THE ROLE OF METABOLIC DISORDERS IN THE PATHOGENESIS AND PROGRESSION OF CHRONIC TUBULOINTERSTITIAL NEPHRITIS IN CHILDREN (LITERATURE REVIEW)

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Abstract

Chronic tubulointerstitial nephritis (CTIN) represents a major contributor to chronic kidney disease (CKD) in the pediatric population, where metabolic disorders increasingly emerge as pivotal pathogenic drivers. This review synthesizes current evidence linking dysmetabolic states—such as hyperuricemia, dyslipidemia, obesity, and insulin resistance—to tubulointerstitial injury and fibrosis in children. Persistent metabolic imbalance triggers oxidative stress, inflammasome activation, and immune dysregulation, initiating a self-perpetuating cycle of inflammation, hypoxia, and extracellular matrix expansion. Crystalline nephropathies caused by urate and oxalate deposition act as potent inducers of the NLRP3 inflammasome, while metabolic syndrome components amplify renal oxidative stress and endothelial dysfunction. Early-life exposure to metabolic stressors further predisposes to structural and functional renal impairment. Despite growing recognition of these mechanisms, pediatric-specific data remain limited, emphasizing the need for early detection of metabolic risk and biomarker-guided preventive interventions. Targeted management of dysmetabolism—including dietary regulation, antioxidant therapy, and metabolic correction—offers promising strategies to halt CTIN progression and preserve renal function in children.

Keywords: Chronic tubulointerstitial nephritis; children; metabolic disorders; hyperuricemia; oxidative stress; inflammation; NLRP3 inflammasome; fibrosis.

Introduction

Chronic tubulointerstitial nephritis (CTIN) is a significant contributor to Chronic Kidney Disease (CKD) worldwide, with progression often beginning in childhood (Harambat et al., 2012; Akhmatov et al., 2025). Acute tubulointerstitial nephritis (ATIN) represents the final common pathophysiological pathway resulting

from diverse insults, leading to characteristic sterile cellular infiltrate, tubular atrophy, and interstitial fibrosis. While acute causes include immunologic reactions, medications, and environmental toxins, metabolic exposures are specifically recognized contributors to this type of kidney injury (Aron & Shirali, 2025).

The pervasive rise in urinary system diseases (USD) among children, coupled with their tendency toward recurrence and chronicity, underscores the necessity of preventive nephrology. Dysmetabolic nephropathies (DMNs), defined by underlying metabolic imbalances, constitute a significant portion of kidney diseases in pediatric practice (Rychkova, 2010; Akhmatov & Akhmatov, 2025). Timely identification of these metabolic factors is essential, as their uncontrolled persistence drives progressive kidney damage, often culminating in CTIN, chronic pyelonephritis (CPN), and eventually, chronic renal failure (CRF), necessitating renal replacement therapy (RRT).

Pathophysiological links between metabolic disorders and CTIN

The progression of CKD, regardless of the underlying etiology, converges on a final common pathway of cellular infiltration and interstitial fibrosis, primarily driven by immune and inflammatory responses (Aron & Shirali, 2025; Huang et al., 2023). Metabolic disorders initiate and propagate CTIN through several interwoven mechanisms:

Crystallization and Inflammasome Activation: Metabolic nephropathies, such as those involving oxalate and urate, often manifest as crystalline nephropathy. These crystals function as Da Damage-Associated Molecular Patterns (DAMPs) that are released intracellularly or in the extracellular space. Uptake of these crystals by phagocytic cells directly activates the innate immune system via Toll-like receptors (TLRs) and the NLRP3 inflammasome (Aron & Shirali, 2025; Knauf et al., 2013). This activation triggers a cascade of inflammation and subsequent fibrosis, characteristic of CTIN (Mulay et al., 2014).

Inflammation and Oxidative Stress (OXSTR): Metabolic imbalances foster a proinflammatory state. Oxidative stress, characterized by an imbalance favoring reactive oxygen/nitrogen species (ROS/RNS) over antioxidant defenses, is recognized as a decisive pathogenetic link in kidney disease (Hsu & Tain, 2021; Maciejczyk et al., 2018; Drożdż et al., 2016). High levels of metabolic byproducts, such as glucose and fatty acids (FA), increase mitochondrial ROS production in endothelial cells, contributing to tissue dysfunction and accelerating atherosclerosis (Litwin & Niemirska, 2014). Oxidative stress has been implicated in the tubulointerstitial compartment due to increased tubular workload and oxygen consumption (Schrier et al., 1988).

Hypoxia and Fibrosis: Severe tubulointerstitial inflammation, a core component of CTIN, is associated with kidney hypoxia (Epstein, 1997). Renal tubular epithelial cells (RTECs) are particularly vulnerable to hypoxia because they depend

highly on aerobic oxidative metabolism. Fibrosis itself creates a detrimental feedback loop: exuberant extracellular matrix (ECM) deposition attenuates peritubular vessels, leading to increased hypoxia, which in turn drives further fibrosis and accelerated renal failure progression (Zeisberg & Neilson, 2010; Clark et al., 2016). Hypoxia is considered a major pathogenetic factor in renal dysfunction in children with DMN (Aib et al., 2024).

Immune System Dysfunction: Children suffering from disorders of purine metabolism (dyspurinosis) are inherently immunocompromised. This is because the disruption of nucleoside metabolism negatively affects the differentiation and proliferation of lymphocytes. This compromised immune background may facilitate infections, such as secondary pyelonephritis, further accelerating the chronic kidney pathology.

Impact of specific metabolic factors

Hyperuricemia and Urate Nephropathy Hyperuricemia (serum uric acid >0.230 mmol/L) and hyperuricosuria (uraturia) are established pathogenetic markers of DMN in children. Uric acid (UA), a product of purine metabolism, acts as a DAMP, activating inflammatory pathways like the NLRP3 inflammasome. UA deposition is associated with interstitial inflammation and giant cell formation in ATIN (Aron & Shirali, 2025).

In the context of CKD, UA is positively correlated with markers of kidney damage (GFR and proteinuria). High levels of UA may intensify inflammation and extracellular matrix remodeling, potentially activating the renin-angiotensin-aldosterone system (RAAS), which is a crucial source of ROS promoting fibrosis (Maciejczyk et al., 2018). Urate nephropathy in children often manifests as interstitial nephritis (IN) and uric acid lithiasis. Studies involving children with secondary chronic pyelonephritis complicated by hyperuricemia and uraturia confirm profound, combined shifts in the body's immune system (Baratova, 2024).

Dyslipidemia, Insulin Resistance, and Obesity-Related Changes

The cluster of abnormalities known as Metabolic Syndrome (MS), which includes visceral obesity, dyslipidemia, and insulin resistance (IR), represents a significant challenge in pediatric nephrology. In children with CKD (stages 2–4), the prevalence of MS may be as high as 13%. MS accelerates CKD progression by inducing hyperfiltration, which precedes the development of overt nephropathy and subsequently decreased GFR.

• Dyslipidemia and Oxidative Stress: Dyslipidemia is a typical metabolic abnormality of CKD. In children with CKD, concentrations of oxidized low-density lipoprotein (oxLDL) correlate strongly with indicators of CKD progression (creatinine, cystatin C) and traditional cardiovascular risk factors, notably hypertension and lipid disturbances (Drożdż et al., 2016). These increased oxLDL

levels are considered valuable markers of oxidative stress, linking lipid oxidation to cardiac damage (left ventricular hypertrophy) in children with CKD.

• Insulin Resistance: IR is central to the pathogenesis of MS. IR and impaired glucose tolerance correlate with microalbuminuria and hyperfiltration in obese children. Furthermore, high glucose and fatty acid levels are responsible for increasing mitochondrial ROS production and promoting oxidative stress, thereby contributing to tissue dysfunction and IR itself.

Biomarkers of Progression

Given the asymptomatic nature and frequent delay in CKD diagnosis in children, non-invasive biomarkers of injury and progression are urgently sought.

• Oxidative Stress Markers: Oxidative damage markers show promise. Salivary Advanced Oxidation Protein Products (AOPP) were found to be significantly higher in CKD children compared to controls, correlating negatively with estimated GFR (eGFR) and positively with proteinuria and serum urea (Maciejczyk et al., 2018). AOPP is a powerful indicator of inflammation and kidney damage in uremia. Other markers like urinary F2-isoprostane (lipid peroxidation) and 8-OHdG (DNA damage) are also studied, though their levels in urine may reflect current kidney function rather than predicting the trajectory of disease progression over time (Jacobson et al., 2020).

• Uric Acid: Uric acid itself is proposed as both a biomarker and a therapeutic target, particularly in contexts involving insulin resistance and cardiovascular risk.

Prevention and Management

The goal of management is protective, focusing on both lifestyle changes and correcting underlying metabolic abnormalities, ideally at the preclinical stage (diathesis).

• Metabolic Correction and Diet: Timely correction of dysmetabolism is considered critical for preventing complications such as interstitial nephritis and pyelonephritis. For uric acid diathesis, key measures include a restricted low-purine diet, controlled fluid regimen, microclimate regulation, vitamin therapy, and sometimes medication such as allopurinol (Akhmatov & Akhmatov, 2025; Akhmatova & Alimova, 2025). Dietary interventions also include protein restriction (0.6 to 0.7 g/kg/day) and low-salt diets, which are crucial for nephropathy management and slowing decline in renal function.

• Targeting Oxidative Stress: Given the central role of OXSTR, compensation for antioxidant deficiency is advised, particularly in vulnerable populations like newborns with a history of maternal kidney pathology. In experimental models, perinatal antioxidant supplementation (e.g., N-acetylcysteine, Vitamins C and E, or synthetic antioxidants like MitoQ) has demonstrated protective effects against programmed hypertension and kidney injury induced by prenatal insults (Hsu & Tain, 2021).

• Lifestyle Interventions: For children with components of MS and CKD, increased physical activity combined with dietary modifications (caloric restriction, low glycemic index) is considered the safest and most effective strategy, yielding better results than pharmacological treatment alone in many cases (Litwin & Niemirska, 2014).

• Immunocorrection: Due to the inherent immunocompromised state associated with dyspurinosis, periodic courses (1–2 per year) of immunocorrective agents may be advisable in affected children (Akhmatova & Alimova, 2025).

Conclusion

Metabolic disorders constitute a major, modifiable risk factor for the pathogenesis and progression of CTIN in children. Key mechanisms involve the induction of crystallization nephropathies (urate, oxalate) leading to DAMP-mediated inflammation and NLRP3 inflammasome activation, combined with systemic inflammation and severe oxidative stress linked to metabolic syndrome and purine dysmetabolism. This cascade ultimately leads to tubulointerstitial fibrosis and progressive renal failure.

While significant progress has been made in identifying these pathogenic pathways, the full etiological and pathogenetic mechanisms underlying the chronicity of many somatic kidney diseases remain complex, necessitating continuous research and refinement of treatment strategies. Future directions must prioritize the validation of non-invasive biomarkers of oxidative damage (e.g., salivary AOPP or oxLDL) to allow for earlier diagnosis, especially given that conventional markers often lag behind the disease process. Crucially, there is an urgent need to develop and implement tailored, evidence-based preventive programs focusing on dysmetabolism correction—particularly addressing uric acid diathesis and metabolic syndrome components—starting from the preclinical stages (Akhmatov & Akhmatov, 2025; Aib et al., 2024).

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