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Nephrotoxicity in Diabetes and Obesity: Mechanisms, Biomarkers, and Therapeutic Interventions

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ABSTRACT

Diabetes and obesity, two closely interlinked metabolic disorders, have emerged as major drivers of chronic kidney disease (CKD) and nephrotoxicity worldwide. Beyond hemodynamic and metabolic stressors, these conditions generate a milieu of hyperglycemia, lipotoxicity, oxidative stress, and low-grade systemic inflammation that progressively damage renal parenchyma. Nephrotoxicity in this context is multifactorial, encompassing glomerular injury, tubulointerstitial fibrosis, endothelial dysfunction, and altered renal drug handling. Immune and metabolic crosstalk further amplify renal vulnerability, with adipokines, advanced glycation end-products, and pro-inflammatory cytokines fueling maladaptive repair responses. This review synthesizes current knowledge on the molecular mechanisms underlying nephrotoxicity in diabetes and obesity, with emphasis on oxidative stress pathways, mitochondrial dysfunction, immune dysregulation, and renin–angiotensin–aldosterone system (RAAS) activation. Emerging biomarkers including proteomic and metabolomic signatures, urinary extracellular vesicles, and novel tubular stress markers are discussed in relation to early detection and risk stratification. Finally, therapeutic interventions are highlighted, ranging from lifestyle and metabolic correction to pharmacologic strategies such as SGLT2 inhibitors, GLP-1 receptor agonists, RAAS modulators, and novel anti-inflammatory or antifibrotic agents. Understanding the intersection of diabetes, obesity, and nephrotoxicity is essential for developing precision approaches to prevention and therapy in high-risk populations.

Keywords: nephrotoxicity, diabetes, obesity, chronic kidney disease, biomarkers

INTRODUCTION

Diabetes mellitus and obesity are global epidemics that significantly contribute to morbidity and mortality through their impact on cardiovascular, hepatic, and renal systems [1]. The kidney, as a highly vascular and metabolically active organ, is especially vulnerable to injury in this setting [2]. Diabetic kidney disease (DKD) remains the leading cause of end-stage renal disease, while obesity itself, even independent of diabetes, predisposes to obesity-related glomerulopathy [3]. Both conditions converge on shared pathological pathways that accelerate nephron loss. The concept of nephrotoxicity in diabetes and obesity extends beyond classical diabetic nephropathy. It includes structural and functional alterations induced by metabolic overload, maladaptive immune responses, and increased susceptibility to xenobiotic-induced renal injury [4]. Understanding these mechanisms is vital for guiding biomarker discovery and therapeutic innovation.

2. Mechanisms of Nephrotoxicity in Diabetes and Obesity

The pathogenesis of nephrotoxicity in diabetes and obesity is multifactorial, driven by the interplay of metabolic overload, hemodynamic alterations, immune dysregulation, and structural remodeling of the kidney [5]. Together, these mechanisms accelerate nephron loss and increase susceptibility to both intrinsic and drug-induced renal injury.

2.1 Hemodynamic and glomerular injury

In the early stages of diabetes and obesity, chronic hyperglycemia, hyperinsulinemia, and excess adiposity lead to glomerular hyperfiltration, characterized by increased renal plasma flow and intraglomerular hypertension [6]. This state is partly mediated by afferent arteriolar vasodilation, impaired autoregulation, and activation of the renin–angiotensin–aldosterone system. Sustained hyperfiltration imposes mechanical stress on glomerular capillaries, resulting in mesangial cell proliferation and expansion of the extracellular matrix [7]. Podocytes, critical for filtration barrier integrity, undergo hypertrophy and detachment under this stress, ultimately leading to proteinuria and glomerulosclerosis [8]. Over time, these maladaptive changes set the stage for progressive decline in glomerular filtration rate and chronic kidney disease.

2.2 Lipotoxicity and metabolic stress

Obesity promotes ectopic lipid accumulation in non-adipose tissues, including the kidney [9]. Renal tubular epithelial cells and podocytes accumulate toxic lipid intermediates such as ceramides, diacylglycerols, and acylcarnitines [10]. These lipids disrupt mitochondrial function and endoplasmic reticulum homeostasis, generating cellular stress and triggering apoptotic cascades. Lipid overload also impairs insulin signaling in renal cells, further exacerbating oxidative stress and inflammation. The combined effects of lipotoxicity lead to tubular atrophy, glomerular damage, and interstitial fibrosis, all of which contribute to nephrotoxicity [11].

2.3 Oxidative stress and mitochondrial dysfunction

Oxidative stress is a central driver of kidney injury in diabetes and obesity [12]. Chronic hyperglycemia and excess lipids increase production of reactive oxygen species through NADPH oxidase activation and mitochondrial respiratory chain overload [13]. Elevated ROS damage DNA, proteins, and lipids, compromising cellular integrity. Endothelial nitric oxide bioavailability is reduced, impairing vasodilation and promoting vascular stiffness [14]. Mitochondrial dysfunction, in turn, exacerbates ROS generation in a vicious cycle, leading to cell death and fibrosis [15]. These processes not only accelerate intrinsic nephron injury but also enhance susceptibility to exogenous nephrotoxins.

2.4 Inflammation and immune dysregulation

Metabolic disorders sustain chronic low-grade systemic inflammation, often termed “metaflammation.” [16] In the kidney, this manifests as infiltration of macrophages, neutrophils, and T cells into glomerular and tubulointerstitial compartments. Activation of inflammatory signaling cascades, including NF- κ B, JNK, and the NLRP3 inflammasome, promotes the secretion of cytokines such as TNF- α , IL-6, and IL-1 β [17]. These mediators stimulate fibroblast activation, extracellular matrix deposition, and epithelial-to-mesenchymal transition, accelerating renal fibrosis. Adipokines such as leptin and resistin further augment inflammation, while reduced adiponectin diminishes anti-inflammatory protection [18]. Thus, immune dysregulation acts as both an initiator and amplifier of nephrotoxicity in obesity and diabetes.

2.5 RAAS and endothelial dysfunction

The renin–angiotensin–aldosterone system is chronically upregulated in obesity and diabetes, driving glomerular hypertension and fibrogenesis [19]. Angiotensin II promotes vasoconstriction, oxidative stress, and pro-inflammatory signaling, while aldosterone contributes to sodium retention, hypertension, and vascular stiffness [20]. In parallel, endothelial dysfunction impairs vascular tone and increases permeability, facilitating proteinuria [21]. Chronic microvascular injury contributes to rarefaction of peritubular capillaries, limiting oxygen delivery and perpetuating tubulointerstitial fibrosis [22].

2.6 Xenobiotic susceptibility

An underappreciated dimension of nephrotoxicity in metabolic disease is heightened sensitivity to xenobiotics [23]. Diabetes and obesity alter the expression and activity of renal drug transporters, including organic anion and cation transporters, and affect phase I and II metabolizing enzymes [24]. These changes modify drug pharmacokinetics, increasing exposure to nephrotoxic agents such as non-steroidal anti-inflammatory drugs, aminoglycosides, and chemotherapeutics [25]. Furthermore, mitochondrial dysfunction and oxidative stress lower the threshold for drug-induced injury, making the diabetic or obese kidney more vulnerable to iatrogenic toxicity.

3. Biomarkers of Nephrotoxicity

Biomarkers provide essential tools for early detection, monitoring, and risk stratification of nephrotoxicity in diabetes and obesity [26]. Traditional measures such as serum creatinine and albuminuria are insufficient to detect subclinical injury, prompting interest in more sensitive and specific indicators [27].

3.1 Traditional markers

Serum creatinine, estimated glomerular filtration rate, and urinary albumin remain the clinical standard for assessing kidney function. However, these markers often rise only after significant nephron loss, limiting their utility for early intervention [28].

3.2 Tubular stress and injury markers

Novel tubular markers offer earlier insights into nephrotoxicity [29]. Kidney injury molecule-1 reflects proximal tubular damage, while neutrophil gelatinase-associated lipocalin increases rapidly in acute injury [30]. Liver-type fatty acid binding protein indicates oxidative tubular stress, and urinary N-acetyl- β -D-glucosaminidase correlates with lysosomal injury [31]. Collectively, these markers improve sensitivity in detecting tubular dysfunction before overt decline in glomerular filtration.

3.3 Inflammatory and oxidative stress markers

Systemic and urinary markers of inflammation and oxidative stress are increasingly recognized. Circulating cytokines, urinary TNF receptors, and oxidative stress biomarkers such as 8-hydroxydeoxyguanosine reflect ongoing injury and immune activation. Their use may help differentiate metabolic nephrotoxicity from other renal insults [32].

3.4 Omics-based and novel biomarkers

Advances in high-throughput technologies have enabled the identification of proteomic and metabolomic signatures specific to diabetic and obesity-related kidney injury [33]. Urinary extracellular vesicles carry proteins, metabolites, and microRNAs, including miR-21 and miR-192, which are emerging as sensitive indicators of renal stress and fibrogenic activity [34]. These biomarkers hold promise for guiding precision medicine approaches and monitoring response to emerging therapies.

4. Therapeutic Interventions

The management of nephrotoxicity in diabetes and obesity requires a multipronged approach that targets both the underlying metabolic disturbances and the downstream pathways of inflammation, oxidative stress, and fibrosis.

4.1 Lifestyle and metabolic correction

Lifestyle interventions remain the cornerstone of nephroprotection. Sustained weight loss through dietary modification and structured physical activity improves insulin sensitivity, reduces systemic inflammation, and alleviates renal hemodynamic stress [35]. Even modest weight reduction is associated with improvements in glomerular filtration and reductions in proteinuria [36]. In severe obesity, bariatric surgery has shown significant renoprotective effects, with evidence of improved albuminuria and stabilization of kidney function. Lifestyle strategies also synergize with pharmacologic therapies, enhancing their long-term efficacy [37].

4.2 Established pharmacologic therapies

Pharmacologic approaches are well established in slowing renal decline. Blockade of the renin-angiotensin-aldosterone system using ACE inhibitors or angiotensin receptor blockers remains first-line therapy, effectively reducing intraglomerular pressure and proteinuria [38]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have revolutionized diabetic kidney disease management, providing glycemic control while reducing hyperfiltration, mitigating tubular stress, and lowering cardiovascular risk [39]. Glucagon-like peptide-1 receptor agonists contribute additional renoprotective effects by improving glycemia, reducing body weight, lowering blood pressure, and exerting anti-inflammatory actions on the kidney [40].

4.3 Emerging therapies

Beyond established treatments, novel agents are under development to address pathways not targeted by conventional drugs. Antifibrotic compounds such as pentoxifylline and pirfenidone show potential in reducing renal scarring [41]. Inhibitors of the NLRP3 inflammasome and other immune-modulating therapies are being explored to counteract chronic metaflammation [42]. PPAR agonists may improve lipid metabolism and attenuate lipotoxicity, while endothelin receptor antagonists offer promise in reducing proteinuria and vascular injury. Microbiome-directed therapies, including prebiotics, probiotics, and postbiotics, represent an innovative frontier aimed at restoring gut-kidney crosstalk and dampening systemic inflammation [43]. Together, these interventions reflect a transition toward integrated, mechanism-based care that combines metabolic control with targeted nephroprotective strategies.

CONCLUSION

Nephrotoxicity in diabetes and obesity reflects the convergence of hemodynamic stress, lipotoxicity, oxidative injury, and immune dysregulation, leading to progressive renal dysfunction. While conventional markers such as creatinine and albuminuria detect late-stage injury, emerging biomarkers and omics-based profiles offer promise for earlier, more precise risk stratification. Current therapeutic strategies emphasize lifestyle modification, metabolic correction, and pharmacologic interventions including RAAS blockade, SGLT2 inhibitors, and GLP-1 receptor agonists. Novel antifibrotic, anti-inflammatory, and microbiome-based therapies represent future directions. Advancing understanding of these mechanisms is essential to develop precision approaches that prevent and mitigate kidney injury in high-risk populations.

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