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DPP-4 Inhibitors Improve Liver Dysfunction in Type 2 Diabetes Mellitus

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Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors might have pleiotropic effects because receptors for incretin exist in various tissues, including liver. We examined whether DPP-4 inhibitors affect liver function in patients with type 2 diabetes.

Material/Methods: A retrospective review of 459 patients with type 2 diabetes who were prescribed DPP-4 inhibitors was performed. After exclusion of patients with hepatitis B or C, steroid use, and other diseases that might affect liver function and diabetes status, 224 patients were included in the analysis.

Results: Forty-four patients (19.6%) with liver injury defined by aspartate transaminase (AST) or alanine transaminase (ALT) over the normal level of 40 U/L. In the patients with liver injury, AST and ALT were significantly decreased after 6 months from the first date of DPP-4 prescription, with mean changes of -6.2 U/L [95% confidence interval (CI) -10.9 to -1.4 , $p=0.012$] and of -11.9 U/L (95%CI -19.5 to -4.2 , $p=0.003$), respectively. Percent changes in AST were significantly and negatively correlated with baseline AST and ALT ($r=-0.27$, $p<0.001$ and $r=-0.23$, $p=0.002$, respectively), and percent changes in ALT were also negatively correlated with them ($r=-0.23$, $p=0.001$ and $r=-0.27$, $p<0.001$, respectively).

Conclusions: DPP-4 inhibitors improved liver dysfunction in patients with type 2 diabetes.

MeSH Keywords: **Diabetes Complications • Diabetes Mellitus • Diabetes Mellitus, Type 2 • Fatty Liver**

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Background

Dipeptidyl peptidase-4 (DPP-4) inhibitors are frequently used all over the world as blood glucose-lowering treatments of patients with type 2 diabetes mellitus. DPP-4 inhibitors prolong the activity of incretin peptides, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), which stimulate glucose-dependent insulin secretion and inhibit glucagon secretion [1]. GLP-1 action is thought to be the main glucose-lowering effect of DPP-4 inhibitors because the GIP receptor is downregulated under the hyperglycemic condition [2]. Because the receptor for GLP-1 has been shown to exist on various cells, including hepatocytes [3,4], DPP-4 inhibitors may have pleiotropic effects independent of lowering plasma glucose level and stimulating insulin secretion.

Non-alcoholic fatty liver disease (NAFLD) describes a disease with excessive deposition of fat within the liver and includes a broad spectrum of liver diseases ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH) and cirrhosis [5]. NAFLD is more prevalent and more severe in patients with type 2 diabetes, and is associated by increased mortality rates [6]. Because liver function is extremely important for glucose metabolism, NAFLD/NASH may lead to poor glycemic control in type 2 diabetes. Moreover, a recent study revealed that NAFLD was associated with increased prevalence of diabetic macroangiopathy and coronary heart disease in elderly Japanese patients with type 2 diabetes [7]. Therefore, it is no less important to maintain the liver function in diabetic patients than in their nondiabetic counterparts.

Recently, several clinical studies have shown that GLP-1 receptor agonists reduced fat deposition in the liver and improved liver function independently of body weight loss in type 2 diabetes [8,9]. These findings suggest that activation of GLP-1 signaling in the liver has beneficial effects on NAFLD and that DPP-4 inhibitors may also affect liver function. However, the impact of improving liver function by DPP-4 inhibitors is still unknown. Therefore, in this study we examined the effects of DPP-4 inhibitors on liver function in patients with type 2 diabetes.

Material and Methods

Subjects

The inclusion criteria are shown in Figure 1. According to the records of our hospital, a total of 459 patients with type 2 diabetes were prescribed DPP-4 inhibitors from September to November 2012. We excluded the patients with glucocorticoid use (n=56), hepatitis B or C, and other diseases that might affect liver function and diabetes status (n=114). We also excluded patients who were not followed-up at our hospital (n=31)

Figure 1. Flow-chart describing the study subjects.

or for whom we could not define when DPP-4 inhibitors were initially prescribed (n=34). Finally, 224 patients were included in this analysis. Prescription was not changed in the participants during the follow-up period.

Demographic and biochemical parameters at the initial date of DPP-4 inhibitors prescription were collected and body weight, parameters of liver function [aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl transpeptidase (γGTP)], and hemoglobin A1c (HbA1c) were followed up to 6 months. The numbers of patients who were prescribed sitagliptin, alogliptin, and vildagliptin were 155, 37, and 32, respectively. This study was retrospective in design, approved by the ethics review board of Shimane University Faculty of Medicine, and complied with the Helsinki Declaration.

Biochemical measurements

All biochemical markers were measured by standard methods at the clinical laboratory in Shimane University Hospital. HbA1c was determined by high-performance liquid chromatography

Table 1. Baseline characteristics and comparison between patients with and without liver injury.

	Total	Liver injury		p
		With	Without	
Number of subjects	224	44	180	
Sex (male/female)	144/80	28/16	116/64	
Age (years)	67±12	61±12	69±11	<0.001
Body height (cm)	159.2±9.3	161.5±9.4	158.9±9.1	0.102
Body weight (kg)	62.9±11.8	69.3±17.8	61.5±11.9	0.001
BMI (kg/m ²)	24.6±4.2	26.4±5.3	24.3±3.8	0.005
AST (U/L)	28±17	51±25	22±6	<0.001
ALT (U/L)	30±25	65±36	21±8	<0.001
γGTP (U/L)	45±49	84±74	37±35	<0.001
HbA1c (%)	7.9±1.2	8.1±1.3	7.8±1.2	0.132
DPP4 inhibitors				
Sitagliptin	155 (69.2%)	29 (65.9%)	126 (70.0%)	0.599*
Alogliptin	37 (16.5%)	10 (22.7%)	27 (15.0%)	0.219*
Vildagliptin	32 (14.3%)	5 (11.4%)	27 (15.0%)	0.538*

and was calculated according to the National Glycohemoglobin Standardization Program (NGSP). The CVs of all measurements were <10%.

Statistical analysis

Data are expressed as mean ±SD. Statistical significance between the patients with and without liver injury was determined using the *t*-test and χ^2 test. Statistical significance between baseline versus 1, 3, and 6 months was determined using the Wilcoxon signed rank test. Pearson's correlation coefficient was used in univariate analyses. All analyses were performed using the StatView (Abacus Concepts, Berkeley, CA) statistical computer program. *P*<0.05 was considered to be significant.

Results

Baseline characteristics and comparison between patients with and without liver injury

Baseline characteristics are shown in Table 1. Forty-four patients (19.6%) had liver dysfunction defined by AST or ALT above the normal level of 40 U/L. We compared the baseline data between the patients with and without liver dysfunction. The patients with liver dysfunction were younger and heavier than those without liver dysfunction. The levels of AST, ALT, and γGTP were significantly higher in the patients with liver

dysfunction than those without it, while HbA1c levels and DPP-4 inhibitors were not different.

Changes in the parameters of liver function

Chronological changes in body weight, AST, ALT, γGTP, and HbA1c are shown in Table 2. In all subjects, HbA1c levels were significantly decreased for up to 6 months, but body weight and the parameters of liver function were not changed. In the patients with liver dysfunction, HbA1c, AST, and ALT were significantly decreased for up to 6 months, whereas body weight and γGTP were not changed. The mean changes of AST and ALT at 6 months were −6.2 U/L [95% confidence interval (CI) −10.9 to −1.4, *p*=0.012] and −11.9 U/L (95%CI −19.5 to −4.2, *p*=0.003), respectively. When changes in AST and ALT levels were compared among sitagliptin, alogliptin, and vildagliptin, there was no significant difference (data not shown). In contrast, AST or ALT levels were not changed in the patients without liver dysfunction, although HbA1c levels were significantly decreased in the same manner as in the patients with liver dysfunction.

Correlation between baseline characteristics versus percent changes in AST and ALT

To find which parameters predict the reduction of AST and ALT, the correlation of percent changes in AST and ALT at 6 months with baseline characteristics was examined (Table 3). Percent changes in AST and ALT were significantly and inversely

Table 2. Chronological changes in body weight, parameters of liver function, and HbA1c.

	Baseline	1 month	3 months	6 months
Total (n=224)				
Body weight (kg)	62.9±13.5	62.4±11.8	63.9±13.5	63.4±14.3
AST (U/L)	28±17	27±17	26±14	28±16
ALT (U/L)	30±25	28±23	27±19	28±22
γGTP (U/L)	46±49	45±49	46±53	48±59
HbA1c (%)	7.9±1.2	7.5±1.0***	7.3±1.0***	7.2±1.0***
With Liver injury (n=44)				
Body weight (kg)	69.3±17.8	69.3±13.7	73.8±19.0	71.7±18.0
AST (U/L)	51±25	45±30*	42±24*	45±29*
ALT (U/L)	65±36	54±38**	49±30***	52±36**
γGTP (U/L)	84±74	76±71	82±91	88±102
HbA1c (%)	8.1±1.3	7.6±1.2***	7.4±1.1***	7.1±1.0***
Without liver injury (n=180)				
Body weight (kg)	61.5±11.9	61.1±11.0	62.1±11.5	61.6±12.5
AST (U/L)	22±6	23±6	23±7	23±7
ALT (U/L)	21±8	22±10	21±10	23±12
γGTP (U/L)	37±35	37±38	36±31	37±34
HbA1c (%)	7.8±1.2	7.4±1.0***	7.3±1.0***	7.2±0.9***

Data are means ±SD. P values were calculated using Wilcoxon test. AST – aspartate transaminase; ALT – alanine transaminase; γGTP – gamma-glutamyl transpeptidase; HbA1c – hemoglobin A1c. * p<0.05; ** p<0.01; *** p<0.001 vs. baseline.

Table 3. Correlation between baseline characteristics versus percentage change in AST or ALT.

	Percentage change in AST		Percentage change in ALT	
	r	p	r	p
Age	–0.06	0.413	–0.06	0.436
BMI	–0.01	0.912	0.02	0.821
AST	–0.27	<0.001	–0.23	0.001
ALT	–0.23	0.002	–0.27	<0.001
γGTP	–0.13	0.105	–0.13	0.09
HbA1c	0.06	0.411	–0.03	0.691

BMI – body mass index; AST – aspartate transaminase; ALT – alanine transaminase; γGTP – gamma-glutamyl transpeptidase; HbA1c –hemoglobin A1c.

correlated with baseline AST and ALT levels, but they were not correlated with age, body mass index, γGTP, or HbA1c.

Discussion

In this study, we found that DPP-4 inhibitors significantly reduced AST and ALT levels in the type 2 diabetes patients with

liver dysfunction, but they did not affect liver function in those without liver dysfunction. The liver injury of the subjects enrolled in the analysis might have been caused by NAFLD because we excluded subjects who had hepatitis B or C. Furthermore, the baseline and subsequent data showed that the patients with liver dysfunction were obese compared to those without liver dysfunction. In addition, γGTP levels were not changed, suggesting that the improvement of AST and ALT was not caused

by restriction of alcohol abuse. These findings also support that NAFLD caused the abnormality of AST and ALT levels in our subjects. Most recently, Iwasaki et al. reported for the first time that liver function was improved by 4-month treatment with sitagliptin in type 2 diabetes patients with NAFLD diagnosed by ultrasonography [10]. Yilmaz et al. examined paired liver biopsies in 15 diabetic patients with NASH and reported that a significant reduction of NASH scores was observed after 1-year treatment with sitagliptin, and that these effects were accompanied by significant decreases in body mass index, AST, and ALT levels [11]. Our present findings are consistent with these previous studies. Moreover, we found that the changes in AST and ALT by DPP-4 inhibitors were independent of HbA1c level and body weight. Thus, DPP-4 inhibitors have a desirable effect on liver function independent of diabetes status.

The pleiotropic effects of incretin-related therapies have recently attracted widespread attention because the receptor for GLP-1 is reported to be expressed in various tissues [1]. Although GLP-1 has a great potential for treatment of type 2 diabetes, its half-life is extremely short because GLP-1 is rapidly inactivated by DPP-4 [1]. It has recently been shown that the receptor for GLP-1 exists in human hepatocytes and administration of GLP-1 analogue directly reduced triglyceride stores compared with control-treated cells in the absence of insulin [3]. Moreover, several clinical studies showed that GLP-1 receptor agonists improved abnormal liver function and hepatic steatosis [8]. On the other hand, it is reported that DPP-4 is ubiquitously expressed, and that DPP-4 inhibitors have direct effects independent of incretin activity. For example, *in vitro* and *in vivo* studies showed that a DPP-4 inhibitor, alogliptin, directly inhibited macrophage migration via suppressing adenosine deaminase on the cell in the absence of incretin signals [12]. A recent study demonstrated that DPP-4 was locally expressed in the liver and that hepatic DPP-4 expression was significantly greater in NAFLD patients than in healthy subjects [13]. These findings suggest that inhibition of local DPP-4 activity in the liver may be important for the treatment of NAFLD. Taken together, these findings suggest that DPP-4 inhibitors improve liver function via increasing

GLP-1 activity, as well as directly inhibiting local DPP-4 activity in the liver. In our study, the effects of DPP-4 inhibitors on the changes in AST and ALT were independent of HbA1c levels, suggesting that DPP-4 inhibitors have pleiotropic effects on liver function, not only in experimental studies, but also in clinical settings. However, there appear to be no studies examining effects of increasing GLP-1 activity and inhibiting hepatic DPP-4 activity by DPP-4 inhibitors on liver function in patients with NAFLD. Further studies are necessary to understand the mechanism for improving liver function of NAFLD by DPP-4 inhibitors.

Conclusions

The present study showed that DPP-4 inhibitors improved the abnormality of AST and ALT, and that percent changes in AST and ALT were inversely associated with baseline AST and ALT levels. In addition, the effects of DPP-4 inhibitors on changes in AST and ALT were independent of HbA1c and body weight. These findings suggest that DPP-4 inhibitors are clinically useful for patients with type 2 diabetes accompanied by liver dysfunction based on fatty liver, and that DPP-4 inhibitors affect liver function regardless of diabetic status and obesity. Moreover, in this study, DPP-4 inhibitors significantly reduced HbA1c levels even in the patients with liver dysfunction. Liver function is quite important for glucose metabolism because the liver is one of the most important target organs of insulin to decrease plasma glucose level. Therefore, DPP-4 inhibitors may be more useful for type 2 diabetes patients with NAFLD than those without it. However, our study is limited because it is retrospective and based on the database of our hospital. Also, other supportive data such as ultrasonography and liver biopsy were not available in this study. Therefore, a large-scale longitudinal clinical trial is warranted in the future.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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