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Impact of GLP-1 receptor agonist therapy on oxidative stress and adiponectin axis: Implications for renal health in adults with obesity

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ABSTRACT

Obesity is a major contributor to the development and progression of chronic kidney disease (CKD) and represents a global health problem. The pathophysiology of obesity-related kidney injury is fundamentally based on a vicious cycle of oxidative stress and the dysregulation of key adipokines, mainly adiponectin. Chronic obesity leads to a greater production of reactive oxygen species (ROS) that damage the glomerular filtration barrier, leading to podocyte loss and albuminuria. Paradoxically, with fat accumulation, the level of the renoprotective hormone adiponectin decreases, depriving the kidney of crucial anti-inflammatory and antioxidant defenses. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have recently become a breakthrough class of drugs with significant renal benefits beyond weight loss. While their indirect metabolic and anti-inflammatory systemic actions are well-established, emerging data from animal and *in vitro* models suggest potential target-specific pathways on the renal microenvironment, potentially modulating oxidative damage and restoring adiponectin signaling. Accumulating clinical trial data, including secondary analyses from cohorts investigating non-diabetic populations with obesity, demonstrate that these therapies effectively mitigate albuminuria and slow progressive glomerular strain, independently of classic metabolic dynamics. The present review gathers available literature to understand the molecular actions of GLP-1 RAs on the adiponectin–oxidative stress axis, emphasizing the relevance of these pathways in maintaining podocyte integrity and preventing tubulointerstitial fibrosis. This integrative paradigm positions GLP-1 RAs as a key element in managing obesity-related nephropathy, providing a promising option to lessen the clinical and economic burden of renal failure.

Implication for health policy/practice/research/medical education:
The increasing prevalence of obesity-related kidney disease requires a transition from traditional weight-management strategies to targeted organ-protective therapies. This review underlines the important mechanisms of renal protection by glucagon-like peptide-1 receptor agonists (GLP-1 RAs) by the regulation of the adiponectin-oxidative stress axis. GLP-1 RAs exert a dual-action pathway that maintains podocyte function and slows the progression of chronic kidney disease (CKD) by increasing systemic adiponectin and reducing renal oxidative damage. These insights support the early integration of GLP-1 RAs not only as metabolic regulators but also as essential renoprotective agents that can significantly reduce the long-term burden of renal failure and the subsequent need for renal replacement therapy in the obese population with respect to clinical practice and health policy.

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Introduction

Obesity has become a pandemic-level leading cause of several metabolic illnesses, including chronic kidney disease (CKD) (1). The kidney is a highly vascularized organ with complex filtration mechanisms and represents an important target in obesity due to its vulnerability to microvascular stress, immune-mediated inflammation, and endothelial dysfunction (1). The physiological consequences of excessive adiposity in obese individuals lead to glomerular hyperfiltration and increased metabolic load, a setting in which the renal microcirculation is particularly susceptible (2,3). In this clinical context, the interaction between oxidative stress, adipokine dysregulation, and cellular damage appears to be a key cascade leading to progressive kidney injury (4).

Proinflammatory mediators that alter vascular tone and

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stimulate immunological activation are major contributors to systemic alterations in chronic obesity (5). A distinctive aspect of this condition is the increase in oxidative stress, which manifests as excessive generation of reactive oxygen species (ROS) that directly damage the glomerular basement membrane and disrupt the energy metabolism of renal cells (4,6). Adiponectin levels are significantly reduced alongside this oxidative stress. Adiponectin, a major collagen-like plasma protein important for renal homeostasis and maintenance of the glomerular filtration barrier, is decreased under conditions of obesity (7,8).

Obesity is associated with increased mechanical and metabolic stress on podocytes, which are terminally differentiated epithelial cells that form the final barrier of the glomerular apparatus, thereby increasing their vulnerability (9). Oxidative stress and reduced adiponectin availability lead to podocyte depletion and foot process effacement, resulting in persistent proteinuria and progressive glomerulosclerosis (7,10). In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been shown to exert important pleiotropic effects beyond weight reduction (11). Recent evidence suggests that GLP-1 RAs may disrupt this cycle of injury by modulating adiponectin signaling and reducing oxidative stress, thereby contributing to renoprotective effects (12,13). While many of these metabolic pathways are classically characterized in diabetic nephropathy, exploring their translation to non-diabetic, obesity-driven renal stress represents a crucial frontier in contemporary research. This review aims to summarize current knowledge on the effects of GLP-1 RAs therapy on the oxidative stress–adiponectin axis in preserving kidney health in adults with obesity. Due to the paucity of molecular data specific to non-diabetic obesity-related glomerulopathy (ORG), this review extrapolates the established adiponectin-oxidative stress axis from diabetic kidney disease (DKD) literature, hypothesizing its applicability to obesity-driven lipotoxicity. Future studies isolating pure ORG models are urgently needed to fully validate these pathways, and the presented mechanisms should be viewed as a translational working hypothesis.

Search strategy

For this narrative review, a literature search was conducted across major electronic databases, including PubMed, Web of Science, Scopus, Google Scholar, and Embase, to identify relevant studies published up to 2025. To ensure methodological rigor and reproducibility, the primary literature was retrieved utilizing a precise Boolean search string constructed with relevant Medical Subject Headings (MeSH) terms and keywords as follows: ("GLP-1 receptor agonists" OR "semaglutide" OR "liraglutide") AND ("obesity" OR "overweight") AND ("oxidative stress" OR "reactive oxygen species" OR "adiponectin") AND ("kidney disease" OR "podocyte" OR "renal protection" OR "nephropathy").

The search focused on literature evaluating the relationships between GLP-1 receptor agonists, obesity, oxidative stress, adiponectin, and markers of renal injury such as podocyte damage and proteinuria. The selection was limited to articles published in English involving adult populations, focusing on identifying key mechanistic pathways and translating clinical outcomes relevant to obesity-driven renal stress. Additionally, the search strategy was expanded to include select in vitro cell culture and preclinical animal models. These non-clinical studies were specifically included to elucidate the underlying molecular and intracellular mechanistic pathways of GLP-1 RAs, which are not always fully captured or measurable within human clinical trials.

Pathophysiology of obesity-related renal injury

The relationship between excess adiposity and renal dysfunction is complex and characterized by a transition from physiological adaptation to irreversible structural damage (9). In the early phase of obesity, the kidney exhibits glomerular hyperfiltration and hypertrophy, which represents a compensatory response to increased metabolic demands and augmented renal plasma flow (1,9). However, this sustained hemodynamic strain ultimately induces mechanical stress on podocytes, as the highly specialized cells responsible for maintaining the filtration barrier (3).

Beyond hemodynamic changes, expansion of white adipose tissue in obesity generates a systemic milieu of low-grade chronic inflammation (5). Adipose tissue functions as an active endocrine organ; however, in obesity it adopts a pro-inflammatory profile, secreting cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (4). These mediators, together with activation of the renin-angiotensin-aldosterone system (RAAS), contribute to increased oxidative stress within the glomerular microenvironment (4).

Lipotoxicity plays a central role in this process. Ectopic lipid accumulation in renal cells leads to mitochondrial dysfunction and increased production of ROS (14). The resulting oxidative stress promotes protein carbonylation and lipid peroxidation, which directly impair the actin cytoskeleton of podocytes, leading to foot process effacement and subsequent proteinuria (2). As podocyte density declines, the exposed glomerular basement membrane becomes susceptible to synechiae formation and focal segmental glomerulosclerosis, a histopathological hallmark of obesity-related nephropathy (1,3). Overall, the kidney in obesity is driven into a self-perpetuating cycle of metabolic, hemodynamic, and inflammatory injury that progressively impairs its filtration capacity (4). Crucially, a distinct pathophysiological line must be drawn between ORG and DKD. Although these conditions share secondary overlapping features, such as elevated oxidative stress and systemic (RAAS) activation, they represent separate clinical and pathological diagnoses.

Classically, ORG is characterized by glomerulomegaly and focal segmental glomerulosclerosis without the profound glomerular basement membrane thickening or nodular intercapillary glomerulosclerosis typical of DKD. Therefore, while substantial mechanistic and biochemical data in the literature are drawn from diabetic populations, translating and extrapolating these findings directly to non-diabetic individuals with obesity requires careful and rigorous clinical interpretation. To date, direct preclinical and clinical evidence characterizing GLP-1 RA modulation of targets like Nrf2 (nuclear factor erythroid 2-related factor 2) or AMP-activated protein kinase (AMPK) specifically within pure, non-diabetic ORG models remains scarce. Consequently, these molecular cascades are primarily hypothesized based on overlapping lipotoxicity pathways shared with DKD literature.

Adiponectin; the protective link in renal homeostasis

Adiponectin is a 30-kDa protein predominantly secreted by adipocytes and serves as an important molecular regulator of renal function (7). In contrast to other adipokines, adiponectin exhibits anti-inflammatory, anti-fibrotic, and insulin-sensitizing properties (7). Under physiological conditions, adiponectin binds to its receptors (AdipoR1 and AdipoR2) in the kidney, primarily on podocytes and glomerular endothelial cells, thereby activating downstream signaling pathways that contribute to the maintenance of cellular integrity (7,8).

Adiponectin exerts its renoprotective effects through activation of AMP-activated protein kinase. This pathway is essential for preserving the podocyte actin cytoskeleton and preventing foot process effacement (7,15,16). In addition, adiponectin acts as an endogenous antioxidant by reducing NADPH oxidase activity and superoxide anion generation within the renal microenvironment (6,8). It also inhibits the nuclear factor kappa B (NF- κB) pathway and the release of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby modulating the inflammatory response (17,18).

In obesity, a paradoxical decline in adiponectin levels has been reported despite increased adipose tissue mass. This hypoadiponectinemia is attributed to reduced adiponectin synthesis driven by the pro-inflammatory environment of hypertrophied adipocytes (5). Consequently, the kidney becomes deprived of this protective adipokine and more susceptible to metabolic and oxidative injury. Reduced adiponectin levels are strongly associated with increased albuminuria and decreased glomerular filtration rate (GFR), as podocytes lose a key protective mechanism against apoptotic and fibrotic signaling (2,19). Restoration or enhancement of adiponectin signaling has therefore emerged as a potential therapeutic target for preventing the development of obesity-related nephropathy (7). Furthermore, while hypoadiponectinemia is a standard feature of early-stage obesity and metabolic syndrome, a clinical phenomenon known as the adiponectin paradox is observed in advanced CKD. In late-stage renal failure, circulating adiponectin levels can paradoxically rise, primarily due to significantly reduced renal clearance and altered adipocyte secretion dynamics, which requires careful baseline stratification when utilizing this adipokine as a biomarker.

GLP-1 receptor agonists; beyond glycemic control

Recent human transcriptomic and single-cell RNA sequencing data demonstrate that human renal GLP-1R expression is exceptionally low or below standard detection limits. Consequently, the established renoprotective effects of GLP-1 RAs including the modulation of the adiponectin-oxidative stress axis should be conceptualized primarily as a result of indirect, systemic metabolic remodeling rather than direct intrarenal receptor activation. While early animal models suggested direct glomerular expression, human clinical evidence strongly reinforces that systemic metabolic improvements drive these intrarenal pathway benefits, secondary to weight loss and reduced systemic inflammation. Through these systemic and tissue-specific modulations, GLP-1 RAs indirectly trigger intracellular signaling pathways within the renal microenvironment. These intrarenal molecular adjustments [such as NADPH oxidase inhibition and superoxide dismutase (SOD)/catalase upregulation] represent a secondary response downstream of enhanced systemic adiponectin secretion from restored adipocytes and the subsequent activation of podocyte AdipoR1 (adiponectin receptor 1), rather than a direct activation of renal GLP-1R (20).

The renal effects of GLP-1 RAs appear to be partly mediated through modulation of adiponectin signaling. Emerging evidence suggests that GLP-1 RAs treatment may increase systemic adiponectin levels by improving adipocyte function and reducing local inflammation in adipose tissue (5,7). As demonstrated by Wang et al (7), liraglutide promotes white adipose tissue browning, which directly enhances the systemic secretion of adiponectin from these remodeled adipocytes. This systemic elevation in circulating adiponectin consequently increases its bioavailability in the renal microenvironment, thereby stimulating the highly expressed AdipoR1 receptors on human podocytes to trigger protective downstream anti-inflammatory cascades. This increase in adiponectin may enhance renal AMPK activation, which contributes to stabilization of the podocyte cytoskeleton and maintenance of slit diaphragm integrity (7,15).

In addition, GLP-1 RAs act as modulators of oxidative stress. They inhibit NADPH oxidase activation and upregulate antioxidant enzymes such as superoxide dismutase and catalase within the renal microenvironment (6,8). This combined effect on adipokine regulation and oxidative stress may help attenuate the lipotoxic environment characteristic of obesity (4). Furthermore, GLP-1 RAs reduce inflammatory cell recruitment and decrease the release of pro-inflammatory cytokines, which

may slow the progression of tubulointerstitial fibrosis and glomerular scarring (12,13). Overall, these agents may provide multifaceted protection against metabolic, inflammatory, and structural pathways involved in renal injury in obesity (11). The proposed interaction between obesity-induced oxidative stress, adiponectin dysregulation, podocyte injury, and the renoprotective effects of GLP-1 RAs is illustrated in Figure 1, while the specific molecular targets are summarized in Table 1.

Clinical evidence and renal outcomes

Several landmark trials and observational studies have supported the translation of GLP-1 RAs therapy from experimental models to clinical practice in patients with obesity. Clinical data consistently show that these agents reduce albuminuria, an early marker of glomerular injury, and slow the decline in estimated glomerular filtration rate (eGFR) (8,11).

Recent cardiovascular and renal outcome trials have provided important evidence supporting the potential renoprotective effects of GLP-1 RAs. In particular, the FLOW trial demonstrated that semaglutide reduced the risk of major composite kidney outcomes, including persistent macroalbuminuria, substantial decline in eGFR, progression to kidney failure, and renal or cardiovascular death by approximately 24% in patients with type 2 diabetes and CKD (12,20,29). Importantly, because the FLOW trial specifically evaluated individuals with type 2 diabetes and pre-existing CKD, its primary findings cannot be directly generalized to non-diabetic populations. To address the clinical impact of these agents in obesity without diabetes, the landmark SELECT trial demonstrated significant renal benefits with semaglutide in non-diabetic overweight and obese individuals with established cardiovascular disease. Specifically, the trial reported clear reductions in composite adverse renal endpoints; however, it is critical to clarify that this composite outcome was predominantly driven by a significant reduction in new-onset macroalbuminuria, as hard renal endpoints such as a sustained ≥50% eGFR decline or end-stage renal disease were expectedly rare within this non-diabetic cohort. While this nuance underscores that the primary early benefit in non-diabetics lies in preventing progressive albuminuria (30), the significant reduction in albuminuria (a surrogate endpoint) provides robust translational evidence for ORG management. In many patients, reductions in proteinuria have been associated with increases in circulating adiponectin and improvements in oxidative stress markers, such as malondialdehyde (19).

In addition, although improvements in blood pressure and weight loss contribute to renal benefit, they do not fully account for the observed effects. Emerging evidence suggests that GLP-1 RAs may exert direct actions on the podocyte–endothelial unit by reducing oxidative stress and inflammatory signaling, which may contribute to improved renal outcomes (7,12). Clinical observations also indicate stabilization of renal function in some patients prior to significant weight reduction, supporting the hypothesis of direct metabolic and renal effects (31). Overall, current evidence supports GLP-1 RAs as an important therapeutic option to slow the progression of obesity-related nephropathy toward end-stage renal disease.

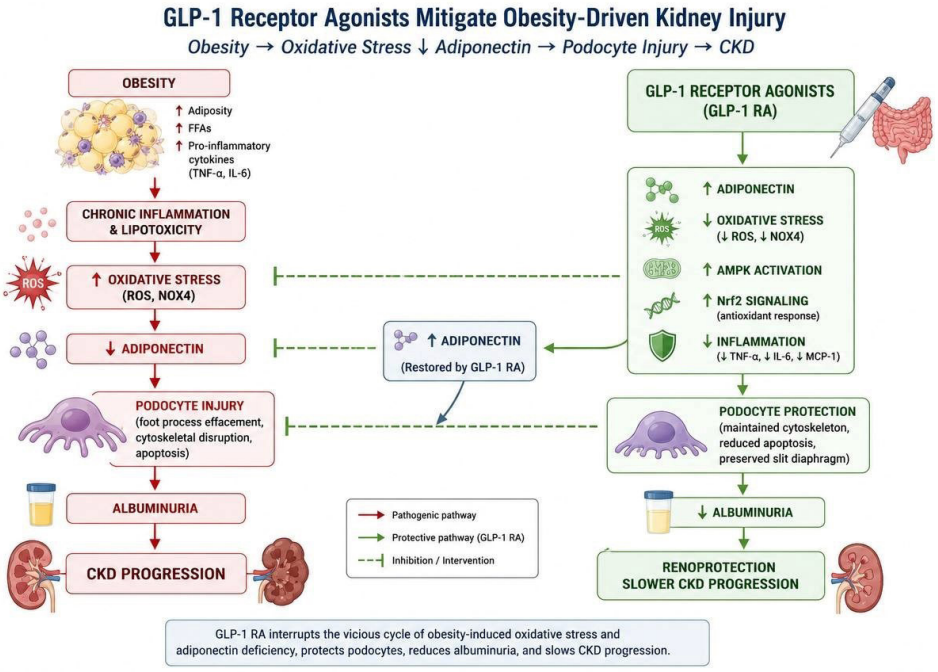

Figure 1. The adiponectin–oxidative stress axis in obesity-related CKD and the protective role of GLP-1 receptor agonists.

Table 1. Molecular mechanisms of GLP-1 RAs and adiponectin signaling in renal protection

Molecular target	Effect of treatment	Impact on renal health	Key references
AdipoR1 expression	Up-regulation in podocytes	Attenuates metabolic-induced cellular apoptosis	(7,16,21)
Nrf2 pathway	Promotion of nuclear translocation	Activates antioxidant genes	(6,13,20,22)
NADPH oxidase	Inhibition of NOX4 activity	Reduces ROS production	(4,8,23)
AMPK signaling	Activation of AMPK/mTOR inhibition	Restores cellular autophagy under metabolic stress	(17,24-26)
Mitochondria	Improved energy metabolism	Prevents apoptosis by upstream adiponectin restoration	(14,27,28)

AdipoR1: Adiponectin Receptor 1; AMPK: Adenosine monophosphate-activated protein kinase; mTOR: Mammalian target of rapamycin; NADPH: Nicotinamide adenine dinucleotide phosphate; NOX4: NADPH oxidase 4; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species.
Note: Molecular pathways (e.g., AdipoR1, Nrf2, and AMPK) are partially generalized from established diabetic kidney disease (DKD) literature due to overlapping lipotoxic and inflammatory cascades; direct validation of these specific molecular targets under isolated non-diabetic obesity-related glomerulopathy (ORG) settings remains limited.

Focus on biomarkers

The identification of reliable biomarkers is important for evaluating the therapeutic effects of GLP-1 RAs and for predicting renal outcomes in individuals with obesity. Conventional markers such as serum creatinine and albuminuria remain clinically relevant; however, they are relatively insensitive to early molecular changes within the renal microenvironment (12,19). Therefore, increasing attention has been directed toward the adiponectin–oxidative stress axis, with markers such as total oxidant status (TOS) and total antioxidant capacity (TAC) (19).

Adiponectin is considered a dual-function biomarker, as increases in circulating levels during GLP-1 RAs therapy may reflect improved adipocyte function and enhanced renal protection (5,7). Therefore, clinicians should note that baseline adiponectin is most useful as a predictive biomarker in early-to-moderate obesity-related kidney disease, whereas its utility diminishes in advanced CKD (stages 4-5) due to this paradox. This creates a distinct clinical dilemma when interpreting rising adiponectin levels in patients with advanced stage 4 CKD undergoing GLP-1 RA therapy, as it becomes challenging to distinguish between a beneficial increase reflecting improved adipocyte function versus a detrimental accumulation caused by declining renal clearance. To resolve this clinical ambiguity, the interpretation of adiponectin in late-stage disease must not be done in isolation; it requires a concurrent assessment of longitudinal eGFR trends alongside complementary redox and structural markers, such as TOS, TAC, or urinary nephrin, to avoid misinterpreting poor renal clearance as a therapeutic success. Furthermore, from a clinical prescribing perspective, because GLP-1 RAs are primarily indicated for early-to-moderate CKD risk reduction, the adiponectin paradox observed in advanced CKD (stages 4-5) remains a largely theoretical concern for late-stage ORG. In clinical reality, the utility of both GLP-1 RA therapy and adiponectin monitoring in advanced stages is limited by pharmacokinetic constraints and dose adjustment requirements, as patients approaching end-stage disease are typically transitioned to renal replacement therapy preparations rather than primary nephroprotection.

Concurrent assessment of oxidative balance using TOS and TAC provides a more comprehensive evaluation of renal redox status. Total oxidant status reflects the overall burden of oxidants associated with lipotoxicity, whereas TAC represents the cumulative capacity of antioxidant defenses to counteract oxidative injury (4,6).

Clinical studies suggest that GLP-1 RAs therapy may modulate this balance by reducing TOS and increasing TAC, thereby potentially limiting oxidative stress–induced injury to podocytes (13,19). Nevertheless, it is important to note that while TOS and TAC serve as valuable systemic markers of redox status, they reflect systemic circulation and may not perfectly mirror the localized, intrarenal microenvironmental redox state. In addition, urinary biomarkers of podocyte injury, such as podocalyxin and nephrin fragments, have been increasingly associated with systemic redox markers, offering a non-invasive approach for assessing glomerular filtration barrier integrity (19). Overall, adiponectin, TOS, and TAC represent promising biomarkers for monitoring renal status in obese patients and may provide mechanistic insight into the efficacy of renoprotective therapies (12). The clinical outcomes and biomarker changes are summarized in Table 2.

Treatment modalities and future perspectives

The integration of GLP-1 RAs into the management of obesity-related renal injury represents a shift toward more proactive approaches to nephroprotection. Current treatment strategies emphasize a multidisciplinary approach in which GLP-1 RAs may be initiated early in adults with obesity, particularly in those with early signs of glomerular hyperfiltration or low-grade albuminuria (11,31). Long-acting GLP-1 RAs (e.g., semaglutide) and novel dual incretin receptor agonists like tirzepatide [a dual GIP (glucose-dependent insulinotropic polypeptide)/GLP-1 RA] remain central therapeutic agents, with evidence suggesting potential benefits in modulating metabolic and oxidative stress–related pathways over time (5).

Future perspectives are increasingly focused on personalized medicine. A biomarker-guided strategy

Table 2. Clinical and biomarker outcomes

Clinical parameter	Observed change	Clinical significance	Key references
Albuminuria (UACR)	Significant reduction	Restored filtration barrier	(11,19)
Urinary nephrin/PCX	Marked decrease	Reduced podocyte injury	(12,19)
Systemic adiponectin	Increase in plasma levels	Anti-inflammatory protection	(50,10,32)
TOS / TAC Balance	Reduced TOS / Increased TAC	Re-established redox balance	(4,19)

PCX: Podocalyxin; TAC: Total antioxidant capacity; TOS: Total oxidant status; UACR: Urine albumin-to-creatinine ratio.

based on adiponectin, TOS, and TAC profiles may help clinicians tailor the intensity and duration of GLP-1 RAs therapy to optimize renal protection (19). In addition, emerging evidence supports the concept of combined therapy, where GLP-1 RAs are used alongside SGLT2 inhibitors or mineralocorticoid receptor antagonists to potentially target hemodynamic, metabolic, and fibrotic pathways in a complementary manner (20).

Furthermore, research into podocyte-specific GLP-1 receptor signaling is expanding, and novel oral formulations as well as dual and triple incretin agonists are being investigated for their potential to enhance metabolic and antioxidant effects (14,26,33). From a health policy perspective, GLP-1 RAs may eventually be considered as part of earlier intervention strategies in high-risk populations with obesity. This approach could potentially delay the progression from obesity-related kidney injury to end-stage renal disease and reduce the long-term burden on renal replacement therapies (8,11).

Conclusion

In summary, the interaction between adipose tissue as an endocrine organ, systemic inflammation, and renal microvascular health is central to understanding obesity-related kidney disease. This review highlights that renal injury in adults with obesity is not solely the result of mechanical overload but is largely driven by dysregulation of the adiponectin–oxidative stress axis. The interplay of hypoadiponectinemia, increased TOS, and reduced TAC may contribute to podocyte dysfunction and progressive glomerular injury. Likewise, GLP-1 RAs represent an important therapeutic advancement in nephropharmacology. These agents act on multiple pathways and may contribute to improving adiponectin signaling and redox balance within the kidney. In conclusion, GLP-1 RAs significantly mitigate early markers of glomerular injury, particularly albuminuria, in non-diabetic obesity. This reduction in surrogate markers suggests potential for long-term preservation of renal function; however, hard endpoint data regarding progression to end-stage renal disease or absolute kidney failure in this specific non-diabetic cohort are still maturing and require further long-term clinical evaluation. Due to the paucity of molecular data specific to non-diabetic ORG, this review extrapolates the established adiponectin-oxidative stress axis from DKD literature, hypothesizing its applicability to obesity-driven lipotoxicity. Future studies isolating pure ORG models are urgently needed to fully validate these pathways, and the presented mechanisms should be viewed as a translational working hypothesis.

Overall, these findings support the emerging clinical relevance of adiponectin, TOS, and TAC as biomarkers of renal oxidative status. Future therapeutic strategies should focus on earlier intervention targeting this axis to potentially reduce the burden of obesity-related renal disease and progression to kidney failure.

Authors' contribution

Conceptualization: Miqat Abdulkadhim Jawad, Hasan Haider Alsalamy, and Mudhafar Sami Khazal.
Data curation: Miqat Abdulkadhim Jawad.
Investigation: Miqat Abdulkadhim Jawad.
Supervision: Hasan Haider Alsalamy and Mudhafar Sami Khazal.
Validation: Hasan Haider Alsalamy and Mudhafar Sami Khazal.
Visualization: Miqat Abdulkadhim Jawad.
Writing–original draft: Miqat Abdulkadhim Jawad.
Writing–review and editing: All authors.

Conflicts of interest

The authors state that there is no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors utilized Gemini (Google) and Grammarly to refine grammar points and language style in writing. Additionally, Canva (Canva Pty Ltd) was utilized solely as a graphic design and layout platform to visually format and organize the manually verified conceptual frameworks presented in Figure 1. No automated generative AI tools or AI-driven image synthesis were employed to create, hallucinate, or modify the underlying biological structures or molecular signaling pathways. All conceptual mechanisms were manually mapped and rigorously verified for scientific accuracy against current literature by the authors, including Miqat Abdulkadhim. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the accuracy and content of the publication.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) were fully observed by the authors.

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