractory NAFLD.

Table 1. Characteristics of the patient

	Reference value	Patient's value
Age, years		64
Gender		female
Height, cm		145.5
Body weight, kg		81.4
Body mass index, kg/m^2		38.5
Body fat mass, kg		43
White blood cell count, /μl	4,000–9,000	9,300
Red blood cell count, /μl	380–500×10^4	506×10^4
Hemoglobin, g/dl	11.0–15.0	16.2
Platelets, /μl	13.0–36.0×10^4	24.8×10^4
Aspartate aminotransferase, U/l	13–33	35
Alanine aminotransferase, U/l	6–30	47
Lactate dehydrogenase, U/l	119–229	203
Alkaline phosphatase, U/l	115–359	194
γ-Glutamyltranspeptidase, U/l	10–47	23
Choline esterase, IU/l	214–466	529
Total protein, g/dl	6.70–8.30	8.35
Albumin, g/dl	4.00–5.00	4.64
Total bilirubin, mg/dl	0.30–1.20	0.65
Blood urea nitrogen, mg/dl	8.0–22.0	14.9
Creatinine, mg/dl	0.40–0.70	0.53
Sodium ion, mEq/l	130–146	138
Potassium ion, mEq/l	3.6–4.9	4.6
Chloride ion, mEq/l	99–109	99
Serum iron, μg/dl	80–170	104
Ferritin, ng/ml	4.9–96.6	102.1
Serum zinc, μg/dl	80–130	94
Amylase, U/l	42–132	81
Fasting glucose, mg/dl	80–109	125
Fasting insulin, μU/ml	5.0–20.0	52.8
HOMA-IR	<2.5	16.3
Hemoglobin A1c, %	4.3–5.8	7.8
Total cholesterol, mg/dl	128–219	223
HDL cholesterol, mg/dl	86.1–40.0	78.7
LDL cholesterol, mg/dl	<139.0	130
Triglyceride, mg/dl	40.0–96.0	118
Free fatty acid, μmol/l	100–540	1,400
3-Hydroxybutyric acid, μmol/l	<76	112
Antimitochondrial antibody	negative	negative
Antinuclear antibody	negative	negative
α-Fetoprotein, ng/ml	<8.7	3.9
Hepatitis B surface antigen	negative	negative
Hepatitis B core antigen	negative	negative
Antibody to hepatitis C virus	negative	negative

HDL = High-density lipoprotein; LDL = low-density lipoprotein.

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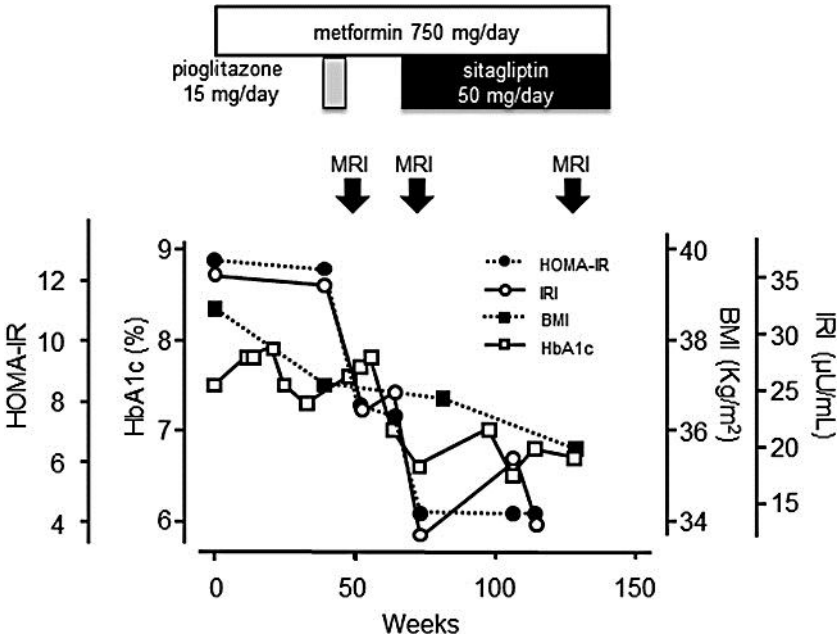

Fig. 1. Time course of body mass index and glucose metabolisms during the medical treatment.

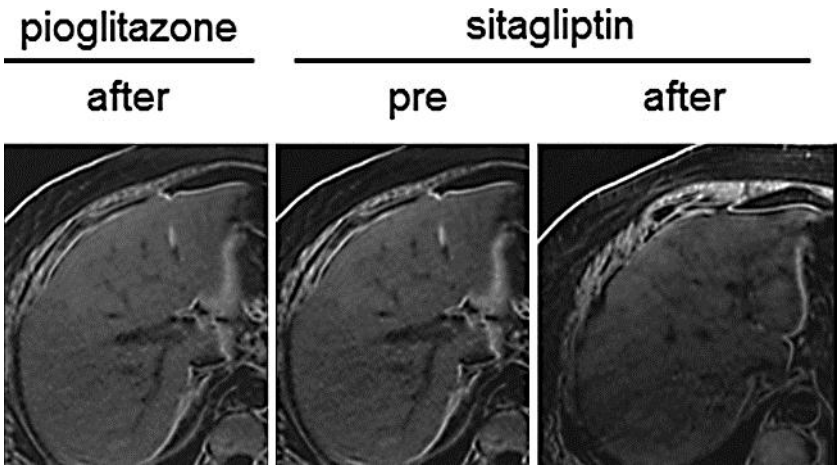

Fig. 2. Changes in MRI imaging during the medical treatment. All images are T1 subtraction images.

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