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Original Article

Liraglutide combined with routine therapy improves renal function, renal fibrosis, immune status, and prognosis of type 2 diabetes patients

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Abstract: Objective: To investigate the effect of Liraglutide in conjunction with routine therapy on renal function, renal fibrosis, immune status, and prognosis in patients with diabetes mellitus. Methods: The clinical data of patients with Type 2 diabetes mellitus (T2DM) treated at the First Affiliated Hospital of Jishou University from March 2021 to March 2022 were retrospectively analyzed. Patients were assigned into a control group (n=42) and a study group (n=42) according to their treatment regimen. The control group received routine treatment, and the study group received Liraglutide in addition to routine treatment. The therapeutic effects, blood glucose levels, renal function, renal fibrosis, and Immunoglobulin (Ig) levels as well as the incidence of adverse reactions, were compared between the two groups. Results: The effective rate was higher in study group (97.62%) than that of the control group (78.57%) (P<0.05). After treatment, the fasting blood-glucose (FBG), 2-hour postprandial plasma glucose (2hPG), and glycosylated hemoglobin (HbA1c) levels were decreased; and the study group displayed a significantly lower blood glucose level than the control group (all P<0.05). Also, the serum creatinine (Scr), blood urea nitrogen (BUN), and 24-hour urinary protein quantification (24h-UPor) were decreased after treatment; and the study group showed more pronounced improvement in renal function index than did the control group (all P<0.05). The levels of IgA, IgM, and IgG were increased after treatment compared to pre-treatment; and the study group exhibited significantly better improvement than the control group (all P<0.05). However, the study group reported a notably higher incidence of adverse reactions than the control group (19.05% vs 2.38%; P<0.05). Conclusion: Liraglutide combined with routine therapy is effective in treating patients with diabetes, which can effectively reduce the levels of blood glucose andurinary protein, and the degree of renal fibrosis, while improving renal and immune functions and the clinical prognosis of diabetic patients.

Keywords: Liraglutide, diabetes mellitus, renal function, renal fibrosis

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease mainly characterized by insulin resistance (IR) and pancreatic islet secretion dysfunction caused by a combination of environmental and genetic factors, resulting in compromised glucose metabolism and elevated blood sugar. As a result, T2DM manifests as a series of metabolic disorders affecting sugar, fat, and protein. Long-term persistent chronic hyperglycemia can damage both large blood vessels and micro-vessels, as well as various tissues and organs of the body, adversely affecting the physical and mental health and overall life quality of patients, and in severe cases, it may be life-threatening [1, 2]. According to International Diabetes Federation, the global prevalence of T2DM has increased significantly, from 151 million people in 2000 to 415 million in 2015 [3]. China has also seen a surge in T2DM prevalence in recent years, from 5.5% in 2001 to 10.9% in 2013 [4]. With approximately 110 million individuals affected, China now has the highest number of T2DM patients worldwide [5]. In view of this situation, the prevention and treatment of T2DM has become a vital public health issue in China.

Effective blood sugar control is crucial for treating T2DM [6, 7]. Traditional hypoglycemic drugs primarily reduce blood sugar levels; however,

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certain medications, such as sulfonylureas, thiazolidinediones (TZD) and insulin, can lead to weight gain, thus aggravating insulin resistance, leading to a vicious circle and increasing the risk of various complications of obese T2DM, especially major cardiovascular adverse events (MACE) [8]. Glucagon-like peptide-1 receptor agonist (GLP-1RA), as a new hypoglycemic drug, has emerged to address these issues [9, 10]. GLP-1RA can stimulate insulin secretion in a glucose-dependent manner, inhibit glucagon secretion, reduce endogenous glucose production, improve nerve conduction function, delay gastric emptying, enhance islet β-cell function and insulin sensitivity, and provide cardiovascular and renal protective effects. It also has a low incidence of hypoglycemia, making it more suitable for patients with abdominal obesity and IR, thus becoming a preferred option for managing T2DM [11-13]. In China, liraglutide is widely used as a long-acting GLP-1RA medication [14]. It shares 97% amino acid sequence homology with natural glucagon-like peptide-1 (GLP-1), enhancing its binding to plasma albumin and extending its half-life through modifications to the native GLP-1 structure. The half-life of liraglutide ranges from 11 to 13 hours [15]. The initial dose of liraglutide is 0.6 mg administered subcutaneously once daily, which can be increased to 1.2 mg after at least one week, and further to 1.8 mg once daily based on clinical assessment [16]. Studies have confirmed that liraglutide not only lowers blood sugar but also regulates blood lipids, reduces body weight, waist circumference, visceral fat and IR, lowers the risk of hypoglycemia, decreases the incidence of diabetic complications, and reduces the risk of MACE [17, 18].

At present, there is limited research on the effects of Liraglutide combined with conventional therapy on renal function, renal fibrosis, immune status and prognosis in patients with diabetes, resulting in the lack of theoretical basis for the promotion and application of this treatment regimen. Thus, it is essential to conduct further research to better demonstrate its therapeutic efficacy and safety, thereby optimizing treatment options for patients. This study aims to analyze the clinical implication of Liraglutide to provide an evidence-based foundation for its use.

Methods

General information

The clinical data of the patients with T2DM treated in the First Affiliated Hospital of Jishou University from March 2021 to March 2022 were retrospectively analyzed. Patients were assigned into a control group (n=42) and a study group (n=42) according to their treatment regimen. The control group received routine treatment, while the study group received additional Liraglutide added to routine treatment. This study was approved by the Ethics Committee of the First Affiliated Hospital of Jishou University.

Inclusion criteria: 1) Patients meeting the diagnostic criteria for type 2 diabetes [19]; 2) Patients aged ≥ 18 years old; 3) No use of slimming drugs or systemic glucocorticoids within the last two months; 4) Patients were conscious with stable vital signs; 5) Available and complete clinical files.

Exclusion criteria: 1) Patients with type 1 diabetes or secondary diabetes; 2) Pregnant or lactating patients; 3) Presence of severe kidney, liver, or heart problems; 4) Patients with other endocrine diseases; 5) Patients with congenital immune deficiency; 6) Patients with severe mental illness and cognitive impairment; 7) Patients who had undergone major surgical operations in the past three months; 8) Patients with incomplete clinical files.

Treatment methods

Upon hospital admission, patients received comprehensive education on diabetes management from the nursing staff. All patients were prescribed metformin tablets (Sino-American Shanghai Squibb Pharmaceutical Co., Ltd., H20023370, 0.5 g*20 tablets) at a dosage of 0.5 g/time, 3 times/day. Based on conventional treatment, the patients in study group received an intravenous injection of liraglutide (sub-packaged by Novo Nordisk (China) Pharmaceutical Co., Ltd., approved by the National Medicines J20160037, 3 ml: 18 mg). The initial dose was 0.6 mg, which was increased to 1.2 mg after one week and maintained until the end of the test period. If the blood sugar was below 3.9 mmol/L, the dose was reduced to 0.6 mg and could be raised

back to 1.2 mg after one week if necessary. Both groups were treated for 2 months continuously.

Observation index

The primary outcome was the therapeutic effect, and secondary outcomes included the change in blood glucose, renal function, and blood biochemical indexes.

(1) Therapeutic Effect. Patients were evaluated for efficacy two months after treatment using the following evaluation criteria: Markedly effective: the clinical symptoms and signs basically disappeared, the 24-hour urinary protein was below 0.5 g or reduced by more than 2-3 times, and the blood glucose and renal function indices improved by more than 30%. Effective: 10% to 30% improvement in aforementioned indices due to reduction in clinical symptoms and signs. Ineffective: no improvement in symptoms or signs, with less than 10% improvement or worsening of indexes. Total effective rate = (number of markedly effective cases + effective cases)/total number of cases × 100%. (2) Blood Glucose Control. The levels of FBG, 2hPG, and HbA1c were compared between the two groups before and two months after treatment. (3) Renal Function. The levels of serum creatinine (Scr), blood urea nitrogen (BUN), and 24-hour urinary protein quantification (24hUPor) were compared between the two groups before treatment and 2 months after treatment. (4) Renal Fibrosis Index. The levels of serum laminin (LN), serum procollagen III (PC-III) and collagen IV (Col-IV) were measured by automatic biochemical analyzer before and 2 months after treatment. (5) Immune Function. The serum levels of IgA, IgM, and IgG was determined using enzyme-linked immunosorbent assay (ELISA) method before and 2 months after treatment. (6) Adverse Reactions. The common adverse reactions including diarrhea, indigestion, constipation, nausea and vomiting during the treatment were compared between the two groups. The incidence of adverse reactions = the total number of adverse reactions/the total number of cases × 100%.

Statistical analysis

SPSS19.0 was used for the data analysis. Measured data with a normal distribution and uniform variance were expressed as ($\bar{x}$±s). A paired sample t-test was used for intragroup comparisons, while an independent sample t-test was used for intergroup comparisons. The counted data were presented as [n (%)], and the comparison between groups was made by χ^2 test. A significant difference was determined at $P<0.05$.

Results

General information of the patients

There were 27 male and 15 female patients in the control group; the age ranged between 56 and 77 years old, with a mean age of (67.41±5.18) years; the BMI ranged from 17.70 to 27.79 kg/m^2, with an average of (23.36±2.25) kg/m^2. The course of disease ranged from 0.2 to 20.4 years, with an average of (8.15±3.71) years. In the study group, there were 25 male and 17 female patients; the age ranged between 55 and 78 years old, with an average age of (66.78±5.21) years. BMI ranged from 17.66 to 27.72 kg/m^2, with an average of (23.41±2.27) kg/m^2; the course of the disease ranged from 0.3 to 20.1 years, with an average of (8.06±7.92) years. There was no significant difference in general data between the two groups (all $P>0.05$, **Table 1**).

Comparison of therapeutic effects between the two groups

In the study group, the treatment was markedly effective for 25 patients, effective for 16 patients, and ineffective for 1 patient, resulting in an effective rate of 97.62%. In the control group, the treatment was markedly effective for 13 patients, effective for 20 patients, and ineffective for 9 patients, with an effective rate was 78.57%. The study group exhibited a higher effectiveness rate compared to the control group ($P<0.05$, **Table 2**).

Comparison of blood glucose levels between the two groups

Initially, there was no significant change in blood glucose levels between the groups prior to treatment ($P>0.05$). After treatment, the levels of FBG, 2hPG and HbA1c were decreased (all $P<0.05$). Furthermore, the blood glucose indicators in the study group were significantly lower than those of the control group (all $P<0.05$, **Table 3**).

Table 1. Baseline data of the two groups

	Control group (n=42)	Study group (n=42)	χ^2/t	P
Gender (Male/Female)	27/15	25/17	0.202	0.653
Age (years)	67.41±5.18	66.78±5.21	0.556	0.580
BMI (kg/m^2)	23.36±2.25	23.41±2.27	0.101	0.919
Course of disease (years)	8.15±3.71	8.06±7.92	0.067	0.947
Hypertension	19 (45.24)	21 (50.00)	0.191	0.662
Hyperlipidemia	16 (38.10)	17 (40.48)	0.050	0.823
Coronary heart disease	12 (28.57)	11 (16.19)	0.060	0.807
Education level			0.293	0.864
Primary and junior high school level	17 (40.48)	19 (45.24)		
Senior high and technical school level	13 (30.95)	13 (30.95)		
College and above	12 (28.57)	10 (23.81)		

Table 2. Comparison of therapeutic effects between the two groups

	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=42)	13 (30.95)	20 (47.62)	9 (21.43)	33 (78.57)
Study group (n=42)	25 (59.52)	16 (38.10)	1 (2.38)	41 (97.62)
χ^2				7.265
P				0.007

Table 3. Comparison of blood glucose levels between the two groups ($\bar{x}$±s)

		Control group (n=42)	Study group (n=42)	χ^2/t	P
FBG (mmol/L)	Before treatment	9.32±1.41	9.24±1.33	0.267	0.790
	After treatment	7.25±0.93[a]	6.08±1.05[b]	5.406	<0.0001
2hPG (mmol/L)	Before treatment	16.87±4.05	16.37±4.24	0.553	0.582
	After treatment	13.56±2.61[a]	11.05±1.72[b]	5.204	<0.0001
HbA1c (%)	Before treatment	9.28±1.04	9.11±1.15	0.711	0.479
	After treatment	7.83±0.81[a]	6.23±0.88[b]	8.670	<0.0001

Note: [a]P<0.05 *vs* before treatment in control group; [b]P<0.05 *vs* before treatment in combination group. FBG, fasting blood glucose; 2hPG, 2-hour postprandial plasma glucose; HbA1c, glycosylated hemoglobin.

Comparison of renal function indexes between the two groups

Before treatment, there were no significant changes in renal function (P>0.05). After treatment, serum levels of Scr, BUN, and 24h-UPor were noticeably decreased (all P<0.05). Additionally, the study group showed more substantial improvement in renal function indexes than the control group (all P<0.05, **Table 4**).

Comparison of renal fibrosis indexes between the two groups

Before treatment, there were no significant differences in the levels of renal fibrosis between the two groups (all P>0.05). After treatment, the levels of COL-iv, PC-iii and LN were decreased (all P<0.05). Moreover, improvements in the renal fibrosis indexes were more pronounced in the study group (all P<0.05, **Table 5**).

Comparison of immune function between the two groups

There were no significant differences in the levels of IgA, IgM, and IgG between the two groups before treatment (all P>0.05). After treatment, the IgA, IgM, and IgG levels were increased (all P<0.05), and the improvements in IgA, IgM, and IgG in the study group were more substantial in the study group (all P<0.05, **Table 6**).

Table 4. Comparison of renal function indexes between the two groups ($\bar{x}\pm s$)

		Control group (n=42)	Study group (n=42)	χ^2/t	P
Scr (μmol/L)	Before treatment	135.64±14.08	134.37±13.71	0.419	0.676
	After treatment	94.55±9.23[a]	78.05±8.01[b]	8.750	<0.0001
BUN (c/μmol·L^{-1})	Before treatment	8.63±1.22	8.46±1.09	0.673	0.503
	After treatment	6.35±0.66[a]	4.08±0.54[b]	17.251	<0.0001
24h-UPor (m/mg)	Before treatment	1462.09±120.36	1465.14±123.41	0.115	0.909
	After treatment	1287.51±179.33[a]	1077.52±103.52[b]	6.572	<0.0001

Note: [a]P<0.05 *vs* before treatment in control group; [b]P<0.05 *vs* before treatment in combination group. Scr, serum creatinine; BUN, blood urea nitrogen; 24h-UPor, 24-hour urinary protein quantification.

Table 5. Comparison of renal fibrosis indexes between the two groups ($\bar{x}\pm s$)

		Control group (n=42)	Study group (n=42)	χ^2/t	P
Col-IV (μg/L)	Before treatment	226.08±10.34	227.14±10.17	0.474	0.637
	After treatment	218.66±20.05[a]	140.55±14.23[b]	20.589	<0.0001
PC-III (μg/L)	Before treatment	23.36±2.38	22.71±2.14	1.316	0.192
	After treatment	21.34±1.38[a]	18.83±1.42[b]	8.215	<0.0001
LN (μg/L)	Before treatment	150.78±12.17	151.06±10.42	0.113	0.910
	After treatment	137.41±13.24[a]	101.42±3.48[b]	17.038	<0.0001

Note: [a]P<0.05 *vs* before treatment in control group; [b]P<0.05 *vs* before treatment in combination group. Col-IV, collagen IV; PC-III, procollagen III; LN, serum laminin.

Table 6. Comparison of IgA, IgM, and IgG levels between the two groups ($\bar{x}\pm s$)

		Control group (n=42)	Study group (n=42)	χ^2/t	P
IgA	Before treatment	1.61±0.18	1.57±0.17	1.047	0.298
	After treatment	2.09±0.38[a]	2.46±0.29[b]	5.016	<0.0001
IgM	Before treatment	0.77±0.09	0.79±0.18	0.644	0.521
	After treatment	1.01±0.25[a]	1.29±0.31[b]	4.557	<0.0001
IgG	Before treatment	11.86±1.96	11.60±1.68	0.100	0.920
	After treatment	12.71±1.45[a]	15.81±1.99[b]	8.159	<0.0001

Note: [a]P<0.05 *vs* before treatment in control group; [b]P<0.05 *vs* before treatment in combination group. IgA, Immunoglobulin A; IgM, Immunoglobulin M; IgG, Immunoglobulin G.

Table 7. Comparison of the incidence of adverse reactions between the two groups

	Diarrhea	Dyspepsia	Constipation	Nausea and vomiting	Incidence of adverse reactions
Control group (n=42)	0 (0)	1 (2.38)	0 (0)	0 (0)	1 (2.38)
Study group (n=42)	2 (4.76)	1 (2.38)	2 (4.76)	3 (7.15)	8 (19.05)
χ^2					6.098
P					0.013

Comparison of adverse reaction incidence between the two groups

In the control group, only one patient had dyspepsia, with an incidence of adverse reactions of 2.38%. In the study group, adverse reactions were reported at a higher rate of 19.05%, including two cases of diarrhea, one of dyspepsia, two of constipation, and three of nausea and vomiting. A significantly lower incidence of adverse reactions was observed in the control group (P<0.05, **Table 7**).

Discussion

Hyperglycemia is a hallmark of diabetes. There are many types of diabetes, with Type 2 diabetes mellitus (T2DM) being the most prevalent. During the past decade, both the incidence and prevalence of T2DM have increased steadily [20]. The main goal of traditional hypoglycemic drugs is to control blood sugar in the ideal range. However, most hypoglycemic drugs do promote weight loss, and some, including insulin, sulfonylureas and TZD, may even contribute to weight gain. The emergence of enteropagin hypoglycemic drugs has addressed this issue by promoting a more potent and sustained insulin release in response to oral glucose [2].

Effective control of blood sugar in T2DM patients has become a major concern of clinicians [21]. This study found that the levels of FBG, 2hPG, and HbA1c were significantly decreased after treatment, with more substantial improvement observed in the study group. Metformin, a first-line drug for diabetes treatment due to its effectiveness, may require supplementation with insulin or sulfonylurea-based hypoglycemic agents when blood glucose control is inadequate [22]. The combination of Liraglutide with metformin has proven particularly effective in treating T2DM, primarily because Liraglutide enhances islet function and lowers blood glucose levels, while synergistically enhancing the hypoglycemic effect of metformin. In addition, post-treatment measurements indicated reduced levels of BUN, Scr, and CysC in the study group compared to both their baseline levels and those observed in the control group, indicating that Liraglutide in combination with routine treatment not only controls blood glucose but also stabilizes it, and prevents renal function damage caused by hemodynamic changes and metabolic disorders induced by hyperglycemia. Cherney's research has shown that Liraglutide cannot only maintain the stability of blood sugar, but also inhibit the activity of kidney oxidase, thus reducing the stress injury of kidney, and play a protective role in renal function [23]. Renal interstitial fibrosis, marked by the accumulation of extracellular matrix such as type IV collagen, laminin, and type III collagen, is closely related to renal function decline. The levels of serum Col-IV, LN and Col-III can be used to judge the degree of renal fibrosis [24]. The results of this study indicated that adding Liraglutide to routine treatment can effectively reduce the levels of Col-IV and LN in patients with diabetic nephropathy, indicating that this therapeutic approach may effectively mitigate renal fibrosis.

T2DM is a progressive disease that disrupts the normal balance of blood structure and diminishes the immune status of patients. Previous studies have reported that the levels of T lymphocyte subsets, immunoglobulins, and complement in peripheral blood of T2DM patients are abnormal, suggesting a compromised immune balance and reduced immunity [25]. An imbalance in immune status can manifest as altered levels of immunoglobulins such as decreased IgA, IgM, and IgG, indicative of a disrupted immune state. Our results indicated that the levels of IgA, IgM, and IgG were noticeably improved after treatment, with more substantial improvements in the study group. This suggests that Liraglutide in combination with metformin is more effective in enhancing IgA, IgM, and IgG levels than metformin alone. It affirms its positive effect in the regulation of immune function in T2DM patients.

The common adverse reactions of liraglutide include nausea, vomiting, diarrhea, and upper respiratory tract infection. Gastrointestinal adverse reactions (GIAR) mostly occur in the first week of treatment and are generally tolerable for most patients, with no evidence suggesting dose-related factors [26]. Wu et al. identified female sex and higher thyroid stimulating hormone levels as independent risk factors for gastrointestinal side effects of Liraglutide treatment in patients with T2DM [27]. Our results revealed that there were no serious adverse reactions after treatment, but the adverse reactions in the control group were lower. However, the adverse events in the study group were mild and their duration was short with most adverse reactions occurred within first 2 weeks of treatment. This may be related to delayed gastric emptying, which reduces hunger and energy intake. It is advisable for clinicians to monitor patients for adverse reactions during treatment and intervene promptly if serious adverse reactions occur [28].

Conclusion

Liraglutide in combination with routine therapy is effective for managing T2DM. It effectively

enhances control over blood glucose levels, improves renal function, and promotes the recovery of immune function. However, the incidence of gastrointestinal adverse reactions of Liraglutide is higher. Therefore, its clinical use necessitates close drug monitoring, especially in elderly patients with T2DM, those with hepatorenal insufficiency and patients with previous history of drug allergy. Despite its effectiveness, this study has some limitations, including the limited study samples, single sourcing center, and relatively short follow-up time. Future studies should therefore aim for a larger, multicenter, prospective design to validate and expand upon these findings.

Disclosure of conflict of interest

None.

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