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Research Progress of Semaglutide Combined with Metformin in the Treatment of Obese Type 2 Diabetes Mellitus

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Abstract: In recent years, the incidence of type 2 diabetes mellitus (T2DM) caused by obesity in China has been increasing continuously, which has become a risk factor for the onset of T2DM and seriously affects the quality of life of patients. The conventional treatment methods include weight loss and regulating the body's metabolism. Semaglutide, as a glucagon-like peptide-1 receptor agonist (GLP-1RA), mainly reduces patients' appetite, decreases their craving for high-fat and high-sugar foods, regulates hypothalamic feeding behavior, inhibits gastric emptying and gastrointestinal motility, and ultimately leads to weight loss. Metformin mainly acts on extra-islet tissues, increasing glucose utilization, reducing glucose production, and ultimately lowering blood glucose levels. Based on this, this article reviews relevant literature on authoritative websites such as CNKI and Wanfang, organizes the data, and analyzes the research progress of semaglutide combined with metformin in the treatment of obese T2DM. The aim is to bring more treatment options for obese T2DM and promote better prognosis for patients.

Keywords: Semaglutide; Metformin; Obese T2DM; Research progress

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1. Introduction

Obese type 2 diabetes mellitus (T2DM) has become a significant challenge in the global public health sector. According to statistics from the International Diabetes Federation, the number of diabetes patients worldwide reached 529 million in 2021, with 96% being T2DM, and approximately 45.4% of T2DM patients having comorbid abdominal obesity [1]. The comorbidity of obesity and T2DM significantly exacerbates the complexity of metabolic disorders, leading to intertwined pathological mechanisms such as insulin resistance, systemic inflammation, and liver fat accumulation, forming a vicious cycle. This complex pathophysiological profile makes it difficult for monotherapy to simultaneously control blood glucose, reduce weight, and improve metabolic complications. Combination therapy strategies have gradually become a hot spot in clinical research

due to their multi-target synergistic effects [2]. Traditional hypoglycemic drugs such as metformin can improve insulin sensitivity, but their regulatory effect on obesity-related metabolic disorders is limited. Semaglutide, as a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA), achieves hypoglycemic and weight loss effects through multiple mechanisms including glucose-dependent stimulation of insulin secretion, inhibition of glucagon release, delay of gastric emptying, and appetite suppression [3]. Its half-life is up to 7 days, and a stable blood concentration can be maintained with once-weekly subcutaneous injection, significantly improving patient compliance. Metformin exerts its hypoglycemic effect by reducing hepatic glucose output, improving insulin sensitivity in peripheral tissues, and regulating gut microbiota. The combination of metformin and semaglutide is expected to produce favorable results. In this regard, this article will explore the research progress of semaglutide combined with metformin in the treatment of obese T2DM, with specific reports as follows.

2. Pathological mechanisms of obese T2DM

Obesity, as a major factor influencing the progression of T2DM, induces insulin resistance in skeletal muscle and liver through the secretion of inflammatory factors and free fatty acids from expanded adipose tissue, and promotes the functional decline of pancreatic beta cells. Moreover, most obese patients develop non-alcoholic fatty liver disease (NAFLD), which has a high prevalence. This not only increases the burden on the liver but also releases hepatogenic inflammatory factors to some extent, thereby affecting the patient's own metabolic state [4]. In the pharmacological treatment of rejuvenation, although it can effectively improve insulin sensitivity, the regulation of related effects on metabolic disorders is very limited. Some studies have directly pointed out that monotherapy with metformin can effectively reduce hemoglobin in patients, but weight loss is very limited, and it is not effective for patients with liver-type inflammation [5]. Not only that, obese T2DM may also be combined with hyperlipidemia, hypertension, and related cardiovascular diseases, and there are significant limitations to monotherapy.

3. Mechanism of action of semaglutide

Semaglutide shares certain similarities with GLP-1. As an endogenous incretin, it has a 94.00% homology in structure. Its main function is to promote the secretion of cells in the intestine, regulate glucose homeostasis, and release postprandial insulin. GLP-1 receptors are widely distributed, mainly in the lungs, brain, gastrointestinal tract, pancreas, cardiovascular system, kidneys, adipose tissue, hypothalamus, skeletal muscles, and more. Semaglutide is highly dependent on glucose, stimulates insulin secretion, prevents the occurrence of glucagon, and achieves the goal of lowering blood sugar. However, when used alone in obese T2DM patients, there was no significant improvement in glucagon. In addition, semaglutide also plays a certain role in the liver and adipose tissue. After increasing its intake, it can effectively inhibit glucose production and ultimately lower blood sugar [6]. Although semaglutide and GLP-1 have high homology, there are also certain differences. Semaglutide can induce blood sugar production, reduce patients' cravings for high-fat and high-sugar foods, improve their own blood sugar levels, and increase the secretion capacity of insulin B cells. Furthermore, semaglutide directly acts on the nerve center to reduce appetite. Relevant studies have directly pointed out that when blood sugar is less than 4.5mmol/L, GLP-1 does not stimulate insulin, blood sugar does not decrease, and there is no risk of hypoglycemia [7].

4. Mechanism of metformin on glucose metabolism

Metformin can increase glucose utilization, reduce glucose production, and increase anaerobic glycolysis of glucose in muscles, ultimately achieving the goal of lowering blood sugar. In addition, metformin can also decompose hepatic glycogen, which has high clinical value for patients with high fasting blood glucose levels. Moreover, studies have found that metformin can directly inhibit glucose, preventing its absorption in the intestine, and only allowing absorption in the small intestine at high concentrations through the gastrointestinal wall [8]. Metformin not only controls hyperglycemia but also does not increase insulin concentration, ultimately reducing patient weight. Another study found that metformin can block the development of liver mitochondria, correct insulin-sensitive tissues, and avoid intracellular metabolic abnormalities [9]. Related research directly points out that metformin reduces ATP production by inhibiting mitochondrial electron transport chain complex I, increases the AMP/ATP ratio, and activates the AMPK signaling pathway. After AMPK activation, it phosphorylates key gluconeogenic enzymes, inhibits key steps of gluconeogenesis, and reduces glucose production [10]. Even if AMPK is not activated, metformin can still directly inhibit gluconeogenesis by inhibiting mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH) and blocking the redox shuttle that converts glycerol and lactic acid into glucose. Metformin can activate LKB1 through the media, which phosphorylates the Thr172 site of the AMPKα subunit, leading to full activation of AMPK [11]. When the AMP cellular level in the body increases, it directly binds to the CBS domain of the AMPKγ subunit, inducing conformational changes and activating AMPK [12].

5. Synergistic mechanism of semaglutide and metformin

Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA), stimulates insulin secretion in a glucose-dependent manner, inhibits glucagon release, delays gastric emptying, and suppresses appetite. Metformin primarily acts by reducing hepatic glucose output, improving insulin sensitivity in extra-pancreatic tissues, and modulating gut microbiota, thereby exerting its hypoglycemic effect. According to research, semaglutide suppresses appetite and decreases energy intake by activating the hypothalamic feeding center, while metformin reduces hepatic glucose production by inhibiting mitochondrial respiratory chain complex I and enhancing muscle glucose uptake [13]. The combination of these two drugs simultaneously targets both energy intake and expenditure, leading to a more significant weight loss. Other studies suggest that these two medications can achieve anti-inflammatory and anti-fibrotic synergies [14]. Semaglutide can lower liver inflammation markers and fibrosis scores, possibly through inhibiting the NF-kB pathway and reducing macrophage infiltration. Metformin, on the other hand, inhibits the activation of hepatic stellate cells and reduces collagen deposition by activating the AMPK pathway [15]. Combined therapy can more comprehensively improve the pathological state of the liver. Additionally, semaglutide enhances beta-cell function by promoting beta-cell differentiation and inhibiting apoptosis, while metformin protects beta-cells by reducing lipotoxicity and oxidative stress [16]. The combination of the two drugs can delay the progression of T2DM and even achieve diabetes remission in some patients.

6. Application of semaglutide combined with metformin in obese type 2 diabetes mellitus

In recent years, multiple clinical studies have confirmed the significant advantages of semaglutide combined with metformin in the treatment of obese type 2 diabetes mellitus (T2DM). One study selected 78 patients with

obese T2DM as the research subjects and conducted a prospective study [17]. The results showed that the treatment of semaglutide combined with metformin has high application value for patients with obese T2DM, effectively improving the treatment efficiency and reducing the relevant indicators of glucose metabolism. Another study included 98 patients with obese T2DM and found that the treatment of semaglutide combined with metformin has significant effects, effectively regulating the relevant levels of glucose and lipid metabolism, reducing body mass index, and possessing high medication safety [18]. Other related research analyzed the application effect of semaglutide combined with metformin in obese type 2 diabetes mellitus, including a total of 132 patients with obese T2DM [19]. The results indicated that semaglutide combined with metformin can effectively improve clinical efficacy and reduce the incidence of adverse reactions. A study analyzed the clinical efficacy of semaglutide + dapagliflozin + metformin in T2DM with nonalcoholic fatty liver disease [20]. The results showed that compared with monotherapy, combination therapy can effectively reduce blood lipids and blood glucose, improve patients' pancreatic beta-cell function, and not increase other adverse reactions.

7. Conclusion

In summary, with the innovation of treatment concepts for metabolic diseases, the combined therapy strategy of semaglutide and metformin has transitioned from theoretical exploration to clinical practice, marking a significant breakthrough in the comprehensive management of obese type 2 diabetes mellitus (T2DM). This combination not only addresses the limitations of single-drug therapy in multi-target regulation but also achieves triple benefits of "lowering blood glucose, reducing weight, and improving metabolic complications" through complementary mechanisms. The combined therapy of semaglutide and metformin signifies a paradigm shift in T2DM management, moving from single-target control to multi-organ protection. With deepening mechanistic research and accumulating clinical evidence, this combination is expected to become one of the standard treatments for obese T2DM. In the future, through precise stratification, multidisciplinary collaboration, and the establishment of a long-term follow-up system, combined therapy will bring more sustained metabolic health benefits to patients, ultimately achieving the dual goals of diabetes remission and improved quality of life.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Lu Y, Li M, 2025, Research Progress on the Treatment of Obese Polycystic Ovary Syndrome with Semaglutide Combined with Metformin. Advances in Clinical Medicine, 15(1): 534–537.

[2] Ni W, You J, Feng X, 2023, A Case of Type 2 Diabetes Mellitus Complicated with Polycystic Ovary Syndrome Treated with Semaglutide Combined with Pioglitazone and Metformin. Chinese Journal of Diabetes Mellitus, 15(Z2): 181–184.

[3] Guo R, Chen Y, 2024, A Case of Type 2 Diabetes Mellitus with Multiple Cardiovascular Risk Factors Treated with Semaglutide. Chinese Journal of Diabetes Mellitus, 16(Z2): 111–114.

[4] Shams AH, Aziz MH, Kuraishy AMH, 2024, The Potential Effects of Metformin and/or Sitagliptin on Leptin/Adiponectin Ratio in Diabetic Obese Patients: A New Therapeutic Effect. JPMA. The Journal of the Pakistan Medical Association, 74(10 Suppl-8): S241–S245.

[5] Díez G, Oliva L, Jiménez P, et al., 2024, Cocoa and Carob Supplementation, Alone or in Combination with Metformin, Protects Against Hepatorenal Injury in Zucker Diabetic Fatty Rats. Nutrients, 16(18): 3087–3087.

[6] Wang H, Peng W, Liu Y, 2024, A Case of Type 2 Diabetes Mellitus Complicated with Acute Coronary Syndrome Treated with Semaglutide. Chinese Journal of Diabetes Mellitus, 16(Z2): 101–103.

[7] Xu Z, Ao W, Huang T, et al., 2025, The Effect of Semaglutide Combined with Metformin in the Treatment of Obese Patients with Type 2 Diabetes Mellitus. China Kangfu Medicine, 37(7): 26–28, 36.

[8] Ye Q, 2024, The Influence of Semaglutide Combined with Metformin on Glucose and Lipid Metabolism Indexes and Body Mass Index Levels in Obese Patients with Type 2 Diabetes Mellitus. Diabetes New World, 27(16): 121–124.

[9] Shi W, Wang J, Liu Y, 2024, The Effect of Semaglutide Combined with Metformin in the Treatment of Obese Patients with Type 2 Diabetes Mellitus. China Kangfu Medicine, 36(1): 25–27.

[10] Ye J, Chen D, Qiu Z, et al., 2024, Efficacy Analysis of Semaglutide Combined with Dapagliflozin and Metformin in Obese Patients with Type 2 Diabetes Mellitus Complicated with Nonalcoholic Fatty Liver Disease. Diabetes New World, 27(1): 19–22.

[11] Xu S, Zhao Z, Zheng G, 2025, The Efficacy of Semaglutide Combined with Insulin in the Treatment of Obese Type 2 Diabetes and Its Impact on Patients' Physical Indicators. Tianjin Pharmaceutical Journal, 37(4): 450–454.

[12] Hu Z, 2025, The Effect of Dapagliflozin Combined with Semaglutide on Glucose and Lipid Metabolism in Obese Patients with Type 2 Diabetes. Modern Diagnosis and Treatment, 36(3): 389–391.

[13] Yu M, Hu Y, 2024, Observation on the Clinical Effect of Dapagliflozin Combined with Semaglutide in the Treatment of Obese Type 2 Diabetes Patients. Tianjin Pharmaceutical Journal, 36(2): 55–58.

[14] Li C, Chen P, Huang Q, et al., 2024, The Effect of Dapagliflozin Combined with Semaglutide in the Treatment of Obese Type 2 Diabetes and Its Impact on Glucose and Lipid Metabolism Indicators. Rational Drug Use in Clinic, 17(35): 28–31.

[15] Ma Z, 2024, Observing the Effects of Semaglutide Combined with Metformin on Glucose and Lipid Metabolism and Body Weight in Obese Patients with Type 2 Diabetes. Modern Diagnosis and Treatment, 35(13): 1946–1948.

[16] Xu X, Jin G, Han J, et al., 2023, Analysis of the Efficacy and Safety of Semaglutide in the Treatment of Overweight or Obese Type 2 Diabetes. Chinese Journal of Diabetes, 15(Z2): 35–39.

[17] Liu Y, Ren J, Ren Z, et al., 2023, A Case of Semaglutide in the Treatment of Type 2 Diabetes with End-Stage Renal Disease. Chinese Journal of Diabetes, 15(Z2): 67–69.

[18] Tan Q, Luo X, Chen Q, 2020, Evaluation of the Efficacy and Safety of Liraglutide Combined with Metformin in Obese Patients with Type 2 Diabetes Mellitus. Chinese and Foreign Medical Research, 18(36): 143–144.

[19] Jiang L, Li J, 2022, The Efficacy of Orlistat Combined with Metformin in Obese Patients with Type 2 Diabetes and Its Impact on Body Mass Index, Beta-Cell Function Index, and Insulin Resistance Index. China Journal of Pharmaceutical Economics, 17(1): 71–74.

[20] Chen Y, Lin X, Chen Y, 2022, The Effect of Dapagliflozin Combined with Metformin in the Treatment of Overweight and Obese Patients with Type 2 Diabetes Mellitus. Fujian Medical Journal, 44(6): 106–108.