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Original Article

Efficacy of sitagliptin on liver function in patients with diabetes and chronic viral hepatitis B

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Abstract: Objective: To evaluate the efficacy and safety of sitagliptin treatment for type 2 diabetes mellitus complicated with chronic hepatitis B. Methods: We retrospectively collected 528 patients with type 2 diabetes mellitus complicated with chronic hepatitis B. They were divided into two groups: the sitagliptin group and the control group. The patient's general data, glycated hemoglobin (HbA1c) values, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, total bilirubin (TBil) values, hypoglycemia, and other adverse events were recorded. Results: Compared with those in the control group, the blood ALT, AST, and TBil values decreased significantly after sitagliptin treatment, and the HbA1c values and insulin doses in the sitagliptin group decreased significantly at week 12 ($p < 0.05$). In addition, compared with those in the control group, the HbA1c values and insulin doses decreased significantly in the sitagliptin group at week 12 ($p < 0.05$). There were also no statistically significant differences in adverse events, such as nausea, dizziness, and rash, between the two groups. Conclusions: In patients with type 2 diabetes and chronic hepatitis B, insulin and sitagliptin could effectively control blood glucose and reduce insulin dosage without further impairing liver function with the administration of antiviral and hepatoprotective drugs that stabilize liver function.

Keywords: Sitagliptin, type 2 diabetes, viral hepatitis B, propensity score

Introduction

A survey in 2010 showed that the prevalence rate of maturity-onset diabetes in China was 11.6%. There may be as many as 113.9 million adults with diabetes and 493.4 million people with prediabetes [1]. Diabetes is often accompanied by liver disease. It has been reported that 70% of patients with diabetes have nonalcoholic fatty livers, the main causes of which are insulin resistance and lipopexia in the liver [2]. Diabetes is also a complication of chronic liver disease; 80% of patients with chronic liver disease have disorders of glucose metabolism and 30% have combined diabetes mellitus [3]. Diabetes can aggravate the progression of chronic liver disease and is a prognostic independent factor in patients with liver disease [4].

The liver acts as the glucose (or fuel) reservoir of human body, and helps to keep the circulating balance of blood glucose. However, the treatment of patients with diabetes and hepatic insufficiency is complicated. Studies have shown that the rate of HB (hepatitis B) patients achieving normal blood glucose levels is about 34.2% [5], and the main reason is hepatotoxicity of drugs. Dietary adjustments and exercises are not suitable for patients with diabetes and hepatic insufficiency. Dietary restrictions may also lead to malnutrition [6]. Most blood glucose-lowering drugs are metabolized by the liver and may impair liver function and increase the occurrence of hypoglycemia and lactic acidosis [7]. Diabetes treatment in patients with diabetes mellitus and hepatic insufficiency mainly relies on insulin [8], but insulin is metabolized in the liver. When liver insufficiency occurs, liver clearance and gluconeogenesis are reduced and hypoglycemia and lactic acidosis may develop [9].

Sitagliptin is currently the most commonly administered dipeptidyl peptidase (DPP)-4

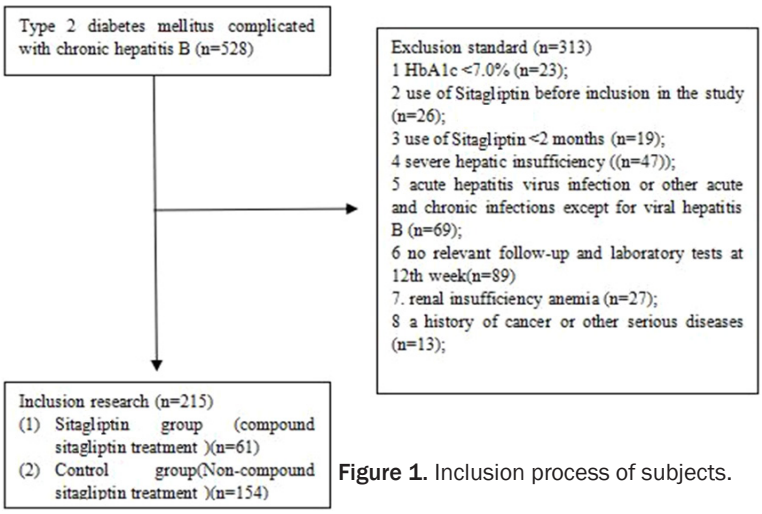

Figure 1. Inclusion process of subjects.

inhibitor and is primarily metabolized by the kidneys. Only a small proportion (approximately 16%) undergoes hepatic metabolism [10]. In an animal experiment, DPP-4 inhibitors can inhibit hepatic fibrosis by attenuating the activity of hepatic stellate cells in mice [11] or improve hepatic steatosis in mice with non-alcoholic fatty liver disease [12]. Another study showed that sitagliptin adapts to the changes in cirrhotic diabetes with moderate hepatic insufficiency and only mild changes in liver function are found [13]. However, there is no evidence for the effectiveness and safety of sitagliptin in patients with diabetes and CHB. Therefore, this study aimed to evaluate the efficacy and safety of sitagliptin as a treatment for type 2 diabetes mellitus complicated with CHB.

Materials and methods

Patients

After obtaining approval from the Institute of Medical Ethics, clinical data of 528 patients with type 2 diabetes mellitus complicated with CHB were retrospectively collected from Xixi Hospital of Hangzhou and the Run Run Shaw Affiliated Hospital of Medical School of Zhejiang University. All the patients conformed to the following conditions: (1) type 2 diabetes fulfilled the 1999 World Health Organization (WHO) diabetes diagnostic criteria [14]. (2) CHB fulfilled the diagnostic criteria and Prevention Scheme of Viral Hepatitis revised by the Institute of Infectious Diseases and Parasites in 2010 with mild or moderate hepatic insufficiency (mild: Child-Pugh grade A, 5-6 points; moderate: Child-Pugh grade B, 7-9 points).

The exclusion criteria were as follows: (1) age < 18 years; (2) HbA1c < 7.0%; (3) administration of sitagliptin before inclusion in the study; (4) administration of sitagliptin for < 2 months; (5) severe hepatic insufficiency (Child-Pugh grade C, ≥10 points); (6) acute hepatitis virus infection or other acute/chronic infections, except for viral hepatitis B; (7) renal insufficiency (creatinine clearance < 50 mL/min), moderate and severe anemia; (8) a history of cancer or other serious diseases; and (9) no relevant follow-up or laboratory tests (blood sugar and renal function tests) in the 12th week. Patients admitted multiple times during the study period were subject to the first admission.

Treatment plan

The treatment plan for patients with viral hepatitis B in this hospital consisted of oral entecavir, 0.5 mg once daily (Baraclude Tablets Bristol-Myers Squibb, 0.5 mg/tablet). The course of treatment was recorded within 12 weeks. According to whether sitagliptin was administered or not, the patients were divided into two groups: the sitagliptin group (X group) and the control group (C group). Liver function grading was based on the Child-Pugh grading standard [14]. HbA1c levels were determined using high-performance liquid chromatography (HPLC) with a D-10 HbA1c analyzer. Blood glucose levels were measured using a Johnson ultra-glucose test meter. Blood biochemical tests such as those for hepatic and renal function were performed using an AV5421 automatic biochemical analyzer.

Outcome indicator

Blood glucose was controlled by administering insulin alone or in combination with oral antidiabetic drugs (OADs). An endocrinologist determined the insulin regimen based on the patient's general condition. OADs were sitagliptin (100 mg, qd), metformin (0.5 g, bid), or acarbose tablets (50 mg, tid). When the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBil) increased to within 2 times of the normal upper

Table 1. Comparison of general data of patients between two groups after propensity score-matching (n = 43)

Indicator	All		*p* value	After propensity score matching		*p* value
	Sitagliptin group (n = 61)	Control group (n = 154)		Sitagliptin group (n = 43)	Control group (n = 43)	
Age (Year, $\bar{x} \pm s$)	54 ± 9	51 ± 11	0.014	53 ± 8	53 ± 11	0.991
Gender (male/female)	32/29	67/87	0.235	20/23	22/21	0.666
BMI (kg/m^2, $\bar{x} \pm s$)	24.7 ± 3.3	23.5 ± 2.1	0.011	23.9 ± 2.9	24.0 ± 2.2	0.752
Diabetes progress (Year, $\bar{x} \pm s$)			0.533			0.468#
< 1 Year	1 (1.6%)	3 (1.9%)		0 (0%)	1 (2.3%)	
1-5 Years	5 (8.2%)	21 (13.6%)		4 (9.3%)	6 (14.0%)	
> 5 Years	55 (90.2%)	124 (84.4%)		39 (90.7%)	36 (83.7%)	
Liver Child-Pugh grading			0.100			0.826
Grade A	40 (65.6%)	82 (53.2%)		26 (60.5%)	25 (58.1%)	
Grade B	21 (34.4%)	124 (84.4%)		17 (39.5%)	18 (41.9%)	
Anti-viral treatment	49 (80.3%)	124 (81.6%)	0.833	36 (83.7%)	34 (79.1%)	0.579
Hypertension history (n, %)	40 (65.6%)	97 (63.0%)	0.755	30 (69.8%)	28 (65.1%)	0.645
Hypotensor						
β receptor blocker (n, %)	15 (24.6%)	43 (27.9%)	0.620	12 (27.9%)	11 (25.6%)	0.808
ACEI drugs (n, %)	26 (42.6%)	65 (42.2%)	0.956	19 (44.2%)	19 (44.2%)	1.000
ARBs drugs (n, %)	9 (14.8%)	15 (9.7%)	0.293	6 (14.0%)	3 (7.0%)	0.483#
CCB drugs (n, %)	16 (26.2%)	37 (24.0%)	0.735	13 (30.2%)	8 (18.6%)	0.209
Diuresis drugs (n, %)	7 (11.5%)	13 (8.4%)	0.490	4 (9.3%)	3 (7.0%)	0.693#
Insulin dosage (IU, $\bar{x} \pm s$)	29 ± 4	30 ± 5	0.110	30 ± 4	30 ± 4	0.527
Insulin project (n, %)			0.481			0.499
Insulin aspart 30 injections	32 (52.5%)	73 (47.4%)		25 (58.1%)	20 (46.5%)	
Protamine zinc reconstitution lispro 25 injections	8 (13.1%)	31 (20.1%)		5 (11.6%)	8 (18.6%)	
Spart insulin combined with glargine insulin	21 (34.4%)	50 (32.5%)		13 (30.2%)	15 (34.9%)	
OADs (n, %)						
Null	8 (13.1%)	23 (14.9%)	0.732	4 (9.3%)	8 (18.6%)	0.351#
Metformin	48 (78.7%)	116 (75.3%)	0.601	35 (81.4%)	29 (67.4%)	0.138
Acarbose	1 (1.6%)	2 (1.3%)	1#	0	0	
Metformin and acarbose	5 (8.2%)	13 (8.4%)	0.953	5 (11.6%)	6 (14.0%)	0.747
Others	0	0		0	0	
HbA1c (%, $\bar{x} \pm s$)	8.4 ± 1.0	8.7 ± 0.9	0.099	8.6 ± 1.0	8.7 ± 1.0	0.584
ALT (U/L, $\bar{x} \pm s$)	122 ± 14	121 ± 15	0.394	121 ± 15	120 ± 15	0.814
AST (U/L, $\bar{x} \pm s$)	91 ± 13	92 ± 12	0.514	92 ± 13	90 ± 14	0.654
TBil (umol/L, $\bar{x} \pm s$)	66 ± 11	77 ± 13	< 0.001	69 ± 10	70 ± 10	0.863
Propensity score ($\bar{x} \pm s$)	0.47 ± 0.25	0.21 ± 0.16	< 0.001	0.34 ± 0.17	0.34 ± 0.17	0.915

#: Fisher's exact probability; BMI = body mass index; ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; OAD = oral antidiabetic drug; HbA1c = glycated hemoglobin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBil = total bilirubin.

limit, administration of sitagliptin was initiated. Insulin was injected subcutaneously with an initial dose of 0.5 U/kg with the following 3 regimens: (1) 30 IU injections of insulin aspart, subcutaneously injected before breakfast and dinner; (2) 25 IU injections of reconstituted protamine zinc recombinant human insulin lispro, subcutaneously injected before breakfast and dinner; and (3) an injection of insulin aspart combined with insulin glargine, subcutaneously injected before bedtime.

Blood glucose adjustments were made at the outpatient or post-hospital admission when fasting plasma glucose (FPG) levels were > 7.0 mmol/L, 2-h postprandial plasma glucose (PPG) levels were > 11.1 mmol/L, and HbA1c was > 7.0%. Patients could adjust levels by 2 U insulin according to blood glucose monitoring every 3 days. Insulin was reduced when (1) FPG levels were < 4.4 mmol/L and 2-h PPG levels were < 5.5 mmol/L or (2) doctors believed that there was a risk of hypoglycemia.

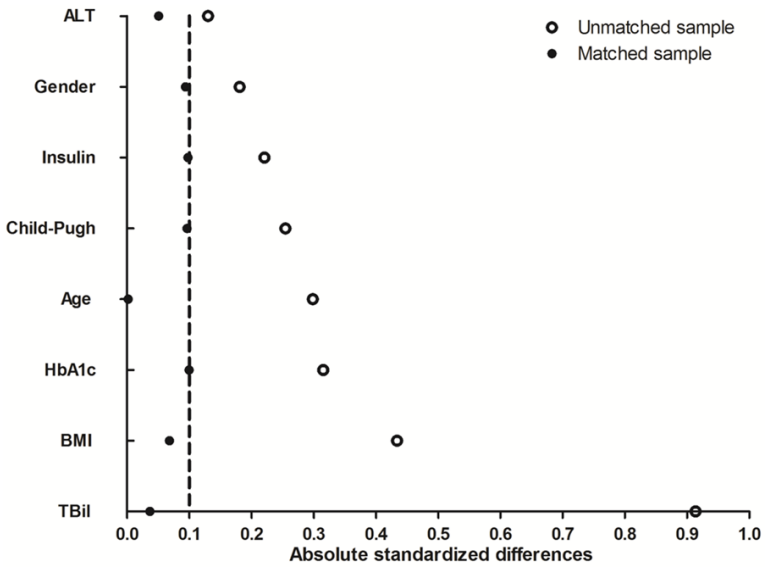

Figure 2. Absolute standardized differences in independent variables before and after matching between sitagliptin and control groups.

The following data were collected: 1. General information: age; gender; body mass index (BMI); diabetes history; hypertension history; insulin dose; history of receiving antihypertension drugs, including beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics, including the history of receiving OADs, such as metformin and acarbose tablets. 2. Observation indicators: (1) Main observation indicators, including HbA1c difference values before and after treatment at week 12 (HbA1cΔ = HbA1c value at week 12-baseline value before treatment) [15]; and (2) Secondary observation indicators, including differences in insulin dose, BMI, ALT, AST, and TBil before and after treatment at week 12 (Δ = value at week 12 after treatment - baseline value before treatment). It also included the BGC target control rate, HbAlc ≤7% [15], and adverse events such as hypoglycemia, with criteria based on blood glucose levels (< 3.9 mmol/L) and at least two of progress records, nursing records, and discharge summaries [15]. Finally, the liver function index at week 12 based on ALT, AST, and TBil levels was recoreded.

Statistical analysis

Propensity score-matching was used to reduce bias, which is a commonly used method to control for confounding factors in retrospective research [16]. P < 0.5 was used to indicate independent variables in the general data of the patients. Depending on whether sitagliptin was administered or not, patients were divided into two groups and propensity scores of each patient were calculated. The caliper was set to 0.1, and matched patients with similar propensity scores were selected according to the ratio of 1:1. Standardization differences of independent variables were calculated to detect matching results. All data were analyzed using SPSS 18.0 statistical software. Measurement data are expressed as mean ± standard deviation ($\overline{\chi}$ ± s), comparison was conducted using the t-test (normal distribution) and nonparametric Mann-Whitney U test (non-normal Distribution). Enumeration data were compared using the χ^2 test or Fisher's exact probability, with $p < 0.05$ representing statistical significance.

Results

Comparison of general patient data

A total of 215 patients were enrolled in the study, of which 61 received sitagliptin and 154 were not (**Figure 1**). The inclusion matching indicators between the two groups included: gender, age, insulin dosage, BMI, HbA1c value, TBil value, ALT value, and Child-Pugh grade. After the propensity score-matching, there were 86 cases in total and 43 patients in each group. Comparison of general patient data before and after matching is presented in **Table 1**. Compared with those in the control group, the age and BMI were higher before matching in the X group, and the B grade was lower in Child-Pugh grading, and the insulin dose, HbA1c value, and TBil value were lower ($p < 0.05$). After matching, there were no significant differences in the general data between the two groups ($p > 0.05$, **Table 1**), and the standard deviation of the matching propensity scores was < 0.1, indicating that the matching results were adequate (**Figure 2**).

Comparison of the treatment effect and liver function index

Comparison of the treatment effect and liver function index before and after treatment in the

Table 2. Comparison of clinical observations before and after treatment in two groups after propensity score-matching (n = 43)

Clinical observation indicator	Sitagliptin group		*P* value	Control group		*P* value
	Prior treatment	12 week post treatment		Prior treatment	12 week post treatment	
HbA1c (%, $\bar{x} \pm s$)	8.6 ± 1.0	7.8 ± 1.2	0.002	8.7 ± 1.0	8.4 ± 1.1	0.189
Insulin dose (IU, $\bar{x} \pm s$)	30 ± 4	28 ± 4	0.041	30 ± 4	28 ± 5	0.223
BMI (kg/m^2, $\bar{x} \pm s$)	24 ± 3	23 ± 3	0.252	24.0 ± 2.2	23.4 ± 2.2	0.187
ALT (U/L, $\bar{x} \pm s$)	121 ± 15	59 ± 6	< 0.001	120 ± 15	58 ± 6	< 0.001
AST (U/L, $\bar{x} \pm s$)	92 ± 13	54 ± 13	< 0.001	90 ± 14	53 ± 13	< 0.001
TBil (umol/L, $\bar{x} \pm s$)	69 ± 10	33 ± 11	< 0.001	70 ± 10	31 ± 8	< 0.001

HbA1c = glycated hemoglobin; BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBil = total bilirubin.

Table 3. Comparison of clinical observations and adverse events between the two groups after propensity score-matching (n = 43)

Outcome indicator	Control group	Sitagliptin group	*p* value
HbA1cΔ, %, *M (QR)*	0.5 (0.2 to 0.7)	0.2 (0.1 to 0.3)	0.031
Insulin doseΔ (IU, $\bar{x} \pm s$)	2.1 ± 0.6	1.5 ± 0.9	0.001
BMIΔ (kg/m^2, $\bar{x} \pm s$)	0.32 ± 0.10	0.30 ± 0.09	0.365
ALTΔ (U/L, $\bar{x} \pm s$)	62 ± 9	62 ± 9	0.981
ASTΔ (U/L, $\bar{x} \pm s$)	37 ± 4	38 ± 5	0.828
TBilΔ (umol/L, $\bar{x} \pm s$)	29 ± 8	30 ± 7	0.246
Glucose-target-rate (n, %)	10 (23.3%)	4 (9.3%)	0.142#
Hypoglycemia rate (n, %)	2 (4.7%)	5 (11.6%)	0.237#
Nausea (n, %)	1 (2.3%)	0 (0%)	1.000#
Dizziness (n, %)	3 (7.0%)	1 (2.3%)	0.616#
Rash	2 (4.7%)	3 (7.0%)	1.000#

#: Fisher's exact probability; Δ = Difference before and after treatment; HbA1c = glycated hemoglobin; BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBil = total bilirubin.

two groups after propensity score-matching is shown in **Table 2**. Compared with the status before treatment, the blood ALT, AST, and TBil values decreased significantly at week 12 after treatment, and the HbA1c value and insulin dose at week 12 in the sitagliptin group decreased significantly ($p < 0.05$), but there were no obvious significant differences in the control group ($p > 0.05$). There was no significant change in BMI before and after treatment in the two groups (both $p > 0.05$).

Comparison of the treatment effect, liver function index, and adverse events

Comparison of the treatment effect, liver function index, and adverse events between the two groups after propensity score-matching is shown in **Table 3**. Compared with those in the control group, HbA1c values and insulin doses decreased significantly at week 12 in the sitagliptin group ($p < 0.05$), but there was no difference in target glucose levels including hypoglycemia rate, ΔBMI, Δblood ALT levels, ΔAST levels, and ΔTBil levels between the two groups. There were also no statistically significant differences in adverse events such as nausea, dizziness, and rash between the two groups.

Discussion

Sitagliptin is a commonly administered DPP-4 inhibitor in recent years. The results of this study show that compared with patients who do not receive sitagliptin, 12 weeks later, HbA1c levels and insulin doses significantly decreased after the administration of sitagliptin. HbA1c levels and insulin doses decreased more significantly at week 12. Regardless of whether sitagliptin was administered, liver function indicators such as blood ALT, blood AST, and TBil values significantly decreased following antiviral and hepatoprotective treatments, and there was no significant difference in liver function index values between the two groups. These results were consistent with the results of previously conducted similar studies [17]. A meta-analysis found that patients treated with vildagliptin for 12 to 104 weeks were not associated with

increased risks of severe increases in liver enzymes or adverse events in the liver.

DPP-4 plays a key role in the development of various chronic liver diseases, while DPP-4 inhibition appears to be beneficial for chronic liver disease [18]. Sitagliptin inhibits DPP-4 to hydrolyze endogenous glucagon-like peptides (GLPs), thereby increasing the plasma concentration of the activated form of GLP-1, optimizing the glucose fluctuations of basal insulin after titration, which regulates blood glucose with glucose dependence. After food intake, carbohydrates, fats, and other substances stimulate the release of GLP-1 and glucose-dependent insulin-releasing peptides from the intestine to increase insulin secretion. A proportion of 50% to 70% of postprandial insulin requires GLP-1 to stimulate insulin secretion. In addition, GLP-1 reduces glucagon secretion, resulting in reduced glucose production, and inhibition of gastric and duodenal motility. Delayed gastric emptying, increased satiety, and inhibition of pancreatic alpha cells to secrete glucagon, thus improves insulin resistance [19], lowering blood sugar levels and hypoglycemia incidence without leading to the risk of weight gain [20].

A recent article on the use of exenatide or liraglutide to improve liver lipopexia in patients has been published. The main finding of this study was that the administration of exenatide or liraglutide in patients who are obese can reduce the development of type 2 diabetes by 42%. It was associated with glucose improvement levels, but this was not associated with weight loss. This study did not show that sitagliptin had an advantage in patients with type 2 diabetes mellitus and chronic hepatitis B. This may be related to the fact that BMI is within the normal range in Chinese individuals, thereby weakening its weight protection effect. The blood ALT, blood AST, and TBil values in both groups were significantly decreased, and the decreasing range was more than 50% on average. There were no statistically significant differences in liver function decreasing values between the two groups, indicating that liver function is more susceptible to antiviral and hepatoprotective drugs. Sitagliptin is mainly metabolized by the kidneys, and about 80% is excreted through the urine as it is administered [21]. There is no need to adjust the dose of sitagliptin for patients with mild or moderate hepatic impairments [22]. This study found that sitagliptin did not increase adverse events such as nausea, dizziness, and rash, but it should be noted that when liver function indicators ALT, AST, and TBil decrease by 2 times the normal value limit, sitagliptin administration should be initiated. The lack of combined treatment in patients with type 2 diabetes mellitus was associated with liver damage data for DPP-4 inhibitors or GLP-1 receptor agonists. There were no statistically significant differences in the incidence of hypoglycemia between the two groups, and hypoglycemia occurred less frequently in the sitagliptin group than that in the control group (4.7% vs. 11.6%, respectively), which is a similar result in most studies [23, 24]. It shows that sitagliptin is well tolerated and safe. However, Vilsbboll et al. reported that compared to insulin alone, sitagliptin combined with insulin treatment increased the incidence of hypoglycemia (16% vs. 8%) [25].

This study has some limitations. First, because there were no clear and strict indications for the administration of sitagliptin, the administration of sitagliptin was determined by an endocrinologist. Second, although bias was minimized using strict exclusion criteria and propensity score adjustments, potential bias factors may not be eliminated completely in retrospective studies. Finally, demographic characteristics and liver function protection strategies of each institution are different, therefore our clinical findings should be interpreted carefully.

In summary, for patients with type 2 diabetes and chronic hepatitis B, insulin and sitagliptin can effectively control blood glucose levels and reduce insulin dosages without further impairing liver function in combination with antiviral and hepatoprotective drugs that stabilize liver function, which provide a new option for these patients.

Disclosure of conflict of interest

None.

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