Journal of Biosciences and Medicines, 2024, 12, 16-24
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

A Retrospective Analysis of Glucagon-Like Peptide 1 Receptor Agonists in Treating Type 2 Diabetes Mellitus Complicated by Nonalcoholic Fatty Liver Disease

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How to cite this paper: Chen, J.Q. and Wu, H.Y. (2024) A Retrospective Analysis of Glucagon-Like Peptide 1 Receptor Agonists in Treating Type 2 Diabetes Mellitus Complicated by Nonalcoholic Fatty Liver Disease. *Journal of Biosciences and Medicines*, **12**, 16-24.
https://doi.org/10.4236/jbm.2024.123002

Received: January 25, 2024
Accepted: March 5, 2024
Published: March 8, 2024

Abstract

Background: The objective of this study was to compare and analyze the variations in clinical indices before and after treatment of type 2 mellitus (T2DM) combined with nonalcoholic fatty liver disease (NAFLD) that were treated with glucagon-like peptide 1 receptor agonists (GLP-1RAs). **Methods:** The electronic medical record system was utilized to search for a total of 16 patients with type 2 diabetes complicated by NAFLD who were hospitalized at the First Affiliated Hospital of Yangtze University from October 2022 to April 2023 and treated with GLP-1RA for the first time. The clinical indices were compared before and after 12 weeks of treatment with GLP-1RA. **Results:** The liver-spleen CT ratio (L/S), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) in all patients treated with GLP-1RA after 12 weeks were significantly different ($P < 0.05$). Aspartate aminotransferase (AST) and high-density lipoprotein cholesterol (HDL-C) levels did not change significantly compared to the levels before treatment ($P > 0.05$). The patients were categorized into two groups based on the types of GLP-1RAs. The changes in L/S, TC, TG, and LDL-C in the long-acting group after treatment were statistically significant ($P < 0.05$), as were the changes in L/S, TC, and TG in the ultra-long-acting group after treatment ($P < 0.05$). LDL-C levels after treatment with ultra-long-acting GLP-1RA showed a difference at the 0.05 significance level from LDL-C levels after treatment with long-acting GLP-1RA. No statistically significant differences were observed in the levels of L/S, ALT, AST, GGT, TC, TG, and HDL-C. **Conclusions:** GLP-1RAs can improve liver function, regulate lipid metabolism, and reduce the severity of fatty liver in patients with T2DM complicated by NAFLD, which demon-

strates the importance of clinical applications.

Keywords

Glucagon-Like Peptide 1 Receptor Agonists, Nonalcoholic Fatty Liver Disease, Type 2 Diabetes Mellitus

1. Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) has rapidly increased, making it the most common chronic liver disease worldwide. NAFLD affects approximately 32.4% of the world population [1]. It is estimated that NAFLD affects approximately 30% of the general population, more than 80% of obese individuals, and more than 60% of patients with type 2 mellitus (T2DM) [2] [3]. Currently, there are no drugs specifically approved for the treatment of NAFLD [4]. In the 2020 international expert consensus, it was noted that NAFLD is a multi-system disease associated with metabolic disorders caused by multiple factors. The consensus suggested that NAFLD should be renamed as metabolic associated fatty liver disease, which further emphasized the correlation between NAFLD and T2DM. A variety of antihyperglycemic medications have been used to treat NAFLD, and promising results have been achieved. Preclinical studies and large-scale randomized controlled trials have demonstrated that glucagon-like peptide 1 receptor agonists (GLP-1RAs) can improve hepatic steatosis, balloon degeneration, and inflammation and prevent the progression of fibrosis [5] [6] [7]. A total of 16 patients were evaluated to determine the effects of GLP-1RA on L/S, liver function, and blood lipids in patients with T2DM and NAFLD.

2. Methods

2.1. Participants

Patients hospitalized in the Endocrinology Department of the First Affiliated Hospital of Yangtze University were searched in the electronic medical record system. Admission dates were set from October 1, 2022 to April 30, 2023. The disease diagnosis was set to fatty liver, and the search results were exported as an excel table. Patients with T2DM and NAFLD who received GLP-1RA treatment for the first time were searched manually.

2.2. Patients Selection

Patients were selected based on the following criteria: 1) met the 1999 WHO diagnostic criteria for T2DM: fasting plasma glucose ≥ 7.0 mmol/L and/or 2-hour post glucose load ≥ 11.1 mmol/L; 2) met the 2010 diagnostic criteria for NAFLD developed by the Chinese Medical Association of Hepatology: no history of alcohol consumption or less than 140 g/week (<70 g/week for female); the CT di-

agnosis of fatty liver was determined by a reduction in liver density and a liver/spleen CT ratio of less than 1.0; 3) treated with GLP-1RA for the first time; 4) had complete data, received continuous treatment with GLP-1RA for 12 weeks.

The patients exclusion criteria were as follows: 1) other types of diabetes besides T2DM, acute complications of diabetes, infections, severe liver and kidney damage and cardiac insufficiency; 2) complicated with viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hereditary liver disease, etc; 3) a history of medullary thyroid cancer; 4) a history of pancreatitis; 5) pregnancy.

2.3. Treatments

Treated with GLP-1RA alone or in combination with other antihyperglycemic medications and lipid-regulating medications, the treatment cycle lasted 12 weeks.

2.4. Observations

The liver-spleen CT ratio (L/S), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured. L/S was measured by radiologists in our hospital on the CT reading system. Biochemical markers were completed by the biochemical laboratory of our hospital, and all results were available on the electronic medical record system.

2.5. Statistical Analyses

The statistical software SPSS version 27.0 was used for data analysis, and quantitative variables were presented as the means ± standard deviations. Paired t tests were used to compare pre-treatment and post-treatment measurements within the same group. Comparisons between groups were conducted with independent sample t tests. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Results of Patients Inclusion

Sixteen patients were included based on the selection and exclusion criteria using the electronic medical record system. Including 12 male patients and 4 female patients, with ages ranging from 22 to 83 years and a mean age of 58.88 ± 16.10 years.

3.2. Comparison of Clinical Indices after 12 Weeks of Treatment with GLP-1RA

Compared the L/S between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the L/S increased from 0.85 ± 0.08 to 1.07 ± 0.15. The mean and 95% confidence interval (CI) of the difference was −0.23 (−0.31, −0.15), t =

−6.396, P = 0.000 < 0.05. Thus, there was a statistically significant difference in the L/S.

Compared the ALT (U/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the ALT decreased from 36.75 ± 33.55 to 17.94 ± 8.96. The mean and 95% CI of the difference was 18.81 (3.72, 33.90), t = 2.657, P = 0.018 < 0.05. Thus, there was a statistically significant difference in the ALT.

Compared the AST (U/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the AST decreased from 31.75 ± 25.23 to 22.81 ± 19.69. The mean and 95% CI of the difference was 8.94 (−1.15, 19.02), t = 1.889, P = 0.078 > 0.05. Thus, there was not a statistically significant difference in the AST.

Compared the GGT (U/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the GGT decreased from 61.13 ± 44.43 to 39.81 ± 22.72. The mean and 95% CI of the difference was 21.31 (7.12, 35.50), t = 3.201, P = 0.006 < 0.05. Thus, there was a statistically significant difference in the GGT.

Compared the TC (mmol/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the TC decreased from 5.18 ± 1.15 to 4.01 ± 1.12. The mean and 95% CI of the difference was 1.17 (0.64, 1.70), t = 4.725, P = 0.000 < 0.05. Thus, there was a statistically significant difference in the TC.

Compared the TG (mmol/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the TG decreased from 4.13 ± 3.89 to 2.20 ± 1.86. The mean and 95% CI of the difference was 1.93 (0.78, 3.08), t = 3.586, P = 0.003 < 0.05. Thus, there was a statistically significant difference in the TG.

Compared the HDL-C (mmol/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the HDL-C increased from 0.98 ± 0.18 to 1.10 ± 0.32. The mean and 95% CI of the difference was −0.11 (−0.30, 0.07), t = −1.323, P = 0.205 > 0.05. Thus, there was not a statistically significant difference in the HDL-C.

Compared the LDL-C (mmol/L) between pre-treatment and post-treatment of GLP-1RA in 16 patients, revealed that the LDL-C decreased from 2.62 ± 0.82 to 2.01 ± 0.66. The mean and 95% CI of the difference was 0.61 (0.25, 0.97), t = 3.588, P = 0.003 < 0.05. Thus, there was a statistically significant difference in the LDL-C (Table 1).

3.3. Comparison of Clinical Indices after 12 Weeks of Treatment with Long-Acting and Ultra-Long-Acting GLP-1RA

Patients were categorized into two groups based on the type of GLP-1RAs, including long-acting group (liraglutide) and ultra-long-acting group (dulaglutide, loxenatide, and semaglutide), and their outcomes were compared after 12 weeks of treatment. Nine patients were treated with liraglutide, four patients with dulaglutide, two patients with loxenatide, and one patient with semaglutide. Nine patients in the long-acting group, including 6 males and 3 females, aged 50 - 83

Table 1. Changes of clinical indices before and after treatment.

Groups	Pre-treatment	Post-treatment	MeanDiff (95%CI)	t value	P value
L/S	0.85 ± 0.08	1.07 ± 0.15	−0.23 (−0.31, −0.15)	−6.396	0.000
ALT (U/L)	36.75 ± 33.55	17.94 ± 8.96	18.81 (3.72, 33.90)	2.657	0.018
AST (U/L)	31.75 ± 25.23	22.81 ± 19.69	8.94 (−1.15, 19.02)	1.889	0.078
GGT (U/L)	61.13 ± 44.43	39.81 ± 22.72	21.31 (7.12, 35.50)	3.201	0.006
TC (mmol/L)	5.18 ± 1.15	4.01 ± 1.12	1.17 (0.64, 1.70)	4.725	0.000
TG (mmol/L)	4.13 ± 3.89	2.20 ± 1.86	1.93 (0.78, 3.08)	3.586	0.003
HDL-C (mmol/L)	0.98 ± 0.18	1.10 ± 0.32	−0.11 (−0.30, 0.07)	−1.323	0.205
LDL-C (mmol/L)	2.62 ± 0.82	2.01 ± 0.66	0.61 (0.25, 0.97)	3.588	0.003

years, with an average age of 66.11 ± 10.18 years. Seven patients in the ultra-long-acting group, including 6 males and 1 female, aged 22 - 70 years, with an average age of 49.57 ± 18.16 years.

The paired sample t test revealed that the changes in L/S, TC, TG, and LDL-C in the long-acting group after treatment were statistically significant ($P < 0.05$). However, the changes in ALT, AST, GGT, and HDL-C were not statistically significant ($P > 0.05$). The changes in L/S, TC, and TG in the ultra-long-acting group after treatment were statistically significant ($P < 0.05$), while the changes in ALT, AST, GGT, HDL-C, and LDL-C were not statistically significant ($P > 0.05$).

Using independent samples t test, there was no statistically significant difference in L/S, ALT, AST, GGT, TC, TG, HDL-C and LDL-C before treatment between the long-acting group and the ultra-long-acting group ($P > 0.05$), which could be compared.

After the treatment, the levels of ALT, AST, GGT, TC, TG and LDL-C in both groups decreased compared to pre-treatment, while the levels of L/S and HDL-C increased compared to pre-treatment. According to Levene's test for assessing the variance, all the significance values were >0.05, indicating that the variance was homogeneous. Examine the outcome of the "Assumed Equal Variance" in the first line. The results indicated that the LDL-C levels after treatment in the ultra-long-acting group differed from those after treatment in the long-acting group at the 0.05 level of significance ($0.01 < P = 0.026 < 0.05$). However, significant statistical difference was not observed in L/S, ALT, AST, GGT, TC, TG and HDL-C (Table 2).

4. Discussions

There is a complex pathogenesis for NAFLD that involves genetics, the environment, nutrition, and lifestyle factors, ultimately leading to the accumulation of fat in the liver [8]. A number of pathophysiological processes contribute to liver disease, including lipid accumulation, insulin resistance, imbalance in fatty acid intake and synthesis, fatty acid oxidation and liver secretion, increased

Table 2. Changes of clinical indices before and after treatment between long-acting group and ultra-long-acting group.

Groups	L/S		ALT (U/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
long-acting	0.86 ± 0.08	1.11 ± 0.17*	29.56 ± 26.43	15.78 ± 9.55
ultra-long-acting	0.83 ± 0.08	1.03 ± 0.13*	46.00 ± 41.30	20.71 ± 7.93
t value	0.627	0.934	−0.971	−1.102
P value	0.541	0.366	0.348	0.289

Groups	AST (U/L)		GGT (U/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
long-acting	29.78 ± 27.78	24.67 ± 26.01	65.89 ± 50.96	42.33 ± 23.64
ultra-long-acting	34.29 ± 23.43	20.43 ± 7.46	55.00 ± 37.34	36.57 ± 22.88
t value	−0.344	0.415	0.474	0.49
P value	0.736	0.684	0.643	0.631

Groups	TC (mmol/L)		TG (mmol/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
long-acting	5.09 ± 0.90	3.96 ± 1.43*	4.93 ± 4.91	2.61 ± 2.38*
ultra-long-acting	5.29 ± 1.49	4.06 ± 0.64*	3.09 ± 1.87	1.67 ± 0.72*
t value	−0.331	−0.171	0.932	1.006
P value	0.746	0.867	0.367	0.331

Groups	HDL-C (mmol/L)		LDL-C (mmol/L)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
long-acting	0.99 ± 0.20	1.05 ± 0.25	2.38 ± 0.55	1.69 ± 0.57*
ultra-long-acting	0.97 ± 0.17	1.16 ± 0.41	2.92 ± 1.04	2.41 ± 0.57
t value	0.153	−0.69	−1.334	−2.487
P value	0.881	0.501	0.204	0.026a

*indicates a significance level of $P < 0.05$ compared to pre-treatment. "a" indicates a difference at the 0.05 level of significance. "b" indicates a difference at the 0.01 level of significance.

hepatic glucose production and lipogenesis, mitochondrial dysfunction induced by oxidative stress, apoptosis and inflammation induced by lipotoxicity, which eventually lead to nonalcoholic fatty liver and can progress to nonalcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma, making it a primary factor contributing to the rise in morbidity and mortality related to liver diseases [9] [10]. GLP-1 is a peptide hormone produced by intestinal endocrine cells. It is found in α cells of the pancreas, certain brain regions, the heart, vascular tissues, as well as the kidneys, lungs, and gastrointestinal tract [11]. However, its expression in liver tissues remains controversial. Currently, it is widely believed that

the role of GLP-1 in the liver is mediated by an indirect pleiotropic mechanism, which encompasses various functions. It inhibits glucagon release, increases insulin secretion, slows gastric emptying, and enhances satiety [12]. Liraglutide has gradually become the first-line treatment for diabetic patients. Several studies have demonstrated that GLP-1RA monotherapy or combination therapy can decrease lipid accumulation and hepatic steatosis, as well as prevent the development of cardiovascular disease, renal disease, and other diseases [13] [14] [15]. This study involved patients treated with GLP-1RA alone or in combination with other antihyperglycemic and lipid-regulating medications, and the changes in imaging and biochemical parameters were analyzed to provide some guidance for clinical application.

In this retrospective analysis, there were 16 patients, including 12 male patients and 4 female patients, it is consistent with the conclusion that the incidence rate of men is higher than that of women [1]. Post-treatment revealed changes in 16 patients with T2DM combined with NAFLD compared to those in the pre-treatment. The changes in L/S, ALT, GGT, TC, TG, and LDL-C were statistically significant and consistent with related studies [16] [17]. However, the changes in AST and HDL-C were not statistically significant, which contradicts the results of related studies. The potential reasons include the retrospective nature of the analysis, lack of intervention in the patients' diet and exercise, variations in treatments, and inconsistencies in the types and dosages of therapeutic drugs administered to the patients. When comparing the observational indices before and after treatment with long-acting and ultra-long-acting GLP-1RA, only LDL-C levels in the ultra-long-acting group differed significantly from those in the long-acting group at the 0.05 level of significance. There was no statistically significant difference in L/S, ALT, AST, GGT, TC, TG and HDL-C. In a meta-analysis, long-acting GLP-1RAs significantly reduced TC and LDL compared with short-acting GLP-1RAs, there was no significant difference in TG and HDL, but the forest plot indicated that long-acting drugs might be more valuable in reducing TG [18]. However, the meta-analysis did not compare the clinical indices between the ultra-long-acting group and the long-acting group.

In the study period, we selected patients from October 1, 2022 to April 30, 2023, based on the high follow-up rate of patients in previous experiences, and to allow sufficient time for consulting the medical record system and collecting data. In the exclusion criteria, we exclude patients with acute complications of diabetes, severe liver and kidney damage, and other specified comorbidities, because they have confounding factors that reduce the reliability of data, and after removal, the homogeneity of the research object is increased, making the sample relatively homogeneous. However, there are also some limitations in this study: this was a retrospective study with individual treatment differences and a small sample size. Only the L/S, liver function, and blood lipids were analyzed. The study did not analyze changes in body weight, blood glucose, insulin content, insulin resistance index, and other parameters. There is a need to expand the

data, increase the number of observations, and conduct further analysis.

In conclusion, treating patients with T2DM and NAFLD with GLP-1RA can improve liver function, regulate lipid metabolism, and alleviate hepatic steatosis and is of great clinical significance in preventing the progression of NAFLD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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