International Journal of Diabetes in Developing Countries (2020) 40:491–499
https://doi.org/10.1007/s13410-020-00857-w

ORIGINAL ARTICLE

The effect of liraglutide on nonalcoholic fatty liver disease in type 2 diabetes mellitus

Xueyang Zhang[1] · Ran Bai[1] · Yong Jia[2] · Junwei Zong[3] · Yongbo Wang[1] · Yanan Dong[1]

Received: 7 January 2020 / Accepted: 29 July 2020 / Published online: 13 August 2020

Abstract

Aims The objective is to investigate the effects of liraglutide on nonalcoholic fatty liver disease in type 2 diabetes mellitus.

Materials and methods Thirty-two patients with T2DM and NAFLD admitted to the Third Affiliated Hospital of Dalian Medical University from December 2014 to December 2016 were selected, including 11 females and 21 males, aged 39.34 ± 8.54 years old. The patients were given liraglutide on the basis of their original hypoglycemic regimen.

Results After 3 months treatment of liraglutide, FPG was reduced from 8.54 ± 2.21 mmol/L to 6.90 ± 1.73 mmol/L. HbA1c was reduced from 9.72 ± 1.95 to 7.78 ± 1.99. WC was reduced from 103.27 ± 9.92 kg to 93.97 ± 8.35 kg. BMI was reduced from 30.56 ± 4.06 kg/m^2 to 28.01 ± 3.12 kg/m^2. FLI was reduced from 79.23 ± 16.56 to 58.83 ± 19.75. The differences were statistically significant ($p < 0.001$). TG was reduced from 2.95 ± 2.13 mmol/L to 2.27 ± 1.31 mmol/L. The difference was significant ($p < 0.01$). Meanwhile, HOMA-IR was reduced from 1.504 ± 0.002 to 1.503 ± 0.002. GGT was reduced from 62.63 ± 71.61 U/L to 38.13 ± 30.13 U/L. AST was reduced from 27.25 ± 13.74 U/L to 25.44 ± 16.69 U/L. The differences were statistically significant ($p < 0.05$). After treatment, FCP, TC, HDL-C, LDL-C, ALT, and HOMA-β were also improved compared with before treatment, but the difference was not statistically significant ($p > 0.05$).

Conclusion In addition to effectively lowering glucose and improving islet resistance, liraglutide could also improve obesity and adjust blood lipids. However, the improvement of islet function might not be significant after 3 months of treatment. Liraglutide could reduce liver fat accumulation in patients with T2DM and NAFLD.

Keywords Liraglutide · Nonalcoholic fatty liver disease · Type 2 diabetes

Introduction

The prevalence of diabetes mellitus (DM), especially type 2 diabetes (T2DM), is increasing markedly worldwide, including in China [1]. In 2013, the overall prevalence of DM in Chinese adult population was 10.4% [2]. Insulin resistance is a metabolic feature of T2DM. Obesity and insulin resistance are key factors in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). The progression of NAFLD is due to the accumulation of triglycerides (TG) in the liver. At the same time, there was evidence that the accumulation of TGs in the liver increased systemic insulin antagonism of cytokine level and also increased insulin resistance in the liver [3]. In addition, metabolic changes accompanying diabetes are also included as a causative factor in nonalcoholic liver disease. Studies have shown that 18 to 33% of patients with impaired glucose tolerance or impaired fasting glucose (> 6 mmol/L) had NAFLD and 62% of patients with T2DM had fatty liver. It can be seen that both T2DM and NAFLD are complications of each other, affect each other, and promote the progress of the disease [4, 5].

Patients with T2DM and NAFLD, compared with those only with T2DM, resulted in more severe hyperlipidemia and high levels of inflammatory markers, as well as more severe insulin resistance and metabolic disorders of visceral

✉ Xueyang Zhang
zhangxueyang_2006@163.com

✉ Ran Bai
ranbaicn@163.com

[1] Department of Endocrinology, The first affiliated Hospital of Dalian Medical University, Dalian, Liaoning, Dalian, Liaoning, China

[2] Institute of Integrative Medicine, Dalian Medical University, Dalian, Liaoning, China

[3] Department of Orthopedics, The first affiliated Hospital of Dalian Medical University, Dalian, Liaoning, Dalian, Liaoning, China

obesity [6]. The mortality of patients with T2DM and NAFLD was increased compared with the one with T2DM without NAFLD. The most common causes of death were ischemic heart disease and liver-related disease [7]. Patients with NAFLD and diabetes were more likely to develop nonalcoholic steatohepatitis (NASH), compared with patients with NAFLD alone [8]. There was increasing evidence that NAFLD was one of the most common causes of death in diabetic patients with vascular disease. Cross-sectional study showed that NAFLD was positively correlated with carotid intima-media thickness, carotid plaque formation, and cardiovascular and cerebrovascular disease prevalence [9].

The treatment of T2DM with NAFLD focuses on reducing body weight and improving insulin resistance. The common drugs in clinical practice are antioxidants, lipid-lowering drugs, cell protective agents, insulin sensitizers, tumor necrosis factor inhibitors, and intestinal microecological preparations. But it is hard to say which drug works better. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used as novel hypoglycemic drugs. The extra benefits of hypoglycemic agents are slowly discovered, significant weight loss caused by reducing gastrointestinal motility, inhibiting the feeding center and losing appetite [10, 11]. Thus, it has been proposed to have a therapeutic effect on fatty liver. Dutch scholars firstly reported in 2006 that GLP-1RAs had improved liver fat content.

Liraglutide is an analog of glucagon-like peptide-1 (GLP-1), which was approved for marketing in the USA in 2010 and is marketed in China the following year. The hypoglycemic effect of liraglutide is undoubted, and its treatment of NAFLD has also been confirmed by research. Liraglutide reduced intrahepatic fat content, alanine aminotransferase (ALT), and TG in 87 T2DM patients with NAFLD [12]. At the same time, it has been confirmed that liraglutide has the effect of improving liver lipid content and then treating NAFLD in the animal model [13]. However, there are few studies on the efficacy of liraglutide in the treatment of T2DM with NAFLD.

Liver biopsy is the golden standard for quantitative measurement of fat content of NAFLD [14]. But it is an invasive test with significant sampling error. Hydrogen proton magnetic resonance spectrum is a noninvasive golden standard for detecting fatty liver. But it is often as a scientific research tool. Due to its complicated operation and high cost, it is difficult to apply to clinical practice. At present, the common fatty liver tests are liver/spleen CT ratio, liver and kidney ultrasound index, and abdominal ultrasound. However, there are still many factors such as radiation, special operation, inconvenient detection, and high price. Therefore, it is clinically necessary to have an easy and accurate evaluation method. The fatty liver index (FLI) was proposed in 2005 and widely accepted. FLI is an indicator to evaluate fatty liver, based on body mass index (BMI), waist circumference (WC), TG, and glutamyl transpeptidase (GGT). Fatty liver is excluded when FLI is lower than 30. Fatty liver is considered when FLI is greater or equal to 60. Studies have shown that FLI, liver/spleen CT ratio, and liver and kidney ultrasound index have a good correlation with the evaluation of liver fat accumulation in NAFLD. FLI as a noninvasive blood test method is cheap, no radiation, easy to operate, and widely screened [15]. In this study, we observed the effects of liraglutide on liver fat metabolism after observing the changes of FLI and blood lipid of patients of T2DM combined with NAFLD after 3 months treatment, in order to understand the effects of liraglutide on nonalcoholic fatty liver disease in type 2 diabetes mellitus. It may provide evidence for clinically applying liraglutide to treat patients of T2DM with NAFLD.

Materials and methods

Objects

Thirty-three patients with T2DM and NAFLD who were inpatients in the third department of The First Affiliated Hospital of Dalian Medical University from December 2014 to December 2016 were selected. The sample size was estimated based on published data [16].

The inclusion criteria were as follows: (1) aged 28–68 years; (2) BMI $\geq$ 25 kg/m^2 and/or male WC > 90 cm, female WC > 85 cm; (3) complying with the 1999 World Health Organization (WHO) diabetes diagnosis and classification criteria; (4) not adjusting the hypoglycemic regimen and dose of hypoglycemic drugs 2 months before admission; (5) meeting the diagnostic criteria of the 2006 NAFLD diagnosis and treatment guidelines; (6) no history of alcohol consumption or alcohol equivalent to alcohol for men < 140 g and women < 70 g per week.

The exclusion criteria were as follows: (1) type 1 diabetes, including adult late-onset autoimmune diabetes (LADA); (2) secondary diabetes; (3) severe acute complications of diabetes and stress state; (4) impaired liver function, transaminase > 3 times; (5) severe renal insufficiency; (6) TG < 9 mmol/L; (7) oral dipeptidyl peptidase IV (DPP-4) inhibitors or secretagogues before or during the observation period; (8) subcutaneous injection of premixed insulin hypoglycemic before or during the observation period; (9) women who are pregnant or breastfeeding or plan to become pregnant within half a year; (10) presence of infection and malignancy; (11) a history of severe cardiovascular and cerebrovascular disease in the past 3 months; (12) various diseases that significantly affect blood sugar; (13) previous pancreatitis; (14) previous medullary thyroid carcinoma and related family history of disease.

The withdrawal criteria were as follows: (1) applying liver-protective drugs and/or lipid-lowering drugs during enrollment; (2) serious adverse drug reactions occur; (3) allergic reactions to the drug; (4) not tolerating the drug; (5) poor compliance; (6) fasting blood glucose (FBG) > 13.3 mmol/L after half a month of treatment.

Methods

Testing methods and testing indicators

Liraglutide injection (3 mL: 18 mg/piece) is produced by Novo Nordisk, Denmark. It can be injected subcutaneously once a day and can be injected into the upper arm, abdomen, or thigh. It is recommended to take the medicine at the same time every day.

Patients with T2DM and NAFLD who met the enrollment criteria were given normal diet and exercise education, and were treated with liraglutide based on their original hypoglycemic regimen (metformin, glycosidase inhibitor, long-acting insulin). The medical history, age, and sex were recorded as baseline information. Height, weight, and WC were measured to calculate BMI. The patients fasted for 12 h, and the elbow median venous blood was drawn in the fasting state in the early morning the next day. The biochemical instrument was used to determine fasting plasma glucose (FPG), total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c), fasting C peptide (FCP), ALT, aspartate transaminase (AST), and glutamyl transpeptidase (GGT). Insulin resistance index (homeostasis model assessment for insulin resistance, HOMA-IR), islet function (homeostasis model assessment for beta cell, HOMA-β), and FLI were calculated.

Related calculation formulas are as follows:

$$\mathrm{BMI}\left(\mathrm{kg/m^2}\right) = \mathrm{weight(kg)} \div \mathrm{height(m)}^2,$$

$$\mathrm{HOMA\text{-}IR} = 1.5 + \mathrm{FPG(mmol/L)} \times \mathrm{FCP(pmol/L)} \div 2800,$$

$$\mathrm{HOMA\text{-}\beta} = 0.27 \times \mathrm{FCP(pmol/L)} \div [\mathrm{FPG(mmol/L)} - 3.5];$$

$$\mathrm{FLI} = \left(e^{(0.953\times\log e(\mathrm{TG})+0.139\times\mathrm{BMI}+0.718\times\log e(\mathrm{GGT})+0.053\times\mathrm{WC}-15.745)}\right) \div \left(1+e^{(0.953\times\log e(\mathrm{TG})+0.139\times\mathrm{BMI}+0.718\times\log e(\mathrm{GGT})+0.053\times\mathrm{WC}-15.745)}\right) \times 100$$

The TG unit is mg/dL, the GGT unit is U/L, and the WC unit is cm.

Experiment procedure

The baseline data of the enrolled patients were recorded and checked the next day. The patients were injected subcutaneously once daily with a starting dose of 0.6 mg. After 3–7 days of observation, if the patient had no obvious adverse reactions (diarrhea, vomiting, nausea, and other gastrointestinal reactions), the liraglutide dose was adjusted to 1.2 mg/day. If the above adverse drug reactions occurred, the dose was reduced back to 0.6 mg. The patients were increased the dose, until the adverse reactions were completely relieved. Patients were followed up for blood glucose control at the second week and the sixth week, respectively. If FBG was higher than 7 mmol/L, and/or 2-h postprandial blood glucose (2hPBG) was higher than 10 mmol/L, other oral drugs and long-acting insulin were not adjusted. Liraglutide's dose was increased to 1.8 mg. Patients were withdrawn from the trial if FBG was higher than 13.3 mmol/L at the second week. In order to avoid the influence of the drug on the experimental results, no lipid-lowering drugs and/or liver-protective drugs were used and the dose of other hypoglycemic drugs except liraglutide was not adjusted in this study. Patients were followed up for 3 months after BMI, HbA1c, FPG, FCP, AST, ALT, GGT, TC, TG, HDL-C, and LDL-C. HOMA-IR, HOMA-β, and FLI were calculated. We observed whether the patient had obvious adverse drug reactions during the whole process. The patient discontinued the drug if the adverse was serious.

Statistical analyses

All data were analyzed using statistical software SPSS21.0. Data are described using mean ± standard deviation ($\bar{x} \pm SD$). When performing hypothesis tests, the comparison of the indicators before and after the intervention was performed using paired sample *t* tests.

Results

Baseline data and follow-up

A total of 33 subjects were enrolled. One patient withdrew from the trial due to poor glycemic control. A total of 32 subjects were analyzed, including 21 males (65.6%) and 11 females (34.38%). The average age was 39.34 ± 8.54 years.

The average duration of disease was 3.59 ± 2.22 years. Eleven patients had comorbidities (10 patients with hypertension, 5 patients with coronary heart disease, 4 both), and 7 with chronic complications of diabetes. After using liraglutide, all the patients experienced nausea and decreased appetite to varying degrees, but they tolerated and symptoms gradually disappeared after 1to 3 days. There was no allergy at the injection site, and no patients had severe hypoglycemia (Table 1).

Effects of liraglutide on blood glucose, islet function, and insulin resistance

FPG decreased from 8.54 ± 2.21 mmol/L before treatment to 6.90 ± 1.73 mmol/L after treatment. The difference was statistically significant ($p < 0.001$). With FPG < 7 mmol/L as the standard, the standard compliance rate was 62.5%. The HbA1c was 9.72 ± 1.95% before treatment and 7.78 ± 1.99% after treatment. The difference was statistically significant ($p < 0.001$). With HbA1c < 7% as the compliance standard, the compliance rate was 31.3%. HOMA-IR decreased from 1.504 ± 0.002 before treatment to 1.503 ± 0.002 after treatment. The difference was statistically significant ($p < 0.05$). The HOMA-β difference was not statistically significant ($p > 0.05$), but it was improved to a certain extent compared with before treatment (Table 2).

Effect of liraglutide on obesity

WC decreased 9%, from 103.27 ± 9.92 cm before treatment to 93.97 ± 8.35 cm after treatment. BMI decreased 8%, from 30.56 ± 4.06 kg/m^2 before treatment to 28.01 ± 3.12 kg/m^2 after treatment. The differences between the two indexes were statistically significant ($p < 0.001$). Liraglutide can significantly reduce BMI and WC. It has the effect of improving obesity (Table 3).

Effects of liraglutide on fatty liver and blood lipids

TG decreased from 2.95 ± 2.13 mmol/L before treatment to 2.27 ± 1.31 mmol/L after treatment, a decrease of 22%, and the difference was statistically significant ($p < 0.01$). Comparing before and after treatment, LDL-C and TC decreased by 3% and 0.2% respectively, and HDL-C increased

Table 1 Baseline and follow-up data

Index		$\bar{x} \pm s$	(min, max)
Gender (male/female)		21/11	
Age (years)		39.34 ± 8.54	(18, 56)
Course of disease (years)		3.59 ± 2.22	(1, 10)
WC (cm)		103.27 ± 9.92	(91, 124.5)
BMI (kg/m^2)		30.56 ± 4.06	(24.29, 38.10)
FPG (mmol/L)		8.54 ± 2.21	(5.29, 16.80)
FCP (pmol/L)		1.27 ± 0.54	(0.55, 3.30)
TG (mmol/L)		2.95 ± 2.13	(1.04, 9.87)
TC (mmol/L)		4.92 ± 1.07	(3.07, 7.41)
HDL-C (mmol/L)		1.12 ± 0.31	(0.64, 1.85)
LDL-C (mmol/L)		3.01 ± 0.75	(1.58, 4.16)
AST (U/L)		27.25 ± 13.74	(12, 59)
ALT (U/L)		48.09 ± 29.21	(8, 113)
GGT (U/L)		62.63 ± 71.61	(11, 287)
HbA1c (%)		9.72 ± 1.95	(6.4, 13.2)
Comorbidities		11	
Chronic complications		7	
Adverse effects of liraglutide	Gastrointestinal reaction	32	
	Hypoglycemia response	2	
	Allergic reaction	0	
Exit group	Poor glycemic control	1	

Demographic parameters and clinical and treatment history data were collected from medical records. Data are shown as mean ± SD

WC, waist circumference; *BMI*, body mass index = body weight (kg)/height (m)^2 ; *FPG*, fasting plasma glucose; *FCP*, fasting C-peptide; *TG*, total triglycerides; *TC*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *ALT*, alanine aminotransferase; *AST*, aspartate transaminase; *GGT*, γ-glutamyl transpeptidase; *HbA1c*, hemoglobin A1c

Table 2 Effects of liraglutide on FPG, HbA1c, islet function, and insulin resistance

Index	Before treatment ($n = 32$)	After treatment ($n = 32$)	Compliance rate	p	95% CI
FPG (mmol/L)	8.54 ± 2.21	6.90 ± 1.73	62.5%	< 0.001	(0.12, 1.66)
HbA1c (%)	9.72 ± 1.95	7.78 ± 1.99	31.3%	< 0.001	(0.86, 2.34)
FCP (pmol/L)	1.27 ± 0.54	1.25 ± 0.74		0.838	(− 0.18, 0.20)
HOMA-IR	1.504 ± 0.002	1.503 ± 0.002		0.008	(0.00, 0.001)
HOMA-β	0.082 ± 0.048	0.134 ± 0.120		0.472	(− 0.06, 0.01)

Clinical history and data from most recent laboratory investigations within the past year were collected from medical records. Data are shown as mean ± SD. Data are presented as odds ratios (95% CI)

FPG, fasting plasma glucose; *HbA1c*, hemoglobin A1c; *FCP*, fasting C-peptide;

HOMA-IR = 1.5 + FPG (mmo/L) × FCP (pmol/L) ÷ 2800;

HOMA-β = 0.27 × FCP (pmol/L) ÷ [FPG (mmo/L) − 3.5];

by 5%. They had no statistical significance ($p > 0.05$) (Table 4).

GGT decreased from 62.63 ± 71.61 U/L before treatment to 38.13 ± 30.13 U/L after treatment, a decrease of 39%. AST decreased from 27.25 ± 13.74 U/L before treatment to 25.44 ± 16.69 U/L after treatment, a decrease of 7%. The differences were statistically significant ($p < 0.05$). Although ALT decreased by 9% compared with that before treatment, the difference was not statistically significant ($p > 0.05$) (Table 5). Analysis of FLI showed a decrease of 26% from 79.23 ± 16.56 before treatment to 58.83 ± 19.75 after treatment. The effect of liraglutide on FLI was statistically significant ($p < 0.001$). Liraglutide can significantly reduce FLI (Table 5).

Discussion

Epidemiology shows that the number of people with diabetes is increasing day by day. The detection rate of NAFLD is increasing with the wide application of ultrasound. In a study in the USA, the prevalence of NAFLD in T2DM population was as high as 70 to 80%, compared with 10 to 24% in the general population [17]. Therefore, there is an urgent need for a drug that simultaneously lowers blood sugar and blood lipids, and has a therapeutic effect on NAFLD. Liraglutide is widely used as a new type of hypoglycemic drug, and its benefits other than hypoglycemic are slowly being explored. Its role in the treatment of fatty liver has been widely concerned.

FPG is the basic sugar, and good FPG level is more conducive to smoothly control of blood sugar. This trial showed that FPG decreased from 8.54 ± 2.21 mmol/L to 6.90 ± 1.73 mmol/L (a decrease of 19%) after 3 months of treatment with liraglutide. The result was consistent with the results of LEAD confirming its hypoglycemic effect [18, 19]. GLP-1 is a kind of incretin, and its blood glucose effect after meal reduction is more significant. Its effect mainly manifests in the stimulation of islet β-cell secretion of insulin after oral administration of glucose, and it has the effect of delaying gastric emptying. Since this study mainly observed the effect of liraglutide on NAFLD, postprandial blood glucose changes were not detected.

HbA1c responds to blood glucose levels for nearly 2–3 months. Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017 Edition) presented HbA1c should remain < 7% for adult nongestational age T2DM patients of expected long-term survival, short history, and no associated complications [20]. This test showed that the pretreatment HbA1c was 9.72 ± 1.95% and HbA1c was 7.78 ± 1.73% after 3 months of treatment with liraglutide, a decrease of 20%, consistent with the results of the LEAD series of tests. The compliance rate of HbA1c in this trial was 31.3%, which was considered to be related to the higher level of HbA1c before application of liraglutide and the shorter follow-up time. HbA1c is clinically used to guide and evaluate hypoglycemic therapy. Recently, clinical studies have shown that HbA1c is an important risk factor for NAFLD, may alert the occurrence of NAFLD. Bae et al. observed 7849 participants of NAFLD and the metabolic syndrome for 4 years. Four hundred thirty-five (5.5%) participants developed diabetes.

Table 3 Effects of liraglutide on obesity

Index	Before treatment ($n = 32$)	After treatment ($n = 32$)	p	95% CI
WC (cm)	103.27 ± 9.92	93.97 ± 8.35	< 0.001	(7.61, 11.05)
BMI (kg/m^2)	30.56 ± 4.06	28.01 ± 3.12	< 0.001	(1.99, 3.10)

History data were collected from medical records. Data are shown as mean ± SD. Data are presented as odds ratios (95% CI)

WC, waist circumference; *BMI*, body mass index = body weight (kg)/height (m)^2

Table 4 Effects of liraglutide on blood lipids

Index	Before treatment ($n = 32$)	After treatment ($n = 32$)	p	95% CI
TG (mmol/L)	2.95 ± 2.13	2.27 ± 1.31	0.010	(0.06,1.05)
TC (mmol/L)	4.92 ± 1.07	4.91 ± 1.00	0.958	(− 0.42,0.47)
HDL-C (mmol/L)	1.11 ± 0.31	1.17 ± 0.28	0.481	(− 0.21,0.10)
LDL-C (mmol/L)	3.01 ± 0.75	2.91 ± 0.79	0.465	(− 0.15,0.34)

Clinical history and data from most recent laboratory investigations within the past year were collected from medical records. Data are shown as mean ± SD. Data are presented as odds ratios (95% CI)

TG, total triglycerides; *TC*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol

NAFLD had an additive effect on the development of diabetes in patients with MetS [21].

Insulin resistance can promote the development of NAFLD [22]. The first hit of the classic "second strike theory" has been confirmed to be related to insulin resistance, which shows that insulin resistance is closely related to the onset of NAFLD. In the LEAD 2, 3, and 4 studies, after 24, 52, and 26 weeks of treatment with liraglutide, the results showed that liraglutide could significantly increase islet β-cell function and improve insulin resistance compared with glimepiride and improve islet function compared with gliclazide [18, 23, 24]. This test uses the C-peptide fitting HOMA-IR formula, which has been shown to be useful for determining insulin resistance in an individual. And the HOMA-IR index is positively correlated with the degree of insulin resistance [25]. Before and after treatment, HOMA-IR decreased from 1.504 ± 0.002 to 1.503 ± 0.002. The difference was statistically significant ($p < 0.05$). HOMA-β difference was not statistically significant ($p > 0.05$), but there is a certain degree of improvement compared with before treatment. Studies have shown that human islet beta cells produce new cells at a limited rate, requiring 6 to 12 months of treatment to alter islet beta cell architecture [26]. However, the treatment time of this experiment was only 3 months and only 8 patients in this experiment used a dose of liraglutide to 1.8 mg, which may cause inconsistency with the LEAD test results.

Studies have suggested that obese and the age of diabetic patients are risk factors for advanced liver fibrosis in NAFLD. And obesity is a common risk factor for T2DM and NAFLD, especially central obesity [27, 28]. WC and BMI can initially reflect central obesity. Central obesity increases the risk of cardiovascular and metabolic diseases, can aggravate insulin resistance and impair beta cell function, and form a vicious circle with T2DM and NAFLD. At present insulin, sulfonylureas, and thiazolidinediones in the treatment of T2DM hypoglycemic drugs can cause weight gain. Glycosidase inhibitors and DPP-4 inhibitors have no significant effect on body weight. Although metformin has a weight-reducing effect, it has limited effect and is related to the gastrointestinal reaction in the initial stage of medication. The GLP-1RA can directly act on the hypothalamus to suppress appetite, and also acts on the autonomic nervous system to delay gastric emptying, and finally achieve the effect of reducing body weight. At the same time, it has the effect of regulating lipid distribution and improving central obesity [29]. The WC of patients in this trial decreased from pre-treatment (103.27 ± 9.92 cm) to post-treatment (93.97 ± 8.35 cm). BMI decreased from pre-treatment 30.56 ± 4.06 kg/m^2 to 28.01 ± 3.12 kg/m^2 after treatment. The differences between the two groups were

Table 5 Effects of liraglutide on liver enzymes and FLI

Index	Before treatment ($n = 32$)	After treatment ($n = 32$)	p	95% CI
FLI	78.40 ± 16.96	57.96 ± 20.08	< 0.001	(15.33, 25.55)
GGT (U/L)	62.63 ± 71.61	38.13 ± 30.13	0.015	(2.79, 45.14)
ALT (U/L)	48.09 ± 29.21	43.63 ± 29.87	0.138	(− 1.64, 11.21)
AST (U/L)	27.25 ± 13.74	25.44 ± 16.69	0.009	(− 1.08, 5.69)

Clinical history and data from most recent laboratory investigations within the past year were collected from medical records. Data are shown as mean ± SD. Data are presented as odds ratios (95% CI)

FLI, fatty liver index; *GGT*, γ-glutamyl transpeptidase; *ALT*, alanine aminotransferase; *AST*, aspartate transaminase

$FLI = (e(0.953 \times \log e(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times WC - 15.745)) \div (1 + e(0.953 \times \log e(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times WC - 15.745)) \times 100$

The TG unit is mg/dL, the GGT unit is U/L, and the WC unit is cm

statistically significant ($p < 0.001$), confirming that liraglutide can improve the WC and BMI of patients, which was consistent with many studies. LEAD 1 suggests that liraglutide can reduce body fat content without reducing muscle mass. In the LEAD 1 to 5 series of studies, increasing the dose of liraglutide to 1.8 mg significantly reduced body weight and the reduction in body weight was positively correlated with dose size and also positively correlated with treatment duration. Liraglutide not only reduces subcutaneous fat but also reduces visceral fat content. It was confirmed in the LEAD 2 and 3 studies using CT analysis of body composition before and after treatment [18, 23, 24, 30, 31].

During the trial, no liver-protecting drugs were used in the patients. The data of ALT, GGT, and AST before and after treatment showed that GGT and AST decreased 39% and 7%. Although the difference between GGT and AST was statistically significant ($p < 0.05$), only a few of them showed abnormalities, so the difference was not clinically significant. ALT decreased by 9% after treatment compared with before treatment. The difference was not statistically significant ($p > 0.05$). At present, there is still a lack of research on the treatment of nonalcoholic steatohepatitis with liraglutide and relevant research is needed. During the trial, no lipid-regulating drugs were used in the patients. The statistical analysis before and after the application of liraglutide showed that TG had statistically significant difference. There were no significant differences in HDL-C, TC, and LDL-C, while the levels after treatment were improved compared with the pre-treatment levels. However, liraglutide reduced TC, LDL-C, TG, HDL-C, and FFAs levels in LEAD 4. This might be related to the application of liraglutide in this test being small (0.6 to 1.8 mg), the application time being short (only 3 months), and the test sample size being small (only 32 cases).

This test uses the FLI to measure the degree of fat accumulation before and after liver treatment. FLI is an indicator based on BMI, WC, TC, and GGT, used to assess liver fat accumulation. When FLI is lower than 30, fatty liver is excluded. While FLI is more than or equal to 60, fatty liver is considered. Studies support the predictive validity of FLI [32, 33]. At present, FLI has not been tested with liver biopsy. FLI, liver/spleen CT ratio and liver and kidney ultrasound index have a good correlation with the evaluation of NAFLD liver fat accumulation. At the same time, FLI assessed liver fat accumulation with quantitative indicators in several studies. Analysis of FLI before and after treatment showed that FLI decreased 26%, from pre-treatment (79.23 ± 16.56) to post-treatment (58.83 ± 19.75). And the difference of liraglutide on FLI was statistically significant ($p < 0.01$), showing that liraglutide can significantly reduce liver fat accumulation. And the difference of liraglutide on FLI was statistically significant ($p < 0.01$), showing that liraglutide can significantly reduce liver fat accumulation.

The mechanism by which liraglutide improves liver fat accumulation has not been elucidated. The possible mechanism is to play a role by improving insulin resistance and regulating liver lipid metabolism. Fibroblast growth factor 21 (FGF-21) is a regulator of insulin regulating sugar and lipid metabolism. It is produced mainly by the liver and to a lesser extent by adipose tissue. The study found that FGF-21 concentration was significantly increased in the plasma of NAFLD patients. At the same time, some studies have shown that the concentration of FGF-21 in T2DM combined with NAFLD plasma is significantly higher than that in the healthy group and the fatty liver group alone [34–36]. The above research suggests that the increase of FGF-21 level may be a compensation mechanism to improve insulin resistance and impaired insulin function. Studies have shown that the plasma FGF-21 concentration level in the GLP-1Ra intervention group is significantly higher than that in the placebo control group, suggesting that it can participate in regulating liver lipid metabolism by regulating FGF-12 levels. At the same time, studies have shown that cAMP-responsive element-binding protein H (CREBH) and peroxisome proliferator activated receptor α (PPARα) in the liver mutual coordination plays an important role in regulating lipid metabolism [37, 38]. The CREBH-PPARα-FGF21 axis is an indispensable part of the liver involved in mediating lipid and sugar metabolism. Some research results show that the mRNA levels of CREBH and PPARα transcripts and related proteins in the liver of diabetic rats are significantly reduced. However, the use of GLP-1Ra significantly increased the expression of CREBH and PPARα.

Hepatic lipid balance is maintained through the β-oxidation of fatty acids after entering the liver, the production of fat from scratch, and secretion of very low-density lipoprotein (VLDL) [39]. Defects on either side can cause liver lipid accumulation. Lipid breakdown causes the concentration of free fatty acids in the blood to rise, leading to impaired insulin signaling, reducing the metabolic clearance of glucose, and increasing the glucose content. Excessive sugar accumulation further increases insulin secretion and eventually unbalances the accumulation and breakdown of lipids. Insulin resistance outside the liver triggers the mobilization of peripheral fats, inhibits the use of free fatty acids, increases the concentration of triglycerides after esterification, and decreases the concentration of TGs secreted by the liver, resulting in liver cells fat accumulation inside. It can be seen that blood glucose, lipid metabolism disorders, and insulin resistance all directly or indirectly promote the occurrence and development of NAFLD.

In this study, we found that liraglutide can well control blood glucose, lipids, and body weight, improve insulin resistance, and combined with in vitro and in vivo, research data show that GLP-1 can directly affect liver cell lipid metabolism by binding to GLP-1 receptors. In summary, liraglutide has the

potential to be used as a new drug to treat NAFLD. Nevertheless, there are still several limitations of our study. Firstly, the number of patients included in the study was small, so the results obtained, to some extent, were not representative. Maybe we should expand the sample size as much as possible in the future studies, in order to get more convincing results. Secondly, due to the cross-sectional, retrospective design of the study, it was not possible to draw conclusions on the cause-and-effect relationship between risk factors and various diabetes-related complications.

Conclusion

In addition to effectively lowering glucose and improving islet resistance, liraglutide could also improve obesity and adjust blood lipids. However, the improvement of islet function might not be significant after 3 months of treatment. Liraglutide could reduce liver fat accumulation in patients with T2DM and NAFLD.

Funding information This study was supported by the National Science Foundation of Liaoning Province of China (No. 2015020310).

Compliance with ethical standards All procedures of the study were approved by the Ethics Committee of The First Affiliated Hospital of Dalian Medical University (YJ-KY-SB-2019-86). All procedures of the study were approved by The First Affiliated Hospital of Dalian Medical University (YJ-KY-SB-2019-86).

Conflict of interest The authors declare that they have no conflict of interest.

Abbreviations DM, diabetes mellitus; T2DM, type 2 diabetes; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; GLP-1, glucagon-like peptide 1; FLI, fatty liver index; BMI, body mass index; WC, waist circumference; WHO, World Health Organization; LADA, adult late-onset autoimmune diabetes; FPG, fasting plasma glucose; FBG, fasting blood glucose; 2hPBG, 2-h postprandial blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; FCP, fasting C-peptide; ALT, alanine transaminase; AST, aspartate transaminase; GGT, glutamyl transpeptidase; DPP-4, dipeptidyl peptidase IV; LEAD, liraglutide effect and action diabetes; FGF-21, fibroblast growth factor 21; IHL, intrahepatic lipids; CREBH, cAMP-responsive element-binding protein H; PPARα, peroxisome proliferator activated receptor α; VLDL, very low-density lipoprotein

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87:4–14.
2. Xu Y, Wang L, He J, Bi Y, Li M, Wang L, et al. 2010 China Noncommunicable Disease Surveillance Group: prevalence and control of diabetes in Chinese adults. JAMA. 2013;310:948–59.
3. Adams LA, Ratziu V. Non-alcoholic fatty liver – perhaps not so benign. J Hepatol. 2015;62:1002–4.
4. Bedi O, Aggarwal S, Trehanpati N, Ramakrishna G, Krishan P. Molecular and pathological events involved in the pathogenesis of diabetes-associated nonalcoholic fatty liver disease. J Clin Exp Hepatol. 2019;9:607–18.
5. Rhee EJ. Nonalcoholic fatty liver disease and diabetes: an epidemiological perspective. Endocrinol Metab (Seoul). 2019;34:226–33.
6. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015;62(1 Suppl):S47–64.
7. Alsabaani AA, Mahfouz AA, Awadalla NJ, Musa MJ, Al Humayed SM. Non-alcoholic fatty liver disease among type-2 diabetes mellitus patients in Abha City, south western Saudi Arabia. Int J Environ Res Public Health. 2018;15.
8. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol. 2019;71:793–801.
9. Sao R, Aronow WS. Association of non-alcoholic fatty liver disease with cardiovascular disease and subclinical atherosclerosis. Arch Med Sci. 2018;14:1233–44.
10. Nuffer WA, Trujillo JM. Liraglutide: a new option for the treatment of obesity. Pharmacotherapy. 2015;35:926–34.
11. Iepsen EW, Torekov SS, Holst JJ. Liraglutide for type 2 diabetes and obesity: a 2015 update. Expert Rev Cardiovasc Ther. 2015;13:753–67.
12. Feng W, Gao C, Bi Y, Wu M, Li P, Shen S, et al. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. J Diabetes. 2017;9:800–9.
13. Moreira GV, Azevedo FF, Ribeiro LM, Santos A, Guadagnini D, Gama P, et al. Liraglutide modulates gut microbiota and reduces NAFLD in obese mice. J Nutr Biochem. 2018;62:143–54.
14. Wong VW, Adams LA, de Lédinghen V, Wong GL, Sookoian S. Noninvasive biomarkers in NAFLD and NASH – current progress and future promise. Nat Rev Gastroenterol Hepatol. 2018;15:461–78.
15. Chen LD, Huang JF, Chen QS, Lin GF, Zeng HX, Lin XF, et al. Validation of fatty liver index and hepatic steatosis index for screening of non-alcoholic fatty liver disease in adults with obstructive sleep apnea hypopnea syndrome. Chin Med J. 2019;132:2670–6.
16. International Diabetes Federation. IDF Diabetes Atlas. 5th ed. Brussels: International Diabetes Federation; 2011.
17. Bellan M, Colletta C, Barbaglia MN, Salmi L, Clerici R, Mallela VR, Castello LM, Saglietti G, Carnevale Schianca GP, Minisini R, Pirisi M. Severity of nonalcoholic fatty liver disease in type 2 diabetes mellitus: relationship between nongenetic factors and PNPLA3/HSD17B13 polymorphisms. Diabetes Metab J 2019;43: 700–710.

18. Nauck M, Frid A, Hermansen K, Thomsen AB, During M, Shah N, et al. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. Diabetes Obes Metab. 2013;15:204–12.
19. Anirban M, Soumyabrata RC, Debmalya S, Bhattacharjee K. Liraglutide – Indian experience. Indian J Endocrinol Metab. 2018;22:818–26.
20. Chinese Diabetes Society. Guidelines for the prevention and treatment of type 2 diabetes in China (2017 edition). Chin J Diabetes Mellitus. 2018;10:4–67.
21. Bae JC, Kim SK, Han JM, Kwon S, Lee DY, Kim J, et al. Additive effect of non-alcoholic fatty liver disease on the development of diabetes in individuals with metabolic syndrome. Diabetes Res Clin Pract. 2017;129:136–43.
22. Kitade H, Chen G, Ni Y, Ota T. Nonalcoholic fatty liver disease and insulin resistance: new insights and potential new treatments. Nutrients. 2017;9.
23. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel treatment trial. Lancet. 2009;373:473–81.
24. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009;32:1224–30.
25. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53:251–60.
26. Chen C, Cohrs CM, Stertmann J, Bozsak R, Speier S. Human beta cell mass and function in diabetes: recent advances in knowledge and technologies to understand disease pathogenesis. Mol Metab. 2017;6:943–57.
27. Younossi ZM, Tampi RP, Racila A, Qiu Y, Burns L, Younossi I, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the United States. Diabetes Care. 2019. https://doi.org/10.2337/dc19-1113.
28. Younossi ZM, Henry L. The impact of obesity and type 2 diabetes on chronic liver disease. Am J Gastroenterol. 2019;114:1714–5.
29. Aroda VR. A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomized controlled trials. Diabetes Obes Metab. 2018;20:22–33.
30. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26:268–78.
31. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52:2046–55.
32. Drinda S, Grundler F, Neumann T, Lehmann T, Steckhan N, Michalsen A, et al. Effects of periodic fasting on fatty liver index – a prospective observational study. Nutrients. 2019;11.
33. Klisic A, Kavaric N, Ninic A. Predictive values of serum uric acid and alanine-aminotransferase for fatty liver index in montenegrin population. J Med Biochem. 2019;38(4):407–17.
34. Su X, Kong Y, Peng D. Fibroblast growth factor 21 in lipid metabolism and non-alcoholic fatty liver disease. Clin Chim Acta. 2019;498:30–7.
35. Wang YS, Ye J, Cao YH, Zhang R, Liu Y, Zhang SW, et al. Increased serum/plasma fibroblast growth factor 21 in type 2 diabetes mellitus: a systematic review and meta-analysis. Postgrad Med J. 2019;95:134–9.
36. Hu Y, Liu J, Zhang H, Xu Y, Hong T, Wang G. Exenatide treatment decrease fasting fibroblast growth factor 21 level in patients with newly diagnosed type 2 diabetes mellitus. Diabetes Metab. 2016;42:358–63.
37. Nakagawa Y, Shimano H. CREBH regulates systemic glucose and lipid metabolism. Int J Mol Sci. 2018;19.
38. Bougarne N, Weyers B, Desmet SJ, Deckers J, Ray DW, Staels B, et al. Molecular actions of PPARα in lipid metabolism and inflammation. Endocr Rev. 2018;39:760–802.
39. Cerk IK, Wechselberger L, Oberer M. Adipose triglyceride lipase regulation: an overview. Curr Protein Pept Sci. 2018;19:221–33.