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Diabetes-Associated Hepatotoxicity and Nephrotoxicity: Roles of Oxidative Stress and Immunomodulation in Organ Crosstalk

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ABSTRACT

Diabetes mellitus is a systemic metabolic disorder that accelerates injury to both the liver and kidneys. Beyond hemodynamic and metabolic derangements, two convergent hallmarks-oxidative stress and immune dysregulation-shape the trajectory of diabetes-associated hepatotoxicity and nephrotoxicity. Hyperglycemia, insulin resistance, and lipid overload drive mitochondrial and NADPH oxidase–derived reactive oxygen species, advanced glycation end-product signaling, endoplasmic reticulum stress, and impaired autophagy. These redox disturbances activate innate and adaptive immune programs, including Toll-like receptor pathways, NLRP3 inflammasome assembly, macrophage polarization, and T-cell skewing, thereby sustaining inflammation and fibrotic remodeling. The liver and kidney communicate through cytokines, chemokines, hepatokines, adipokines, bile acid–FXR signaling, extracellular vesicles, and uremic toxins, creating a feed-forward hepato–renal axis that amplifies injury in both organs. This review synthesizes current mechanistic understanding of oxidative and immune pathways in diabetic liver and kidney disease, highlights emerging biomarkers and noninvasive assessment tools, and outlines therapeutic strategies-metabolic, antioxidant, and immunomodulatory for interrupting shared nodes of pathobiology and organ crosstalk.

Keywords: diabetes, hepatotoxicity, nephrotoxicity, oxidative stress, immunomodulation

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that exerts systemic effects extending far beyond glucose dysregulation [1]. Among the most affected organs are the liver and kidney, both of which are highly susceptible to the metabolic, hemodynamic, and inflammatory insults associated with persistent hyperglycemia and insulin resistance [2]. Type 1 and type 2 diabetes markedly increase the risk of developing nonalcoholic or metabolic dysfunction–associated fatty liver disease (NAFLD/MAFLD), nonalcoholic steatohepatitis (NASH), and hepatic fibrosis, while also accelerating the onset of diabetic kidney disease (DKD), characterized by albuminuria, progressive decline in glomerular filtration rate, glomerulosclerosis, and tubulointerstitial fibrosis [3]. These complications often coexist in the same patient, reinforcing each other and magnifying overall morbidity and mortality. The coexistence of hepatic and renal complications in diabetes also carries broader clinical implications. Patients with both conditions are at significantly higher risk of cardiovascular disease, heart failure, and systemic metabolic decompensation [4]. While traditional models of DKD emphasized hemodynamic stress, such as renal hyperfiltration, and those of NAFLD highlighted lipid accumulation as the primary driver of hepatocellular injury, contemporary insights reveal that these conditions cannot be viewed in isolation [5]. Instead, they are increasingly recognized as manifestations of shared molecular and cellular disturbances rooted in oxidative stress and immune dysregulation.

This systems-level perspective emphasizes that diabetes-associated hepatotoxicity and nephrotoxicity are not parallel processes but part of an interconnected hepato–renal axis. Metabolic stress in one organ produces signals-reactive oxygen species, inflammatory cytokines, hepatokines, uremic toxins, or extracellular vesicles—that propagate injury in the other [6]. As a result, organ crosstalk amplifies damage, accelerates fibrosis, and sustains chronic inflammation. This paradigm has significant therapeutic implications: interventions targeting oxidative

stress and immune modulation may simultaneously mitigate both liver and kidney injury, shifting clinical care toward integrated management strategies.

2. Molecular Drivers of Oxidative Stress in Diabetes

Oxidative stress arises when the generation of reactive oxygen species (ROS) and reactive nitrogen species overwhelms endogenous antioxidant defenses [7]. In the diabetic milieu, multiple pathways converge to increase ROS production, affecting hepatocytes, Kupffer cells, podocytes, mesangial cells, and tubular epithelial cells [8]. Hyperglycemia is the central instigator of oxidative imbalance [9]. Elevated intracellular glucose enhances mitochondrial electron transport chain activity, leading to electron leakage and superoxide formation [10]. At the same time, glucose flux through the polyol pathway consumes NADPH, thereby reducing the availability of this essential cofactor for regenerating reduced glutathione, a major antioxidant [10]. The accumulation of advanced glycation end-products (AGEs) and their binding to the receptor for AGEs (RAGE) activate nuclear factor-kappa B (NF-κB), increasing the transcription of inflammatory and oxidative genes [11]. Other contributors include activation of protein kinase C (PKC) isoforms, which stimulate NADPH oxidase (NOX) enzymes, further amplifying ROS generation [12]. Lipid overload in hepatocytes and renal tubular cells enhances fatty acid oxidation and promotes lipid peroxidation, generating toxic aldehydes that perpetuate oxidative injury [13]. In addition, excess polyunsaturated fatty acids may trigger ferroptosis, a form of regulated necrosis linked to iron-dependent lipid peroxidation [14].

Endoplasmic reticulum (ER) stress adds another layer of complexity [15]. In diabetes, chronic nutrient excess activates the unfolded protein response (UPR), which intersects with c-Jun N-terminal kinase (JNK) and CHOP signaling to induce oxidative stress and apoptosis [16]. Meanwhile, the endogenous antioxidant defense system is weakened, with reduced activity of superoxide dismutase, catalase, and glutathione peroxidase, along with impaired activation of the transcription factor Nrf2, a key regulator of cellular antioxidant responses [17]. Collectively, these mechanisms create a sustained redox imbalance that underpins tissue damage in both liver and the kidney.

3. Hepatotoxicity in Diabetes: From Steatosis to Fibrosis

The liver is a primary target of diabetic injury, progressing from simple steatosis to inflammation, fibrosis, and cirrhosis [18]. Insulin resistance is the initiating factor, as hyperinsulinemia drives de novo lipogenesis through sterol regulatory element–binding protein-1c (SREBP-1c) [19]. At the same time, impaired fatty acid β-oxidation and increased lipolysis in adipose tissue deliver excessive free fatty acids to hepatocytes, overwhelming metabolic capacity [20]. This imbalance results in hepatic steatosis, which serves as a fertile ground for oxidative injury.

Mitochondrial dysfunction, often exacerbated by cytochrome P450 2E1 (CYP2E1) induction, generates ROS that promote lipid peroxidation [21]. Reactive products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) covalently modify proteins, impairing their function and perpetuating hepatocellular injury [22]. Damaged hepatocytes release danger-associated molecular patterns (DAMPs), including mitochondrial DNA and HMGB1, which activate innate immune receptors such as Toll-like receptors (TLRs) and the NLRP3 inflammasome in Kupffer cells [23]. This results in the production of cytokines including TNF-α, IL-1β, and IL-6, which sustain hepatic inflammation. Simultaneously, hepatic stellate cells respond to oxidative and inflammatory cues by transforming into myofibroblasts that deposit extracellular matrix proteins, driving fibrogenesis [24]. Thus, the transition from steatosis to steatohepatitis and fibrosis reflects an interplay of metabolic stress, oxidative damage, and immune activation. Importantly, the liver also functions as an endocrine organ. Hepatokines such as fetuin-A, fibroblast growth factor 21 (FGF21), and angiopoietin-like proteins (ANGPTLs) influence systemic insulin sensitivity and inflammatory responses [25]. In diabetes, dysregulated hepatokine secretion not only worsens hepatic pathology but also contributes to renal inflammation and injury, underscoring the role of the liver as both a target and a driver of multisystem toxicity [26].

4. Nephrotoxicity in Diabetes: Glomerular and Tubular Injury

Diabetic kidney disease initiates with glomerular hyperfiltration and progresses through podocyte loss, mesangial expansion, thickening of the glomerular basement membrane, and tubular atrophy [27]. Hyperglycemia-induced mitochondrial and NOX-derived reactive oxygen species, AGE-RAGE signaling, and local RAAS activation converge to amplify oxidative damage [28]. Macrophage and T-cell infiltration, chemokines such as MCP-1/CCL2, and the NLRP3–caspase-1–IL-1β axis sustain inflammation [29]. Tubular epithelial cells suffer from lipotoxicity and ER stress, releasing NGAL and KIM-1, while fibroblast activation drives interstitial fibrosis [30]. Reduced renal Klotho expression diminishes antioxidant capacity and favors calcification and fibrosis [31].

5. Organ Crosstalk: The Hepato–Renal Axis

Liver and kidney interact bidirectionally. Hepatic inflammation elevates circulating cytokines and hepatokines that aggravate renal oxidative stress and leukocyte recruitment [32]. Conversely, reduced renal clearance increases uremic toxins such as indoxyl sulfate and p-cresyl sulfate, which activate hepatic oxidative pathways and stellate cells [33]. Bile acids signal through FXR and TGR5 to influence glucose and lipid metabolism in both organs; the

FXR–FGF19 axis links intestinal signals to hepatic and renal targets [34]. Adipokines mediate systemic tone: low adiponectin and elevated leptin favor oxidative stress, endothelial dysfunction, and fibrosis [35]. Extracellular vesicles and microRNAs shuttle injury signals across organs, while altered gut microbiota metabolites contribute to both NAFLD/NASH and kidney disease, completing a gut–liver–kidney triangle [36].

6. Immunomodulation in Diabetic Liver and Kidney Disease

Innate immune activation via TLR2/4 and cGAS–STING detects danger signals from oxidized lipids and mitochondrial DNA [37]. Macrophages polarize toward an M1 phenotype in early injury, secreting TNF-α and IL-1β, with later M2-like states supporting fibrogenesis through TGF-β. T-cell skewing toward Th1/Th17 and relative Treg deficiency perpetuate inflammation [38]. Complement activation and NETosis add further tissue damage [38]. Redox signaling intertwines with immunity: reactive oxygen species drive NF-κB and MAPK pathways, while Nrf2 activation restrains both oxidative and inflammatory cascades.

7. Therapeutic Strategies Targeting Shared Nodes

Foundational measures include intensive glycemic control, weight reduction, blood pressure and lipid management, and RAAS blockade, which collectively reduce oxidative and inflammatory triggers [39]. Glucose-lowering agents with organ benefits are central: SGLT2 inhibitors improve kidney outcomes and favorably affect hepatic steatosis and inflammation [40]; GLP-1 receptor agonists promote weight loss and can improve steatohepatitis parameters [41]. Statins are safe in fatty liver and reduce vascular oxidative stress [42]. Antioxidant and redox-directed approaches-N-acetylcysteine, vitamin E in select noncirrhotic NASH, mitochondria-targeted antioxidants, NOX inhibitors, and Nrf2 activators—aim to restore redox balance, while lifestyle interventions enhance endogenous antioxidant systems [43]. Immunomodulatory strategies under investigation include CCR2/CCR5 blockade, IL-1β pathway inhibition, and agents that rebalance macrophage polarization or enhance Treg function [44]. Modulators of bile acid signaling (FXR/TGR5 agonists) and FGF-based therapies target metabolic–inflammatory nodes relevant to both organs [45].

CONCLUSION

Future work should prioritize integrative trials that enroll patients with concurrent liver and kidney involvement and use mechanistic biomarkers to gauge target engagement across organs. Single-cell and spatial multiomics can map redox–immune niches and reveal shared druggable hubs. Therapeutic success will likely require multi-target regimens that dampen oxidative stress, recalibrate immune tone, and correct metabolic drivers simultaneously. Recognizing and treating the hepato–renal axis as a coupled system offers the best prospect for altering the natural history of diabetes-associated hepatotoxicity and nephrotoxicity.

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