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Effect of Semaglutide on C-peptide levels in patients with type 2 diabetes

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Abstract: The study evaluated the effect of semaglutide treatment for type 2 diabetes mellitus (T2DM), specifically examining its effect on C-peptide levels. A total of 80 patients hospitalized for T2DM were included (January 2022–December 2023), and all patients had conventional treatment with oral metformin. Patients in the control group received subcutaneous insulin aspart, while patients in the observation group received subcutaneous semaglutide. Key variables, fasting blood glucose (FBG), 2-hour postprandial blood glucose (2h-PBG), and time to target blood glucose, were assessed at the baseline and again after three months. Serum endothelin-1 (ET-1), functional vasodilation (FMD), fasting C-peptide, fasting insulin (FINS), and the insulin resistance index (Homa-IR) were also measured. At the end of three months, the observation group had significantly lower 2h-PBG (9.01±0.53 mmol/L) and FBG (6.13±0.68 mmol/L) than the control group ($P<0.05$). Additionally, the time to target glucose was shorter in the observation group (3.88±0.69 vs. 5.73±1.01 days, $P<0.05$). The observation group also had lower ET-1, higher FMD, and increased Homa-IR ($P<0.05$). In conclusion, semaglutide optimizes glycemic control, lowers insulin resistance, and increases vasorelaxation function. Semaglutide has great potential as a therapeutic agent in T2DM.

Keywords: Type 2 diabetes mellitus, semaglutide, long-acting GLP-1 analogues, C-peptide levels, insulin resistance.

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INTRODUCTION

As living standards continue to rise, the prevalence of diabetes has increased significantly, becoming a major global public health issue. Diabetes is primarily caused by insufficient insulin secretion and insulin resistance, leading to metabolic dysregulation. In 2021, approximately 537 million people worldwide were diagnosed with diabetes, and this number is projected to rise to 783 million by 2045, with 95% of these cases being type 2 diabetes mellitus (T2DM) (Ma *et al*., 2022). T2DM is influenced by multiple factors, including genetics and environmental conditions and its complex pathophysiological mechanisms. Key contributors include insulin resistance, pancreatic β-cell dysfunction and chronic inflammation, which ultimately lead to vascular complications such as cardiovascular disease, renal impairment, and retinopathy (Henson *et al*., 2022). Despite significant advancements in diabetes treatment over the past two decades, cardiovascular disease remains a leading cause of morbidity and mortality among T2DM patients (Husain *et al*., 2019).

Clinical studies have established a strong link between T2DM and various risk factors, with insulin resistance being the most significant. Normally, insulin inhibits glycogenolysis and promotes glucose uptake by peripheral tissues, thereby maintaining blood glucose levels within a normal range (Misra *et al*., 2023). In T2DM patients, adipocytes secrete inflammatory factors that attract macrophages to adipose tissue, perpetuating a cycle of inflammation that disrupts insulin signaling pathways and exacerbates insulin resistance (Khan *et al*., 2020).

Semaglutide, a GLP-1 receptor agonist, shares 94% structural homology with natural glucagon-like peptide-1 (GLP-1) and is secreted primarily by intestinal L cells in the ileum, rectum, and colon. It plays a crucial role in glucose homeostasis, stimulating 50% to 70% of postprandial insulin release (Wang *et al*., 2023). GLP-1 receptors are widely distributed in various tissues, including the pancreas, gastrointestinal tract, lungs, brain, kidneys, hypothalamus, cardiovascular system, liver, adipose tissue, and skeletal muscle (Nauck *et al*., 2021). Semaglutide lowers blood glucose levels by inhibiting glucagon secretion and enhancing insulin secretion. However, it does not alter the counter-regulatory response of glucagon in T2DM patients and does not reduce C-peptide levels. Additionally, it promotes glucose uptake in adipose tissue and muscle while inhibiting hepatic glucose production (Drucker and Nauck, 2006).

C-peptide, a 31-amino-acid polypeptide, is released into the bloodstream in equimolar amounts with insulin from pancreatic β-cells (Fu *et al*., 2013). Compared to insulin, C-peptide has a longer half-life (approximately 20-30 minutes) and is present in the systemic circulation at about five times the concentration of insulin (Maddaloni *et al*., 2022). Fasting C-peptide levels serve as a standardized measure of pancreatic β-cell function and their ability to respond to stimulation. While C-peptide was historically considered biologically inert, emerging

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evidence suggests it possesses bioactive properties (Chen *et al*., 2023). It exhibits anti-inflammatory, anti-apoptotic, antioxidant, and vascular protective effects, potentially preventing or delaying diabetic microvascular complications, improving acute metabolic abnormalities, regulating gene expression, and protecting damaged tissues (Chen *et al*., 2023). Studies in animal models have demonstrated that C-peptide can influence microcirculation and enhance blood flow in tissues such as the retina, kidneys, and peripheral nerves, significantly reducing glomerular ultrafiltration, increasing renal plasma flow, and improving renal function, nerve conduction, and systemic glucose utilization (Wahren, and Jornvall, 2002; Johansson *et al*., 1992). This study aims to evaluate the clinical therapeutic effect of semaglutide, a long-acting GLP-1 receptor agonist, on T2DM and to analyze its impact on improving patients' C-peptide levels.

MATERIALS AND METHODS

Inclusion and exclusion criteria

Inclusion criteria: (1) Clearly diagnosed of T2DM; (2) There is significant insulin resistance, that is, when the patient's fasting insulin level is higher than 80 pmol/L, there is also: blood pressure greater than 140/90 mmHg, triglycerides exceeding 1.70mm/L, central obesity, and urinary microalbumin exceeding 200 μg, two of the indicators are consistent and can be assessed as insulin resistance.

Exclusion criteria: (1) Use of GLP-1 analogs and GLP-1 receptor agonists within 1 month before enrollment; (2) Moderate to severe renal insufficiency; (3) Personal or family history of thyroid dysfunction and medullary thyroid tumor; (4) Multiple endocrine neoplasia syndrome types 2; (5) Mental illness; (6) Immune system dysfunction or autoimmune disease; (7) Severe systemic infection; (8) Combined respiratory infectious diseases.

Methods

After admission, both groups received routine treatment such as diet control and health training and maintained oral treatment with metformin hydrochloride sustained-release tablets, 0.25 g each time, 3 times a day. The control group received 30 subcutaneous injections of insulin aspart based on conventional treatment, and the dose was adjusted according to daily blood glucose levels. Efficacy was assessed after 3 months of maintenance therapy. The observation group was treated with a 0.25-mg-starting-dose subcutaneous injection of semaglutide based on conventional treatment once a week. After 28 days, the dose became 0.5 mg frequency once every seven days. Efficacy was assessed after 3 months of maintenance therapy.

Observation indicators

Roche ACCU-CHEK blood glucose meter was used to detect the patient's level of fasting blood glucose and 2-hour postprandial blood glucose, and the time to reach the target of blood glucose before treatment and 3 months after treatment. Fasting cubital venous blood (4ml) was collected and centrifuged for 10 minutes. The supernatant was taken and enzyme-linked immunoassay was used to determine levels of serum endothelin-1 (ET-1). The HS-1500 acoustic wave diagnostic instrument was used to detect the parameters of the basic inner diameter of the artery and the inner diameter of the arterial reactive hyperemia and calculate the vasodilation function (FMD), FMD = (the inner diameter of the arterial reactive hyperemia - the basic inner diameter of the artery) / the basic inner diameter of the artery × 100%. Use the biochemical immune all-in-one machine to detect the patient's fasting C-peptide and fasting insulin (FINS) levels, and calculate the insulin resistance index (Homa-IR). The arising of adverse reactions to drugs during the treatment in both groups was also recorded.

STATISTICAL ANALYSIS

We use the SPSS 26.0 software package to perform statistical analysis. The patient's measurement data were all consistent with normal distribution and were expressed as x±s. We compared differences between multiple groups by using a one-way analysis of variance and made a comparison between both groups by using the SNK-q test. Researchers expressed Adverse reactions as the number of cases or incidence rate. We used the χ^2 test to compare between groups. We considered $P<0.05$ as a significant statistical difference.

RESULTS

Basic information

We selected 80 T2DM patients our hospital accepted as early as January 2022 and as late as December 2023 as the research subjects. The patients were distributed 40 cases to the observation group and 40 cases to the control group randomly and on average. In the control group, there were 26 female cases and 14 male cases; their average age was (53.2±6.8) years; the duration of the disease lasted 2-6 years, and the average disease duration was (4.1±1.2) years. In the observation group, there were 25 female and 15 male cases; the average age of patients was (52.4±7.2) years; the disease duration ranged from 2 to 6 years, and the average duration of the disease was (4.0±1.5) years. The comparison between patients' general information in both groups made sense ($P>0.05$).

Comparison of fasting blood glucose, 2-h postprandial blood glucose level, and time to reach blood glucose target before treatment and 3 months after treatment

Compared with before treatment, the 2-hour postprandial blood glucose level and fasting blood glucose level of patients in both groups dropped into a lower situation after treatment; after three-month treatments, the patients

in the observation group had a lower fasting blood glucose level and a lower 2-hour postprandial blood glucose level and a shorter blood-glucose-reaching-target time than patients in the control group. There were significant differences (P<0.05) (table 1).

Comparison of serum ET-1 and FMD levels before treatment and 3 months after treatment

Compared with before treatment, the serum ET-1 level of patients in both groups after 3-months of treatment dropped, and the FMD level rose; after three months of treatment, the difference in serum ET-1 and FMD of the patients between both groups had significant meaning (P<0.05) (table 2).

Comparison of fasting insulin, C-peptide levels, and insulin resistance index before treatment and 3 months after treatment

Before treatment, there was little difference in FINS, fasting C-peptide levels, and Homa-IR between both groups (P>0.05); in comparison with before treatment, levels of FINS and fasting C-peptide were lower after three-month treatment (P<0.05); the insulin resistance index was also significantly lower (P<0.05); the observation group dropped more significantly (P<0.05) (table 3).

Comparison of adverse reaction rates

In the observation group, two cases had symptoms of nausea and vomiting, one case had diarrhea and constipation, and one case had hypoglycemia. The gross adverse reaction incidence was 10.00%. In the control group, one case had symptoms of nausea and vomiting, two cases had hypoglycemia, and the total adverse reaction rate was 7.50% (P>0.05) (table 4).

DISCUSSION

Diabetes is a disease that requires long-term treatment and is also one of the three major diseases that threaten human physical and mental health. Chronic complications mainly cause the disability and death of patients with diabetes. Therefore, how to prevent and treat diabetes has become a problem that cannot be ignored by the medical community and even the whole society, and it is also an urgent task to be solved. For the moment, it is clinically held that the main pathogenesis of T2DM patients is due to insulin resistance and abnormal function of pancreatic islet B cells, which in turn leads to elevated fasting and postprandial blood glucose. At the same time, hyperlipidemia and hyperinsulinemia are important components of resistance to insulin and are independent factors of risk for cardiovascular problems (Sanches *et al.*, 2023; Solis-Herrera *et al.*, 2021).

Studies have found that GLP-1 hormone can directly stimulate and promote the synthesis of local intestinal insulin cells and secrete active hormones. It has a significant hypoglycemic effect and reduces the risk of cardiovascular death (Begic and Causevic, 2021). It is a hypoglycemic drug with multiple benefits. Previous pathological studies (Berman *et al.*, 2023; Alavi *et al.*, 2019) have shown that human endogenous GLP-1 is an intestinal L cells-excreted peptide hormone, which can act on pancreatic beta cells, pancreatic isl*et al*pha cells, pancreatic islet delta cells, etc. to regulate insulin expression. Promote insulin synthesis and secretion, inhibit glucagon synthesis, enhance insulin sensitivity, slow gastric emptying and exert a hypoglycemic effect. In patients with T2DM, the load of pancreatic β cells increases, and the glucose metabolism capacity decreases, thus showing blood glucose fluctuations. Relevant studies (Sloan, 2019) believe semaglutide, a GLP-1 analogue, has 94% homology with endogenous GLP-1. While promoting insulin production, it can also promote the synthesis of endogenous GLP-1 and enhance the hypoglycemic effect. This study shows that after 3-month treatment, the patients in the observation group had lower fasting blood glucose and postprandial blood glucose levels and shorter time taken to reach the blood glucose target than the patients in the control group did. It indicates that semaglutide can effectively regulate blood glucose levels in the treatment of T2DM.

ET-1 is a type of active peptide that has a strong vasoconstrictive effect and can participate in the angiogenesis process. As its expression increases, it can cause vascular damage. It has a strong positive inotropic effect on cardiomyocytes and induces cardiovascular diseases. In this study, after 3-month treatment, the patients in the observation group had a lower level of serum ET-1 than patients in the control group did and had a higher level of FMD than the control group, suggesting that semaglutide can help promote the vascular endothelial cell function of patients when used in the treatment of T2DM. C-peptide and insulin share the same preproinsulin. When proinsulin is cleaved into 1 molecule of insulin, 1 molecule of C-peptide is produced. Therefore, the molar mass of self-insulin is consistent with the level of C-peptide. The liver does not easily degrade C-peptide, so this indicator can accurately reflect the patient's insulin secretion. For T2DM patients with insulin resistance, fasting insulin and C-peptide levels are often higher than the normal range (Yuzugulen *et al.*, 2017). However, as the disease progresses, pancreatic islet function gradually decreases, and secretion capacity may decline. The study indicated that, in comparison with before treatment, the fasting insulin levels and fasting C-peptide of both groups of patients significantly improved, and the level of insulin resistance declined significantly. This is consistent with the above analysis. Therefore, semaglutide has a significant improvement effect on insulin resistance. In addition, the percentage of adverse drug reactions was similar between both groups in this

Table 1: Comparison of fasting blood glucose, 2-hour postprandial blood glucose level and blood glucose reaching target time before treatment and 3 months after treatment (x±s, n=40)

Group	Time	Fasting blood glucose/ (mmol·L-1)	2h postprandial blood glucose/(mmol·L-1)	Blood glucose reaching target time/d
Observation group	before treatment	8.50±1.02	14.35±1.35	3.88±0.69$^{\triangle}$
	3 months later	6.13±0.68$^{\#\triangle}$	9.01±0.53$^{\#\triangle}$	
Control group	before treatment	8.41±1.11	14.30±1.44	5.73±1.01$^{\triangle}$
	3 months later	6.80±0.94$^{\triangle}$	9.57±1.08$^{\triangle}$	

NOTE: Compared with the control group, $^{\#}P<0.05$; compared with before treatment, $^{\triangle}P<0.05$

Table 2: Comparison of serum ET-1 and FMD levels before treatment and 3 months after treatment ($\bar{x}$±s, n=40)

Group	Time	ET-1/(ng·L-1)	FMD/%
Observation group	before treatment	93.12±9.25	3.70±0.30
	3 months later	70.48±5.20$^{\#\triangle}$	5.13±0.54$^{\#\triangle}$
Control group	before treatment	92.89±8.26	3.84±0.35
	3 months later	77.48±5.64$^{\triangle}$	4.74±0.50$^{\triangle}$

NOTE: Compared with the control group, $^{\#}P<0.05$; compared with before treatment, $^{\triangle}P<0.05$

Table 3: Comparison of fasting insulin, C-peptide levels and insulin resistance index before treatment and 3 months after treatment (x±s, n=40)

Group	Time	FINS (mU/L)	fasting C-peptide (ng/ml)	Homa-IR
Observation group	before treatment	13.20±1.35	1.76±0.12	6.91±0.67
	3 months later	8.20±1.02$^{\#\triangle}$	0.52±0.04$^{\#\triangle}$	5.31±0.50$^{\#\triangle}$
Control group	before treatment	13.34±1.30	1.72±0.14	7.04±0.60
	3 months later	9.34±1.01$^{\triangle}$	0.70±0.05$^{\triangle}$	5.97±0.47$^{\triangle}$

NOTE: Compared with the control group, $^{\#}P<0.05$; compared with before treatment, $^{\triangle}P<0.05$

Table 4: Comparison of adverse reaction rates

Group	feel sick and vomit	diarrhea and constipation	hypoglycemia	adverse reaction incidence rate /%
Observation group (n=40)	2	1	1	10.00
Control group (n=40)	1	0	2	7.50
χ^2				0.157
P				0.692

study, suggesting that the application of semaglutide in the treatment of T2DM did not significantly subjoin adverse drug reactions. The study analysis may be related to the good pharmacokinetics of semaglutide.

CONCLUSION

In summary, semaglutide can significantly improve the treatment efficiency of T2DM, help regulate blood glucose levels while reducing fasting C-peptide and fasting insulin levels, and improve insulin resistance, which has a high clinical application value.

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