WEP Warwick Evans Publishing

International Journal of Public Health and Medical Research

ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online) | Volume 3, Number 3, Year 2025
DOI: https://doi.org/10.62051/ijphmr.v3n3.08
Journal homepage: https://wepub.org/index.php/IJPHMR/index

Application and Mechanism of GLP-1 Receptor Agonists in the Treatment of Obesity Complicated with Type 2 Diabetes Mellitus

Xingyu Liu, Mao Shu *

School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, China

*Corresponding Author: Mao Shu

ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) are the main metabolic diseases in the world, and they are closely related in pathogenesis. Obesity can induce insulin resistance and chronic inflammation, while T2DM is often accompanied by abnormal distribution of body fat, which further aggravates metabolic disorder. Traditional treatment methods have some problems, such as hypoglycemia risk, weight gain and limited long-term curative effect. Therefore, the development of new hypoglycemic and weight-reducing drugs has become a clinical demand. GLP-1 receptor agonists (GLP-1 RAs), as a new generation of hypoglycemic drugs, has become a breakthrough in the treatment of obesity complicated with T2DM with its unique glucose-dependent hypoglycemic mechanism, significant weight loss effect and potential cardiovascular protection. By activating GLP-1 receptors, GLP-1 RAs enhance insulin secretion, suppress glucagon release, delay gastric emptying, and inhibit appetite, thereby improving glycemic control and reducing energy intake. Multiple clinical trials have confirmed that GLP-1 RAs can significantly lower glycated hemoglobin (HbA1c) levels, reduce body weight by 5%-15%, and decrease the risk of cardiovascular events by 13%-26%. However, their mechanism of action has not been fully elucidated, and differences in efficacy and long-term safety still require further investigation. This article reviews the current application of GLP-1 RAs in the treatment of obesity combined with T2DM, explores their multi-faceted mechanisms of action in glycemic control, weight loss, and cardiovascular protection, and analyzes their efficacy and safety based on the latest clinical research data to provide a reference for rational clinical use.

KEYWORDS

T2DM; GLP-1 RAs; Obesity complicated; GLP-1; HbA1c

1. INTRODUCTION

In recent years, the incidence of obesity and type 2 diabetes mellitus (T2DM) is on the rise worldwide, and they have become the main metabolic diseases that threaten public health. According to the latest statistics of WHO, the global adult obesity rate has exceeded 13%, and the prevalence rate of T2DM is as high as 9.3%, and they are closely related in pathogenesis [1]. Obesity is an important inducement of T2DM by promoting insulin resistance (IR) and chronic low-grade inflammation. T2DM patients are often accompanied by abnormal distribution of body fat, which further aggravates metabolic disorder and forms a vicious circle.

Although traditional treatment can effectively control blood sugar, there are limitations such as hypoglycemia risk, weight gain and limited long-term curative effect. For example, sulfonylurea drugs may cause hypoglycemia events, and β cell function declines significantly after long-term use;

Although metformin has no significant effect on body weight, some patients have poor compliance due to gastrointestinal reaction. Therefore, it is urgent to develop new drugs that can not only reduce blood sugar but also lose weight and have multiple metabolic protective effects.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs), as a new generation of hypoglycemic drugs, has become a breakthrough in the treatment of obesity complicated with T2DM due to its unique glucose-dependent hypoglycemic mechanism, significant weight loss effect and potential cardiovascular protection. By activating GLP-1 receptor, GLP-1 RAs can not only enhance insulin secretion and inhibit glucagon release, but also delay gastric emptying and inhibit appetite, thus improving blood sugar control and reducing energy intake.

In recent years, many large-scale clinical trials have confirmed that GLP-1 RAs can not only significantly reduce the level of glycosylated hemoglobin (HbA1c), but also reduce the weight of patients by 5%~15%, and reduce the risk of cardiovascular events by 13% ~ 26% [2]. However, the mechanism of GLP-1 RAs has not been fully clarified, and the difference in curative effect and long-term safety of GLP-1 RAS in different populations still need further discussion.

In this paper, the application status of GLP-1 RAs in the treatment of obesity complicated with T2DM is systematically reviewed, and its multiple mechanisms of hypoglycemic, weight loss and cardiovascular protection are discussed in depth. Combined with the latest clinical research data, its efficacy and safety are analyzed to provide reference for rational clinical medication.

2. MECHANISM OF GLP-1 RAS

2.1. Hypoglycemic Mechanism

GLP-1 RAs activate the GLP-1 receptor on the surface of pancreatic β-cells, which in turn activates adenylate cyclase (AC) to generate cyclic adenosine monophosphate (cAMP), thereby activating the protein kinase A (PKA) pathway. This process promotes the opening of L-type voltage-gated calcium channels, enhances calcium ion influx, and triggers the exocytosis of insulin granules. The glucose-lowering effect of GLP-1 RAs is "glucose-dependent": when blood glucose levels are above a certain threshold, GLP-1 RAs significantly stimulate insulin secretion; once blood glucose returns to the normal range, insulin secretion automatically ceases, thus minimizing the risk of hypoglycemia. For example, semaglutide can reduce fasting blood glucose by 1.8–2.5 mmol/L and postprandial glucose peaks by 4–6 mmol/L [3].

GLP-1 RAs inhibits glucagon release in a glucose concentration-dependent manner by directly acting on islet α cells or indirectly through bypass effect. When blood sugar rises, the secretion of glucagon decreases by about 30%~50%, thus inhibiting liver gluconeogenesis and glycogen decomposition and reducing fasting blood sugar level [4].

GLP-1 RAs inhibits gastric antrum contraction and pyloric sphincter relaxation by activating GLP-1 receptors in the central nervous system (CNS) and peripheral gastrointestinal tract, and delays gastric emptying. This effect can reduce postprandial blood glucose fluctuation and make the blood glucose curve more stable. For example, Liraglutide can prolong gastric emptying time by 30%~50%, and delay the appearance of postprandial blood glucose peak by 1~2 hours [5].

2.2. Weight Loss Mechanism

GLP-1 RAs activates satiety center of hypothalamic arcuate nucleus through blood-brain barrier, and enhances satiety signal transmission. At the same time, it inhibits the hunger center in the lateral hypothalamus and reduces appetite. For example, Tirzepatide can reduce the daily energy intake of patients by 500~800 kcal, and the weight loss can reach 15% ~ 20% [6]. Inhibit gastroparesis and intestinal peristalsis, prolong the residence time of food in gastrointestinal tract, and enhance the

perception of satiety signal. Reduce gastric acid secretion and pancreatic exosecretion, and further reduce appetite. GLP-1 RAs can improve insulin sensitivity, promote glucose uptake by adipocytes and reduce fat accumulation. At the same time, it activates brown adipose tissue to generate heat and increases energy consumption.

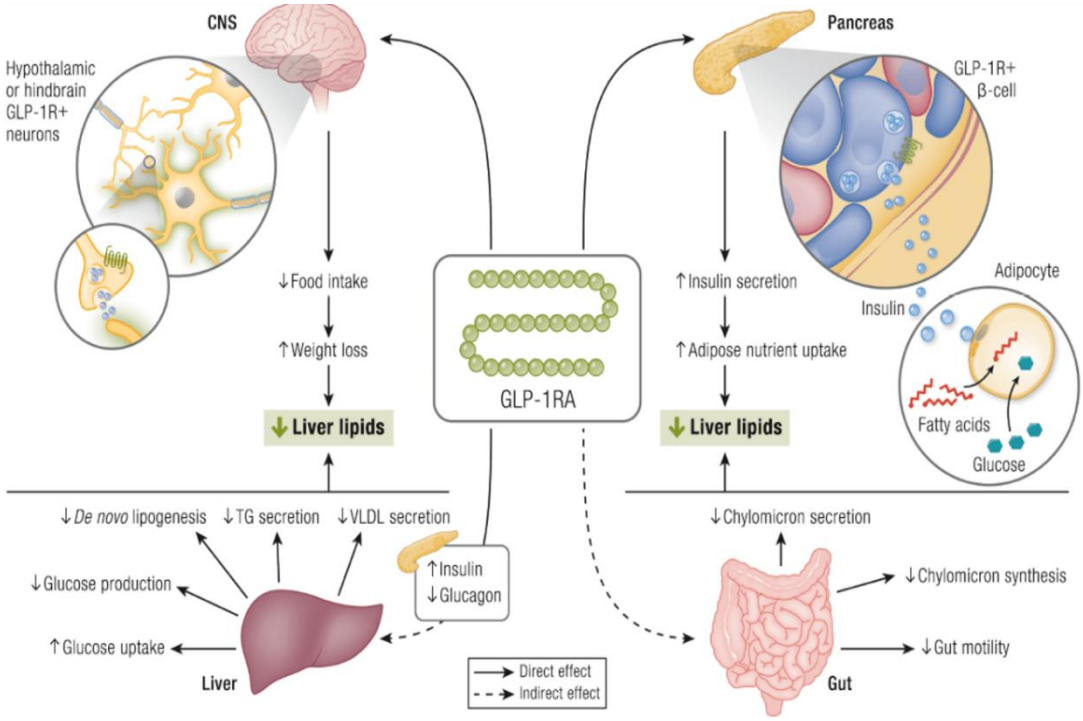

Figure 1. GLP-1RA reduces liver lipid through indirect and direct mechanisms involving CNS, pancreas, liver and intestine

Intestinal cells do not express GLP-1R, but the effect of GLP-1 is related to the synthesis, secretion and decrease of intestinal peristalsis [7]. Common direct and indirect mechanisms link GLP-1R activity with biological pathways in CNS, pancreas, liver and intestine, reducing liver lipid level and maintaining liver homeostasis (Figure 1).

2.3. Cardiovascular Protection Mechanism

GLP-1 RAs provides cardiovascular protection through various mechanisms, including direct myocardial protection, anti-inflammatory and anti-atherosclerosis effects and improving vascular endothelial function. In terms of direct myocardial protection, GLP-1 RAs activates receptors on the surface of myocardial cells, enhances contractility and reduces apoptosis, which can significantly reduce the infarct area in acute myocardial infarction models [8]. They also have anti-inflammatory effects, which can inhibit the adhesion of monocytes to vascular endothelium, reduce the foaming of macrophages, thereby reducing the formation of atherosclerotic plaques, and reduce circulating inflammatory markers such as C-reactive protein and tumor necrosis factor-α. GLP-1 RAs can promote the production of nitric oxide by activating nitric oxide synthase in endothelial cells and enhance vasodilation function, which is especially effective in improving vascular endothelial dysfunction related to diabetes.

2.4. Renal Protection Mechanism

GLP-1 RAs provide renal protection through multiple mechanisms, including reducing urinary protein excretion and slowing the decline in glomerular filtration rate. By inhibiting the activation of the renin-angiotensin-aldosterone system (RAAS), GLP-1 RAs lower intraglomerular pressure, thereby reducing proteinuria. In patients with diabetic nephropathy, they significantly decrease the

urinary albumin-to-creatinine ratio (UACR) [9]. Additionally, they suppress tubulointerstitial fibrosis and reduce glomerulosclerosis, helping to slow the progression of kidney function deterioration.

3. EFFICACY AND SAFETY OF GLP-1 RAS IN OBESITY COMPLICATED WITH T2DM

GLP-1 RAs, as a new type of hypoglycemic drug, has shown remarkable efficacy in the treatment of obesity complicated with T2DM (Table 1). These drugs can promote insulin secretion and inhibit glucagon secretion in a glucose concentration-dependent manner by activating GLP-1 receptor, thus achieving hypoglycemic effect. GLP-1 RAs can also delay gastric emptying and enhance satiety, thus helping to lose weight.

Table 1. Research achievements in current fields

Drug Names	Hypoglycemic effect (HbA1c change%)	Weight loss effect (weight change%)
Exenatide	-1.0-1.5	-2.5-3.5
Liraglutide	-1.5-2.0	-3.0-4.0
Semaglutide	-1.8-2.5	-8.5-10.0
HRS9531	-2.1-2.7	-5.4-16.8
Tirzepatide	-2.0-2.5	-15.0-20.0

3.1. Curative Effect Analysis

(1) Hypoglycemic effect

GLP-1 RAs can significantly reduce the level of HbA1c and improve blood sugar control. For example, drugs such as exenatide and liraglutide have shown significant hypoglycemic effects in clinical trials. Phase II clinical study of a new GLP-1/GIP double receptor agonist such as HRS9531 in patients with T2DM shows that after 20 weeks of treatment, the change of HbA1c can reach -2.7% compared with the baseline, which significantly improves the blood glucose compliance rate [10].

(2) Weight loss effect

GLP-1 RAs can slow down gastric emptying and enhance satiety, thus suppressing appetite and achieving the purpose of losing weight. For example, in a large-scale clinical trial, somarutin reduced the weight of patients by an average of 8.5% [11]. Phase II clinical study of new GLP-1/GIP double receptor agonists such as HRS9531 in obese adults showed that after 24 weeks of treatment, the percentage of body weight change from baseline could reach -16.8%, and the proportion of subjects who lost weight ≥5% reached 92% [12].

3.2. Security Analysis

The most common adverse reactions of GLP-1 RAs are gastrointestinal reactions, such as nausea, diarrhea, loss of appetite, etc., but most of them are mild to moderate, and will be relieved over time. A few patients may have allergic reactions, but most of them are mild rashes, and very few cases of severe allergies [13]. Some patients may have pain, redness and swelling at the injection site, but they are usually mild and will not affect the treatment. GLP-1 RAs promotes insulin secretion in a glucose concentration-dependent manner, so the risk of hypoglycemia is low. However, the dosage should be adjusted according to the patient's specific situation to avoid hypoglycemia.

4. FUTURE RESEARCH DIRECTION

4.1. Mechanism Exploration and Target Optimization

In-depth analysis of the molecular mechanism of GLP-1/GIP/GCG (glucagon) and other multi-receptor agonists, to explore the synergistic effect of triple receptor activation in hypoglycemic, weight loss and metabolic protection. To develop a new type of double/triple receptor agonist and optimize the dosage ratio to balance the efficacy and safety. To reveal the long-term effect of GLP-1 RAs on hypothalamic appetite center through blood-brain barrier, and explore its potential mechanism of improving cognitive function and reducing the risk of neurodegenerative diseases.

4.2. Clinical Application Development

For special populations such as the elderly, those with hepatic or renal insufficiency, and patients with cardiovascular diseases, research on dose optimization and safety of GLP-1 RAs should be conducted. The potential application of GLP-1 RAs in metabolic-related conditions such as non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS) should be explored. Additionally, combination therapy regimens involving GLP-1 RAs with SGLT-2 inhibitors, DPP-4 inhibitors, or basal insulin should be studied to enhance efficacy and reduce the limitations of single-agent therapy.

4.3. Drug Delivery and Dosage form Innovation

Break through the technical bottleneck of low oral bioavailability of GLP-1 RAs, develop new penetration enhancers or nano-delivery systems, and improve patient compliance. Explore a longer-acting GLP-1 RAs dosage form, such as once a month, to reduce the frequency of administration and improve the quality of life of patients.

4.4. Safety and Long-Term Risk Assessment

Establish a safety database for the long-term use of GLP-1 RAs, with a focus on potential risks such as pancreatitis and thyroid C-cell tumors. Conduct larger-scale cardiovascular outcome trials (CVOTs) with longer follow-up periods to validate the cardiovascular protective effects of GLP-1 RAs across diverse populations.

4.5. Cost-Effectiveness and Medical Policy

To analyze the cost-benefit of GLP-1 RAs in different medical systems, and provide basis for making medical insurance policies. Promote the research and development of generic GLP-1 RAs in low-income countries, reduce the cost of treatment and expand the coverage of patients.

5. CONCLUSION

GLP-1 RAs shows remarkable curative effect and multiple metabolic protection in the treatment of obesity complicated with T2DM. By activating GLP-1 receptor, GLP-1 RAs can not only promote insulin secretion and inhibit glucagon release in a glucose-dependent manner to achieve hypoglycemic effect, but also delay gastric emptying and enhance satiety, thus helping to lose weight. GLP-1 RAs also has potential cardiovascular protection, which can improve vascular endothelial function and provide comprehensive metabolic support through direct myocardial protection, anti-inflammatory and anti-atherosclerosis mechanisms. In terms of safety, the most common adverse reaction of GLP-1 RAs is gastrointestinal reaction, but most of them are mild to moderate, and will be relieved over time. The risk of hypoglycemia is low, but the dosage should be adjusted according

to the specific situation of patients. The safety of long-term use still needs further study, especially the potential risks such as pancreatitis and thyroid C-cell tumor. Future research directions include in-depth analysis of the molecular mechanism of multi-receptor agonists such as GLP-1/GIP/GCG, exploration of the development of new double/triple receptor agonists, and dose optimization and safety research for special populations. At the same time, breaking through the technical bottleneck of low oral bioavailability, developing long-acting dosage forms and improving patient compliance are also important development directions in the future.

REFERENCES

[1] Nauck, M. A., & D'Alessio, D. A. (2022). Tirzepatide, a dual gip/glp-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovascular Diabetology, 21(1), 1-16.

[2] Karagiannis, T., Avgerinos, I., Liakos, A., Del Prato, S., Matthews, D. R., & Tsapas, A., et al. (2022). Management of type 2 diabetes with the dual gip/glp-1 receptor agonist tirzepatide: a systematic review and meta-analysis. Diabetologia, 65(8), 1251-1261.

[3] Shabil, M., Khatib, M. N., Ballal, S., Bansal, P., Tomar, B. S., & Ashraf, A., et al. (2024). Risk of hepatocellular carcinoma with glucagon-like peptide-1 receptor agonist treatment in patients: a systematic review and meta-analysis. BMC Endocrine Disorders, 24(1), 1-11.

[4] Palecek, E. J., Kimzey, M. M., Zhang, J., Marsden, J., Bays, C., & Moran, W. P., et al. (2024). Glucagon-like peptide-1 receptor agonist therapy effects on glycemic control and weight in a primary care clinic population. Journal of Investigative Medicine, 72(8), 911–919.

[5] Zhao, M. B. T., Tifei Xu Tifei XuState Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai , ChinaMore by Tifei Xu, Xu, T., Xu, M. B. T., &, et al. (2023). Discovery of novel 5, 6-dihydro-1, 2, 4-triazine derivatives as efficacious glucagon-like peptide-1 receptor agonists. Journal of Medicinal Chemistry, 66(12), 7988-8010.

[6] Tuersun, A., Hou, G., & Cheng, G. (2024). Efficacy and safety of the combination or monotherapy with glp-1 receptor agonists and sglt-2 inhibitors in type 2 diabetes mellitus: an update systematic review and meta-analysis. The American Journal of the Medical Sciences, 368(6), 579-588.

[7] Neves, J. S., Borges-Canha, M., & Vasques-Novoa, FranciscoGreen, Jennifer B.Leiter, Lawrence A.Granger, Christopher B.Carvalho, DavideLeite-Moreira, AdelinoHernandez, Adrian F.Del Prato, StefanoMcMurray, John J. V.Md, Joao Pedro Ferreira. (2023). Glp-1 receptor agonist therapy with and without sglt2 inhibitors in patients with type 2 diabetes. Journal of the American College of Cardiology, 82(6), 517-525.

[8] Klein, K. R., Clemmensen, K. K. B., & Lingvay, A. I. (2024). Occurrence of gastrointestinal adverse events upon glp-1 receptor agonist initiation with concomitant metformin use: a post hoc analysis of leader, step 2, sustain-6, and pioneer 6. Diabetes care, 47(2), 280-284.

[9] Jagome, T., Velling, S., Tikva, T. B., Maksimtuk, V., Gaur, N., & Reimets, R., et al. (2025). Gaba and glp-1 receptor agonist combination therapy modifies diabetes and langerhans islet cytoarchitecture in a rat model of wolfram syndrome. Diabetology & Metabolic Syndrome, 17(1), 1-15.

[10] Hintze, S. C., & Terkamp, C. (2022). New therapeutic developments in the treatment of type 2 diabetes mellitus. Deutsche medizinische Wochenschrift (1946), 147(10), 626-636.

[11] Lincoff, A. M., Colhoun, H., Emerson, S., Hovingh, G. K., Kabakci, G., & Kahn, S., et al. (2025). Effect of the glp-1 receptor agonist semaglutide on total cardiovascular events in patients with cardiovascular disease and overweight or obesity but no diabetes in the select trial. Journal of the American College of Cardiology, 85(12), 378-378.

[12] Malin, J., Melo, M. H. S. T. D., John, T. A., Wattanachayakul, P., Lo, K. B., & Amanullah, A. M. (2025). Impact of glucagon-like peptide-1 receptor agonist (glp-1a) use in patients with obesity and heart failure with reduced ejection fraction (hfref): a propensitymatched us population based cohort study. Journal of the American College of Cardiology, 85(12), 1658-1658.

[13] He, L., Wang, J., Ping, F., Yang, N., Huang, J., & Li, Y., et al. (2022). Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases: a systematic review and meta-analysis of randomized clinical trials. JAMA internal medicine, 182(5), 513-519.