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Efficacy and Clinical Value of Liraglutide for Treatment of Diabetes Mellitus Complicated by Non-Alcoholic Fatty Liver Disease

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Background: The aim of this study was to investigate the efficacy and clinical value of liraglutide for the treatment of patients with diabetes mellitus (DM) complicated by non-alcoholic fatty liver disease (NAFLD).

Material/Methods: Patients with DM complicated by NAFLD (n=835) were enrolled. Patients were divided into 2 groups: 424 patients were included in the liraglutide group and 411 patients were included in the conventional drug group. Venous blood was collected to test blood glucose levels, blood lipid levels, and liver function. After discharge, patients were followed up for between 6 months and 1 year and assigned a quality-of-life score.

Results: The blood glucose levels of patients in both groups were improved after treatment (P<0.05). The blood lipid levels of patients in both groups improved after treatment (P<0.05). Various blood lipid parameters of patients in the liraglutide group were significantly better than in the conventional drug group (P<0.05). The liver function of patients in the conventional drug group was not significantly different before or after treatment (P>0.05), while in the liraglutide group it improved significantly after treatment (P<0.05). The average quality-of-life score at follow-up in the liraglutide group was 81.00±9.33 points, which was significantly higher than the 68.53±8.44 points in the conventional drug group (P<0.05).

Conclusions: Liraglutide for the treatment of DM complicated by NAFLD can effectively improve the blood glucose and lipid levels as well as liver function of patients.

MeSH Keywords: Blood Glucose • Diabetes Complications • Drug-Induced Liver Injury

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Background

Worldwide, diabetes mellitus (DM) is a common metabolic disorder, with one of the highest morbidity rates of all diseases [1]. A study by Zinman et al. [2] found that the global incidence of DM was 25.6% in 2015 [3]. As living standards improve and society progresses, the incidence of DM is increasing. An analysis of DM morbidity rates by Green et al. [4] revealed that the morbidity will approximate 50% within the next 50 years. Moreover, in some countries with a high population density, such as China, India, and the United States, the number of people older than 50 years with DM will account for more than 60% of the population. Although the morbidity of DM is extremely high, the improvement of available treatments has resulted in a better prognosis [5].

DM is accompanied by a number of complications, of which a fatty liver is one of the most common [6]. A statistical analysis by Lonardo et al. [7] demonstrated that 78.2% of patients with DM also suffer from a fatty liver. A fatty liver frequently causes insulin resistance, resulting in irritable liver damage and promoting the development of hepatitis, liver cirrhosis, and even liver cancer [8]. Insulin is an important drug used for the treatment of DM; however, developing strategies to avoid serious damage to patients as a result of the reaction between insulin and fatty liver cells are key in curing DM. Liraglutide is a new glucagon-like peptide hypoglycemic agent which not only has an excellent inhibitory effect on blood glucose but also has a very strong regulatory effect on pancreatic β cells and has recently been under the spotlight as a drug for the treatment of DM [9]. We hypothesized that liraglutide is a more effective drug for the treatment of DM complicated by non-alcoholic fatty liver disease (NAFLD) than is the conventional drug.

Therefore, the aim of this study was to investigate the efficacy and clinical value of liraglutide to provide a reference for future clinical treatment of patients with DM complicated by NAFLD.

Material and Methods

Patients data

Eight hundred thirty-five patients with DM complicated by NAFLD treated in our Hospital of Integrated Traditional and Western Medicine were selected as the subjects of this retrospective study. Five hundred twenty-seven patients were men and 308 were women. The patients ranged in age between 45 and 65 years, and the mean age was 52.73±10.26 years. The patients were divided into 2 groups: the liraglutide group (receiving conventional and liraglutide treatment) consisting of 424 patients and the conventional drug group (receiving conventional treatment only) consisting of 411 patients, according to the different therapeutic drugs used during treatment in our hospital. The following inclusion criteria applied: a diagnosis of DM made in our hospital, the presence of NAFLD, undergoing treatment in our hospital after diagnosis, having a complete case, and an age 45–65 years. Patients were excluded if they suffered from cardiovascular, cerebrovascular, or digestive tract diseases; were physically disabled, pregnant, or bedridden over a long period; were transferred to another hospital halfway through the study period; or received or used other drug therapies without the doctors' permission. Written informed consent was obtained from all patients in the study.

Treatment approach and analysis of clinical variables

Patients in the conventional drug group were treated with metformin (dimethylbiguanide; Suzhou Erye Pharmaceutical Co., Ltd., Suzhou City, China) as the main therapeutic drug, 3 times per day (500 mg/time), for 3 months continuously. Patients in the liraglutide group were treated with liraglutide (Novo Nordisk A/S, Bagsvaerd, Denmark) once per day (1.2 mg/time), administered via subcutaneous injection for 3 months continuously. Venous blood (4 ml per patient) was collected from each patient. An automatic biochemical analyzer (Beckman Coulter, Inc., CA, USA) was used to test the blood glucose levels (fasting blood glucose [FBG], 2-h postprandial blood glucose [2hPG], and glycosylated hemoglobin [HbAlc]), blood lipid levels (serum total cholesterol [TC], triglyceride [TG], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), and liver function (aspartate transaminase [AST], alanine transaminase [ALT], and gamma-glutamyl transpeptidase [GGT]). Patients were followed up for between 6 months and 1 year after discharge and assigned a quality-of-life score (body, activities, and mood). Finally, the 2 groups were compared to identify differences in these parameters.

Statistical analyses

SPSS version 22.0 (IBM Corp., Armonk, NY) was used for data processing. Clinical data of patients were represented by ratios. The chi-square test and *t* test were used for comparisons between the 2 groups: blood glucose levels, blood lipid levels, liver function, and quality-of-life scores were represented by mean ± standard deviation. A P value <0.05 was considered statistically significant.

Results

Patient data

To ensure the accuracy and credibility of the results, age, sex, residence, marital status, smoking habits, exercise habits, body weight, and disease status of patients in the 2 groups were

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Table 1. Clinical data of patients in the 2 groups (%).

	Liraglutide group (n=424)	Conventional drug group (n=411)	χ^2(t)/P
Age	51.27±8.16	52.05±7.84	1.41/0.16
Sex			0.14/0.71
Male/Female	62.5/37.5	63.7/36.3	
Residence			0.03/0.86
City/countryside	64.6/35.4	65.2/34.8	
Marriage			0.48/0.49
Married/unmarried	92.5/7.5	93.7/6.3	
Smoking			0.28/0.60
Yes/no	58.3/41.7	56.4/43.6	
Body weight			0.26/0.61
<60 KG/≥60 KG	38.7/61.3	37.0/63.0	
Exercise habits			0.58/0.45
Yes/no	32.1/67.9	34.5/65.5	
Course of disease			0.01/0.94
<15d/≥15d	38.4/61.6	38.7/61.3	

compared (Table 1). There was no significant difference between the 2 groups (P>0.05), demonstrating that the patients in the 2 groups were comparable.

Test results of parameters before and after treatment

To compare the efficacy of liraglutide and the conventional drug for the treatment of patients with DM complicated by NAFLD, the blood glucose levels, blood lipid levels, and liver function of patients in both groups were tested using an automatic biochemical analyzer. Before treatment, blood glucose levels, blood lipid levels, and liver function were not significantly different between the 2 groups (P>0.05). In both groups, the blood glucose and lipid levels improved after treatment. The FBG of patients in the liraglutide group was 6.52±0.54 mmol/L after treatment, which was not significantly different (P>0.05) from the FBG of the conventional drug group. After treatment, the 2hPG and HbAlc were 9.53±1.01 mmol/L and 7.20±0.46% in the liraglutide group, respectively, and 10.07 ± 0.63 mmol/L and 7.72±0.56% in the conventional drug group, respectively, which were also not significantly different (P>0.05) (Table 2). These results indicate that both metformin alone and liraglutide plus metformin are effective in improving blood glucose levels.

Regarding blood lipid function, after treatment, the TC, TG, LDL-C, and HDL-C in the liraglutide group were 3.92±0.64 mmol/L, 1.01±0.45 mmol/L, 1.54±0.83 mmol/L, and 0.54±0.41 mmol/L, respectively, which were significantly better than in the conventional drug group (TC, 4.95±0.92 mmol/L; TG, 1.96±0.84 mmol/L; LDL-C, 2.68±0.73 mmol/L; HDL-C, 1.08±0.57 mmol/L; P<0.05), demonstrating the efficacy of liraglutide in reducing the blood lipid levels of patients with DM complicated by NAFLD (Table 3).

The liver function parameters of patients in the liraglutide group improved significantly: AST, ALT, and GGT were 17.24±4.52 IU/L, 25.33±4.92 IU/L, and 26.14±7.28 IU/L, respectively, after treatment, compared to 27.34±6.25 IU/L, 38.52±9.27 IU/L, and 39.62±9.87 IU/L, respectively, before treatment (P<0.05). In contrast, the parameters of liver function of patients in the conventional drug group did not change significantly after treatment (P>0.05) (Table 4). These results indicate that liraglutide effectively improves liver function.

Prognosis related to quality-of-life score

To study the long-term condition of patients in both groups, patients were followed up for between 6 months and 1 year after treatment by phone call or review and a quality-of-life score was assigned to each patient. Eight hundred twenty-four of 835 patients were followed up; 4 patients in the liraglutide group and 7 in the conventional drug group were lost to follow-up.

Table 2. Results of blood glucose tests before and after treatment.

	Liraglutide group (n=424)		Conventional drug group (n=411)	
	Before treatment	After treatment	Before treatment	After treatment
FPG (mmol/L)	11.54±1.27	6.52±0.54*	11.62±1.34#	6.57±0.63*$
2Hpg (mmol/L)	15.26±1.82	9.73±1.01*	15.08±2.01#	10.07±0.63*$
HbAlc (%)	11.04±1.08	7.20±0.46*	11.53±0.82#	7.62±0.56*$

* Refers to the comparison between the 2 groups after treatment and the corresponding group before treatment, P<0.05; # refers to the comparison of values test levels between the 2 groups before treatment, P>0.05; $ refers to the comparison of test levels between the 2 groups after treatment, P>0.05.

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Table 3. Results of blood lipid tests before and after treatment (mmol/L).

	Liraglutide group (n=424)		Conventional drug group (n=411)	
	Before treatment	After treatment	Before treatment	After treatment
TC	5.48±1.27	3.92±0.64*	5.53±1.31#	4.95±0.92*$
TG	2.52±0.92	1.31±0.45*	2.48±1.03#	1.96±0.84*$
LDL-C	3.08±1.09	1.94±0.83*	3.06±0.82#	2.68±0.73*$
HDL-C	1.28±0.53	0.74±0.41*	1.30±0.67#	1.08±0.57*$

* Refers to the comparison between the 2 groups after treatment and the corresponding group before treatment, P<0.05; # refers to the comparison of test levels between the 2 groups before treatment, P>0.05; $ refers to the comparison of test levels between the 2 groups after treatment; all parameters in the liraglutide group were significantly higher than those in the conventional drug group (P<0.05).

Table 4. Results of liver function tests before and after treatment (IU/L).

	Liraglutide group (n=424)		Conventional drug group (n=411)	
	Before treatment	After treatment	Before treatment	After treatment
AST	27.34±6.25	17.24±4.52*	28.01±6.57#	28.34±6.83*$
ALT	38.52±9.27	25.33±4.92*	39.01±8.92#	39.27±9.53*$
GGT	39.62±9.87	26.14±7.28*	38.86±9.21#	39.62±9.53*$

* Refers to the comparison between the 2 groups after treatment and the corresponding group before treatment, in which all parameters in the liraglutide group before treatment were significantly different from those after treatment (P<0.05), while all the parameters in the conventional drug group before and after treatment were not significantly different (P>0.05); # refers to the comparison of test levels between the 2 groups before treatment, P>0.05; $ refers to the comparison of test levels between the 2 groups after treatment; all parameters in the liraglutide group were significantly higher than those in the conventional drug group (P<0.05).

Table 5. Comparison of quality-of-life scores between groups.

	Liraglutide group (n=420)	Conventional drug group (n=404)	t/P
Body	75.24±8.24	65.84±9.24	15.53/0.01
Activities	89.62±9.52	71.53±8.54	28.87/0.01
Mood	78.15±10.23	68.23±7.54	15.91/0.01
Average score	81.00±9.33	68.53±8.44	20.23/0.01

The results showed that the average score of the liraglutide group (81.00±9.33) was significantly higher than the score of the conventional drug group (68.53±8.44) (P<0.05). The largest difference in the quality-of-life score between the 2 groups was observed in the social activities category; the liraglutide group performed significantly better than the conventional drug group (89.62±9.52 *vs.* 71.53±8.54, respectively; P<0.05). Body and mood function scores were also better in the liraglutide group than that in conventional drug group (P<0.05) (Table 5).

Discussion

DM commonly causes injury to vital organs and has been proven to trigger heart, brain, liver, eye, and other diseases [10–13]. NAFLD is one of the most common complications of DM. A study by Younossi et al. [8] demonstrated that long-term exposure to high glucose levels directly impacts the detoxification function of the liver, causing the occurrence of a series of liver diseases. NAFLD is the form of the disease which is not caused by high alcohol consumption; instead, it results from fatty degeneration of the liver parenchymal cells [14,15]. At present, there is no evidence of the pathogenesis of NAFLD; however, the "second strike" theory by Day and James is accepted in the clinical setting. According to this theory, insulin resistance, oxidative stress, and lipid peroxidation are the main causes of inflammatory liver necrosis and fibrosis. DM is typically characterized as a glucose and lipid metabolism disorder which increases insulin resistance [16,17]. Conventional therapeutic drugs for DM often result in abnormal liver enzymes, which further aggravate insulin resistance in DM patients [18]. Therefore, the condition of patients with DM complicated by NAFLD may worsen due to the effects of the drugs used during

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treatment, forming a vicious circle. Liraglutide, the latest antidiabetic drug, has a strong regulatory effect on the proliferation and differentiation of pancreatic β cells, can promote the secretion rate of endogenous insulin, and has a strong inhibitory effect on insulin resistance [19,20]. The present study intended to provide a reference and guide for future clinical treatment of patients with DM complicated by NAFLD by analyzing the therapeutic effect of liraglutide on these patients.

Our results showed that both liraglutide and the conventional drug effectively improved the blood glucose and lipid levels of patients with DM complicated by NAFLD; however, the conventional drug had no significant effect on the liver function of patients and even appeared to aggravate the liver. In contrast, liraglutide greatly improved liver function. Based on their quality-of-life scores, the follow-up investigation suggested that the prognosis of patients treated with liraglutide was significantly better than that of patients treated with the conventional drug. The key reasons for the differences between the 2 groups were the improvement of insulin resistance; insulin resistance induces the synthesis of free fatty acids in adipose tissues, causing the elevation of glucagon-like peptide (GLP-1), which aggravates the liver and worsens NAFLD [10]. The seriousness of NAFLD is directly related to the elevation of GLP-1 levels. The capacity of the nervous system to absorb nutrients is lowered by GLP-1 and the ability of the patient to function during drug therapy gradually declines, which ultimately causes the condition to fail to improve. Liraglutide has very high sequence homology with GLP-1 and is able to interact with the GLP-1 receptor [21], which greatly increases the synthesis and metabolism of cyclic adenosine monophosphate. Insulin secretion is stimulated when blood glucose levels increase, thus inhibiting the secretion of pancreatic glucagon. In contrast, the secretion of insulin is reduced when blood glucose levels decrease, thereby maintaining the normal metabolism of pancreatic glucagon. Meanwhile, liraglutide promotes the proliferation and differentiation of β cells, which play an essential role in the improvement of fatty liver degeneration, hepatocyte injury, and other conditions. In addition, liraglutide can activate the protective effect of GLP-1 receptors in the liver during treatment [22] to prevent secondary liver injury caused by DM. The significant difference in patients' prognoses according to their quality-of-life score observed in our study could be ascribed to this protective effect. Our results confirmed those of a study by Rotman and Sanyal [23] in which they prove the therapeutic effect of liraglutide on liver cirrhosis. However, the mechanism underlying the protection of the liver by liraglutide is not known and further research is necessary.

In this study we compared the efficacy of liraglutide and the conventional drug for the treatment of patients with DM complicated by NAFLD. Our study has several limitations, including the small number of patients and the small range in patients' ages, which means that we cannot exclude the possibility that the efficacy of liraglutide may be different in different age groups. To achieve optimal experimental results, patients will be followed up for a longer period and the experimental design will be improved.

Conclusions

Liraglutide for the treatment of patients with DM complicated by NAFLD can effectively improve blood glucose and lipid levels, as well as liver function; therefore, it should be popularized and applied clinically.

Conflict of interests

None.

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