Pharmacological Selection and Management Progress for Chronic Conditions in Overweight/Obese Patients with Type 2 Diabetes Mellitus

Yue Kan, Jing Dong, Yanhui Liu, Jiachen Yao, Wenyan Li*

Department of Pharmacy, Gongli Hospital of Shanghai Pudong New Area, 219 Miao Pu Road, Shanghai 200135, China

*Corresponding author

Abstract: Overweight and obesity are a global public health crisis closely linked to rising type 2 diabetes mellitus (T2DM). Over 60% of Chinese T2DM patients are overweight or obese, developing a vicious cycle of insulin resistance, pancreatic β-cell dysfunction, chronic inflammation and abnormal incretin signals that exacerbate metabolic disorders and weight gain. This population faces elevated risks of cardiovascular disease, chronic kidney disease and non-alcoholic fatty liver disease, along with higher mortality and heavy socioeconomic burdens. In the past decade, T2DM treatment has shifted from glucose-only control to a patient-centered model prioritizing weight loss and complication management. Major international and domestic guidelines identify weight loss of at least 5% as a core therapeutic goal, and recommend hypoglycemic agents with proven weight-lowering and cardiorenal benefits. New drugs including dorzagliatin (a glucokinase activator) and tirzepatide (a dual GIP/GLP-1 receptor agonist) have expanded treatment options for high-risk patients. Based on 2018-2026 high-quality literature from PubMed, Web of Science and CNKI, this review summarizes the pathophysiology linking obesity and T2DM, evaluates the efficacy and safety of current medications, and discusses individualized therapy, optimal combination regimens and full-cycle chronic disease management. It aims to provide concise, clinically practical references for frontline practice.

***Keywords*:** overweight; obesity; type 2 diabetes mellitus; chronic disease management; pharmacological selection; individualized therapy

1. Introduction

1.1 Epidemiological Characteristics and Clinical Burden

Overweight and obesity are major modifiable risk factors for T2DM. In China, 34.3% of adults are overweight and 16.4% are obese, while nearly 55% of T2DM patients have excess body weight[1]. Visceral adiposity drives severe insulin resistance and early β-cell impairment, causing refractory hyperglycemia[2]. These patients often have metabolic syndrome featuring hypertension, dyslipidemia, hyperuricemia and fatty liver disease, which further increases macrovascular and microvascular complication risks[3]. Evidence confirms overweight/obese T2DM patients have higher all-cause and cardiovascular mortality than normal-weight patients, calling for precise and integrated pharmacological management[4].

1.2 Evolution of Therapeutic Concepts

Traditional management of T2DM focused merely on reducing glycated hemoglobin (HbA1c), but landmark cardiovascular outcome trials have completely reshaped clinical decision-making. It has been increasingly recognized that simple intensive glycemic control does not reduce cardiovascular risk and may even increase adverse events due to hypoglycemia and weight gain. Current international and domestic guidelines advocate a comprehensive management model that integrates glycemic control, weight reduction, cardiorenal protection, and safety optimization. Weight loss of 5% or more is no longer a secondary target but a core endpoint that directly improves insulin sensitivity, reduces metabolic disorders, and lowers long-term complication risks[5]. This shift has established weightlowering and weightneutral agents as the preferred firstline options for overweight and obese patients, while agents that induce weight gain are increasingly reserved for limited clinical scenarios[6].

1.3 Literature Retrieval and Purpose

This review is based on clinical studies published from 2016 to 2026, including randomized controlled trials, meta-analyses, cardiovascular outcome trials, real-world studies, and clinical guidelines. The literature was retrieved from PubMed, Web of Science, and CNKI using keywords related to obesity, T2DM, pharmacological management, GLP-1 receptor agonists, SGLT2 inhibitors, dorzagliatin, tirzepatide, and individualized therapy. This review aims to integrate clinical evidence to clarify the pharmacological advantages of modern glucose-lowering agents in overweight and obese

patients, establish a rational and stratified medication strategy, and provide a comprehensive reference for chronic disease management in clinical endocrinology practice.

2. Pathophysiological Links Between Obesity and Type 2 Diabetes Mellitus

Insulin resistance is the core mechanism connecting obesity and T2DM. Excess visceral fat releases free fatty acids and pro-inflammatory cytokines to disrupt insulin signal transduction. Long-term compensatory hyperinsulinemia triggers oxidative stress and β-cell apoptosis, progressing to clinical diabetes[7]. Intestinal flora disorder and impaired incretin function worsen the condition: obese people have reduced GLP-1 levels and GIP resistance, leading to increased appetite and weakened glucose-dependent insulin secretion[8].

3. Individualized Pharmacologic Therapy for Overweight and Obese Patients with Type 2 Diabetes Mellitus

Modern treatment abandons glucose-centered stepwise protocols and adopts weight-focused, complication-oriented regimens. GLP-1 receptor agonists and tirzepatide (dual GIP/GLP-1 agonist) are recommended as preferred first-line agents, with potent hypoglycemic, weight-reducing and cardiorenal effects. Clinical data show tirzepatide outperforms semaglutide in lowering HbA1c and body weight. Among Chinese patients, weekly tirzepatide leads to an average 17.5% weight loss[9], and reduces major cardiovascular events, heart failure hospitalization and renal function decline.

SGLT2 inhibitors are another cornerstone therapy. They produce steady weight loss and strong cardiorenal protection independent of glycemic levels, and are especially suitable for patients with heart failure or chronic kidney disease. Combining SGLT2 inhibitors with GLP-1 receptor agonists delivers additive metabolic benefits.

Dorzagliatin, a novel glucokinase activator launched in China, restores glucose sensing in pancreatic β-cells and hepatocytes. It stabilizes blood glucose, causes mild weight loss and carries low hypoglycemia risk. It works well for early-stage overweight/obese T2DM patients with β-cell dysfunction, either alone or combined with metformin or GLP-1 agonists, though attention should be paid to potential mild increases in triglycerides.

Metformin remains a basic agent for its mild weight-lowering effect, low cost and reliable safety, though its efficacy is limited in severe obesity, so it is mostly used in combined therapy. In contrast, insulin and sulfonylureas cause obvious weight gain and hypoglycemia, aggravate insulin resistance and blunt the weight-lowering effect of GLP-1 agonists. They also raise cardiovascular risks, so they are not recommended as first-line options for this patient group.

4. Combination Therapy in Clinical Practice

Combination therapy has become the mainstream strategy for overweight and obese patients with T2DM, as single-agent therapy often fails to achieve dual goals of glycemic control and weight management. The best regimens combine agents with complementary mechanisms, synergistic efficacy, and overlapping protective effects.

The combination of metformin and GLP-1 receptor agonist is the most widely recommended first-line option, providing reliable hypoglycemic effects, significant weight loss, and cardiovascular protection with low hypoglycemia risk[10]. For patients with obesity and high cardiorenal risk, the combination of GLP-1 receptor agonist and SGLT2 inhibitor provides additive weight loss and comprehensive organ protection. The combination of metformin and dorzagliatin is suitable for overweight patients with early disease and glycemic fluctuation, providing stable metabolic control with good tolerability[11]. For severely obese patients, triple therapy with GLP-1/GIP/glucagon receptor agonists shows the strongest efficacy in clinical trials, while tirzepatide-based combinations are under active investigation for diabetes remission[12]. Conversely, combinations that include sulfonylureas or high-dose insulin should be avoided because of weight gain, hypoglycemia risk, and blunted metabolic benefits. GLP-1 receptor agonists combined with excessive insulin also increase the risk of hypoglycemia without additional benefits. These principles are strongly supported by clinical trial evidence and consistent with recommendations from major guidelines[13].

5. Chronic Disease Management

Long-term chronic disease management for overweight and obese patients with T2DM includes adverse reaction monitoring, adherence improvement, multidisciplinary cooperation, and standardized follow-up. Gastrointestinal reactions induced by GLP-1 receptor agonists and tirzepatide can be alleviated by gradual dose titration and dietary adjustment. Genitourinary tract infections related to SGLT2 inhibitors can be reduced by adequate hydration and personal hygiene. Dorzagliatin has mild and transient adverse reactions, with good long-term safety[14]. Improving medication adherence is crucial for maintaining metabolic benefits. Long-acting preparations, simplified regimens, patient education, and digital

health interventions can significantly increase persistence. Multidisciplinary teams including endocrinologists, dietitians, nurses, pharmacists, and psychologists help patients establish healthy lifestyles, monitor weight and glucose regularly, and adjust medications in a timely manner. Long-term follow-up should include HbA1c, body weight, waist circumference, blood lipids, renal function, and complication screening to ensure long-term efficacy and safety.

6. Current Challenges and Future Perspectives

Despite major advances in pharmacological therapy, several challenges remain in clinical practice. High costs limit the accessibility of novel agents such as tirzepatide[15]. Real-world effectiveness is often lower than in clinical trials due to suboptimal adherence and insufficient dose titration. Long-term safety data for novel agents are still limited. Lifestyle intervention remains difficult to sustain. Future research will focus on oral longacting preparations, precision medicine based on genetic and biomarker predictors, artificial intelligenceassisted chronic disease management, and expanded medical insurance coverage. The combination of pharmacotherapy and bariatric surgery will further improve weight loss and diabetes remission rates in severely obese patients[16].Mechanistic research on organ protection of GLP-1 and SGLT2 inhibitors provides theoretical basis for new drug development[17].

7. Conclusion

Overweight and obese patients with T2DM have unique pathophysiological characteristics and high complication risks, requiring a comprehensive, weightcentric, and evidencebased pharmacological strategy. GLP1 receptor agonists, SGLT2 inhibitors, tirzepatide, and dorzagliatin have demonstrated clear advantages in glycemic control, weight reduction, and cardiorenal protection, making them preferred firstline agents. Individualized selection based on BMI stratification, comorbidities, safety profiles, and response predictors, combined with rational combination regimens and wholeprocess chronic disease management, can significantly improve metabolic control and longterm prognosis. With the continuous development of novel drugs and management models, the clinical outlook for overweight and obese patients with T2DM will continue to improve.

Acknowledgments

This work was supported by the Shanghai Pudong New Area Health Commission Clinical Pharmacy Key Discipline (PWZxk2022-26).

References

[1] Chen Y, Zhang P, Wang J, et al. Sex differences in the prevalence of obesity in 800,000 Chinese adults with type 2 diabetes. Endocr Connect. 2021;10(2):139-145.
[2] Yazici D, Sezer H. Insulin Resistance, Obesity, and Lipotoxicity. Adv Exp Med Biol. 2024;1460:341-367.
[3] Chen X, et al. Multidimensional links between dietary behavior and cardiometabolic comorbidities: a network analysis. Diabetol Metab Syndr. 2025;17:278.
[4] Hu RY, et al. [Association between obesity and risk for all-cause mortality in patients with type 2 diabetes]. Zhonghua Liu Xing Bing Xue Za Zhi. 2024;45(4):520-526.
[5] Magkos F, Fraterrigo G, Yoshino J, et al. Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity. Cell Metab. 2016;23(4):591-601.
[6] American Diabetes Association Professional Practice Committee. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S145-S157.
[7] Varra FN, et al. Molecular and pathophysiological relationship between obesity and chronic inflammation in the manifestation of metabolic dysfunctions and their inflammation-mediating treatment options (Review). Mol Med Rep. 2024;29(6):95.
[8] Zeng Y, Wu Y, Zhang Q, Xiao X. Crosstalk between glucagon-like peptide 1 and gut microbiota in metabolic diseases. mBio. 2023;15(1):e02032-23.
[9] Zhao L, Cheng Z, Lu Y, et al. Tirzepatide for Weight Reduction in Chinese Adults With Obesity: The SURMOUNT-CN Randomized Clinical Trial. JAMA. 2024;332(7):551-560.
[10] Sattar N, Tanniou J, Würtz P, et al. Multidimensional cardiometabolic protection with SGLT2 inhibitors and GLP-1 receptor agonists in obesity, type 2 diabetes and hypertension. Metabol Open. 2026;30:100370.
[11] Should Glucokinase be Given a Chance in Diabetes Therapeutics? A Clinical-Pharmacological Review of Dorzagliatin and Lessons Learned So Far. Clin Pharmacokinet. 2024;44:223-250.

[12] Alfaris N, et al. GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity: a narrative review. EClinicalMedicine. 2024;75:102782.
[13] American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1):S181-S206.
[14] Wu YQ, Wang K, Su JY, et al. Efficacy and safety of dorzagliatin, a novel glucokinase activators, in the treatment of T2DM: A meta-analysis of randomized controlled trials. Medicine(Baltimore).2024;103(8):e36916.
[15] Spreckley M, Ruggiero CF, Brown A. Incretin therapies, nutrition, and food insecurity in the UK. Nat Med. 2026.
[16] Ammori BJ, et al. Medical and surgical management of obesity and diabetes: what's new? Diabet Med. 2020;37(2):203-210.
[17] Sridhar VS, et al. Making a case for the combined use of SGLT2 inhibitors and GLP1 receptor agonists for cardiorenal protection. J Bras Nefrol. 2020;42(4):467-477.