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Effect of liraglutide treatment on vascular endothelial function and pancreatic β−cell function in elderly type 2 diabetic patients

Xiao−Yan Gao[1], Dong−Xing Liu[2]✉, Feng−Hua Li[3]

[1]*Medical Ward, Jinan Bridge People's Hospital, Shandong, Jinan 250031, China*
[2]*Emergency Center, Provincial Hospital Affiliated to Shandong University, Jinan 250021, Shandong, China*
[3]*Department of Endocrinology, Dezhou People's Hospital, Dezhou 253000, Shandong, China*

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ABSTRACT

Objective: To observe the effects of liraglutide treatment on vascular endothelial function and pancreatic β cell function in elderly patients with type 2 diabetes mellitus (T2DM). **Methods:** A total of 100 cases of elderly patients with type 2 diabetes mellitus were selected and randomly divided into observation group and control group, each group was 50 cases, the control group received conventional therapy of metformin hydrochloride combined with glimepiride based on blood glucose levels, the observation group was given liraglutide treatment on the basis of conventional treatment. The improvements of endothelial function and pancreatic β-cell function in two groups were observed for 1 month and 3 months. **Results:** (1) The levels of ET-1, NO and FMD in both groups were not statistically significant before treatment. After treatment for 1 month and 3 months, the levels of NO and FMD in the observation group increased and was higher than that in the control group, the level of ET-1 in the observation group decreased and was lower than that in the control group with statistical difference; (2) The levels of FPG, 2hPBG and HbA1c in both groups were not statistically significant before treatment. After treatment for 1 month and 3 months, the levels of FPG, 2hPBG and HbA1c in the observation group were significantly lower than that in the control group; (3) The levels of FIns, HOMA-IR and HOMA-B in both groups were not statistically significant before treatment. After treatment for 1 month and 3 months, the levels of FIns and HOMA-B in the observation group increased and were significantly higher than that in the control group, the level of HOMA-IR in the observation group decreased and was significantly lower than that in the control group. **Conclusion:** Liraglutide treatment in elderly patients with T2DM can effectively improve endothelial function and islet β cell function.

1. Introduction

Many studies confirmed that vascular endothelial dysfunction and impaired pancreatic β cell function existed in elderly patients with type 2 diabetes (T2DM), vascular endothelial dysfunction is an independent risk factor of leading to atherosclerosis and cardiovascular disease[1,2], meanwhile, the extent of impaired pancreatic β cell function has sterner influences on the treatment of T2DM. In recent years, the researches of new medication for improving vascular endothelial function and pancreatic β cell function have attracted extensive concern in clinic[3]. Liraglutide is a new generation of hypoglycemic drug which is a receptor stimulant of glucagon-like peptide 1 (GLP-1) and starts to apply in clinical. Our study showed that liraglutide can effectively improve endothelial function and islet β cell function. Details as follows.

2. Clinical data and methods

2.1. General data

From January 2014 to December 2015, 100 cases of elderly patients with type 2 diabetes from Medical ward of Jinan Bridge people's Hospital were collected and randomly divided into observation group and control group, with 50 cases in each group. This study was approved by the Ethics Committee, all patients volunteered for the study and signed the informed consent. In the

✉Corresponding author: Dong-Xing Liu, Emergency Center, Provincial Hospital Affiliated to Shandong University, Jinan.
Tel: 13789812918
E-mail: gaoxiaoyan888225@163.com
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observation group, total of 50 cases were composed of 27 male and 23 female, who were 61-72 (65.83±3.76) years old, body mass index (BMI) was 22.36-28.62 kg/m^2 and the average was (25.65±2.21) kg/m^2, the level of fasting blood-glucose (FPG) was 7.23-10.21 mmol/L and the average was (8.45±1.22) mmol/L. In the control group, total of 50 cases were composed of 28 male and 22 female, who were 61-74 (65.69±3.73) years old, BMI was 22.06-28.75 kg/m^2 and the average was (25.71±2.28) kg/m^2, the level of FPG was 7.22-11.07 mmol/L and the average was (8.47±1.36) mmol/L. The gender, age, course of disease, FPG and BMI levels were not statistically different (P>0.05).

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) The diagnosis of T2DM was according to the diagnostic criteria of <China Guideline for Type 2 Diabetes>[4] enacted by Chinese Diabetes Society in 2010, FPG 7.0 mmol/L or random blood sugar 11.1 mmol/L; (2 h blood glucose, 2 h PBG) 11.1 mmol/L. (2) Age>60 years. (3) Incipient patients. (4) Medical behaviors are good and cooperate with treatment and follow-up. (5) With complete medical records and laboratory examination indexes.

Exclusion criteria: (1) High blood sugar or type 1 diabetes caused by other diseases. (2) Combined liver and kidney dysfunction, other endocrine disease, cardiovascular disease or malignant tumor. (3) Combined contraindication of liraglutide, such as inflammatory bowel disease and thyroid tumor.

2.3. Therapeutic method

Patients in both groups were given T2DM diet prescription control according to individual circumstance, received basic treatments including health education and individual movement scheme.

Control group: Patients were given peroral treatment of metformin hydrochloride combined with glimepiride tablets, the initial metering of metformin hydrochloride (Produced by Sino-American Shanghai Squibb co., LTD. approved by H20023370, batch number was 20131115, 20141020) was 0.25 g•once^{-1}, 2 times•d^{-1}, the amount was gradually added according to the curative with generally 1^{-1}.5 g•d^{-1}. The initial metering of glimepiride tablets (Produced by Sanofi (Beijing) Pharmaceutical co., LTD, approved by H20057672, batch number was 20131022, 20141206) was 0.2 mg•once^{-1}, once•d^{-1}, the amount was gradually added according to the curative with generally 4 mg•once^{-1}, once•d^{-1}, the largest maintenance dose should not exceeded 6 mg•once^{-1}, once•d^{-1}.

Observation group: Liraglutide (Produced by Danish Novo Nordisk, approved by J20110026, batch number was 20131206, 20141109) was used on the basis of conventional therapy in control group with subcutaneous injections, 1.2 mg•once^{-1}, once•d^{-1}.

Patients in both groups were continuously treated for 3 months. Pay close attention to drug adverse reactions during the treatment, and deal with complications actively.

2.4. Obvervational index

(1)Endothelial function indexes in both groups were compared before treatment, treatment for 1 month and 3 months, including Endothelin-1 (ET-1), Nitric oxide (NO), Flow-mediated vasodilation (FMD); Blood NO was detected by nitrate reduction method, ET-1 was detected by radioimmunoassay, FMD was detected by Doppler ultrasound instrument (GE Logiq S8 type, USA) and radio frequency probe of blood vessels. (2)Blood sugar indexes in both groups were compared before treatment, treatment for 1 month and 3 months, including FPG, 2hPBG and HbA1c. Blood sugar was detected by glucose oxidase method, HbA1c was detected by chromatography. (3)Pancreatic β cell function indexes in both groups were compared before treatment, treatment for 1 month and 3 months, including fasting insulin (Fins), homeostasis model assessment-insulin resistance index (HOMA-IR), homeostasis model assessment-B (HOMA-B). Blood sugar was detected by glucose oxidase method, insulin was detected by radioimmunoassay, HOMA-IR＝FPG FINS/22.5, HOMA-B＝20×FINS/(FPG-3.5).

2.5. Statistics

Measurement data were described as mean ± standard deviation after normality test, comparison between the different points was adopted by analysis of variance with single factor and repeated measurements, inter-group comparison was carried out by t test. SPSS 17.0 statistical software was adopted for data analysis, values of P<0.05 were considered to be statistically significant.

3. Results

3.1. Comparison of endothelial function indexes before and after treatment

The levels of ET-1, NO and FMD in both groups were not statistically significant before treatment (P>0.05). After treatment for 1 month and 3 months, level of ET-1 in both groups decreased significantly, level of NO in both groups increased significantly, and the comparison between different points was considered to be statistically significant (P<0.05). The level of FMD in the observation group increased significantly after treatment for 1 month and 3 months, and the comparison between different points was considered to be statistically significant (P<0.05), while the level of FMD in the control group was not statistically significant (P>0.05). After treatment for 1 month and 3 months, level of ET-1 in the observation group was significantly lower than that in the control group, levels of NO and FMD in the observation group were significantly higher than that in the control group, and the comparison between two groups was considered to be statistically significant (P<0.05). See Table 1.

3.2. Comparison of blood sugar indexes before and after treatment

The levels of FPG, 2hPBG and HbA1c in both groups were not statistically significant before treatment (P>0.05). After treatment for 1 month and 3 months, levels of FPG, 2hPBG and HbA1c in both groups decreased significantly, and the comparison between different points was considered to be statistically significant (P<0.05). After treatment for 1 month and 3 months, levels of FPG, 2hPBG and HbA1c in the observation group were significantly lower than that in the control group, and the comparison between two groups was considered to be statistically significant (P<0.05). See Table 2.

3.3. Comparison of pancreatic β cell function indexes before and after treatment

The levels of Fins, HOMA-IR and HOMA-B in both groups were not statistically significant before treatment (P>0.05). After

treatment for 1 month and 3 months, levels of Fins and HOMA-B in both groups increased significantly, level of HOMA-IR in both groups decreased significantly, and the comparison between different points was considered to be statistically significant (P<0.05). After treatment for 1 month and 3 months, levels of Fins, HOMA-IR and HOMA-B in control group were not statistically significant compared with that before treatment (P>0.05). After treatment for 1 month and 3 months, levels of Fins and HOMA-BFMD in the observation group were significantly higher, while level of HOMA-IR was significantly lower than that in the control group, and the comparison between two groups was considered to be statistically significant (P<0.05). See Table 3.

4. Discussion

In 2013, the diabetes map published by International Diabetes Federation (IDF) showed that China has become the country with the largest population of diabetes all over the world, T2DM patients account for upwards of 90[5]. Clinical studies have confirmed that elderly T2DM patients have different degrees of impaired endothelial function, which are key independent risk factors of leading to atherosclerosis and cardiovascular disease[6,7]. In addition, function and quantity of pancreatic β cell gradually decline with the development of T2DM, resulting in more and more difficult to control the stability of the blood sugar level, and decrease of body's sensitivity due to endogenous insulin secretion gradually reduce[8]. Numerous elderly T2DM patients adopt the simple oral medication which could achieve the purpose of hypoglycemic by promoting insulin secretion and increasing insulin sensitivity, but combined insulin therapy gradually replace it in 10 years[9], while this therapy method has poor effects on improvement of vascular endothelial function and pancreatic β cell function in elderly T2DM patients and still cannot achieve clinical satisfaction. In recent years, liraglutide was used as a new diabetes drug, began to applied in clinical and received good effects.

Clinical researches at home and abroad reported that vascular endothelial injury was closely related to the regulation of vascular active substances, such as ET-l and NO[10,11]. The abnormal levels of ET-l and NO could lead to abnormal vasomotor function, the level of serum ET-1 increased when arterial endothelial function damage exits, and decrease of NO is of great significance to predict endothelial injury severity. Dai Yao et al[12] have studied and confirmed that liraglutide as a receptor stimulant of glucagon-like peptide 1 (GLP-1) had remarkable effects on vascular endothelial dysfunction induced by high blood sugar, could effectively decrease the level of ET-1 and improve FMD. This study found that levels of ET-l and NO have been improved in elderly T2DM patients which were given peroral treatment of metformin hydrochloride combined with glimepiride tablets, while the improvement of FMD was not obvious. While the extents of ET-l decrease, NO and FMD increase in the patients given with liraglutide were significantly higher than that in the control group, adequately confirmed that liraglutide had remarkable effects on improvement of endothelial function. Analyzing the reasons, in one hand, it is confirmed that liraglutide can effectively inhibit the expression of plasminogen

Table 1.
Comparison of endothelial function indexes before and after treatment.

Index	Group	n	Before treatment	Treatment for 1 month	Treatment for 3 months	F	P
ET-1(ng•L^{-1})	Observation	50	106.47±8.17	85.68±7.26*	53.11±4.09*	65.34	<0.05
	Control	50	108.36±8.21	95.64±7.53	67.09±5.17	51.31	<0.05
NO(umol•L^{-1})	Observation	50	48.67±3.74	60.15±4.19*	68.61±5.28*	35.19	<0.05
	Control	50	47.84±4.02	51.22±5.06	59.37±5.36	24.38	<0.05
FMD(%)	Observation	50	3.14±0.23	3.35±0.31*	5.12±0.91*	14.27	<0.05
	Control	50	3.19±0.27	3.28±0.46	3.43±0.47	3.15	>0.05

Note: compared with control group: *P<0.05.

Table 2.
Comparison of blood sugar indexes before and after treatment.

Index	Group	n	Before treatment	Treatment for 1 month	Treatment for 3 months	F	P
FPG (mmol/L)	Observation	50	8.45±1.22	6.90±0.66*	6.08±0.45*	11.32	<0.05
	Control	50	8.47±1.36	7.12±1.38	6.73±0.42	8.52	<0.05
2hPBG (mmol/L)	Observation	50	12.46±2.29	8.96±0.62*	8.15±0.66*	13.45	<0.05
	Control	50	12.51±2.21	11.08±0.71	9.09±0.67	9.37	<0.05
HbA1c(%)	Observation	50	7.59±1.23	6.82±1.06*	6.23± 0.85*	8.25	<0.05
	Control	50	7.54±1.18	7.11±1.05	6.77±0.92	7.15	<0.05

Note: compared with control group: *P<0.05.

Table 3.
Comparison of pancreatic β cell function indexes before and after treatment.

Index	Group	n	Before treatment	Treatment for 1 month	Treatment for 3 months	F	P
Fins (mIU/L)	Observation	50	7.26±0.91	9.16±1. 67*	10.58±1.63*	22.32	<0.05
	Control	50	7.38± 0.85	7.61±1.02	7.65±1.21	3.65	>0.05
HOMA-IR	Observation	50	4.62±0.52	3.75±0.45*	3.06±0.38*	9.25	<0.05
	Control	50	4.64±0.61	4.25±0.63	4.21±0.72	3.23	>0.05
HOMA-B	Observation	50	32.52±12.86	51.65±14.32*	60.11±16.37*	22.37	<0.05
	Control	50	32.45±11.39	32.72±12.08	33.86±11.59	3.12	>0.05

Note: compared with control group: *P<0.05.

activator inhibitor type-1 (PAI-1) and vascular adhesion molecule (VAM) by cultivating human umbilical vein endothelial cells in vitro, PAI-1 and VAM are both important basis of occurrence and development in diabetic atherosclerosis[13]. In the other hand, increase of inflammatory factors could stimulate the release of vascular active substances including ET-l and NO which have correlation, and liraglutide could effectively reduce the inflammatory reaction of diabetic patients and maybe the reason of preventing vascular endothelial dysfunction[14]. In addition, liraglutide could inhibit the increase of intracellular reactive oxygen species induced by intermittent high glucose, and ccould inhibit endothelial cell apoptosis rate and activation of Caspase-3 protein, indicated that liraglutide ccould effectively improve vascular endothelial cell oxidative damage induced by intermittent high glucose[15,16].

Chen Pin et al[17] have studied and confirmed that liraglutide had remarkable effects on stabilization and improvement of sugar metabolism, recovering islet β cell secretory function and improving insulin sensitivity in newly diagnosed T2DM patients with glycosylated HbA1c > 9%. This study found that levels of FPG, P2hPG and HbA1c decreased in elderly T2DM patients which were given peroral treatment of metformin hydrochloride combined with glimepiride tablets, while the improvements of the indexes in the patients given with liraglutide were better than that in the patients with conventional drug treatment. Further observation on pancreatic β cell function indexes found that the levels of Fins, HOMA-IR and HOMA-B in elderly T2DM patients which were given peroral treatment of metformin hydrochloride combined with glimepiride tablets had no significant effects after treatment ($P>0.05$), but the levels of Fins, HOMA-IR and HOMA-B in the patients given with liraglutide improved significantly compared with that before treatment ($P<0.05$), and the levels of Fins and HOMA-B in the patients given with liraglutide were higher, level of HOMA-IR was lower than that in the patients with conventional drug treatment, indicated that hypoglycemic drugs including liraglutide, biguanides and sulfonylureas had effective synergy on controlling blood glucose level in elderly T2DM patients, also indicated that liraglutide had a significant effect on improving pancreatic β cell function. Analyzing the reasons, in one hand, it is confirmed that GLP-1 receptor stimulant could improve the secretion of FIns in β cells and inhibit secretion of glucagon by glucose concentration dependent, and could effectively delay gastric emptying and suppresses appetit[18]. In the other hand, it is found that liraglutide could inhibit the degradation of glucose-dependent insulinotropic polypeptide in the restoration of glucose tolerance by some examples of animals, and promote the regeneration of pancreatic β cell[19,20], and contribute to improve levels of Fins, HOMA-IR and HOMA-B.

In conclusion, liraglutide can effectively reduce the blood sugar level, improve vascular endothelial function and pancreatic β cell function in elderly T2DM patients on the basis of hypoglycemic drugs, and is worthwhile for spreading in clinical practice.

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