MEDICINE AND MATERIALS
Volume 6, Issue 2, 2026: 153-160 | ISSN: 2784 – 1499 & e-ISSN: 2784 – 1537
DOI: 10.36868/MEDMATER.2026.06.02.07 | www.medicineandmaterials.com |

SEMAGLUTIDE IN TYPE 2 DIABETES MELLITUS: GLYCEMIC CONTROL, CARDIOMETABOLIC BENEFITS, RENAL PROTECTION, AND SAFETY CONSIDERATIONS

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Abstract

Type 2 diabetes mellitus is a complex metabolic disorder associated with chronic hyperglycemia, excess adiposity, cardiovascular morbidity, and progressive renal impairment, and semaglutide, a long-acting glucagon-like peptide-1 receptor agonist, has emerged as an important therapeutic option because it combines effective glucose lowering with clinically relevant weight reduction and broader cardiometabolic benefits. This review summarizes the pharmacological rationale, glycemic efficacy, weight-related outcomes, cardiovascular relevance, renal protection, and safety considerations of semaglutide in patients with type 2 diabetes mellitus, and evidence from clinical trials, real-world studies, and outcome-focused analyses supports its role in reducing glycated hemoglobin and body weight, while recent data also highlight its potential value in high-risk populations, including patients with cardiovascular disease or chronic kidney disease. Nevertheless, semaglutide therapy requires individualized clinical decision-making, particularly regarding oral versus injectable formulation, gastrointestinal tolerability, hypoglycemia risk in combination therapy, adherence, cost, and use in older or frail patients, and overall, semaglutide is more than a glucose-lowering agent, offering an integrated approach to reducing metabolic, cardiovascular, and renal risks.

Keywords: semaglutide, type 2 diabetes mellitus, GLP-1 receptor agonist, glycemic control, cardiometabolic risk, renal protection.

Introduction

Type 2 diabetes mellitus is a chronic metabolic disease characterized by insulin resistance, progressive β-cell dysfunction, hyperglycemia, and a high burden of cardiovascular, renal, and obesity-related complications, and despite the availability of multiple glucose-lowering therapies, long-term disease control remains challenging because treatment must address not only glycated hemoglobin reduction, but also body weight, cardiometabolic risk, renal protection, tolerability, and adherence, and in this context, glucagon-like peptide-1 receptor agonists have become an important therapeutic class due to their glucose-dependent insulinotropic effect and broader metabolic benefits [1].

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist designed to improve glycemic control in patients with type 2 diabetes mellitus, and its pharmacological activity is based on stimulation of insulin secretion and suppression of glucagon release in a glucose-dependent manner, thereby reducing the risk of hypoglycemia when used without

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insulin or sulfonylureas, and in addition, semaglutide slows gastric emptying and promotes satiety through central and peripheral mechanisms, contributing to clinically relevant weight reduction, and these effects make semaglutide particularly valuable in patients with type 2 diabetes and excess adiposity, where weight loss is an important therapeutic objective [1,2].

Beyond glycemic control, semaglutide has attracted attention because of its potential cardiometabolic and renal benefits, and its actions may involve improvements in body weight, blood pressure, lipid profile, inflammation, endothelial function, and metabolic stress, supporting its role as more than a conventional antihyperglycemic agent, and therefore, semaglutide represents a modern therapeutic option for type 2 diabetes mellitus, integrating glucose-lowering, weight-management, and organ-protective perspectives into an individualized treatment strategy [2,3].

Glycemic control, weight reduction, and real-world effectiveness

Semaglutide has become one of the most clinically relevant glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus because it addresses two major therapeutic objectives: improving glycemic control and reducing body weight, and in routine practice, these effects are particularly important because many patients with type 2 diabetes present with obesity or overweight, insulin resistance, metabolic syndrome, and increased cardiovascular risk, and real-world evidence confirms that semaglutide use is associated with clinically meaningful reductions in glycated hemoglobin and body weight, supporting its effectiveness beyond controlled trial environments. Such data are valuable because they reflect broader patient populations, variable adherence patterns, heterogeneous comorbidities, and treatment decisions closer to daily clinical practice [4].

Both injectable and oral semaglutide formulations have expanded therapeutic flexibility. Oral semaglutide is especially relevant because it provides a non-injectable GLP-1 receptor agonist option for patients reluctant to use injectable therapy, systematic reviews and meta-analyses have shown that oral semaglutide improves glycemic parameters and body weight in patients with type 2 diabetes, with efficacy varying by dose, baseline metabolic status, background therapy, and adherence to dosing requirements. Its oral formulation may improve acceptance in selected patients, although absorption conditions and dosing instructions remain important determinants of real-world effectiveness [5,6].

Comparative real-world studies assessing oral and subcutaneous semaglutide show that both formulations can be effective in routine clinical care, but they may serve different patient profiles, and subcutaneous once-weekly semaglutide offers a practical dosing schedule and has been associated with robust reductions in HbA1c and body weight, whereas oral semaglutide may be preferred by patients who avoid injections or require a more acceptable initiation strategy, and these observations emphasize that the choice between oral and injectable semaglutide should be individualized based on patient preference, metabolic targets, gastrointestinal tolerability, adherence capacity, and prior treatment history [7,8].

Prospective observational evidence further supports the effectiveness of oral semaglutide in real-world management of type 2 diabetes, and such studies are important because they document outcomes under routine clinical conditions, where patients often have multiple comorbidities, polypharmacy, and variable lifestyle patterns, and improvements in glycemic control and body weight observed in these settings reinforce the clinical applicability of semaglutide, although persistence, proper administration, and gastrointestinal adverse effects may affect long-term outcomes [9].

Real-world comparisons between oral and subcutaneous semaglutide also suggest that treatment effectiveness may depend on clinical context rather than formulation alone, and injectable semaglutide may provide stronger or more consistent weight and glycemic reductions in some cohorts, while oral semaglutide offers a valuable alternative when acceptability and

convenience are prioritized, and these findings support a patient-centered approach, in which efficacy is balanced against adherence, route of administration, tolerability, and therapeutic goals [10].

Beyond HbA1c and body weight, semaglutide may improve broader metabolic and patient-centered outcomes, and changes in body composition, waist circumference, metabolic parameters, and patient-reported outcomes are clinically relevant because type 2 diabetes management increasingly focuses on cardiometabolic health rather than glucose-lowering alone, and weight reduction may also improve insulin resistance, mobility, quality of life, and treatment satisfaction, making semaglutide particularly useful in patients with obesity-associated type 2 diabetes [11].

More recent comparative evidence also situates semaglutide within an evolving incretin-based therapeutic landscape, and tirzepatide has shown greater weight-loss effects in some analyses, but semaglutide remains a well-established GLP-1 receptor agonist with substantial evidence for glycemic improvement, weight reduction, cardiovascular relevance, and renal benefit, and therefore, semaglutide should be considered a central option in modern type 2 diabetes therapy, particularly when the treatment goal extends beyond glycemic control to the integrated reduction of cardiometabolic risk [12], and the principal evidence domains supporting the use of semaglutide for glycemic control, weight reduction, and real-world effectiveness we have summarized in Table 1.

Table 1. Evidence domains for semaglutide effectiveness in type 2 diabetes mellitus

Evidence domain	Main findings relevant to type 2 diabetes	Clinical interpretation	Ref.
Real-world effectiveness	Reductions in HbA1c and body weight in routine practice	Supports external validity beyond randomized trials	[4]
Oral semaglutide efficacy	Improves glycemic control and body weight	Useful non-injectable GLP-1 receptor agonist option	[5,6]
Oral versus subcutaneous use	Both formulations are effective, with different practical advantages	Route should be individualized according to preference and adherence	[7,10]
Once-weekly subcutaneous semaglutide	Clinically meaningful HbA1c and weight reduction	Convenient option with strong metabolic effect	[8]
Prospective real-world oral data	Confirms effectiveness under routine clinical conditions	Important for patients with comorbidities and polypharmacy	[9]
Body composition and patient-reported outcomes	Improvements extend beyond HbA1c and body weight	Supports cardiometabolic and quality-of-life relevance	[11]
Comparative incretin therapy	Tirzepatide may produce greater weight loss in some analyses	Places semaglutide within modern incretin-based treatment strategies	[12]

Cardiovascular and renal protection in high-risk type 2 diabetes populations

Cardiovascular and renal complications represent major determinants of morbidity and mortality in patients with type 2 diabetes mellitus, and for this reason, modern diabetes management has moved beyond isolated glycemic control toward therapies capable of reducing cardiometabolic and kidney-related risk, and semaglutide is particularly relevant in this context because its benefits appear to extend across multiple interconnected pathways, including weight reduction, improved glycemic control, blood pressure modulation, and potential effects on inflammation, endothelial function, and metabolic stress. In high-risk patients, these pleiotropic effects may contribute to clinically meaningful cardiovascular and renal outcomes [13].

Recent cardiovascular outcome evidence with oral semaglutide has strengthened the role of GLP-1 receptor agonist therapy in patients with type 2 diabetes and elevated cardiovascular risk, and in such populations, therapeutic decisions must consider not only HbA1c reduction but also major adverse cardiovascular events, background medication, renal status, obesity, and global risk burden, and the demonstration that oral semaglutide can be evaluated within cardiovascular outcome frameworks is important, as it supports the clinical relevance of both injectable and oral incretin-based approaches for patients requiring integrated risk reduction [13].

The interaction between semaglutide and other cardioprotective drug classes is also clinically important, and in contemporary diabetes care, many high-risk patients receive sodium-glucose cotransporter-2 inhibitors because of their cardiovascular and renal benefits. Analyses evaluating oral semaglutide according to concomitant SGLT2 inhibitor treatment are relevant because they reflect real-world combination strategies and help clarify whether GLP-1 receptor agonists may provide additive or complementary protection, and this is especially important in patients with established cardiovascular disease, chronic kidney disease, or multiple metabolic risk factors [14].

Renal protection has become one of the most important recent areas of research on semaglutide, and the FLOW trial provided essential evidence regarding semaglutide in patients with type 2 diabetes and chronic kidney disease, a population at particularly high risk of kidney failure and cardiovascular death, amd in this setting, semaglutide was associated with reduced risk of clinically important kidney outcomes and cardiovascular death, supporting its role as an organ-protective therapy rather than only a glucose-lowering agent, and these findings are highly relevant because diabetic kidney disease remains a leading cause of end-stage renal disease worldwide [15].

Additional analyses from FLOW examining semaglutide with or without concomitant SGLT2 inhibitor use further support the need to understand combined therapeutic strategies in diabetic kidney disease, and since SGLT2 inhibitors and GLP-1 receptor agonists may act through distinct yet complementary mechanisms, their integration could provide broader risk reduction in selected patients, and however, treatment selection must remain individualized, considering kidney function, tolerability, cardiovascular risk, body weight, glycemic targets, and concomitant therapies [16].

The rationale, design, and baseline characteristics of the FLOW trial are also important for interpreting evidence on renal outcomes and provide context on patient selection, disease severity, endpoints, and the clinical relevance of semaglutide in chronic kidney disease associated with type 2 diabetes. Overall, the available evidence suggests that semaglutide may contribute to a broader therapeutic paradigm in which glucose lowering, cardiovascular protection, renal preservation, and weight management are addressed simultaneously in high-risk populations with type 2 diabetes [17], and the main cardiovascular and renal evidence domains supporting the use of semaglutide in high-risk populations with type 2 diabetes we have summarized in Table 2.

Table 2. Cardiovascular and renal evidence domains for semaglutide in type 2 diabetes mellitus

Evidence domain	Main relevance	Clinical interpretation	Ref.
Cardiovascular outcomes with oral semaglutide	Evaluates semaglutide in patients with high cardiovascular risk	Supports incretin-based therapy beyond glucose lowering	[13]
Concomitant SGLT2 inhibitor use	Assesses semaglutide effects according to background SGLT2 inhibitor therapy	Relevant for modern combination strategies in high-risk patients	[14]
Chronic kidney disease outcomes	Evaluates kidney and cardiovascular endpoints in T2DM with CKD	Supports semaglutide as a potential organ-protective therapy	[15]
Semaglutide with or without SGLT2 inhibitors in CKD	Explores complementary treatment effects in diabetic kidney disease	Helps guide individualized therapy in patients with CKD	[16]
FLOW trial rationale and design	Provides context for patient selection, endpoints, and baseline risk	Strengthens the interpretation of renal outcome evidence	[17]

Safety, tolerability, adherence, and clinical limitations

The clinical value of semaglutide in type 2 diabetes mellitus depends not only on glycemic efficacy, weight reduction, and organ-protective effects, but also on safety, tolerability, treatment persistence, and appropriate patient selection and as with other glucagon-like peptide-1 receptor agonists, the most frequent adverse effects of semaglutide are gastrointestinal, including nausea, vomiting, diarrhea, abdominal discomfort, constipation, and reduced appetite. These reactions are usually dose-dependent and more frequent during treatment initiation or dose escalation. Although often transient, they may reduce adherence, lead to dose interruption, or require slower titration in susceptible patients [19].

The safety profile of semaglutide has been evaluated across both the SUSTAIN and PIONEER clinical trial programs, which included subcutaneous and oral formulations, and these data support an overall acceptable tolerability profile but also highlight the importance of monitoring gastrointestinal events, the risk of hypoglycemia when co-administered with insulin or sulfonylureas, gallbladder-related events, and treatment discontinuation, and because semaglutide acts through glucose-dependent insulin secretion, hypoglycemia is generally uncommon when used as monotherapy or with agents that do not independently cause hypoglycemia, however, the risk increases when semaglutide is co-administered with insulin secretagogues or insulin therapy, necessitating dose adjustment and patient education [19].

Age is an important factor when evaluating semaglutide safety, and post hoc cardiovascular outcome analyses according to age suggest that semaglutide may remain clinically relevant across age groups, but older patients often require individualized assessment because of frailty, polypharmacy, reduced renal reserve, gastrointestinal vulnerability, sarcopenia risk, and higher susceptibility to dehydration during vomiting or diarrhea, and therefore, therapeutic benefit must be balanced against tolerability and functional status, especially in elderly patients with multiple comorbidities [18].

Evidence in older patients receiving oral semaglutide further emphasizes this need for individualized treatment, and in this population, improvements in glycemic control can be achieved, but adverse events, discontinuation, nutritional status, and the risk of hypoglycemia require careful monitoring, excessive appetite suppression or rapid weight loss may be

undesirable in frail older adults, particularly when associated with reduced muscle mass or inadequate protein intake, therefore, semaglutide should be integrated into a broader clinical plan that includes nutritional counseling, medication review, renal monitoring, and assessment of treatment goals [20].

Adherence is another practical limitation, oral semaglutide requires specific administration conditions, including fasting and a small amount of water, as well as delayed food or medication intake, which may be difficult for some patients, and conversely, once-weekly injectable semaglutide may improve convenience but can be limited by injection reluctance, access, cost, or gastrointestinal intolerance, and these practical aspects influence real-world effectiveness and should be considered when selecting the formulation, and overall, semaglutide is a highly valuable therapeutic option for type 2 diabetes mellitus, but its use requires individualized risk-benefit assessment, and clinical decision-making should consider age, comorbidities, renal function, background glucose-lowering therapy, gastrointestinal tolerance, body composition, adherence capacity, cost, and patient preference, and the main safety and tolerability considerations relevant to semaglutide therapy, we have summarized in Table 3.

Table 3. Safety, tolerability, and clinical limitations of semaglutide in type 2 diabetes mellitus

Safety domain	Main clinical issue	Practical implication	Ref.
Gastrointestinal adverse effects	Nausea, vomiting, diarrhea, constipation, abdominal discomfort	May require gradual dose escalation, counseling, or temporary interruption	[19]
Hypoglycemia risk	Generally low with monotherapy, higher with insulin or sulfonylureas	Adjust background therapy and educate patients	[19,20]
Treatment discontinuation	May occur due to gastrointestinal intolerance or poor adherence	Monitor tolerability during initiation and escalation	[19,20]
Older age	Frailty, polypharmacy, reduced renal reserve, dehydration risk	Individualize dose escalation and treatment goals	[18,20]
Weight loss in frail patients	Possible loss of appetite and lean mass concerns	Assess nutrition, muscle status, and functional reserve	[20]
Oral formulation requirements	Strict fasting administration conditions	May affect adherence and real-world effectiveness	[20]
Injectable formulation limitations	Injection reluctance, cost, access, gastrointestinal intolerance	Choose formulation according to preference and feasibility	[18,19]

Conclusions

Semaglutide represents a major therapeutic advancement in type 2 diabetes mellitus because it integrates effective glycemic control with clinically relevant weight reduction and potential cardiometabolic and renal benefits, thereby addressing several interconnected dimensions of diabetes-related risk; however, its optimal use requires individualized patient selection, careful assessment of cardiovascular and kidney status, consideration of oral versus

injectable formulation, and active monitoring of gastrointestinal tolerability, hypoglycemia risk in combination therapy, adherence barriers, cost, and frailty-related concerns in older adults, so that semaglutide should be positioned not merely as a glucose-lowering agent, but as part of a broader, patient-centered strategy for metabolic, cardiovascular, and renal risk reduction.

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Received: March 15, 2026
Accepted: May 24, 2026