Journal of Hainan Medical University

http://www.hnykdxxb.com

Regulating effect of liraglutide therapy on metabolic disorders in patients with newly diagnosed type 2 diabetes complicated with obesity

Dong−Mei Gao[1]✉, Shan−Dan Bao[2]

[1.] *Department of General Practice, Puhuangyu Community Health Service Center of Fengtai District Beijing, Fengtai District, Beijing 100075*

[2.] *Department of Endocrine, the First Hospital of Fangshan District Beijing, Fangshan District, Beijing 102400*

ARTICLE INFO

Article history:
Received 28 Jul 2017
Received in revised form 9 Aug 2017
Accepted 19 Aug 2017
Available online 28 Aug 2017

Keywords:
Type 2 diabetes mellitus
Obesity
Liraglutide
Lipid metabolism
Inflammatory response

ABSTRACT

Objective: To investigate the regulating effect of liraglutide therapy on metabolic disorders in patients with newly diagnosed type 2 diabetes complicated with obesity. **Methods:** A total of 118 patients with newly diagnosed type 2 diabetes complicated with obesity who were treated in the hospital between September 2014 and January 2017 were collected and divided into the control group (n=59) and observation group (n=59) by random number table. Control group received metformin therapy and the observation group received liraglutide therapy. The differences in levels of glucose metabolism indexes, lipid metabolism indexes and inflammatory factors were compared between the two groups before and after 4 months of treatment. **Results:** Before treatment, the differences in serum levels of glucose metabolism indexes, lipid metabolism indexes and inflammatory factors were not statistically significant between the two groups. after 4 months of treatment, serum FPG, FIN, F-CP, TC, TG, IL-1β, IL-6, CRP and TNF-α levels of both groups of patients were lower than those before treatment while HDL-C levels were higher than those before treatment, and serum FPG, FIN, F-CP, TC, TG, IL-1β, IL-6, CRP and TNF-α levels of observation group were lower than those of control group while HDL-C level was higher than that of control group. **Conclusion:** Liraglutide therapy can effectively optimize the glucose lipid metabolism and reduce the microinflammatory response in patients with type 2 diabetes mellitus complicated with obesity.

1. Introduction

In recent years, the probability of obesity in patients with newly diagnosed type 2 diabetes is higher and higher, obesity can further increase the risk of future cardiovascular events in patients with type 2 diabetes, and increase the difficulty of glycemic control, and the treatment of such patients has been the clinical difficulties[1,2]. Metformin is the most common clinical oral hypoglycemic drug, it was considered as the preferred drug for patients with obese type 2 diabetes, it lowers the blood sugar and also reduces the energy supply of glucose to the muscle tissue so as to cause weight loss in a lot of diabetic patients, but it causes serious gastrointestinal discomfort, and its effectiveness weakens with the extension of application time[3,4]. Liraglutide is the new hypoglycemic drug that inhibits glucagon secretion, promotes the islet β cell hyperplasia, and so on, and many scholars believe that the drug can more effectively control the blood sugar of patients with newly diagnosed type 2 diabetes[5,6]. In the research, metformin and liraglutide were used in clinical treatment of patients with type 2 diabetes associated with obesity respectively, and the application value was explored from the glucolipid metabolism, micro-inflammatory state and other aspects, now reported as follows.

2. Information and methods

2.1 General information

A total of 118 patients with newly diagnosed type 2 diabetes complicated with obesity who were treated in the hospital between September 2014 and January 2017 were selected as the research subjects, and the family members signed informed consent. The enrolled patients were divided into the control group (n=59)

✉Corresponding author: Dong-Mei Gao, Department of General Practice, Puhuangyu Community Health Service Center of Fengtai District Beijing, Fengtai District, Beijing 100075.
Tel: 18911713539
Fund Project: The Capital Health Development Research Project (No.: 2016-1-2057); the Capital Health Development Research Project (No.: 2016-2-2054); the Capital Clinical Characteristic Application Research Project (No.: Z151100004015021).

and observation group (n=59) by random number table. Control group included 31 men and 28 women that were 41-78 years old; observation group included 30 men and 29 women that were 43-79 years old. The gender and age distribution of the two groups were not significantly different (P>0.05), subsequent data were comparable, and the hospital ethics committee approved the study.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with type 2 diabetes mellitus for the first time; (2) BMI was in line with the obesity standard; (3) not receiving independent treatment before admission; (4) cooperating with the whole treatment and with complete data.

Exclusion criteria: (1) combined with hyperthyroidism, hypothyroidism and other endocrine diseases; (2) with long-term use of glucocorticoids; (3) combined with systemic inflammatory disease caused by pathogen infection; (4) combined with severe heart, liver and kidney insufficiency.

2.3 Therapy

Both groups received lifestyle interventions, including regular diet, reducing intake of foods rich in sugar and lipid, increasing quality protein intake, and appropriate exercise. Control group, on the basis of lifestyle intervention, received metformin treatment, specifically as follows: oral metformin (Yangzhou Zhongbao Pharmaceutical Co., Ltd., approved by H20052503), 1.0 g/time, 2 times/d, for continuous 4 months of treatment. Observation group of patients, on the basis of lifestyle intervention, received liraglutide treatment, specifically as follows: subcutaneous injection of liraglutide (Novo Nordisk Pharmaceuticals Co., Ltd., approved by J20160037), 0.6 mg/time, 1time/d, increasing the dose to 1.2 mg if there was no adverse reaction after 1 week, for continuous 4 months of treatment.

2.4 Observation indexes

Before treatment and after 4 months of treatment, 3.0 mL fasting cubital venous blood was extracted from two groups of patients, anti-coagulated, let stand at room temperature for stratification and centrifuged at low speed to get upper serum, which was frozen at -80 ℃ for test. Automatic biochemical analyzer (Abbott Pharmaceutical Co., Ltd., specifications Aeroset) was used to determine plasma glucose (FPG) levels, and automatic electrochemical luminescence analyzer (Roche Diagnostics GmbH, specifications Elecsys 2010) was used to determine insulin (FIN) and F-CP levels. Automatic biochemical analyzer was used to determine the serum contents of lipid metabolism indexes, including total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C). Enzyme-linked immunosorbent assay (ELISA) was used to determine the serum contents of inflammatory cytokines, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor (TNF- α).

2.5 Statistical processing

Statistical software was SPSS 24.0. Glucose metabolism indexes, lipid metabolism indexes and inflammatory factors belonged to measurement data and were in terms of mean ± standard deviation, and comparison was by t test. P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Glucose metabolism indexes

Before treatment and after 4 months of treatment, comparison of glucose metabolism indexes FPG (mmol/L), FIN (μU/mL) and F-CP (ng/mL) between two groups of patients was as follows: before treatment, serum FPG, FIN and F-CP levels were not statistically different between the two groups (P>0.05). Compared with same group before treatment, serum FPG, FIN and F-CP levels of both groups of patients decreased significantly after 4 months of treatment (P<0.05), and compared with those of control group after 4 months of treatment, serum FPG, FIN and F-CP levels of observation group decreased significantly after 4 months of treatment (P<0.05).

Table 1.
Comparison of glucose metabolism indexes before and after treatment.

Groups	n	Time	FPG	FIN	F-CP
Control group	59	Before treatment	12.17±1.84	25.28±4.19	9.38±1.56
		After 4 months of treatment	6.94±0.71*	15.62±1.53*	6.17±0.75*
Observation group	59	Before treatment	12.23±1.95	25.17±4.24	9.36±1.48
		After 4 months of treatment	5.16±0.53*#	8.35±1.93*#	3.62±0.45*#

Note: comparison of indexes within group before and after treatment, *P<0.05; comparison of indexes between groups after 4 months of treatment, #P<0.05.

Table 2.
Changes in lipid metabolism index levels before and after treatment (mmol/L).

Groups	n	Time	TC	TG	HDL-C
Control group	59	Before treatment	5.93±0.75	2.74±0.35	0.82±0.09
		After 4 months of treatment	4.67±0.54*	1.92±0.25*	0.97±0.15*
Observation group	59	Before treatment	5.91±0.73	2.72±0.37	0.83±0.09
		After 4 months of treatment	3.15±0.38*#	1.36±0.18*#	1.29±0.17*#

Note: comparison of indexes within group before and after treatment, P<0.05; comparison of indexes between groups after 4 months of treatment, #P<0.05.

Table 3.
Changes in inflammatory factor levels before and after treatment.

Groups	*n*	Time	IL-1 β	IL-6	CRP	TNF- α
Control group	59	Before treatment	16.29±2.17	19.32±2.45	2.46±0.31	37.27±4.51
		After 4 months of treatment	12.06±1.53*	13.13±1.59*	1.75±0.19*	20.63±2.77*
Observation group	59	Before treatment	16.21±2.09	19.27±2.38	2.43±0.34	37.19±4.37
		After 4 months of treatment	7.15±0.86*#	8.74±0.92*#	1.21±0.16*#	11.58±1.64*#

Note: comparison of indexes within group before and after treatment, *$P<0.05$; comparison of indexes between groups after 4 months of treatment, #$P<0.05$.

3.2 Lipid metabolism indexes

Before treatment and after 4 months of treatment, comparison of lipid metabolism indexes TC, TG and HDL-C between two groups of patients was as follows: before treatment, serum TC, TG and HDL-C levels were not statistically different between the two groups ($P>0.05$). Compared with same group before treatment, serum TC and TG levels of both groups of patients decreased significantly while HDL-C levels increased significantly after 4 months of treatment ($P<0.05$), and compared with those of control group after 4 months of treatment, serum TC and TG levels of observation group decreased significantly while HDL-C level increased significantly after 4 months of treatment ($P<0.05$).

3.3 Inflammatory factors

Before treatment and after 4 months of treatment, comparison of inflammatory factors IL-1 β (pg/mL), IL-6 (pg/mL), CRP (mg/L) and TNF- α (ng/L) between two groups of patients was as follows: before treatment, serum IL-1 β, IL-6, CRP and TNF- α levels were not statistically different between the two groups ($P>0.05$). Compared with same group before treatment, serum IL-1 β, IL-6, CRP and TNF- α levels of both groups of patients decreased significantly after 4 months of treatment ($P<0.05$), and compared with those of control group after 4 months of treatment, serum IL-1 β, IL-6, CRP and TNF- α levels of observation group decreased significantly after 4 months of treatment ($P<0.05$).

4. Discussion

At present, the number of newly diagnosed type 2 diabetes is increasing in our country each year, those combined with obesity have more difficult glycemic control than those with normal body weight and also higher probability of long-term complication of coronary heart disease, myocardial infarction and other serious cardiovascular events, and the glycemic control of such patients is the emphasis and difficulty in clinical research. Metformin was considered as the preferred hypoglycemic drug for patients with obese type 2 diabetes mellitus because it not only realizes hypoglycemic effect, but also reduce the patients' body weight to a certain extent, but along with the increase in its clinical application, many cases show that metformin is weak in reversing the progress of the diabetes, and looking for more efficient and safer oral hypoglycemic drugs is the key of clinical research. Liraglutide belongs to the human glucagon-like peptide 1 (GLP-1) analogue that combines and activates GLP-1 receptors to promote glucose concentration-dependent insulin secretion, and it has longer plasma half-life and can exert positive hypoglycemic effect for a long time[7-9]. In order to choose more efficient and reasonable hypoglycemic drugs, metformin and liraglutide were both used for the treatment of patients with newly diagnosed type 2 diabetes associated with obesity in this study, and their roles in glucolipid metabolism, micro-inflammation state and other aspects were explored.

Sugar metabolism disorder is a typical feature of newly diagnosed type 2 diabetes, it is specifically characterized by higher fasting plasma glucose, lower insulin sensitivity, higher insulin levels and so on, and detecting the changes in their levels is also the most common means to judge patients′ disease severity and drug control effect[10,11]. In this study, the differences in glucose metabolism indexes were compared between the two groups, and it was found that serum FPG, FIN and F-CP levels of both groups of patients were lower than those before treatment; further compared with control group, the observation group were with lower serum levels of FPG, FIN and F-CP after treatment, indicating that both metformin and liraglutide can optimize the levels of glucose metabolism, but the liraglutide treatment can more effectively reduce fasting plasma glucose and optimize the insulin sensitivity.

There is significantly abnormal lipid metabolism in patients with type 2 diabetes complicated with obesity, which leads to the accumulation of fat molecules in the body and aggravates the condition of diabetes[12]. TC and TG are the most typical indexes of lipid metabolism, and their levels are positively correlated with the abnormal degree of lipid metabolism. They are the specific forms of lipid accumulation in the body. HDL-C is a specific molecule with the role of "de-fat", and obese diabetic patients generally have a decrease in HDL-C content, and its content is negatively correlated with the abnormal degree of lipid metabolism[13,14]. In the study, the differences in serum levels of above lipid metabolism indexes were compared between the two groups before and after treatment, and it was found that compared with those before treatment, serum TC and TG contents reduced while HDL-C contents increased after treatment; further compared with the control group, the observation group were with lower contents of serum TC and TG as well as higher HDL-C content, showing that metformin and liraglutide can promote the lipid metabolism of patients with newly diagnosed

type 2 diabetes associated with obesity to different extent, but the liraglutide can more effectively balance the lipid metabolism process.

In recent years, it is believed that inflammation plays a media role in the occurrence of type 2 diabetes mellitus, and the relationship between inflammation and diabetes has received attention at present[15]. More and more scholars support that type 2 diabetes mellitus is a chronic low inflammatory state, and the contents of inflammatory markers can predict the occurrence of type 2 diabetes and determine the severity of the disease. It has been confirmed that the contents of the typical inflammatory factors such as CRP and TNF-α increase in patients with type 2 diabetes mellitus, and those with poor disease control have higher levels. IL-1β and IL-6 are the most commonly studied clinical pro-inflammatory mediators, and high blood glucose can induce their secretion, further induce the accumulation of neutrophil cells and continuously secrete other inflammatory factors[16-18]. In this study, the levels of inflammatory factors in serum were compared between the two groups, and it was found that compared with those before treatment, serum IL-1β, IL-6, CRP and TNF-α levels of both groups of patients decreased after treatment; further compared with those of control group, serum IL-1β, IL-6, CRP and TNF-α levels of observation group were lower after treatment, suggesting that both metformin and liraglutide treatment can relieve the patient's micro-inflammation state, and the role of liraglutide is more significant.

Liraglutide can be more effective to optimize glucose and lipid metabolism disorder and further ease the micro-inflammatory state in patients with newly diagnosed type 2 diabetes mellitus complicated with obesity, it is a more ideal oral hypoglycemic drug, and it is worth active application in clinical intervention of such patients in the future.

References

[1] Elkhidir AE, Eltaher HB, Mohamed AO. Association of lipocalin-2 level, glycemic status and obesity in type 2 diabetes mellitus. *BMC Res Notes* 2017; **10**(1): 285.

[2] Gorgojo-Martínez JJ, Feo-Ortega G, Serrano-Moreno C. Effectiveness and tolerability of liraglutide in patients with type 2 diabetes mellitus and obesityafter bariatric surgery. *Surg Obes Relat Dis* 2016; **12**(10): 1856-1863.

[3] Lee KT, Yeh YH, Chang SH, See LC, Lee CH, Wu LS, et al. Metformin is associated with fewer major adverse cardiac events among patients with a new diagnosis of type 2 diabetes mellitus: A propensity score-matched nationwide study. *Medicine (Baltimore)* 2017; **96**(28): e7507.

[4] Li J, Gong Y, Li C, Lu Y, Liu Y, Shao Y. Long-term efficacy and safety of sodium-glucose cotransporter-2 inhibitors as add-on to metformintreatment in the management of type 2 diabetes mellitus: A meta-analysis. *Medicine (Baltimore)* 2017; **96**(27): e7201.

[5] Vega-Hernandez G, Wojcik R, Schlueter M. cost-effectiveness of liraglutide versus dapagliflozin for the treatment of patients with type 2 diabetes mellitus in the UK. *Diabetes Ther* 2017; **8**(3): 513-530.

[6] Alatorre C, FernandezLando L, Yu M, Brown K, Montejano L, Juneau P, et al. Treatment patterns in patients with type 2 diabetes mellitus treated with glucagon-like peptide-1 receptor agonists: Higher adherence and persistence with dulaglutide compared with once-weekly exenatide and liraglutide. *Diabetes Obes Metab* 2017; **19**(7): 953-961.

[7] Hunt B, Vega-Hernandez G, Valentine WJ, Kragh N. Evaluation of the long-term cost-effectiveness of liraglutide vs lixisenatide for treatment of type 2 diabetes mellitus in the UK setting. *Diabetes Obes Metab* 2017; **19**(6): 842-849.

[8] Ericsson A, Lundqvist A. Cost effectiveness of insulin degludec plus liraglutide (ideglira) in a fixed combination for uncontrolled type 2 diabetes mellitus in Sweden. *Appl Health Econ Health Policy* 2017; **15**(2): 237-248.

[9] Dilla T, Alexiou D, Chatzitheofilou I, Ayyub R, Lowin J, Norrbacka K. The cost-effectiveness of dulaglutide versus liraglutide for the treatment of type 2 diabetes mellitus in Spain in patients with BMI 30 kg/m^2. J *Med Econ* 2017; **20**(5): 443-452.

[10]Lee CJ, Iyer G, Liu Y, Kalyani RR, Bamba N, Ligon CB, et al. The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: A systematic review and meta-analysis of intervention studies. *J Diabetes Complications* 2017; **31**(7): 1115-1126.

[11]Tanaka K, Okada Y, Mori H, Miyazaki M, Kuno F, Sonoda S, et al. Comparative analysis of the effects of alogliptin and vildagliptin on glucose metabolism in type 2 diabetes mellitus. *Endocr J* 2017; **64**(2): 179-189.

[12]Chen Y, Zhao Q, Du G, Xu Y. Association between serum osteocalcin and glucose/lipid metabolism in Chinese Han and Uygur populations with type 2 diabetes mellitus in Xinjiang: two cross-sectional studies. *Lipids Health Dis* 2017; **16**(1): 139.

[13]Sun LL, Zhang SJ, Chen MJ, Elena K, Qiao H. Relationship between modulator recognition factor 2/at-rich interaction domain 5b gene variations and type 2 diabetes mellitus or lipid metabolism in a northern Chinese population. *Chin Med J (Engl)* 2017; **130**(9): 1055-1061.

[14]Kelany ME, Hakami TM, Omar AH, Abdallah MA. Combination of sitagliptin and insulin against type 2 diabetes mellitus with neuropathy in rats: neuroprotection and role of oxidative and inflammation stress. *Pharmacology* 2016; **98**(5-6): 242-250.

[15]Liu Y, Liu SX, Cai Y, Xie KL, Zhang WL, Zheng F. Effects of combined aerobic and resistance training on the glycolipid metabolism and inflammationlevels in type 2 diabetes mellitus. *J Phys Ther Sci* 2015; **27**(7): 2365-2371.

[16]Gomez Garcia A, Rivera Rodriguez M, Gomez Alonso C, Rodriguez Ochoa DY, Alvarez Aguilar C. Myeloperoxidase is associated with insulin resistance and inflammation in overweight subjects with first-degree relatives with type 2 diabetes mellitus. *Diabetes Metab J* 2015; **39**(1): 59-65.

[17]Kalninova J, Jakus V, Glejtkova M, Kuracka L, Sandorova E. Impact of glycemic control on advanced glycation and inflammation in overweight and obese patients with type 2 diabetes mellitus. *Bratisl Lek Listy* 2014; **115**(8): 457-468.

[18]Jakus V, Sandorova E, Kalninova J, Krahulec B. Monitoring of glycation, oxidative stress and inflammation in relation to the occurrence of vascular complications in patients with type 2 diabetes mellitus. *Physiol Res* 2014; **63**(3): 297-309.