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Obesity-Related Nephropathy in the Pediatric Population: Pathophysiology, Clinical Manifestations, and Management - A Review

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Abstract

Background: Obesity has become a serious problem among children in recent decades. This condition causes metabolic and cardiovascular complications, as well as affects the kidneys. The role of excessive weight has been established as a risk factor for renal disease among adults, but more and more research shows similar outcomes in obese children. The incidence of diagnosed cases of obesity-related nephropathy is constantly on the rise.

Aim of the study: This research aims to highlight the importance of renal complications and their monitoring among the group of high-risk patients in the pediatric population. It also presents the latest evidence supporting the use of early biomarkers for detecting and further monitoring the progression of kidney damage among this group of patients.

Material and methods: Review of scientific literature published within the last fifteen years was conducted to evaluate the influence of obesity among children on renal complications, especially chronic kidney disease.

Results: Complications of obesity, such as hypertension and diabetes, as well as metabolic syndrome, are factors that contribute to the development of chronic kidney disease in children. However, if this condition is not monitored, it can lead to severe kidney damage and rapid disease progression, ultimately resulting in end-stage renal failure. Although researchers view obesity-related glomerulopathy as the result of various mechanisms, the most significant factors are considered to be lipid accumulation, insulin resistance, dysfunction of the renin-angiotensin-aldosterone system, and podocyte damage.

Conclusions: Early detection of nephropathy allows slowing disease progression through lifestyle modification and pharmacotherapy, although the existing changes are not reversible. Chronic, progressive kidney disease can reduce not only the quality but also the length of life for young patients.

Key words: obesity, obesity-related glomerulopathy, nephropathy, chronic kidney disease, oxidative stress, lipotoxicity, insulin resistance

1.1 Introduction

Obesity, defined by the World Health Organisation (WHO) as a body mass index (BMI) ≥30 kg/m² for adults and ≥ 95th percentile for age and gender- specific percentiles in the pediatric population, has become a major global health concern affecting not only adults but also children and adolescents. The prevalence of childhood obesity has increased markedly over the last decades, prognosis says that 51% of the population may be obese by 2030. The continuing upward trend continues highlights the importance of early identification of children above the 95th percentile, allowing implementation of preventive strategies and monitoring for potential complications (Mangat et al. 2022; Apovian et al. 2016)

Excess body weight in childhood is associated with multiple systemic consequences involving cardiovascular (hypertension), liver (nonalcoholic fatty liver disease) orthopedic and psychological complication, metabolic and endocrine (T2DM, dyslipidemia, insulin resistance (IR), metabolic syndrome), but also renal system. Among these, kidney involvement is particularly concerning because chronic kidney disease (CKD) often develops silently. Early stages are typically asymptomatic, yet progressive renal injury may ultimately lead to end-stage kidney disease (ESRD), a severe condition linked to markedly increased mortality and a high burden of cardiovascular complications. In pediatric patients, additional challenges such as growth impairment and difficulties with psychosocial development further contribute to a substantial reduction in quality of life (Mangat et al. 2022; Harambat 2011).

Chronic kidney disease is commonly classified using the Kidney Disease Outcomes Quality Initiative (K/DOQI) staging system, which divides disease severity into five stages based on glomerular filtration rate (GFR). CKD is defined as evidence of kidney damage, including structural or functional abnormalities detected by laboratory or imaging studies, persisting for at least three months, or a GFR below 60 ml/min/1.73 m² for the same period (Harambat et al. 2012). Although widely adopted, this framework has important limitations in pediatric populations. Estimation of GFR in children remains challenging, particularly in early kidney injury, and creatinine-based formulas may be less reliable due to age-dependent changes in muscle mass and growth (Jančič 2022 et al. 2022). Moreover, the K/DOQI classification does not apply to children younger than two years, as GFR increases physiologically after birth and reaches values comparable to adults around this age. In addition, children born with significant congenital renal anomalies may be considered to have CKD without waiting three months for diagnosis (Harambat et al. 2012).

Reliable epidemiological data on CKD in children remain limited. Earlier estimates suggested that the prevalence of chronic kidney disease ranged from 15 to 74.7 cases per million children, depending on the population studied (Warady & Chadha 2007). More recent analyses indicate that kidney abnormalities may be present in a substantial proportion of children with obesity, with reported prevalence reaching approximately 20.9% in this group (Forcina et al. 2024). However, the true burden of CKD in pediatric populations is likely underestimated because early disease often follows an asymptomatic course and remains undiagnosed (Carullo et al. 2023). With the rising prevalence of childhood obesity, the risk of long-term renal complications and progression represents an increasingly important clinical problem.

Studies conducted in different populations demonstrate an association between obesity and both development and progression of CKD. Elevated BMI has been linked to proteinuria in individuals without previously diagnosed kidney disease, and some reports indicate that higher BMI is associated with reduced estimated GFR and progressive decline in renal function leading to end-stage renal disease (Kovesdy et al. 2017). These findings suggest that obesity may contribute directly to kidney injury even before clinically overt disease is recognized.

Childhood obesity is increasingly considered a significant risk factor for chronic kidney damage. Although the relationship between obesity and CKD has been well established in adults, growing evidence indicates that similar mechanisms operate in children. Obesity-related pathophysiological changes, including IR, metabolic syndrome, hypertension, and chronic low-grade inflammation, may lead to glomerular hyperfiltration, structural renal injury, and progressive nephron loss. Early disease - frequently asymptomatic may delay the diagnosis. For this reason, children with obesity should be regarded as a high-risk population requiring careful monitoring of renal function.

Evaluation of kidney involvement in this group typically relies on assessment of albuminuria and estimated GFR over time. Albuminuria is most commonly detected using the albumin-to-creatinine ratio (ACR), with values ≥30 mg/g considered abnormal, while decreased eGFR may indicate impaired renal function. These markers, although imperfect in pediatric populations, remain widely used for early detection of obesity-related nephropathy. (Carullo et al. 2023; Mangat et al. 2022; Martínez 2022; Yim et al. 2021)

1.2 Material and methods

A comprehensive narrative literature review was conducted to summarize the current evidence regarding obesity-related nephropathy in the pediatric population. Reliable publications were identified through systematic searches of the PubMed, Google Scholar, and ResearchGate databases. The search strategy incorporated combinations of the following keywords: “obesity-related glomerulopathy,” “chronic kidney disease,” “obesity-related kidney disease,” “nephroprotection,” and “renal biomarkers” focused on pediatric analyses.

The review primarily focused on studies involving both pediatric and adult populations to provide a broader understanding of the disease spectrum and its clinical implications. Relevant publications included randomized controlled trials, meta-analyses, observational studies, cohort studies, systematic reviews, and case reports. The selected articles were critically analyzed and categorized according to their relevance to the major aspects of obesity-related kidney disease, including pathophysiological mechanisms, diagnostic approaches and biomarkers, as well as current treatment and therapeutic strategies.

2. Pathophysiology of Obesity-related Glomerulopathy (ORG)

The pathogenesis of kidney disease (KD) among children seems to have its onset in early childhood, before the symptoms of diabetes and hypertension, or other renal-conditions (such as nephrolithiasis, rarely kidney cancers) are detected. Therefore, while comparing to normal-weight children, young individuals suffering from obesity tend to have significantly larger kidneys as well as the renal flow is increased (Carullo et al. 2023)

Obesity causes increased glomerular filtration rate (GFR), which conclude in glomerulomegaly (enlargement of glomerulus). Diabetes type 2 (DM2) predisposes to hyperfiltration and enhances further development of the nephropathy, leading to the end stage of renal disease (RD). Genrally, about ⅓ of patients with DM2 over time progress to chronic kidney disease (Sharma et al. 2021).

Disruption in metabolism caused by obesity concluding in oxidative stress, adipokine dysregulation, insulin resistance and chronic inflammation has been identified as leading to kidney damage. The exact pathophysiology has not yet been fully understood.

In literature, obesity - related KD has been known as obesity-related glomerulopathy (ORG) specified as enlargement of the glomeruli and its progressive sclerosis worsening renal function. Key mechanisms implicated in ORG include insulin resistance (IR), toxicity of lipids, oxidative stress and RAAS (renin-angiotensin-aldosterone system) upregulation.

2.1 Renin–angiotensin–aldosterone system

Obesity increases both hemodynamic and metabolic demands on the kidneys. These changes are associated with afferent arteriolar vasodilation and enhanced tubular sodium reabsorption, which promote activation of the RAAS. Increased sodium reabsorption in the proximal tubule contributes to volume expansion, glomerular hyperfiltration, and elevated intraglomerular pressure. This mechanism increases the risk of hypertension and proteinuria. Persistent hyperfiltration leads to glomerular hypertrophy and may progress to focal segmental glomerulosclerosis (FSGS). Progressive glomerular injury further alters intrarenal hemodynamics, maintaining afferent vasodilation and promoting efferent arteriolar vasoconstriction, which amplifies intraglomerular hypertension.

In addition, angiotensin II acts as a pro-inflammatory and pro-oxidative mediator, contributing to renal injury progression through contribution to oxidative stress. Hyperactivity of RAAS, particularly the dysbalance between increased angiotensin II and ACE2/Ang (1–7) axis activity, is also associated with impaired metabolism of glucose. Angiotensin II stimulates adipokine production, interferes with insulin signaling, and reduces GLUT4-mediated glucose uptake, thereby promoting insulin resistance (Forcina et al. 2024).

2.2 Lipid metabolism and toxicity

One of the roles of kidneys is to filter lipids from the bloodstream and take part in their synthesis, as well as oxidation. Excessive adipose tissue causes dysregulation of lipid metabolism, secreting substances, such as adipokines, which are cytokines that promote inflammation, and dyslipidemia, leading to the accumulation of fat deposits in renal tissue. This mechanism is recognised as primary, driving damage of kidneys. Nephrotoxic influence triggers mitochondrial stress and inflammation, actin cytoskeleton remodeling, insulin resistance, endoplasmic reticulum stress and further cellular apoptosis (Mitrofanova et al. 2023). The resulting pro-inflammatory milieu may lead to glomerulosclerosis and tubulointerstitial damage. Dyslipidemia and lipidotoxicity affect renal tissue, particularly podocytes, damaging the glomerular filtration barrier and resulting in proteinuria and microalbuminuria (Forcina et al. 2024). These mechanisms lead to impaired filtration, a decline in renal function, and the promotion of fibrosis contributing to KD. Ceramides and free fatty acids (FFAs) can induce oxidative stress, but also dysfunction of mitochondria which intensifies the damage of the kidney. Current research focuses on molecular mechanisms and possible implication of transcriptional regulators (such as PPARs and SREBP-1) in dysregulation of lipid metabolism (Xu et al. 2024).

Lipid-related toxicity is considered one of the key mechanisms contributing to renal injury in individuals with obesity. Dyslipidemia is observed more frequently in patients with chronic kidney disease than in the general population, and children with obesity tend to present with higher concentrations of circulating lipids and lipoproteins compared with those of normal weight. Worsening lipid profiles are also associated with declining kidney function, for each 10 mL/min/1.73 m² reduction in GFR, triglyceride and non-HDL cholesterol show positive correlation, on the contrary to HDL cholesterol levels (Carullo et al. 2023). Patients in early stages of chronic kidney disease may present increased levels of oxidized low-density lipoprotein (oxLDL), triglycerides, and small dense low-density lipoprotein (sdLDL), while high-density lipoprotein- cholesterol (HDL-C) is reduced (Mitrofanova et al. 2023).

Understandment of lipid metabolism and its alteration among obese individuals may help to find target- oriented therapies, while for clinicians this knowledge allows to monitor the stage of kidneys (thus albuminuria and lipid profile), before the patients report symptoms suggesting advanced renal dysfunction.

2.3 Hypoxia and Oxidative stress

Oxidative stress caused by a disproportion between production of ROS and scavenging occurs through a dysfunction of mitochondrial respiration. Impaired mitochondrial function can be caused by kidney damage resulting from various factors, such as inflammation or diabetes (Honda et al. 2019).

Physiologically, nitric oxide (NO) modulates mitochondrial respiration and limits oxygen consumption. A decrease of NO may therefore enhance mitochondrial activity, as well as oxygen consumption, ultimately leading to tissue hypoxia (Liu et al. 2022; Honda et al. 2019). Oxidative stress is increased among patients with CKD. Particularly those with diabetic kidney disease (DKD), experience increased oxidative stress because chronic hyperglycemia in diabetes leads to the production of reactive oxygen species (ROS).

Kidney inflammation and fibrosis induced by ROS contribute to the development of DKD through numerous signaling pathways involving transforming growth factor β (TGF-β), connective tissue growth factor (CTGF), monocyte chemotactic protein 1, TNF-α (tumor necrosis factor α), interleukin (IL) 1, IL-6, IL-18, and cell adhesion molecules (Elmarakby et al. 2012; Honda et al. 2019).

As kidney function deteriorates, erythropoietin (EPO) synthesis decreases, resulting in renal anemia that further worsens oxygen delivery to tissues. Reduced oxygen availability promotes tubular fibrosis and loss of peritubular capillaries, which intensifies hypoxia. At the same time, the remaining glomerular and peritubular capillaries are exposed to altered renal blood flow (RBF) and elevated hydrostatic pressure, contributing to additional structural damage and progression of fibrosis. Consequently, both reduced and abnormally increased RBF within the peritubular microcirculation may lead to tubulointerstitial hypoxia. A critical level of interstitial hypoxia triggers progressive decline in kidney function. In this context, hypoxia and oxidative stress create a self-perpetuating cycle that accelerates renal dysfunction and fibrotic remodeling of the kidney (Liu et al. 2022; Friederich-Persson et al. 2013).

Several markers that are associated with oxidative stress are used to predict the course of kidney disease - such as advanced glycation end products (AGEs), which are uremic toxins, 8-hydroxy-2′-deoxyguanosine (8-OHdG) and malondialdehyde (MDA). Studies show that the severity of DKD is reflected by levels of urinary 8-OHdG (Honda et al. 2019; Xu et al. 2004) In patients with CKD without diabetes, there is a tendency for the accumulation of AGEs, which are formed during glycation and oxidative stress. The deposition of AGEs in the skin reflects systemic accumulation of these toxins, and this parameter is predicted to become a new risk marker for CKD (Honda et al. 2019; Arsov et al. 2014)

2.4 Insulin resistance

Obesity-related complications, particularly diabetes mellitus (DM), are established additional risk factors for kidney disease. In the pediatric population, DM increases the risk of early-onset kidney disease (KD) by 154% compared with healthy peers. Furthermore, renal conditions and kidney damage, including urolithiasis, renal failure, tubulointerstitial diseases, and glomerular diseases, are reported to occur more frequently in children with type 2 DM than in those with type 1 DM. Obesity-related metabolic syndrome and insulin resistance (IR) are considered critical contributors to the development of kidney disease in the pediatric population (Sun et al. 2022; Carullo et al. 2023).

IR has been identified as a key factor in the pathogenesis of obesity-related glomerulopathy (ORG), particularly through podocyte injury and subsequent impairment of the glomerular filtration barrier. Podocytes express both leptin and insulin receptors on their surface. Obesity is characterized by elevated leptin levels and reduced adiponectin levels, which promote a pro-inflammatory immune response mediated by IFN-γ+/IL-17+/CD4+ T cells, while simultaneously reducing the population of regulatory Foxp3+/CD4+ T cells that normally modulate inflammation. In addition, insulin resistance impairs insulin receptor signaling, disrupting the integrity of the filtration barrier through alterations in the PI3K-Akt-mTOR pathway.

Hyperinsulinemia contributes to development of glomerular hyperfiltration and hypertension by stimulating the renin–angiotensin–aldosterone system (RAAS). Insulin can elevate the glomerular filtration rate (GFR) through its vasodilatory properties as well as by enhancing sodium retention. In individuals with type 2 diabetes mellitus, hyperinsulinemia has been linked to increased urinary albumin excretion, despite having minimal or no effect on systemic albumin permeability. Moreover, the severity of insulin resistance correlates with elevated oxidative stress, which contributes to the progression of renal damage (Nakamichi et. al. 2021; Mangat et. al. 2022, Yang et al. 2024).

3. Clinical implications

Obesity-related kidney disease in children, including obesity-related glomerulopathy (ORG) and obesity-associated nephropathies, is increasingly recognized. A robust biomarker strategy-encompassing predictive, diagnostic, and monitoring utilities requires solid evidence from pediatric studies that demonstrate statistical significance and clinical relevance.

3.1 Biomarkers

In pediatric populations, creatinine-based estimation of GFR has limited reliability. Alternative biomarkers such as cystatin C are increasingly recommended, as it is less affected by age-related physiological variability and provides a more accurate assessment of kidney function in children (Skidmore 2024; Golob Jančič 2022). In addition, several emerging biomarkers-including urinary kidney injury molecule-1 (KIM-1), MCP-1, FGF-23, TNFR-1, TNFR-2, suPAR and urinary EGF-have been proposed as predictors of CKD progression in pediatric patients (Sandokji et al. 2021). In the pediatric population, overexpression of these biomarkers has been observed in patients with obesity.

Early diagnosis and ongoing monitoring of obesity-related kidney disease (ORG) in children are significant due to subclinical renal injury that can precede overt CKD and cardiovascular comorbidity, yet pediatric kidneys respond differently to obesity-related insults than adults, making timely detection challenging. Conventional adult biomarkers and thresholds often misclassify or miss subclinical disease in youth, prompting a shift toward pediatric-specific filtration markers and toward panels that capture tubular injury, inflammation, and adipose–kidney axis dysfunction (Hanna & Brophy 2015; Pozzoli et al. 2018; Carullo et al. 2023; Močnik & Varda 2021). Several contemporary pediatric studies have pursued biomarker discovery with statistical significance to predict, detect, or monitor ORG. Mackowiak-Lewandowicz et al. evaluated 142 adolescents to identify predictive factors of CKD development in obesity and metabolic risk contexts. They reported that higher serum cholesterol, triglycerides, and uric acid, together with elevated urinary NGAL (neutrophil gelatinase-associated lipocalin), distinguished those at higher risk of CKD despite normal or reduced GFR. Highlighting a tubular injury axis and the potential utility of NGAL as an early predictor, while cautioning that results varied by GFR status and obesity phenotype. Goknar et al. examined urinary kidney injury markers in obese children and adolescents, including NGAL, KIM-1, NAG, and albuminuria, and found higher concentration of urinary NAG and KIM-1 in obesity/IR groups relative to lean controls, with mixed results across markers across cohorts. Some studies suggest that urinary NGAL and KIM-1 are associated with a rapid decrease in eGFR in such patients (Mangat et. al. 2022).

Importantly, NGAL elevations were sometimes present even when microalbuminuria was not detected, supporting a role for a multi-marker approach in risk stratification but also underscoring inconsistent single-marker performance across populations. Multi-center or sizeable pediatric cohort focusing on obesity and renal risk, biomarker panels incorporating cystatin C (filtration marker independent of muscle mass) alongside tubular markers (NGAL, KIM-1, NAG), inflammatory mediators (MCP-1, TNFR-1/2), and exosomal or proteomic signatures have shown statistically significant associations with renal endpoints or subclinical injury, though with noted heterogeneity and a need for standardized assays and obesity-specific thresholds. These studies collectively emphasize that relying on albuminuria or creatinine-based GFR alone is insufficient in children and that panels better capture the multi-pathway nature of ORG (Hanna & Brophy 2015; Pozzoli et al. 2018; Korecka et al. 2024). Large reviews and meta-syntheses in the pediatric context highlight emerging exosomal and multi-omics approaches that promise improved predictive performance when incorporated into panels, but validating these in longitudinal pediatric cohorts remains an ongoing priority. Findings consistently indicate that combining filtration markers (cystatin C) with tubular/inflammatory/exosomal biomarkers improves discrimination for early ORG and progression risk compared with single markers (Korecka et al. 2024; Zhang 2025). Across these large pediatric experiences, a recurring theme is that obesity-related kidney injury in youth often overlaps with metabolic comorbidities, which can confound single-marker interpretations. Hence, robust, multi-marker strategies with obesity-specific interpretation guidelines and prospective endpoints are essential to translate statistical associations into clinical decision-making for prediction, early detection, and monitoring of obesity-related nephropathy in children (Carullo et al. 2023; Rybi-Szumińska et al 2023; González-Covarrubias 2022).

Current perspective supports a transition from creatinine-centric approaches toward integrated, pediatric-tailored biomarker panels that combine cystatin C with urinary NGAL, KIM-1, and NAG, complemented by exosomal proteomics and multi-omics data, to achieve meaningful predictive and prognostic performance in obese children, while recognizing the need for harmonization, standardization, and longitudinal validation to establish clinically actionable thresholds (Hanna & Brophy 2015; Pozzoli et al. 2018; Korecka et al. 2024; Ding & Mak 2015; Şen et al. 2021; Nagoba et al. 2025)

3.2 Prevention and treatment

Treatment of obesity-related nephropathy in children focuses on a multipronged strategy that prioritizes nephroprotection, metabolic risk reduction, and prevention of progression, while acknowledging that established structural kidney damage may be partially irreversible. First-line management emphasizes nonpharmacologic interventions sustained weight reduction through family-centered lifestyle modification, with dietary energy balance. Additionally, implementation of regular aerobic and resistance exercise, which can reduce proteinuria and improve associated metabolic risk factors (hypertension, dyslipidemia, insulin resistance) though direct reversal of established CKD is uncommon (Delgado et al. 2021; Coronel & Vivar 2022; Pinto et al. 2011).

When ORG coexists with hypertension or proteinuria, pharmacologic nephroprotection is employed to slow progression and preserve renal function. Angiotensin receptor blockers (ARBs) or ACE inhibitors are commonly used to reduce proteinuria and protect glomerular integrity, alongside optimization of lipid and glucose parameters, as well as avoidance of nephrotoxins, recognizing that these interventions aim to delay decline rather than reverse advanced sclerosis of glomeruli (López-Jaramillo 2013; Delgado et al. 2021; Coronel & Vivar 2022; Carpio-Troya et al. 2023)

In the pediatric population, the emphasis remains on preserving growth and development, with therapy tailored to the child's stage of disease and comorbidities. While some pediatric cases may respond to weight loss and blood pressure (BP) control with reductions in albuminuria, established CKD characterized by glomerulosclerosis tends to progress despite therapy, underscoring the priority of early prevention and timely nephroprotection (Carballeda et al. 2018; Delgado et al. 2021; Coronel & Vivar 2022; Carpio-Troya et al. 2023)

From a public health perspective, primordial prevention-early-life nutrition and physical activity strategies are fundamental to reducing the lifetime risk of obesity-related nephropathy and its renal sequelae in youth, reinforcing that pharmacologic options are adjuncts rather than replacements for lifestyle strategies (López-Jaramillo 2013; Delgado et al. 2021; Coronel & Vivar 2022; Rojas et al. 2023). Regarding novel pharmacotherapies specifically for ORG in children, current guidelines emphasize evidence-based management of obesity and comorbidities rather than a single outstanding pediatric-approved agent dedicated to ORG. Metformin remains the cornerstone for obesity-related diabetes risk in youth when indicated, while GLP-1 receptor agonists or other obesity drugs are explored in adults and older adolescents under careful pediatric consideration, with no universally recommended pediatric ORG-specific drug established in the cited sources (Amatruda et al. 2021; Ortiz-Vilchis 2022). In severe, refractory cases where obesity and metabolic disease drive diabetic or hypertensive kidney injury, bariatric surgery may be considered in appropriately selected adolescents as part of a multidisciplinary program, reflecting a shift toward weight-centric strategies in advanced disease when conventional therapy fails (Ackermann et al. 2015).

3.3.Pharmacotherapy

The pharmacological management of obesity-related nephropathy and CKD in adults relies on a combination of renin–angiotensin system blockade (ACE inhibitors and ARBs), SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs), and non-steroidal mineralocorticoid receptor antagonists (ns-MRAs). These classes of medications provide renoprotective and cardioprotective benefits beyond glycemic control, including reductions in albuminuria, slowed eGFR decline, and reduced progression to ESKD. Additionally statins and PCSK9 inhibitors are frequently considered alongside RAAS blockade and antidiabetic therapies in comprehensive risk reduction strategies (Rabbani et al. 2025; Avgoustou et al. 2025; Anumas & Inagi 2025; Biglari et al. 2025; Yang et al. 2025; Dira et al. 2025; Alicic et al. 2024; Amatruda et al. 2021)

Pediatric data on these agents are variable: GLP-1 RAs have pediatric obesity trials and research increasingly examines renal outcomes indirectly through metabolic improvements. However, direct, robust pediatric obesity-related CKD-specific outcome data for SGLT2 inhibitors and GLP-1 RAs remain limited. Several reviews discuss potential applicability and mechanistic rationale in pediatric populations with obesity, T2DM or ORG risk, but

high-quality randomized pediatric CKD outcomes are sparse (Grant & Bell 2025; Dira et al. 2025; He et al. 2021; Amatruda et al. 2021; Oliva-Dámaso et al. 2021).

Adjunctive therapies targeting oxidative stress and mitochondrial dysfunction, including coenzyme Q10 and the mitochondrial-targeted peptide SS-31, have shown potential supportive roles in experimental models of kidney disease. However, clinical evidence in pediatric populations remains insufficient, and their role is currently limited to investigational or supportive contexts. Current literature emphasizes harsh evidence for RAAS blockade, SGLT2i, GLP-1 RA, and ns-MRA as mainstays in adults with CKD or DKD, with pediatric data featuring more limited but evolving evidence, particularly for GLP-1 RAs in youth with obesity-related nephropathy and DKD risk (Oliva-Dámaso 2021; Avgoustou et al. 2025; Ball et al. 2025)

3.3.1 ACE inhibitors (ACEIs) and ARBs

ACEIs/ARBs reduce efferent arteriolar resistance, lower intraglomerular pressure, reduce proteinuria, and slow CKD progression by blocking the RAAS. These effects extend beyond BP lowering and are foundational for proteinuric CKD, including DKD and ORG contexts. In obesity-associated kidney disease, barer data support RAAS blockade as foundational therapy. Those medications remain a first-line approach in proteinuric CKD and are often continued alongside SGLT2i and GLP-1 RA therapies (Sandino et al. 2021; Haider et al. 2024; Avgoustou et al. 2025).

The pediatric-specific CKD literature frequently discusses ACEIs/ARBs as standard care for proteinuric CKD, though the obesity-specific nephropathy pediatric literature is more limited. The general principle of RAAS blockade for nephroprotection in children with CKD is reflected in literature reviews on risk factors and the treatment of diabetic kidney disease in children (Haider et al. 2024; Katsi et al.2025; Avgoustou et al. 2025)

3.3.2 Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2 inhibitors restore tubuloglomerular feedback, reduce intraglomerular hypertension, and attenuate pathways of inflammation, fibrosis and oxidant stress. These medications remit proteinuria and slow eGFR decline in DKD and CKD populations, with benefits in diabetic and non-diabetic CKD (Rabbani et al. 2025; Anumas & Inagi 2025; Avgoustou et al. 2025; Haider et al. 2024). Large trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY) demonstrate reduced risk of kidney failure, kidney-related and cardiovascular death with SGLT2i in DKD and CKD, with benefits observed in diverse populations; combination with GLP-1 RAs may offer additive benefits (Oliva-Dámaso et al. 2021; Haider et al. 2024; Avgoustou et al. 2025; Anumas & Inagi 2025).

Pediatric data on SGLT2 inhibitors for obesity-related nephropathy or DKD are less robust. Some reviews discuss potential utility in pediatric DKD/ORG contexts, but reliable randomized controlled trial pediatric data are lacking. Pediatric-CKD-oriented research may illuminate safety and efficacy among children in the future (Amatruda et al. 2021; Oliva-Dámaso et al. 2021; Grant & Bell 2025). SGLT2 inhibitors also reduce renal inflammation and fibrosis, contributing to cardio-renal protection in DKD and CKD contexts. However drug-related initial eGFR dip and volume status changes require monitoring. Hypovolemia and rare cases of AKI can occur in susceptible individuals, overall renal outcomes tend to be favorable with continued therapy in DKD/CKD (Avgoustou et al. 2025; Anumas & Inagi 2025; Rabbani et al. 2025)

3.3.3 Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

Incretin-based therapies (GLP-1 RAs, and dual GLP-1/GIP agonists like tirzepatide) show robust metabolic and weight-loss benefits, with emerging renal outcomes suggesting reduced albuminuria and slower CKD progression in adults with T2D and obesity. Many trials (FLOW, LEADER/SUSTAIN/AWARD-7, TREASURE-CKD) illuminate potential nephroprotection and synergy with SGLT2 inhibitors (Tuttle et al. 2018; Oliva-Dámaso et al. 2021; Simental-Mendía et al. 2022; Bulum 2022; Alicic et al. 2024; Rabbani et al. 2025; Yang et al. 2025; Biglari et al. 2025)

GLP-1 RAs lower glucose, promote weight loss, improve BP control, and exert anti-inflammatory and anti-fibrotic effects. For renal benefits include slowed decline in renal function and reduced albuminuria in DKD. Possible direct renal tubular effects include increased sodium excretion and modifications to renal hemodynamics, while potential pleiotropic effects may involve inflammatory markers and FGF23 pathways. (He et al. 2021; Bulum 2022; Simental-Mendía 2022; Alicic et al. 2024; Begum et al. 2024; Katsi et al. 2025, Anumas & Inagi 2025; Avgoustou 2025; Rabbani et al. 2025; Yang et al. 2025)

GLP-1 RAs have demonstrated kidney and cardiovascular benefits in large cardiovascular outcome trials (LEADER, SUSTAIN, AWARD-7) and in CKD outcomes. The FLOW trial (semaglutide) focuses on CKD with T2DM, showing reno-/cardioprotective signals. Meta-analytic data suggest reduced albuminuria with GLP-1 RAs, though effects on eGFR/creatinine are variable across studies. However, there have been reports of associated renal complications, including rare reports of acute interstitial nephritis/podocytopathy associated with the use of GLP-1 receptor agonists. Therefore, patients treated with these medications should be closely monitored (Begum et al. 2024)

Research have shown that GLP-1 receptor agonist therapy, prescribed to people with diabetes and obesity, reduced levels of markers of inflammation and oxidative stress, such as interleukin-6, interleukin-1β, monocyte chemotactic protein-1, prostaglandins, and tumor necrosis factor-α. As for animal models of DKD - the GLP-1 receptor agonist was associated with reduced activation of pro-inflammatory cytokines and profibrotic factors, as well as with inhibition of oxidative stress and inflammatory cell infiltration in the kidneys (Alicic et al. 2024)

Subset of reviews focuses on GLP-1 RAs in obese youth, including potential nephroprotective rationale given obesity-related nephropathy. Studies suggest GLP-1 receptor agonists are potential, promising solution especially for adolescents 12 years of age and older, the data concerning younger individuals are limited (Oliva-Dámaso et al. 2021; Amatruda et al. 2021; Dira et al. 2025; Katsi et al. 2025;). Ryan P. M. et al. that analysed 574 subjects across nine studies reports significant reductions in body weight, BMI, and BMI z-score and improvement of the cardiometabolic profile of obese adolescents, children, and young people in a relatively safe manner. Worth acknowledgment, compared with other drugs in this class, semaglutide demonstrated the strongest effect on weight loss in adolescents (aged 12-17), resulting in a significant improvement in BMI z-scores and improvement in health-related quality of life (Ryan et al. 2021; Ball et al. 2025)

3.3.4 PCSK9 inhibitors and lipid-lowering therapies (statins)

PCSK9 inhibitors and statins reduce LDL-C and ASCVD risk. In CKD patients, lipid-lowering therapy is part of comprehensive risk reduction, data directly addressing ORG-specific nephroprotection are limited but expected via cardiovascular risk reduction and potential secondary renal benefits through improved perfusion and reduced inflammation (Avgoustou et al. 2025; Ponte-Negretti et al. 2021)

Class of medication	Example	Mechanism	Health effect(s)	Additional warnings
ACE inhibitors (ACEIs) and ARBs	Lisinopril (ACEI); Losart (ARB)	reduce intraglomerular pressure, slow CKD progression	slower CKD progression; reduced albuminuria; cardiovascular protection; BP reduction	potential AKI with volume depletion
SGLT2i	Empagliflozin Dapagliflozin	remit proteinuria and slow eGFR decline	reduction of CV risk, slower eGFR decline; albuminuria reduction	pediatric data less robust;
GLP-1 RAs	Semaglutide Dulaglutide	anti-inflammatory/anti-fibrotic renal effects; potential FGF23 modulation	mild reductions in body weight, BMI and BMI z-score; improvement of the cardiometabolic profile	acute interstitial nephritis associated with the use of GLP-1
PCSK9 inhibitors and lipid-lowering therapies (statins)	Evolocumab(PCSK9i); Atorvastatin (statin)	LDL-C reduction	cardiovascular risk reduction in CKD; possible renal benefits via reduced inflammation	PCSK9 inhibitors: pediatric trials ongoing; statins generally well tolerated in children;

Table 1. Specification of selected medications

3.3.5 Possible future additional therapies needing further research

CoQ10 and SS-31 are discussed as mitochondrial-targeted strategies that may mitigate oxidative stress and mitochondria-related injury in CKD contexts. However, pediatric ORG-focused evidence is limited, and these agents are not standard first-line therapies for CKD progression in the pediatric population (Mauriello et al. 2024).

Hypoxia-inducible factor (HIF) stabilizers are considered in CKD contexts as potential agents to address tubulointerstitial hypoxia and nephron protection. Pediatric CKD data and obesity-specific nephropathy data are

not well established in the provided sources. This remains an area of ongoing research (Haider et al. 2024; Rabbani et al. 2025; Katsi et al. 2025).

3.3.6 Summary

Pediatric data specifically addressing KD outcomes with these agents are sparse for SGLT2 inhibitors and GLP-1 RAs, though there is increasing interest in using incretin-based therapies for pediatric obesity and metabolic health, with ongoing research into renal outcomes as part of the broader cardiometabolic risk reduction framework (Oliva-Dámaso et al. 2021; Amatruda et al. 2021; Dira et al. 2025; Katsi et al. 2025)

Amatruda et al. discuss youth-onset T2DM and DKD risk, highlighting aggressive DKD progression in youth and the need for therapies that address obesity and metabolic control (Amatruda et al. 2021). Dira et al. review pediatric obesity and entero-insular axis therapies, including GLP-1 RAs, and discuss pediatric trials of incretin-based therapies, with an emphasis on mechanistic rationale and ongoing clinical trial exploration in children (Dira et al. 2025)

Across pharmacological classes, pediatric data on RAAS blockade, SGLT2 inhibitors, and GLP-1 RAs emphasize safety monitoring but are less robust for long-term CKD-specific outcomes. Guidelines emphasize cautious use with close monitoring and consideration of growth effects, while evidence from ongoing pediatric trials is expected to clarify their role in obesity-related nephropathy and CKD progression in children.

(Amatruda et al. 2021; Oliva-Dámaso et al. 2021; Katsi et al. 2025)

4. Conclusions

Mechanisms that drive ORG are not yet fully understood, further research may prove helpful in developing effective pharmacological therapies. Currently used medications have not been extensively studied in the pediatric population. Therefore, clinicians may, with some caution, attempt pharmacotherapy that is effective in obese adults. Studies suggest that CKD caused by obesity-related nephropathy tends to progress despite optimal medical therapy, underscoring the importance of early intervention and prevention rather than attempts to reverse the process after damage has developed.

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