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NEPHROPROTECTIVE POTENTIAL OF SEMAGLUTIDE IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE: CLINICAL EVIDENCE AND THERAPEUTIC PERSPECTIVES

POTENCIAL NEFROPROTETOR DA SEMAGLUTIDA EM PACIENTES COM DIABETES TIPO 2 E DOENÇA RENAL CRÔNICA: EVIDÊNCIAS CLÍNICAS E PERSPECTIVAS TERAPÊUTICAS

POTENCIAL NEFROPROTECTOR DE LA SEMAGLUTIDA EN PACIENTES CON DIABETES TIPO 2 Y ENFERMEDAD RENAL CRÓNICA: EVIDENCIA CLÍNICA Y PERSPECTIVAS TERAPÉUTICAS

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ABSTRACT

Chronic kidney disease (CKD) is one of the most prevalent and impactful complications of type 2 diabetes mellitus (T2DM), associated with high morbidity and mortality rates. Although conventional therapies, such as RAAS inhibitors and SGLT2 inhibitors, provide recognized

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benefits, many patients still experience progressive kidney function decline. In this context, semaglutide, a GLP-1 receptor agonist, has gained attention for its potential nephroprotective effects beyond glycemic control.This article aims to critically review current scientific evidence on the renal effects of semaglutide in patients with T2DM and CKD. A narrative review was conducted based on clinical trials, observational studies, mechanistic analyses, and meta-analyses published between 2018 and 2025. The main findings indicate significant benefits in reducing albuminuria, stabilizing estimated glomerular filtration rate (eGFR), lowering progression to end-stage renal disease, and reducing cardiovascular events.The underlying mechanisms include glomerular hemodynamic modulation, anti-inflammatory and antifibrotic effects, and improved insulin sensitivity. The consistency of results across various clinical contexts reinforces the emerging role of semaglutide as a cardio-renal therapeutic agent. In conclusion, semaglutide represents a promising therapeutic approach with potential to transform the management of CKD in patients with T2DM.

Keywords: Semaglutide. Chronic Kidney Disease. Type 2 Diabetes. GLP-1 Receptor Agonists. Nephroprotection. Albuminuria.

RESUMO

A doença renal crônica (DRC) é uma das complicações mais prevalentes e impactantes do diabetes mellitus tipo 2 (DM2), estando associada a altos índices de morbimortalidade. Embora terapias tradicionais, como os inibidores do SRAA e os inibidores de SGLT2, ofereçam benefícios reconhecidos, ainda há significativa progressão da DRC em muitos pacientes. Nesse cenário, a semaglutida, um agonista do receptor GLP-1, tem se destacado por seus potenciais efeitos nefroprotetores além do controle glicêmico.Este artigo tem como objetivo revisar criticamente as evidências científicas atuais sobre os efeitos renais da semaglutida em pacientes com DM2 e DRC. Trata-se de uma revisão narrativa baseada em ensaios clínicos, estudos observacionais, análises mecanísticas e meta-análises publicadas entre 2018 e 2025. Os principais achados apontam para benefícios significativos na redução da albuminúria, estabilização da taxa de filtração glomerular (TFG), menor progressão para insuficiência renal terminal e redução de eventos cardiovasculares.Os mecanismos subjacentes envolvem modulação hemodinâmica glomerular, efeitos anti-inflamatórios e antifibróticos, e melhora na sensibilidade à insulina. A consistência dos dados em diferentes contextos clínicos reforça o papel emergente da semaglutida como agente cardiorrenal. Conclui-se que a semaglutida representa uma abordagem terapêutica promissora, com potencial para transformar o manejo da DRC em pacientes com DM2.

Palavras-chave: Semaglutida. Doença Renal Crônica. Diabetes Tipo 2. Agonistas do GLP-1. Nefroproteção. Albuminúria.

RESUMEN

La enfermedad renal crónica (ERC) es una de las complicaciones más frecuentes e impactantes de la diabetes mellitus tipo 2 (DM2), asociada a altas tasas de morbilidad y mortalidad. Si bien las terapias tradicionales, como los inhibidores del SRAA y los inhibidores del SGLT2, ofrecen beneficios reconocidos, muchos pacientes aún experimentan una progresión significativa de la ERC. En este contexto, la semaglutida, un agonista del receptor GLP-1, se ha destacado por sus potenciales efectos nefroprotectores, además de su capacidad para controlar la glucemia. Este artículo tiene como objetivo revisar críticamente la evidencia científica actual sobre los efectos renales de la semaglutida en pacientes con DM2 y ERC. Se trata de una revisión narrativa basada en ensayos clínicos, estudios

observacionales, análisis mecanísticos y metaanálisis publicados entre 2018 y 2025. Los principales hallazgos apuntan a beneficios significativos en la reducción de la albuminuria, la estabilización de la tasa de filtración glomerular (TFG), el retraso en la progresión a la insuficiencia renal terminal y la reducción de eventos cardiovasculares. Los mecanismos subyacentes incluyen la modulación hemodinámica glomerular, efectos antiinflamatorios y antifibróticos, y una mayor sensibilidad a la insulina. La consistencia de los datos en diferentes contextos clínicos refuerza el papel emergente de la semaglutida como agente cardiorrenal. Se concluye que la semaglutida representa una opción terapéutica prometedora con el potencial de transformar el manejo de la enfermedad renal crónica en pacientes con diabetes tipo 2.

Palabras clave: Semaglutida. Enfermedad Renal Crónica. Diabetes Tipo 2. Agonistas del GLP-1. Nefroprotección. Albuminuria.

1 INTRODUCTION

Chronic kidney disease (CKD) is one of the most prevalent and impactful microvascular complications of type 2 diabetes mellitus (DM2), associated with high cardiovascular morbidity and mortality and progressive loss of renal function. It is estimated that about 40% of individuals with T2DM will develop some degree of renal impairment throughout their lives, which highlights the need for more effective therapeutic strategies to delay the progression of the disease (BIOMEDICINES, 2022; MAHAFFEY et al., 2024).

Historically, the treatment of CKD in diabetic patients has been based on intensive glycemic control, the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, and, more recently, sodium-glucose cotransporter type 2 (SGLT2i) inhibitors (NEFROLOGIA, 2023; BUENO et al., 2022). Although these approaches have reduced the rate of progression in some patients, many continue to experience renal functional decline, which drives the search for additional interventions with proven nephroprotective action (LONG et al., 2024).

Among emerging therapies, glucagon-like peptide receptor agonists type 1 (GLP-1 RAs) have gained prominence, not only for metabolic control, but also for their extrapancreatic effects. Semaglutide, belonging to this class, was initially approved for the management of T2DM and obesity, but has been progressively studied for its potential direct benefit on the renal parenchyma, regardless of the hypoglycemic action (PRATLEY et al., 2024; RAO et al., 2024).

Recent clinical studies suggest that the renal effects of semaglutide are mediated by multiple mechanisms, including reduction of glomerular inflammation, hemodynamic modulation, decrease of interstitial fibrosis, and preservation of glomerular filtration rate (GFR). In addition, a sustained reduction in albuminuria was observed at different stages of CKD, even in patients at high cardiovascular risk (KRAJEWSKA et al., 2024; PHARMACEUTICS, 2025; APPERLOO et al., 2024).

The FLOW Trial, the main randomized clinical trial to directly address the renal outcomes of semaglutide in patients with T2DM and CKD, demonstrated a significant reduction in compound events related to disease progression, such as the need for renal replacement therapy, worsening albuminuria, and a sharp decline in GFR (PERKOVIC et al., 2024; MAHAFFEY et al., 2024). Sub-analyses of the study showed maintenance of the protective effect even among patients with heart failure and increased cardiovascular risk (PRATLEY et al., 2024).

Observational studies have also contributed with relevant data, pointing to the consistency of the renal and cardiovascular effects of semaglutide in different populations, including among patients already using other therapeutic classes, such as SGLT2i and RAAS inhibitors. These results suggest a possible additive and synergistic effect in the management of diabetic nephropathy (DE LUCAS et al., 2022; HADJADJ et al., 2025; GARCÍA DE LUCAS et al., 2023).

In view of the current panorama and the growing clinical and pathophysiological evidence base, this article aims to critically review the available scientific literature on the use of semaglutide in patients with DM2 and CKD. Its mechanisms of renal action, potential therapeutic benefits, and clinical implications in the context of contemporary nephrology practice will be discussed.

2 METHODOLOGY

This study is a **narrative review of the literature** with a qualitative, descriptive and exploratory approach, whose objective was to gather, analyze and critically discuss the clinical, pathophysiological and therapeutic evidence on the use of semaglutide in patients with type 2 diabetes mellitus (DM2) and chronic kidney disease (CKD), with emphasis on its potential nephroprotective effects. This type of review was chosen because it allows the integration of different types of studies, clinical trials, observational studies, systematic reviews, meta-analyses, and preclinical investigations, offering a broad and up-to-date view of the topic.

The search for scientific articles was carried out between August and October 2025 in the following databases: **PubMed/MEDLINE, Scopus**, **Web of Science**, **SciELO,** and **Google Scholar**. Search strategies were used with combinations of the controlled descriptors (DeCS/MeSH): *"Semaglutide*", *"Chronic Kidney Disease", "Type 2 Diabetes Mellitus", "Diabetic Nephropathy*", *"Renal Outcomes", "Nephroprotection",* in addition to related free terms.

The **inclusion** criteria were:

(a) original articles published between **2018 and 2025**,

(b) studies in humans and animal models with translational relevance,

(c) publications in **Portuguese, English or Spanish**,

(d) access to the full text, and

(e) studies with data related to renal function, nephroprotection, or renal outcomes in patients with T2DM treated with semaglutide.

The following were **excluded**:

(a) duplicate articles,

(b) studies focusing exclusively on other pharmacological classes,

(c) opinion publications not based on scientific evidence (e.g. editorials, letters to the editor),

(d) studies with insufficient data on renal function, and

(e) studies exclusively focused on type 1 diabetes.

Screening was initially performed by reading the titles and abstracts, followed by reading the eligible texts in full. The selection and analysis of the articles were carried out by two reviewers independently. Divergences were resolved by consensus, based on the relevance and methodological quality of the studies. After the selection process, **35 articles** that met the established criteria were included, divided into five thematic categories: (1) clinical trials and observational studies; (2) systematic reviews and meta-analyses; (3) mechanistic and preclinical studies; (4) narrative reviews and clinical guides; (5) complementary and regional studies.

The present study did not involve primary data collection from human beings and, therefore, **did not require approval by a research ethics committee**. The review respected the ethical principles of scientific integrity, with rigor in the identification and citation of the sources used.

3 RESULT AND DISCUSSION

3.1 PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES

The functional and structural alterations that characterize diabetic nephropathy result from a complex set of hemodynamic, metabolic, and inflammatory alterations, which lead to progressive nephron injury and loss of renal function. In many cases, the process is silent in its initial phase, with persistent microalbuminuria as the first detectable marker of glomerular dysfunction (MAHAFFEY et al., 2024).

Chronic hyperglycemia plays a central role in the pathophysiology of the disease, inducing glycotoxicity and oxidative stress, which activate inflammatory pathways and promote the formation of advanced glycation end products (AGEs). These compounds trigger endothelial dysfunction, mesangial expansion, and impaired basement membrane integrity

(ZHOU et al., 2024). In parallel, there is activation of the renin-angiotensin-aldosterone system (RAAS), with consequent vasoconstriction of the efferent arteriole and increased intraglomerular pressure, favoring hyperfiltration and podocyte damage (TUTTLE et al., 2020).

The progression of CKD is strongly associated with the expression of pro-inflammatory cytokines (such as IL-6 and TNF-α) and fibrogenic factors, such as TGF-β, which stimulate tubulointerstitial fibrosis and glomerular sclerosis (BJORNSTAD et al., 2022; KOVESDY et al., 2024). This cascade leads to a gradual decrease in glomerular filtration rate (GFR), often culminating in the need for renal replacement therapy.

Other aggravating factors include insulin resistance, which favors lipotoxicity in the proximal tubules, and mitochondrial dysfunction (CHRISTENSEN et al., 2023), in addition to arterial hypertension, which is highly prevalent in this group, which aggravates hemodynamic damage and accelerates the evolution of the disease (DE LUCA et al., 2024).

Clinically, CKD in diabetic patients remains underdiagnosed in the early stages, compromising opportunities for early intervention. Routine assessment of estimated GFR and albuminuria is essential for risk stratification and definition of therapeutic strategy. In recent decades, agents with direct effects on the kidney, such as SGLT2 inhibitors and GLP-1 agonists, have demonstrated additional benefits to conventional treatment with RAAS inhibitors (LIU et al., 2024; KRAJEWSKA et al., 2024).

Given this multifactorial scenario, understanding the pathophysiology of CKD associated with DM2 is crucial to justify the use of interventions that act on multiple fronts, such as semaglutide, whose effects are not restricted to glycemic control, but also reach inflammatory, oxidative, and fibrogenic pathways. However, despite the solid theoretical basis, there is still a need for studies that elucidate the efficacy of these therapies in more advanced stages of the disease and in specific subgroups of patients.

3.2 RENAL MECHANISMS OF ACTION OF SEMAGLUTIDE

Semaglutide is a glucagon-like peptide receptor agonist type 1 (GLP-1 RA), initially developed for the treatment of type 2 diabetes mellitus (T2DM), with proven efficacy in glycemic control and weight reduction. However, recent evidence points to a multifactorial role of the molecule in renal protection, which goes beyond its traditional hypoglycemic effects (APPERLOO et al., 2024; KRAJEWSKA et al., 2024).

The main mechanisms involved in this renoprotective action include glomerular hemodynamic modulation, attenuation of intrarenal inflammation, inhibition of interstitial fibrosis, and improvement of the systemic metabolic profile. Together, these effects contribute to slowing the progression of chronic kidney disease (CHRISTENSEN et al., 2023). One of the most studied pathways refers to the reduction of intraglomerular pressure, mediated by vasodilation of the afferent arteriole and relaxation of vascular smooth muscle, which helps prevent hyperfiltration, a common phenomenon in the early stages of diabetic nephropathy (BJORNSTAD et al., 2022).

From an inflammatory point of view, studies in animal models have demonstrated reduced expression of pro-inflammatory cytokines such as IL-6 and TNF-α, as well as inhibition of the transcription factor NF-κB pathway, one of the main mediators of chronic renal inflammation (CHRISTENSEN et al., 2023). In addition, there is evidence of decreased oxidative stress and apoptosis in the proximal tubules, with consequent preservation of renal architecture (PHARMACEUTICS, 2025).

As for interstitial fibrosis, semaglutide seems to act negatively on the TGF-β1/Smad3 pathway, responsible for extracellular matrix deposition and progressive glomerular sclerosis (KRAJEWSKA et al., 2024). This antifibrotic potential has been correlated with functional preservation in preclinical models and in sub-analyses of large clinical trials (APPERLOO et al., 2024).

Another relevant mechanism involves the improvement of insulin sensitivity, with a consequent reduction in lipotoxicity and accumulation of triglycerides in the renal tubules, a particularly useful effect in patients with metabolic syndrome or obesity (BJORNSTAD et al., 2022). The sustained reduction in albuminuria, observed in both experimental and clinical studies, represents a robust indirect marker of the drug's protective action on the renal parenchyma (MAHAFFEY et al., 2024; DE LUCAS et al., 2023).

Thus, semaglutide acts in an integrated manner on multiple pathophysiological axes of CKD progression in DM2, being considered a promising candidate within the contemporary concept of multifunctional cardiorenal therapies. However, despite these plausible and well-described mechanisms, translational and clinical studies are still needed to confirm the extent and durability of these effects in more diverse populations and in advanced stages of the disease.

3.3 CLINICAL EVIDENCE: RANDOMIZED TRIALS

Randomized controlled trials represent the highest level of scientific evidence for the evaluation of therapeutic interventions. In the context of chronic kidney disease (CKD) associated with type 2 diabetes (T2DM), studies with semaglutide have shown consistent and promising results regarding its nephroprotective efficacy. The main one was published in 2024, under the acronym **FLOW** (*Finding the Effect of Semaglutide in Diabetic Kidney Disease*), a multicenter, double-blind, placebo-controlled study that included more than 3,500 patients with T2DM and CKD at different stages (PERKOVIC et al., 2024). Participants were followed for a median period of 3.4 years, receiving subcutaneous semaglutide once weekly (1 mg or 2 mg) or placebo in addition to standard treatment (including SGLT2i and RAAS inhibitors when indicated). The results showed a 24% reduction in the risk of composite renal outcomes, such as progression to renal replacement therapy, doubling of serum creatinine, and death from renal causes. However, it is worth noting that the study excluded patients in more advanced stages of CKD, such as those with GFR below 30 mL/min/1.73m² or on hemodialysis, which limits the direct applicability of the findings to this population. In addition, renal outcomes, while significant, were analyzed as a composite outcome, which may obscure the magnitude of the effect on each component individually.

Sub-analyses derived from the same research showed that the benefits of semaglutide were consistent across all stages of kidney disease, with particularly relevant effects on reducing albuminuria and preserving the estimated glomerular filtration rate (eGFR) over time (MAHAFFEY et al., 2024). There was also a positive impact on the reduction of major cardiovascular events (MACE), such as acute myocardial infarction and stroke, especially among individuals with greater renal impairment.

In another analysis focused on cardiac outcomes, a significant reduction in hospitalization for heart failure was observed among patients treated with semaglutide (PRATLEY et al., 2024). These data reinforce the profile of integrated cardiorenal protection of the molecule, aligning with the contemporary concept of multisystem therapeutic approaches for high-risk populations.

In addition to this pivotal trial, complementary evidence comes from secondary analyses of previous studies, such as SUSTAIN-6. Although it did not have renal outcomes as the primary focus, this study identified a significant reduction in the progression of albuminuria, suggesting early effects on the kidney (WANNER et al., 2019).

It is important to highlight that many of these trials included participants in concomitant use of drugs recognized for renal protection, such as SGLT2i and RAAS inhibitors, which highlights the additive effect of semaglutide in already established therapeutic regimens. These findings support the combined and individualized use of the drug in patients with CKD and T2DM (YANG; LIU, 2024).

Thus, the most recent randomized studies strengthen the understanding of semaglutide as an agent with robust and clinically significant renal benefits, with the potential to modify the course of CKD in diabetic patients.

3.4 OBSERVATIONAL STUDIES WITH SEMAGLUTIDE IN DIABETIC KIDNEY DISEASE

In addition to randomized controlled trials, observational studies have played an important role in evaluating the efficacy and safety of semaglutide in patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD), especially in real-world clinical practice settings. These studies provide complementary data on relevant clinical outcomes, such as the evolution of albuminuria, variations in glomerular filtration rate (GFR), and therapeutic response in subgroups with different stages of the disease.

In a retrospective study conducted by Long et al. (2024), which evaluated electronic medical records of patients with renal failure, semaglutide demonstrated good tolerability, with improved glycemic control and stabilization of renal function, even in individuals with GFR less than 30 mL/min/1.73m². The findings are relevant because they indicate the possible safety of the drug in more advanced stages of CKD, a population often excluded from clinical trials.

Similarly, Bueno et al. (2022) followed 312 patients with T2DM and CKD on outpatient semaglutide use, observing significant reductions in albuminuria and glycated hemoglobin (HbA1c) levels, with no record of serious renal adverse events. Conducted in Brazil, the study reinforces the applicability of the treatment in public and private health contexts.

In Spain, García de Lucas et al. (2023) stratified the results according to the stage of CKD and identified improvement in estimated GFR and less need for insulin intensification among patients with moderately reduced renal function. These data suggest maintenance of glycemic efficacy and potential renal benefit even in more compromised stages of renal function.

Additionally, Yabe et al. (2023) evaluated Asian patients with T2DM and CKD, observing a sustained reduction in albuminuria, improvement in HbA1c, and less progression

to end-stage renal disease. The presence of metabolic syndrome or obesity did not compromise the response to treatment, which expands the applicability of semaglutide in different ethnic and metabolic profiles.

Another relevant piece of data was brought by Wang and Xie (2025), who analyzed more than 1,200 medical records and reported a lower rate of hospitalizations for renal and cardiovascular causes among semaglutide users. The study also identified potential clinical benefit in combination with SGLT2 inhibitors, suggesting therapeutic synergism between classes.

This observational evidence reinforces the consistency of the safety and efficacy profile of semaglutide in diverse clinical settings. Despite the limitations inherent to the non-randomized design, these data corroborate the findings of clinical trials and support the use of the molecule as a relevant component of expanded therapeutic strategies for patients with T2DM and CKD.

3.5 SYSTEMATIC REVIEWS AND META-ANALYSES

The growing scientific evidence on the effects of glucagon-like peptide receptor agonists type 1 (GLP-1 RAs), especially semaglutide, has motivated several systematic reviews and meta-analyses in recent years, focusing on renal outcomes in patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD). These analyses, by consolidating data from multiple clinical and observational studies, offer evidence of greater methodological robustness and broaden the understanding of the nephroprotective profile of semaglutide in different clinical contexts.

In a systematic review conducted by Rao et al. (2024), we included 18 studies investigating the effects of semaglutide on renal outcomes. The authors reported a significant reduction in the progression of albuminuria, improvement in estimated glomerular filtration rate (GFR), and less need for renal replacement therapy. These effects were maintained even after adjusting for glycemic control, suggesting that the renal benefits of semaglutide are not restricted to its hypoglycemic action.

Similarly, Zhou et al. (2024) conducted a meta-analysis of randomized controlled trials with GLP-1 RAs, including semaglutide, and observed a 21% reduction in compound renal events (including new or worsened albuminuria, ≥40% drop in GFR, and initiation of dialysis). Semaglutide demonstrated superiority over liraglutide and exenatide in subgroups with moderate to severe CKD, reinforcing its differential potential within the class.

In another meta-analysis, Akabane et al. (2024) evaluated the cardiovascular and renal safety of semaglutide in individuals with T2DM and elevated cardiovascular risk. In addition to reducing renal outcomes, the drug promoted improvement in inflammatory markers, such as C-reactive protein, and in hemodynamic parameters such as blood pressure, suggesting a possible anti-inflammatory and hemodynamic effect associated with cardiorenal protection.

The publication of the *Annals of Medicine & Surgery* (2025) conducted a comparative meta-review between semaglutide and other antidiabetic agents in patients with CKD. It was concluded that semaglutide was one of the interventions with the greatest combined impact on renal, cardiovascular, and metabolic outcomes, maintaining a favorable safety profile even in patients with significantly reduced renal function.

In addition, the pooled analysis of data from the SUSTAIN-6 and LEADER studies, conducted by Shaman et al. (2021), found that semaglutide was associated with lower progression of albuminuria and preservation of kidney function over time, despite the fact that renal outcomes were not the primary endpoints of these trials. These data suggest a sustained renal benefit, which reinforces the interest in long-term analyses.

Finally, a critical review conducted by Kovesdy et al. (2024) discussed that the renal effects of semaglutide can be amplified when used in combination with other therapeutic classes, such as SGLT2 inhibitors. The authors argue that the convergence of antifibrotic, anti-inflammatory, and hemodynamic mechanisms may explain the synergy observed in clinical studies and reinforce the need for further studies focusing on combination therapy.

In general, systematic reviews and meta-analyses reinforce the emerging role of semaglutide as a nephroprotective agent. Its efficacy in different population subgroups, combined with the safety profile, supports the progressive inclusion of the drug in clinical guidelines for the integrated management of patients with T2DM and CKD. Still, gaps remain on its use in specific populations, such as dialysis patients or those with non-diabetic CKD, signaling priority areas for future investigation.

4 CONCLUSION

Chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (DM2) is a highly complex clinical challenge, with significant repercussions on morbidity and mortality and care costs. Although traditional therapeutic strategies, such as intensive glycemic control and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, have proven

benefits, there are evident limitations, especially in individuals with more advanced stages of renal dysfunction.

In this context, glucagon-like peptide receptor agonists type 1 (GLP-1 RAs), especially semaglutide, have been consolidated as promising therapeutic agents. Evidence from randomized controlled trials, notably the FLOW Trial, and large-scale observational studies demonstrates that the drug is associated with reduced albuminuria, preservation of glomerular filtration rate (GFR), and reduced need for renal replacement therapy. In addition to nephrological outcomes, relevant cardiovascular benefits are observed, especially in high-risk populations.

From the pathophysiological point of view, the renal effects of semaglutide result from multifactorial mechanisms, involving anti-inflammatory action, glomerular hemodynamic modulation, antifibrotic properties, and improvement of insulin resistance. These actions have been corroborated by mechanistic and experimental studies, aligning with clinical findings and supporting the biological plausibility of the observed effects.

In addition, recent systematic reviews and meta-analyses reinforce the efficacy of semaglutide in different population subgroups and therapeutic contexts, including when combined with other pharmacological classes such as SGLT2 inhibitors. This versatile profile broadens its practical applications and suggests potential therapeutic synergy.

Despite the advances, important gaps persist in the literature, such as the scarcity of data on patients on dialysis therapy, the need for prolonged follow-up, and cost-effectiveness evaluations in different socioeconomic realities. These aspects require continuous investigation in order to consolidate the role of the drug as a central axis in the treatment of diabetic nephropathy.

In summary, semaglutide emerges as an innovative therapeutic intervention, with the ability to modify the clinical course of CKD in DM2, exceeding the limits of traditional glycemic control. Its incorporation into integrated, evidence-based care strategies may represent a new paradigm in cardiorenal management, promoting better outcomes and rationalization of health care.

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