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Efficacy and safety of ligliptin in treatment of fragile diabetes mellitus complicated with early diabetic nephropathy

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Abstract

At present, the treatment approaches for patients with diabetes and early nephropathy are still mainly based on insulin. Drugs with lower renal excretion rate such as repaglinide and acarbose were commonly applied control the continued loss of urinary protein. However, the current treatment effect of patients with brittle diabetes complicated with early kidney disease is still unsatisfactory. Therefore, it is urgently required to control blood glucose smoothly and delay the progression. Eighty patients with brittle diabetes mellitus complicated with early diabetic nephropathy were randomly assigned into treatment group and control group. Apart from insulin and benazepril, the treatment group took oral linagliptin and control group took oral placebo for 12 weeks followed by analysis of the fasting blood glucose (FPG), postprandial 2h blood glucose (2hPBG), glycosylated hemoglobin (HbA1C), blood lipid level, urinary albumin excretion rate (UAER), and Cystatin C (Cys C). Meanwhile, the serum C-reactive protein (CRP), IL-6, IL-10, and TNF-α levels before and after treatment were determined by ELISA. There were no significant differences in FPG, 2hPBG, HbA1C, UAER, Cys C, CRP, and IL-6 levels before treatment ($P > 0.05$), but they were significantly decreased after treatment ($P < 0.05$). IL-10 and TNF-α showed no difference before or after treatment between two groups ($P > 0.05$). IL-10 was increased and TNF-α was reduced after treatment ($P < 0.05$). There were 8 patients with adverse reactions in treatment group (20%) and 7 cases in control group (17.5%) ($P > 0.05$). Linagliptin can effectively control the blood glucose level of patients with brittle diabetes complicated with early diabetic nephropathy and improve the UAER by reducing inflammatory response.

Keywords: linagliptin, brittle diabetes, diabetic nephropathy, efficacy, safety

Introduction

According to statistics, the number of diabetic patients worldwide reached 250 million in 2010 and incidence is still increasing. The number of patients with brittle diabetes is also significantly increased [1, 2]. Brittle diabetes is characterized as being prone to hypoglycemia and ketoacidosis. It is suffered from fluctuate blood glucose and easy to develop diabetic microvascular complications in a short time [3, 4]. Diabetic nephropathy (DN) is a common microvascular complication.

Dipeptidyl peptidase 4 (DPP-4) inhibitor is a newly oral hypoglycemic agent based on incretin [5]. It can reduce glucagon-like peptide-1 in vivo by inhibiting DPP-4, thereby increasing endogenous GLP-1 level, enhancing insulin secretion, restraining glucagon secretion, and thereby controlling blood glucose [6]. In China, DPP-4 inhibitor has become one of the second-line selection for hypoglycemic treatment of patients with type 2 diabetes [7]. It was found that DPP-4 inhibitors not only block the promotion of hyperglycemia on diabetic nephropathy by lowering blood glucose levels, but also has a protective effect on renal function in GLP-1 independent manner. Therefore, DPP-4 inhibitor is of great significance in the treatment of diabetes and DN [8].

At present, a number of studies confirmed that DPP-4 inhibitor has protective effects on DN, stabilizing blood glucose, reducing blood glucose fluctuations and hypoglycemia, and improving weight and protecting pancreatic function. However, its role in brittle diabetes with early nephropathy is still unclear because of the islet function and the

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earlier appeared complications. Our study aims to investigate DPP-4 inhibitor's role in brittle diabetes with early nephropathy.

Materials and methods

General information

Eighty patients with brittle diabetes mellitus and early diabetic nephropathy admitted to our hospital from January 2015 to December 2016 were enrolled, including 48 males and 32 females (average age: 50.67±10.28) years. The inclusion criteria were based on the American Diabetes Association (ADA) and Practical Endocrinology and the 2nd edition of diagnostic criteria for brittle diabetes. No patients suffered from heart failure, hypertension, or primary renal disease. Blood urea (BUN) and creatinine (SCr) levels were in the normal range. All cases met the diagnostic criteria of the 2006 WHO early diabetic nephropathy as UAER at 20-200 μg/min or 30-300 mg/24h. Acute complications of diabetes such as ketoacidosis and hyperosmolar coma, heart disease, renal failure, malignant or cachexia, long-term use of glucocorticoids, and recent use of ACEI or ARB and other drugs affecting urinary UAER were excluded. Patients were equally assigned into treatment group and control group by double-blind method. 23 males and 17 females were in treatment group with an average age of (49.83±10.57) years, systolic blood pressure (SBP) of (120.37±6.51) mmHg, diastolic blood pressure (DBP) of (74.08±5.47) mmHg, body mass index (MBI) of (24.13±1.58) Kg/m^2, and the duration of diabetes of (8.37±2.52) years. The control group contained 25 males and 15 females (average age: 51.03±10.72 years old), SBP of (121.16±6.73) mmHg, DBP of (73.82±5.88) mmHg, MBI of (24.39±1.76) Kg/m^2, and the duration of diabetes of (8.91±2.74) years. There were no differences of basic information between two groups ($P > 0.05$). The study was approved by the Ethics Committee of our hospital and informed consent was obtained.

Methods

All patients admitted to the hospital were stopped from the original hypoglycemic regimen and changed to insulin (recombinant glargine combined with aspartic insulin) to control blood glucose, benazepril to improve renal arterial pressure, together with strictly controlling diet and appropriate exercise. After blood glucose was stabilized, the treatment group received oral 5 mg linagliptin (Shanghai Boehringer Ingelheim Pharmaceutical Co., Ltd., batch number 462469H) once a day, and the control group took oral placebo for 12 weeks.

Adverse reaction observation

Adverse reactions were recorded during treatment, especially hypoglycemia.

Statistical analysis

SPSS 13.0 software analyzed data and the measurement data were displayed as mean ± standard deviation and assessed by t test. The enumeration data were shown as the number or percentage and compared by chi-square test. $P < 0.05$ indicates a significance.

Results

Comparison of blood glucose control effects

No differences in FPG and 2hPBG were found between two groups ($P > 0.05$), but they were significantly decreased after treatment ($P < 0.05$) with more reduction in treatment group ($P < 0.05$) (Table 1).

Comparison of biochemical indicators

HbA1C showed no difference before treatment ($P > 0.05$), but reduced after treatment ($P < 0.05$) with more decrease in treatment group ($P < 0.05$). TC, LDL-C, and TG levels showed no differences after treatment (Table 2).

Comparison of renal function

The UAER and Cys-C levels in two groups were similar before treatment ($P > 0.05$) and decreased after treatment ($P < 0.05$) with more reduction for treatment group ($P<0.05$) (Table 3).

Comparison of inflammatory cytokines

No differences in UAER, CRP, and IL-6 were observed between two groups before treatment ($P > 0.05$), which were declined significantly after treatment ($P < 0.05$) with more reduction for treatment group ($P < 0.05$). There was no difference of IL-10 and TNF-α before treatment ($P > 0.05$). After treatment, IL-10 was significantly increased, while TNF-α was reduced ($P < 0.05$) (Table 4).

Adverse reaction analysis

A total of 8 patients in treatment group exhibited adverse reactions (20%) and 7 cases in control group suffered from adverse reactions (17.5%) ($P > 0.05$) (Table 5).

Discussion

In recent years, the incidence of diabetes in the world keeps increasing year by year. Persistent high blood glucose often leads to several serious complications, such as cardiovascular disease and nerves systematic and renal damage, etc [9-12]. Therefore, the prevention and treatment of

diabetes and its chronic complications is a major public health problem worldwide. At present, patients with diabetes and early-stage nephropathy are still treated with insulin. Drugs which lower renal excretion rate such as repaglinide and acarbose are commonly selected through ACEI/ARB to control renal arterial pressure, so as to control the continued loss of urinary protein [1, 13]. Brittle diabetes, also known as "unstable diabetes", is a type of diabetes that is difficult to control blood glucose. The condition is extremely unstable, and blood glucose fluctuations are large, which is prone to develop several complications such as hypoglycemia and ketoacidosis [4]. Therefore, it is of great significance to seek a new type of effective hypoglycemic agent while improving the prognosis of diabetic nephropathy.

Linagliptin is a novel DPP-4 inhibitor that competitively inhibits DPP-4. GLP-1 can induce insulin release, thereby effectively controlling blood glucose but not increasing the incidence of hypoglycemia [14, 15]. The advantage is that it is mainly excreted by feces and does not impair kidney function. It is not necessary to adjust the dosage for diabetic patients with impaired renal function [16]. Current research confirms that linagliptin has a potential therapeutic effect on diabetic nephropathy. Takashima S *et al*. [17] showed that linagliptin can delay the progression of diabetic nephropathy. The rat model of diabetes prepared by Kanasaki *et al.* [18] demonstrated that linagliptin can decrease oxidative stress in kidney and effectively improve the pathological changes of extracellular matrix aggregation and glomerular basement membrane thickening. However, the clinical effect of linagliptin on brittle diabetes complicated with early diabetic nephropathy is still not fully understood.

It was found that DPP-4 inhibitors have a good therapeutic effect on brittle diabetes [19]. Luo *et al.* [20] found that sitagliptin can effectively control blood glucose levels and blood glucose fluctuations in brittle diabetes. They believed that the mechanism may be that sitagliptin can reduce glucose secretion. Our study observed decreased FPG and 2hPBG after treatment with more reduction for treatment group, indicating that linagliptin showed better effect in controlling blood glucose level in brittle diabetes compared with traditional insulin therapy. The biochemical indicators in this study exhibited that linagliptin had little effect on the blood lipid index, but it could improve the glycated hemoglobin level. UAER and Cys C are important diagnostic indicators for early diabetic nephropathy [21]. This study examined the effects of two treatments on UAER. It was revealed no significant difference before treatment. It was significantly declined after treatment with more decrease for treatment group, suggesting that linagliptin has a better effect on early diabetic nephropathy. It was considered that the pathogenesis of DN is closely related to inflammatory response and renal fibrosis [22]. CRP is one of the indicators reflecting the acute and chronic inflammatory response. Serum CRP level in DN is higher than the normal population with severity dependent [23]. IL-6, IL-10, and TNF-α are closely related to inflammatory response [24]. Our results found that CRP and IL-6 had no difference before treatment. They were significantly decreased after treatment. There was no statistical difference of IL-10 and TNF-α before treatment. IL-10 was significantly increased, while TNF-α was reduced in the treatment group. It was indicated that linagliptin can effectively improve the inflammatory response in patients with brittle diabetes complicated with early diabetic nephropathy. In addition, we found that linagliptin did not increase adverse reactions. However, due to a small number of patients in our study, which is a main limitation, more patients are required to confirm the findings.

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Disclosure of conflict of interest

None.

Conclusion

Linagliptin can effectively control the blood glucose level of patients with brittle diabetes complicated with early diabetic nephropathy, and improve the UAER by reducing the inflammatory response, indicating that it might be a novel approach for the treatment of brittle diabetes with early diabetic nephropathy

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Table legends

Table 1. **Comparison of blood glucose control effects between the two groups.**

	Time	FPG (mmol/L)	2hPBG (mmol/L)
Treatment group	Before treatment	8.24±0.83	16.24±3.08
	After treatment	6.15±0.62[ab]	7.73±1.28[ab]
Control	Before treatment	8.07±0.91	16.51±3.25
	After treatment	6.79±0.68[a]	11.06±1.79[a]

a $P < 0.05$, compared with before treatment; b $P < 0.05$, compared with control.

Table 2. **Comparison of biochemical indicators before and after treatment between the two groups.**

	Time	HbA1C (%)	TC (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)
Treatment group	Before treatment	8.19±0.46	6.83±2.12	4.57±1.43	3.36±1.17
	After treatment	6.65±0.31[ab]	6.47±1.84	4.41±1.26	3.25±1.03
Control	Before treatment	8.07±0.41	6.91±2.17	4.52±1.38	3.42±1.11
	After treatment	7.14±0.38[a]	6.56±2.03	4.39±1.17	3.30±0.99

a $P < 0.05$, compared with before treatment; b $P < 0.05$, compared with control.

Table 3. **Comparison of renal function before and after treatment between the two groups.**

	Time	UAER (ug/min)	Cys-C (mg/L)
Treatment group	Before treatment	724.61±231.38	2.43±0.31
	After treatment	501.44±182.72[ab]	1.71±0.16[ab]
Control	Before treatment	739.43±217.85	2.51±0.29
	After treatment	598.74±165.29[a]	2.03±0.20[a]

a $P < 0.05$, compared with before treatment; b $P < 0.05$, compared with control.

Table 4. **Comparison of inflammatory cytokines before and after treatment between the two groups.**

	Time	CRP (mg/L)	IL-6 (ng/L)	IL-10 (ng/L)	TNF-α (ng/L)
Treatment group	Before treatment	15.34±2.52	10.13±2.94	9.38±1.42	8.14±0.93
	After treatment	10.08±2.14[ab]	6.37±1.69[ab]	11.56±1.81[ab]	6.72±0.87[ab]
Control	Before treatment	14.96±2.73	9.91±2.75	9.47±1.26	7.91±0.82
	After treatment	12.85±2.09[a]	8.24±1.83[a]	9.68±1.35	7.85±0.88

a $P < 0.05$, compared with before treatment; b $P < 0.05$, compared with control.

Table 5. **Adverse reaction analysis.**

	Gastrointestinal adverse reactions (n, %)	Infection (n, %)	Hypoglycemia (n, %)	Total adverse reaction (n, %)
Treatment group	4(10.00)	3(7.50)	1(2.50)	8(20.00)
Control	3(7.50)	3(7.50)	1(2.50)	7(17.50)
χ^2	0.082			
P	0.775			