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Involvement of bile circulation and hepatic inflammation in glucose homeostasis in a case of primary biliary cholangitis

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ABSTRACT

Primary biliary cholangitis (PBC) is characterized by the impaired enterohepatic circulation of bile acids caused by immune-mediated destruction of the intrahepatic bile ducts, leading to progressive liver dysfunction. This report describes the case of a patient with PBC accompanied with diabetes mellitus who exhibited a remarkable improvement in glycemic control after treatment with ursodeoxycholic acid (UDCA) and bezafibrate. A 51-year-old woman initially referred our department with poorly controlled diabetes during the previous 2 years. The patient had failed to achieve a favorable glycated hemoglobin (HbA_{1c}) level (8.7%) despite treatment with oral glucose-lowering agents, and abnormal liver biochemistry findings indicated predominant increases in serum alkaline phosphatase and γ-glutamyltranspeptidase levels. The patient was diagnosed with PBC based on the presence of cholestatic liver profile and positive tests for anti-mitochondrial antibody, and treatment with UDCA and bezafibrate was then initiated. After a 5-week treatment with these agents, all liver biochemistries and hallmarks of inflammation showed immediate improvement. Notably, her HbA_{1c} level was remarkably ameliorated to 6.3% within 5 weeks after the initiation of treatment, and adequate glycemic control (HbA_{1c} level $<$ 6.5%) was maintained without any additional glucose-lowering agents for the succeeding 3 years. Metabolic profiles revealed that the glucose-lowering effect of the treatment was due to improved pancreatic β cell function and insulin sensitivity possibly via incretin effects and eliminating hepatic inflammation. This case may be interesting when considering the relationship between bile acids and glucose metabolism, and may offer an option for the treatment of glucose intolerance accompanied with cholestatic liver diseases.

1. Introduction

Bile acids act as gut hormones in the ileum; they activate the transmembrane G protein-coupled receptor 5 (TGR5)–glucagon-like peptide-1 (GLP-1) and the nuclear receptor farnesoid X receptor (FXR)–fibroblast growth factor 19 (FGF19) axes, and then regulate pancreatic β cell function and insulin sensitivity [1]. Bile acids also have an antimicrobial effect of restraining commensal microbial species in the ileum and colon [2]. Compositional and functional alterations of the gut microbiome, namely dysbiosis, may allow metabolic endotoxemia followed by insulin resistance via hepatic sterile inflammation [2].

Primary biliary cholangitis (PBC) is a progressive disease characterized by the destruction of small intrahepatic bile ducts, which leads to the decreased biliary secretion and the accumulation of toxic bile acids and their metabolites within hepatocytes [3]. This leads to cholangitis, hepatic fibrosis, cirrhosis, and eventually liver failure [3]. The prevalence of diabetes mellitus (DM) in patients with early-stage PBC appears to be equivalent to that of the age-matched general populations [4]. However, the metabolic functions of bile acids considered, the disturbed enterohepatic bile circulation potentially affects glucose homeostasis in PBC patients.

Ursodeoxycholic acid (UDCA), a naturally occurring hydrophilic bile acid, can ameliorate postprandial intestinal bile flow, affect the hydrophobicity of the bile acid pool, and may lead to intestinal microbial distortion [2,3]. UDCA is the first-line drug for treating PBC, and it extends transplant-free survival, especially when initiated early in the course [3]. Bezafibrate, a hepatic peroxisome proliferator-

Abbreviations: Primary biliary cholangitis, PBC; Ursodeoxycholic acid, UDCA; The transmembrane G protein-coupled receptor 5, TGR5; Glucagon-like peptide-1, GLP-1; The nuclear receptor farnesoid X receptor, FXR; Fibroblast growth factor 19, FGF19; Type 2 diabetes mellitus, T2DM; Peroxisome proliferator-activated receptor-α, PPAR-α; Anti-mitochondrial antibody, AMA; The homeostatic model assessment of β cell function, HOMA-β; The homeostatic model assessment of insulin resistance, HOMA-IR

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activated receptor-α (PPAR-α) agonist, diminishes lipid toxicity through changes in the lipoprotein phenotypes that are characterized by hypertriglyceridemia [5]. Bezafibrate also normalizes liver biochemistry in ~40% of PBC patients with no biochemical response to UDCA [3]. Thus, treatment with UDCA and/or bezafibrate is utilized as a standard practice against PBC; however, the effect of these drugs on glucose homeostasis in such patients remains unclear.

The present report describes a patient with PBC who presented with poorly controlled diabetes despite treatment with oral glucose-lowering agents. To determine the drug effects on glucose homeostasis, metabolic profiles with liver biochemistries were investigated pre- and post-treatment with UDCA and bezafibrate.

2. Case report

A 51-year-old female referred our department and presented with poorly controlled DM. The patient was a non-smoker and social drinker. Her mother had a history of type 2 DM (T2DM), but there was no family history of liver or autoimmune disorders. The patient was diagnosed with T2DM at the age of 41 years; however, she was left untreated for 9 years before visiting a nearby clinic. The patient had been obese since the age of 23 years, and insulin resistance was considered the main factor responsible for her glucose intolerance. Therefore, in addition to a nutritious diet (1,600 kcal daily), metformin hydrochloride (750 mg daily), a biguanide, was administered at the clinic as the first-line oral glucose-lowering agent 2 years before the first visit to our department (Fig. 1). Monotherapy with metformin failed to achieve adequate glycemic control during the first 3 months of the treatment. Treatment with miglitol (150 mg daily), an α-glucosidase inhibitor, was then initiated as the second drug after considering the drug-specific and patient-specific factors such as the necessity of preventing weight gain and cost of medication (Fig. 1). The patient's glycemic control gradually improved, with glycated hemoglobin (HbA_{1c}) level of 7.2% (reference range: 4.6–6.2%) achieved after 9 months of this combination therapy; however, the control began to worsen again, concomitant with the deterioration of the levels of liver biochemistry markers. GLP-1 receptor agonists possess appetite-inhibitory and body weight-reducing properties, which were considered desirable when a third glucose-lowering agent was required to achieve the patient's glycemic target. However, the patient did not allow the initiation of this treatment because it is an expensive injectable therapy. Sodium-glucose cotransporter 2 inhibitors were not commercially available then. Consequently, the patient's diabetic condition was maintained only by metformin and miglitol despite inadequate glycemic control until the first visit to our department.

Table 1
Laboratory findings before and after the 5-week treatment with ursodeoxycholic acid and bezafibrate.

Variable	Pre-treatment	Post-treatment	Reference range
Erythrocyte sedimentation rate (mm/1h)	61	32	3–15
Biochemistry			
Aspartate aminotransferase (IU/l)	86	67	8–40
Alanine aminotransferase (IU/l)	96	57	5–35
Alkaline phosphatase (IU/l)	796	199	100–324
γ-glutamyltranspeptidase (IU/l)	598	108	12–48
Thymol turbidity test (U)	37.9	23.2	0–5.0
Zinc sulphate turbidity test (U)	36.7	20.0	4.0–12.0
Triglycerides (mg/dl)	272	179	< 150
Non-esterified fatty acids (mEq/l)	0.47	0.81	0.14–0.81
Serological test			
C-reactive protein (mg/dl)	0.73	0.25	0–0.40
Immunoglobulin M (mg/dl)	563	363	46.0–260
Endocrine test			
Glycated hemoglobin (%)	8.7	6.3	4.6–6.2
Glucose (mg/dl)	168	109	< 110
Immunoreactive insulin (μU/ml)	14.1	13.5	1.84–12.2
C-peptide immunoreactivity (ng/ml)	3.07	2.61	0.61–2.09
HOMA-β	48	106	40–60
HOMA-IR	5.8	3.6	≤ 1.6
Total glucagon-like peptide-1 (pmol/l)	11	16	NA

HOMA-β, the homeostatic model assessment of β cell function; HOMA-IR, the homeostatic model assessment of insulin resistance.

The patient's body weight at the first visit to our hospital was 87.2 kg (body mass index: 33.5 kg/m^2). Her blood pressure was 142/64 mmHg in the supine position and 100/62 mmHg in the standing position. Physical examination results revealed xanthomas involving the right medial canthus, an umbilical hernia in the abdomen, bilateral

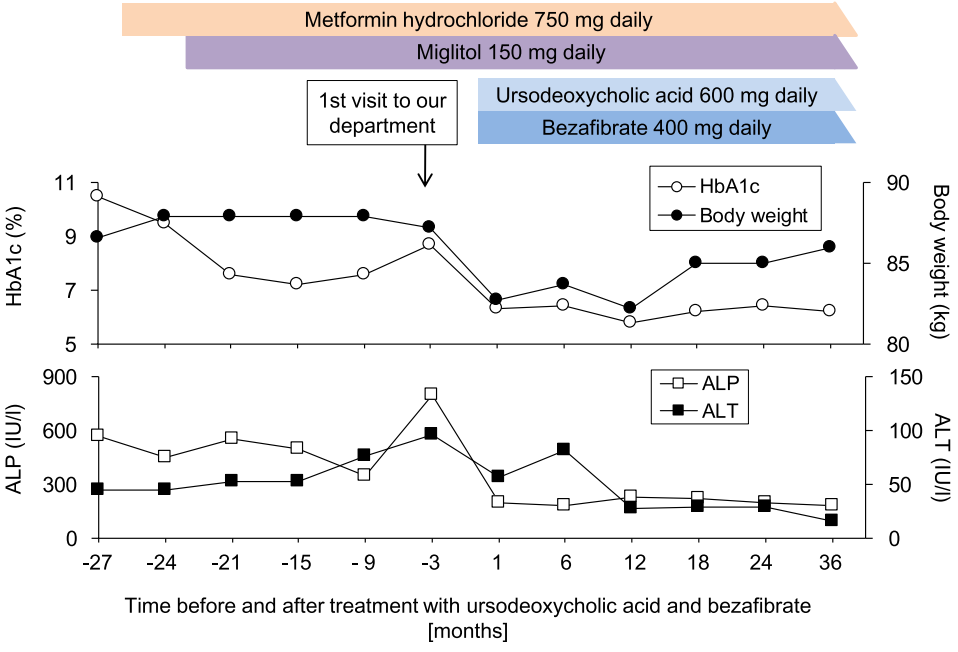

Fig. 1. Clinical course of the patient with primary biliary cholangitis and diabetes mellitus. The lines show the glycated hemoglobin levels (HbA_{1c}, *open circles*), body weight (*closed circles*), serum alkaline phosphatase levels (ALP, *open squares*), and alanine aminotransferase levels (ALT, *closed squares*) observed before and after treatment with ursodeoxycholic acid and bezafibrate. The reference ranges for each item are stated in the text.

dulled perception of vibration, and a loss of Achilles' tendon reflex, along with other unremarkable physical findings. Laboratory examinations revealed high HbA_{1c} level (8.7%) with elevated fasting plasma glucose level (168 mg/dl, reference range: < 110 mg/dl) (Table 1). Test for anti-glutamic acid decarboxylase antibody was negative for type 1 DM (< 0.4 U/ml, negative: ≤ 1.4 U/ml). Her serum low- and high-density lipoprotein cholesterol, and triglycerides levels were 101, 45, and 272 mg/dl, respectively (target or reference range: < 120, ≥ 40, and < 150 mg/dl, respectively). Liver biochemistries indicated marked increases in alkaline phosphatase (ALP: 796 IU/l, reference range: 100–324 IU/l) and γ-glutamyltranspeptidase (γGTP: 598 IU/l, reference range: 12–48 IU/l) levels in conjunction with high aspartate aminotransferase (AST: 86 IU/l, reference range: 8–40 IU/l) and alanine aminotransferase (ALT: 96 IU/l, reference range: 5–35 IU/l) levels. The total bilirubin level was normal (0.4 mg/dl, reference range: 0.2–1.2 mg/dl), and screening tests for hepatitis B and C viruses were negative. High levels of ALP and γGTP were predominant in abnormal liver biochemistries, indicating PBC as a differential diagnosis. Serological findings revealed that both the anti-mitochondrial antibody (AMA) and AMA M2 component were positive (×1,280 and 144 U/ml, respectively, reference range: < ×20 and < 7 U/ml, respectively), with high levels of serum immunoglobulin M (IgM: 563 mg/dl, reference range: 46.0–260 mg/dl), thymol turbidity test (TTT: 37.9 U, reference range: 0–5.0 U), and zinc sulphate turbidity test (ZTT: 36.7 U, reference range: 4.0–12.0 U). Platelet counts were 373,000 per mm^3 (reference range: 120,000–350,000 per mm^3). Abdominal ultrasonography revealed a diffuse bright liver, but no signs of extrahepatic bile duct obstruction, advanced fibrosis, or portal hypertension were observed.

Based on the presence of cholestatic liver profile and the positive tests for AMA, a diagnosis of asymptomatic PBC was made [3], and treatment with UDCA (600 mg daily) was initiated (Fig. 1). Bezafibrate (400 mg daily) was additionally administered for treating PBC and hypertriglyceridemia. No adverse events such as diarrhea, abdominal discomfort, and myopathy were observed during the treatment.

After the 5-week treatment with UDCA and bezafibrate, serum ALP level was normalized (199 IU/l), and all the other liver biochemistry values (γGTP, 108 IU/l; AST, 67 IU/l; ALT, 57 IU/l; TTT, 23.2 U; and ZTT, 20.0 U) were improved (Table 1). Notably, the 5-week treatment apparently reduced the body weight (from 87.6 to 83.2 kg, the average body weight values of two consecutive measurements), and markedly lowered the levels of HbA_{1c} (6.3%) and fasting plasma glucose (109 mg/dl) (Fig. 1). No changes in factors such as diet, alcohol intake, physical activity/exercise, and stress management were observed during the patient's clinical course according to the information provided by the patient. Serial hematological findings revealed no marked change in hemoglobin (Hb) levels 1 and 6 months after the initiation of treatment (before treatment: 12.7 g/dl, after 1 month: 13.1 g/dl, and after 6 months: 12.8g/dl); therefore, a fluctuation in Hb levels could not explain the lowered HbA_{1c} levels in the patient.

Administration of UDCA and bezafibrate resulted in higher fasting serum non-esterified fatty acids level (from 0.47 to 0.81 mEq/l, reference range: 0.14–0.85 mEq/l) (Table 1), predicting higher plasma GLP-1 levels [6]. Indeed, the sum of fasting plasma GLP-1 (7–36) amide and GLP-1 (9–36) amide levels measured by an ELISA kit (Yanaihara Institute, Shizuoka, Japan) suggested that the secretory rate of GLP-1 from ileal L cells of the patient was increased after the 5-week treatment (total GLP-1: from 11 to 16 pmol/l). Erythrocyte sedimentation rate (ESR: from 61 to 32 mm/1h, reference range: 3–15 mm/1h), serum C-reactive protein (CRP: from 0.73 to 0.25 mg/dl, reference range: 0–0.40 mg/ml), IgM (363 mg/dl), and triglycerides (179 mg/dl) levels were decreased after the 5-week treatment. The 5-week treatment ameliorated pancreatic β cell function and insulin sensitivity, as estimated by the homeostatic model assessment of β cell function (HOMA-β: from 48 to 106, reference range: 40–60) and the homeostatic model assessment of insulin resistance (HOMA-IR: from 5.8 to 3.6, reference range: ≤ 1.6), respectively. Taken together, these data suggest that treatment with UDCA and bezafibrate results in improved pancreatic β cell function and insulin sensitivity, possibly via incretin effects and eliminating hepatic inflammation, which is implicated in the favorable outcome on glucose intolerance of the patient (Supplementary Fig. 1).

The patient maintained her adequate glycemic control for reducing the risk of diabetic microvascular complications (HbA_{1c} levels < 6.5%). Furthermore, she did not undergo any flare-up of liver dysfunction, thus avoiding the advancement of liver fibrosis/cirrhosis [3]. Hence, no additional treatment was required in the succeeding 3 years (Fig. 1).

3. Discussion

The course of this case provides two clinical suggestions. First, a disturbed enterohepatic bile circulation and hepatic sterile inflammation along with PBC potentially affect glucose homeostasis. Second, treatment with UDCA and bezafibrate for PBC may exhibit glucose-lowering properties, which are associated with favorable effects on both pancreatic β cell function and insulin sensitivity.

In the present case, treatment with UDCA and bezafibrate resulted in improved β cell function, possibly through UDCA-induced alteration of the TGR5–incretin (GLP-1) pathway. The potency of UDCA for directly activating bile acid receptors is far less than those of other bile acids such as lithocholic, deoxycholic, and chenodeoxycholic acids [2]. A study of patients who underwent bariatric surgery revealed that treatment with UDCA failed to affect plasma GLP-1 and glucose levels [7]. However, oral UDCA therapy with a mixed meal has shown to yield lower plasma glucose levels concomitant with higher postprandial plasma GLP-1 levels to healthy subjects [8]. Orally administered UDCA could indirectly modulate the enterohepatic bile circulation through the following mechanisms: (i) increasing biliary secretion from the liver, (ii) facilitating contraction of the gall bladder, (iii) interfering with the absorption of endogenous bile acids and free fatty acids in the proximal small intestine, and (iv) altering the composition of ileal bile acids [2,3]. Therefore, treatment with UDCA for the patient may restore the postprandial delivery of bile species showing a higher affinity for binding with TGR5 in the ileal L cells as shown in the cases treating non-absorbable resins, colesevelam [9]. Postprandial bile flow into the intestine was possibly blunted in the patient because of dampened gallbladder motility and a decreased gastric emptying rate caused by her diabetic autonomic neuropathy, which may enhance the effectiveness of UDCA treatment.

Treatment with UDCA and bezafibrate also succeeded in eliminating insulin resistance of the patient in parallel with the amelioration of liver biochemistries and systemic inflammatory biomarkers. The activation of the FXR–FGF19 pathway in the ileal epithelium increases energy expenditure [1]. Therefore, UDCA-mediated modulation of enterohepatic bile circulation may influence factors associated with weight loss during the patient's clinical course. The patient started gaining weight again 18 months after the initiation of treatment; however, she could maintain appropriate glycemic control, irrespective of her body weight. The continuous successful management of her insulin resistance was demonstrated by the HOMA-IR index of 1.6 after the 18-months treatment, suggesting that the favorable effects of these agents on her insulin sensitivity could not be fully explained by the weight loss. Hepatic sterile inflammation, along with PBC, exacerbates insulin resistance due to oxidative stress, endoplasmic reticulum stress, and dysbiosis-mediated metabolic endotoxemia, which can be alleviated by treatment with UDCA [2,3]. The activation of hepatic PPAR-α by bezafibrate eliminates lipid toxicity and oxidative stress through the modulation of peroxisomal and mitochondrial β-oxidation [5]. Collectively, treatment with UDCA and bezafibrate possibly played an important role in the improved hepatic insulin sensitivity in the patient.

4. Conclusion

The disturbed enterohepatic bile circulation and hepatic sterile inflammation possibly affects glucose homeostasis in a part of PBC patients. Administration of UDCA and bezafibrate for the treatment of such patients may result in a favorable outcome of glucose metabolism through an improvement in pancreatic β cell function and hepatic insulin sensitivity. These findings emphasis the role of bile acids in glucose homeostasis and may offer an option for the treatment of glucose intolerance accompanied with cholestatic liver diseases.

Disclosure statement

The author declares no conflicts of interest in association with this case report.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jecr.2019.100051.

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