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Tubular Injury in Diabetic Kidney Disease: Early Diagnosis and Intervention Strategies

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ABSTRACT

Diabetic kidney disease (DKD) is the most severe complication of diabetes mellitus and has poor prognosis, often progressing to end-stage renal disease, causing substantial morbidity and mortality globally. While the pathogenesis of DKD has been extensively characterised, including glomerular hyperfiltration, podocyte injury, and tubulointerstitial fibrosis, recent findings underscore renal tubular injury as a pivotal contributor to DKD progression. High glucose levels and lipid accumulation result in tubular injury, followed by oxidative stress, endoplasmic reticulum stress, inflammation, activation of the renin–angiotensin–aldosterone system, programmed cell death, epithelial–mesenchymal transition, and intercellular crosstalk, all of which exacerbate tubular dysfunction in DKD. Notably, biomarkers of renal tubular injury, including kidney injury molecule-1, cystatin C, neutrophil gelatinase-associated lipocalin, liver fatty acid-binding protein, monocyte chemoattractant protein-1, N-acetyl-beta-glucosidase, and retinol-binding protein, along with other promising novel biomarkers, emerge earlier than microalbuminuria and serve as novel diagnostic indicators for early DKD detection. Therapeutically, we critically evaluate both established agents and emerging strategies, including hypoglycemic agents, anti-oxidative stress therapies, anti-inflammatory therapies, anti-cell death therapies, and stem cell therapy, showing promise for mitigating DKD-related tubular damage. This comprehensive review constructs a logical framework linking molecular mechanisms, novel biomarkers, and emerging therapeutic strategies for renal tubular injury in DKD. By bridging molecular mechanisms with actionable therapeutic strategies, this review highlights the pivotal role of tubulopathy in DKD pathogenesis and its implications for early diagnosis and intervention strategies.

1 | Introduction

Diabetic kidney disease (DKD) is the primary cause of end-stage renal disease (ESRD). The Diabetes Atlas of the International Diabetes Federation estimates that there were 366 million people across 110 countries living with diabetes in 2011, a figure projected to reach 552 million by 2030 [1]. Approximately 40% of those with type 2 diabetes (T2D) and 30% with type 1 diabetes (T1D) experience kidney damage [2]. The mortality rate after diabetes with renal complications is high, with a 10-year cumulative mortality rate of 31.1% [3, 4]. The high morbidity, mortality, and economic burden of DKD place a tremendous strain on individuals and public health systems. Contemporary research has emphasised prevention, early detection, and

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effective treatment strategies to mitigate the incidence and progression of DKD.

The traditional pathogenesis of DKD emphasises glomerular injury as the centre of proteinuria, and microalbuminuria is considered an early diagnostic indicator. Chronic hyperglycemia induces profound structural and functional alterations in glomeruli, including mesangial matrix expansion, glomerular basement membrane (GBM) thickening, podocyte depletion, and endothelial dysfunction, all of which contribute to albuminuria and progressive glomerulosclerosis [5–7]. Nonetheless, glomerular injury and urinary albumin excretion rate may have limitations in predicting renal function in DKD [8]. Recent findings suggest that proximal tubule injury also plays an indispensable role in the pathogenesis of DKD and is intimately linked to the gradual loss of renal function [9]. In the early stages of DKD, some biomarkers of proximal tubular cell injury can be detected in urine without obvious glomerular injury, indicating that proximal tubular cell injury may be an early lesion of DKD and is not completely secondary to glomerular injury [10]. Furthermore, it has been reported that the biomarkers of tubular injury appear earlier than microalbuminuria [9, 11].

Therefore, this review aims to evaluate the crucial role of renal tubular injury in DKD pathogenesis, going beyond the traditional focus on the glomerulus. Elucidating the molecular mechanisms underlying renal tubular injury is of great significance for developing novel therapeutic interventions, identifying drug intervention targets, and halting DKD progression.

A comprehensive literature search was conducted using the PubMed and Web of Science databases for articles published from inception until 30 June 2025. The search terms included combinations of ‘diabetic kidney disease’, ‘diabetic nephropathy’, ‘tubular injury’, ‘proximal tubule’, ‘mechanism’, ‘biomarker’, ‘therapy’, and ‘treatment’. The search was focused on original research articles, systematic reviews, and meta-analyses. Articles were selected based on their relevance to the molecular mechanisms, biomarkers, and therapeutic interventions specific to tubular injury in DKD.

2 | Mechanism of Renal Tubular Injury During DKD Progression

Numerous studies indicate that hyperglycemia is the fundamental pathological trigger for renal tubular injury in DKD. Notably, recent mechanistic studies have demonstrated that hyperglycemia can coordinate multiple pathological processes. In this review, we outline the latest advancements in our understanding of the mechanisms of renal tubular injury in DKD from the following perspectives: hyperglycemia and lipid accumulation, oxidative stress, endoplasmic reticulum (ER) stress, inflammation, activation of the renin–angiotensin–aldosterone system (RAAS), epithelial–mesenchymal transition (EMT), programmed cell death (PCD), and intercellular crosstalk (Figure 1). In summary, these findings suggest that hyperglycemia is the main cause leading to the progression of renal tubular injury in DKD.

The primary cause of DKD is chronic hyperglycemia, which is also the principal driver of renal tubular injury. On one hand, chronic hyperglycemia triggers mitochondrial fragmentation, excessive production of reactive oxygen species (ROS), mitotic defects, and ER stress in various cell types, including endothelial cells, where early cell-specific responses have been detected [12–14]. On the other hand, high glucose levels facilitate the formation of advanced glycation end products (AGEs) [15], which is a specific mechanism triggered directly by high glucose in DKD. AGEs accumulate in renal tubular cells and bind to and activate the receptor for AGE (RAGE). The AGE-RAGE interaction activates multiple signalling pathways, including nuclear factor-kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), PI3K/Akt, and NADPH oxidase (Nox). This activation results in ROS overproduction, exacerbating oxidative stress, ER stress, inflammation, and fibrosis in renal tubular epithelial cells [16–21]. Additionally, the formation and aggregation of AGEs inhibit protein synthesis in proximal tubular epithelial cells (PTECs) and stimulate transforming growth factor beta (TGF-β) expression, promoting DKD progression [22]. Hyperglycemia induces oxidative stress, activates pathways such as the polyol and hexosamine biosynthetic pathways, and promotes AGE production and protein kinase C (PKC) activation. These metabolic abnormalities damage renal tubular epithelial cells (TECs), exacerbating DKD progression [15, 23, 24].

Meanwhile, abnormal serum lipids and ectopic lipid accumulation in the kidney are particularly implicated in DKD development [25]. It has been confirmed that impaired lipid phagocytosis, along with ectopic lipid accumulation, occurs in the proximal tubules of patients with DKD and db/db mice [26]. Notably, lipid deposition primarily affects the proximal renal tubules [27]. Both the abnormal quantity and quality of lipids activate inflammation, oxidative stress, mitochondrial dysfunction, and cell death, ultimately leading to proximal tubular damage [28].

2.1 | Oxidative Stress

Recently, an increasing number of studies have focused on the role of oxidative stress in renal tubular injury during the progression of DKD. High glucose levels trigger mitochondrial dysfunction and ROS overproduction in the proximal tubules [29]. The primary endogenous sources of ROS include mitochondrial ROS production, nicotinamide adenine dinucleotide phosphate oxidases (Nox), uncoupled endothelial nitric oxide synthase (eNOS), xanthine oxidase (XO), and cytochrome P450 (CYP450) [30]. While various studies have shown that xanthine oxidase is an important source of ROS in DKD, a recent genetic study demonstrated that certain risk variants in the promoter region of xanthine oxidoreductase (XOR) are associated with elevated XOR activity and progressive DKD in both animal models and human cohorts, further implicating XOR as a key source of ROS in diabetic renal injury [31]. Additionally, the NOX family of enzymes exhibits isoform-specific roles in DKD pathogenesis [32]. NOX4, highly expressed in renal tubules, has been identified as a major source of ROS in the diabetic kidney and is critical mediator of redox signalling in tubulointerstitial cells exposed to the diabetic milieu [33–35]. Conversely, NOX5 has been identified as expressed in glomerulus. In a mouse

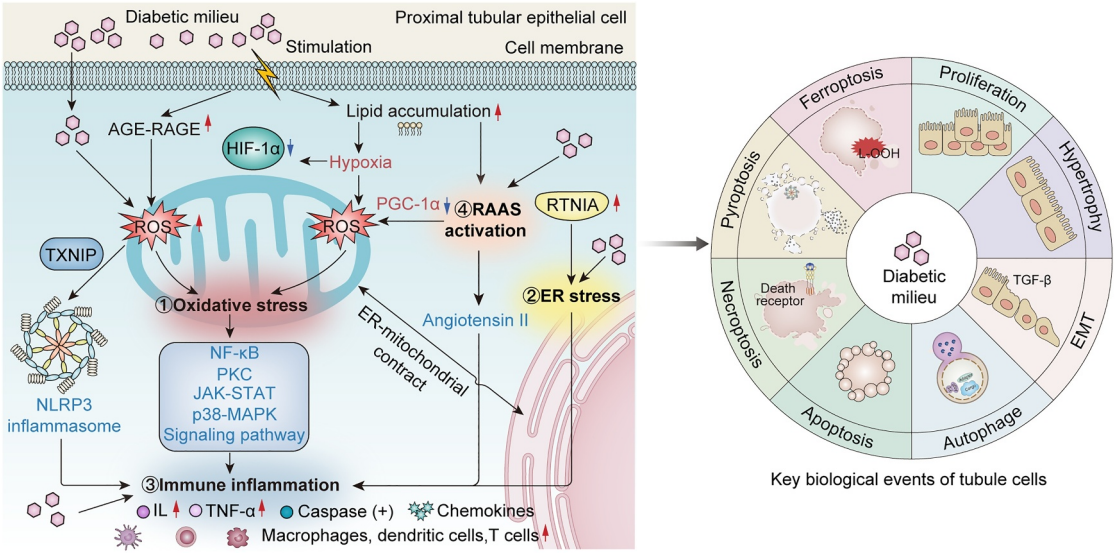

FIGURE 1 | Mechanisms of renal tubular injury in DKD. The diabetic milieu (encompassing high glucose, high lipids, AGEs, and other factors) leads to oxidative stress, hypoxia, ER stress, immune inflammation and RAAS activation, consequently contributing to proximal tubules functional and morphological changes. The proximal tubules undergo proliferation, hypertrophy, EMT and programmed cell death, eventually leading to tubulointerstitial fibrosis and the progression of DKD to ESRD. AGEs, advanced glycation end products; DKD, diabetic kidney disease; ER, endoplasmic reticulum; ESRD, end-stage renal disease; HIF-1α, hypoxia-inducible factor 1a; IL, interleukin; JAK-STAT, janus kinase/signal transducer and activator of transcription; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-kappa-B; NLRP3, NOD-like receptor protein 3; PGC-1α, peroxisome proliferator activated receptor gamma coactivator 1-alpha; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; RTN1A, reticulon-1A; TGF-β, transforming growth factor beta; TNF-α, tumour necrosis factor α; TXNIP, thioredoxin-interacting protein.

model of DKD, the specific overexpression of Nox5 in vascular smooth muscle cells/interstitial cells indicates an increase in glomerular ROS production, suggesting that Nox5 and its derived ROS promote the progression of DKD [36]. Besides, studies have also found that NOX1 modulates the p38/p27 (Kip1) signalling pathway by activating PKC and promotes premature senescence in early stage DKD [37]. These isoform-specific roles highlight the complexity of NOX-mediated oxidative damage in DKD, thus, therapeutic strategies targeting specific NOX isoforms may offer precision in mitigating oxidative damage. ROS activation is critical during oxidative stress caused by mitochondrial damage. Briefly, oxidative stress and ROS accumulation activate multiple signalling pathways, such as nuclear factor-kappa-B (NF-κB), PKC, Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), TGF-β/p38/MAPK, and mammalian target of rapamycin (mTOR), among others [30, 38, 39], contributing to tubular injury. Acetyl-CoA synthetase 2 (ACSS2) demonstrates heightened expression in diabetic PTECs, suppressing Sirtuin 1 (SIRT1) expression and consequently inducing mitochondrial oxidative stress and inflammation within the renal tubules [40]. Furthermore, the activation of mitochondrial ROS/thioredoxin-interacting protein (TXNIP)/NLRP3/IL-1β [41] and TLR4/NF-κB signalling pathways [42], coupled with the depletion of disulfide-bond A oxidoreductase-like protein (DsbA-L) or PTEN-induced serine/threonine kinase 1 (PINK1), exacerbates mitochondrial fragmentation and oxidative stress, culminating in exacerbated tubular injury [43, 44].

Moreover, renal tubular cells, characterized by their elevated energy demands and reliance on aerobic metabolism, become vulnerable to hypoxia in high glucose conditions. Hypoxia-inducible factor 1 α (HIF-1α) is a major regulator of the adaptive response to hypoxia. In the presence of hypoxia, high glucose concentrations in proximal tubular cells hinder HIF-1 activity, resulting in inadequate activation of HIF signalling, subsequently impairing the adaptive response to hypoxia and ultimately contributing to tubular atrophy and interstitial fibrosis [45]. In conclusion, mitochondrial dysfunction triggers excess production of ROS, which in turn intensifies oxidative stress within renal tubular cells and subsequently impairs mitochondrial integrity and function. In this process, excessive ROS production initiates the apoptotic pathway, leading to renal tubular cell death in DKD.

2.2 | ER Stress

In DKD, hyperglycemia, proteinuria, increased AGEs, and free fatty acids all induce ER stress [46]. Notably, ER-mitochondrial-associated membranes (ER-MAMs) may play an important role in the pathogenesis of DKD [47, 48]. Under high glucose conditions, the endoplasmic reticulum-resident protein Reticulon-1A (RTN1A) is highly expressed, aggravating ER stress in TECs. By modulating ER-mitochondrial contact, RTN1A promotes PTEC injury and tubulointerstitial fibrosis in DKD. Importantly, RTN1A overexpression does not worsen glomerular injury or proteinuria in DKD [49]. Furthermore, ER stress

can initiate ferroptosis-related EMT in DKD by mediating the XBP1/Hrd1/Nrf2 signalling pathway [50].

2.3 | Immune Inflammation

Inflammation is crucial in the initiation and progression of DKD. Mitochondrial dysfunction and lipid accumulation augment ROS production and activate relevant signalling pathways and transcription factors. Renal tubular cells exposed to high glucose levels have enhanced production of pro-inflammatory factors such as intercellular adhesion molecule 1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and osteopontin (OPN), which facilitate the infiltration and recruitment of inflammatory cells such as macrophages and monocytes. Moreover, hyperglycemia induces the secretion of inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumour necrosis factor α (TNF-α). Collectively, these processes lead to renal tubular injury and exacerbate the progression of DKD [51–54]. The NOD-like receptor protein 3 (NLRP3) inflammasome is a multimeric protein complex that is primarily activated by ROS. Its activation triggers the caspase-1-mediated cleavage of pro-IL-1β and pro-IL-18, subsequently leading to the secretion of their mature forms from cells, thereby aggravating further inflammatory process and oxidative stress [55]. Predominantly secreted by circulating monocytes, IL-1β is a major proinflammatory cytokine linked to renal tubulointerstitial inflammation. NLRP3 inflammasome activation can drive IL-1β secretion and caspase-1 activation within proximal tubules [56]. In addition, IL-6 appears to be a central mediator in the inflammatory process of DKD, potentially via a gp130-STAT3 signalling axis [57]. Moreover, IL-17 can upregulate proinflammatory and profibrotic genes, including IL-6, TNF-α, and TGF-β [58]. Under high glucose conditions, both activated caspase-1 and caspase-3 levels are increased. Caspase-1 activation promotes IL-1β maturation, whereas caspase-3 activation mediates Gasdermin E (GSDME) cleavage, resulting in the formation of plasma membrane pores and subsequent cytosolic release of IL-1β [59]. Furthermore, a study has revealed a significant increase in TNF-α in the renal tubules of patients with DKD, and TNF-α inhibition can significantly reduce NLRP3 inflammasome expression, along with IL-6 and IL-17 [60]. This suggests that TNF-α also plays a promoting role in the pathogenesis of renal tubular injury in DKD.

The innate immune system employs pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and nucleotide-binding oligomerisation domain (NOD)-like receptors (NLRs), can recognise pathogen-and damage-associated molecular patterns (PAMPs/DAMPs) in extracellular and intracellular compartments [61], thereby triggering a series of inflammatory responses, promoting renal fibrosis, and finally causing renal impairment in DKD [62, 63]. DAMPs, released from injured renal cells under hyperglycaemic stress, are pivotal drivers of sterile inflammation in DKD [64]. For instance, high-mobility group box 1 (HMGB1) is one of the key DAMPs involved in renal and systemic inflammation, with TLR4 and RAGE serving as its primary receptors [65]. A clinical trial showed that HMGB1 levels are significantly higher in patients with DKD. Moreover, elevated HMGB1 was identified as an independent risk factor for DKD progression and significantly correlated with DKD severity [66]. Similarly, High mobility group nucleosome-binding protein 1 (HMGN1), a novel DAMP that contributes to generating the innate immune response, is upregulated in renal tubular epithelial cells of diabetic models, activating the TLR4/MyD88/NF-κB signalling pathway to promote renal tubular epithelial cells injury and inflammatory infiltration [67]. These findings underscore the central role of DAMPs and TLR2/TLR4 signalling in bridging cellular damage to inflammatory responses in DKD.

Chemokines and their receptors (CCRs) critically mediate immune cells infiltration and tubulointerstitial inflammatory response in DKD. Transcriptomic profiling reveals upregulated CCRs (CXCL2, CXCL8, CXCL10, CCL20) in DKD patients, orchestrating immune infiltration of pathogenic immune subsets, including CD56bright natural killer cells, effector memory CD8+ T cells, memory B cells, monocytes, regulatory T cells (Tregs), and T follicular helper cells [68]. Macrophage inflammatory protein-3 alpha (MIP-3α), a CC chemokine, is a significant pathogenic mediator of inflammation in the progression of DKD [69]. It is markedly upregulated in proximal tubular cells under hyperglycemia. In diabetic rodent models, MIP-3α overexpression localises to dilated tubules and drives CD3+ T lymphocyte infiltration via TGF-β1-dependent pathways. Notably, its production is suppressed by angiotensin-converting enzyme (ACE) inhibitors, linking RAAS modulation to chemokine regulation [70]. Similarly, CC motif chemokine 5 (CCL5), also known as regulated upon activation normal T cell expressed and secreted (RANTES), exhibits elevated expression in renal tubular cells and facilitates the recruitment of T cells, macrophages, and monocytes, thereby driving inflammation and fibrosis in DKD [71–74]. Genetic polymorphisms in RANTES signalling axis (ligand/receptors) are independent risk factors for DKD progression, and RANTES and MCP-1 upregulation can also drive macrophage-mediated renal inflammation during DKD progression [75].

Complementing this, an X-cell analysis identified immune cells that showed significant changes in the DKD tubulointerstitium. In particular, CD4+ T cells, Th2 cells, CD8+ T cells, M1 macrophages, activated dendritic cells (DCs) and conventional DCs increased significantly [76]. Activated macrophages produce Th1/Th17-attracting chemokines (CXCL9/10 and CCL20) via TLR4/TRIF and TLR2/4/MyD88 pathways, fostering immune cell infiltration and cytokine release in early DKD [77]. Furthermore, Activated/conventional DCs and pathogenic CD103+ DCs are enriched in DKD, promoting tubulointerstitial inflammation. Mesenchymal stem cell (MSC) therapy reduces CD103+ DC abundance, suppresses inflammatory cytokines (IL-1β, IL-6, TNF-α, MCP-1) and CD8+ T cell infiltration, thereby alleviating fibrosis and improving renal function [78]. In the immune pathogenesis of DKD, pro-inflammatory T helper cells (Th1 and Th17) are particularly prominent, exacerbating tubulointerstitial inflammation and fibrosis via IL-17 secretion. Preclinical studies have shown IL-17 inhibition (e.g., mycophenolate mofetil) alleviates early renal injury and tubulointerstitial fibrosis, suggesting Th17's independent role in DKD progression [79].

Meanwhile, the expression of CXCL1 and its receptor (CXCR2) is significantly increased in DKD. The CXCL1/CXCR2 axis may lead to inflammatory injury by phosphorylating NF-κB and subsequently activating the NLRP3 inflammasome [80]. Besides, several other signalling pathways, including NF-κB, Wnt, PKC, TLR2/4, AGE/RAGE, JAK/STAT, TXNIP, CCL2, and Alpha-kinase 1 (ALPK1), are also activated during immune inflammatory activation [81–85]. Strikingly, in the early stages of DKD, the expression of the Klotho protein is downregulated by pro-inflammatory factors [86]. Research has demonstrated that Klotho overexpression inhibits the production of inflammatory cytokines. However, Klotho levels were significantly reduced in the renal TECs of db/db mice [87].

2.4 | RAAS Activation

2.4.1 | Classical RAAS (ACE/Ang II/AT1R)

The RAAS plays a crucial role in maintaining hemodynamic stability by regulating extracellular fluid volume, preserving sodium balance, and optimising tissue perfusion. RAAS activation occurs in DKD and contributes to disease progression. Several clinical and experimental studies have reported that RAAS activation is closely associated with renal tubulointerstitial injury. Specifically, angiotensin II, the pivotal effector of the RAAS, is elevated in DKD [88], and functions as both a local hormone and a growth factor to regulate tubulointerstitial structure and function. It facilitates monocyte and macrophage infiltration and mediates the activation of a variety of cytokines and chemokines, ultimately leading to proximal tubular cell apoptosis [89]. Moreover, angiotensin II promotes ROS production, releases proinflammatory cytokines, and induces fibrosis by promoting aldosterone expression [90, 91]. Specifically, aldosterone reduces peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) expression, inducing mitochondrial dysfunction and ultimately leading to abundant ROS generation and accumulation [92]. Additionally, studies have shown that angiotensin II stimulates the expression of sodium-glucose cotransporter 2 (SGLT2) in renal proximal tubules, enhancing sodium and water reabsorption and leading to an increase in body fluid volume and hypertension, subsequently exacerbating renal tubule damage in DKD [93, 94]. Furthermore, angiotensin II type 1 receptor-associated protein (ATRAP), which is abundantly expressed in proximal tubules, negatively regulates intracellular angiotensin II signalling [95, 96].

2.4.2 | Counter-Regulatory Role of Alternative RAAS

In addition to the classical RAAS, alternative RAAS components also play an important role in DKD. While the classical RAAS axis (ACE/Ang II/AT1R) promotes inflammation and fibrosis, the alternative RAAS pathway exerts counter-regulatory effects. For instance, activating the AT2 receptor can alleviate the negative impacts of AT1 receptor-induced vasoconstriction and extracellular matrix deposition by promoting nitric oxide production and sodium excretion [97, 98]. Furthermore, angiotensin-(1-7), a heptapeptide generated from angiotensin II (Ang-II) by the action of angiotensin-converting enzyme 2 (ACE2), has vasodilatory properties and can antagonise the growth-promoting signalling pathways in renal tubular epithelial cells by activating protein tyrosine phosphatase [99, 100]. The biologically active peptide Ang-(1-7) then binds to and activates Mas receptors, forming the ACE2/Ang-(1-7)/Mas axis system, which counteracts vasoconstriction, inflammation, oxidative stress and cell proliferation, and has a protective effect in DKD [101, 102]. Similarly, alamandine, a novel endogenous peptide of the RAAS, primarily exerts its effects by activating the Mas-related G protein-coupled receptor D (MrgD) receptor [103]. It may exert renoprotective effects by inhibiting oxidative stress, inflammation (suppressing iNOS expression and reducing inflammatory factors such as IL-1β, IL-6, and TNF-α) [104–106], fibrosis, and apoptosis (inhibiting the PI3K/Akt/MAPK, PKC/ROS signalling pathways, and reducing activated caspases and Bax) [106–109]. In DKD, excessive activation of the classic RAAS aggravates renal damage, while the alternative RAAS pathways have a protective effect. The imbalance between the two may accelerate the progression of DKD.

2.5 | Key Biological Events of Renal Tubule Cells

In the early phases of diabetic mellitus, high glucose levels, AGEs, and lipid accumulation facilitate oxidative stress, ER stress, inflammatory responses, and RAAS activation, which contribute to functional and morphological changes in the proximal tubules. Proximal tubules undergo proliferation, hypertrophy, EMT, autophagy and programmed cell death (apoptosis, necroptosis, pyroptosis, and ferroptosis), eventually leading to tubulointerstitial fibrosis and the progression of DKD to ESRD [110, 111].

2.5.1 | Tubular Hypertrophy

Tubular hypertrophy is one of the earliest structural changes observed during DKD progression. Under high glucose conditions, proximal tubular cells are mediated by cyclin-dependent kinase inhibitors such as p27Kip1 and p21, then arrested in the G1 phase, and ultimately undergo hypertrophy [112–114]. Likewise, TGF-β activation is another vital cause for proximal tubular hypertrophy. The activation of the JAK/STAT [115], extracellular signal-regulated kinase (ERK), and p38 signalling pathways [116] induces TGF-β synthesis in DKD. TGF-β activation promotes cell hypertrophy and stimulates extracellular matrix accumulation [112, 117, 118].

2.5.2 | EMT

EMT in proximal tubular cells occurs during DKD progression, which is the core pathological mechanism of renal tubulointerstitial fibrosis [119]. TGF-β serves as the pivotal cytokine for EMT induction [119, 120]. AGEs activate TGF-β1, along with the activation of the JAK/STAT and ERK1/2-MAPK pathways, thereby initiating EMT in proximal tubules [121, 122]. In DKD, faced with oxidative stress and inflammation, these cells undergo EMT mediated by multiple signalling pathways, including JAK/STAT, PKC, MAPK, PI3K/Akt, Notch, Epac/Rap1, and

Wnt/β-Catenin [123, 124]. Additionally, the generation of IL-1 and TNF-α induces EMT by enhancing TGF-β1 expression [125, 126]. Meanwhile, the RAAS is activated during DKD, and aldosterone induces EMT in renal tubular cells through a ROS-dependent activation of ERK1/2 [127].

2.5.3 | Autophagy

Autophagy is also important in the pathogenesis of tubular injury in DKD. Regulated by nutrient-sensing pathways, including AMPK, mTOR, and SIRT1, autophagy dysfunction exacerbates DKD development [128]. SIRT1, an NAD+-dependent class III histone deacetylase, is downregulated during DKD progression. It regulates autophagy to protect cells, exhibiting anti-apoptotic, anti-oxidative, and anti-inflammatory properties [129–131]. Moreover, extensive studies have demonstrated that during DKD progression, p53 is upregulated and participates in cell autophagy by mediating the SIRT1 or miR-214/ULK1 axis [132, 133]. Furthermore, autophagy of the ER (ER-phagy) can selectively remove damaged ER through the autophagy-lysosomal pathway. Phosphofurin acidic cluster sorting protein 2 (PACS-2), which is involved in autophagy, is downregulated in the renal tubular cells of diabetic mice and can inhibit ER-phagy by mediating the TFEB/FAM134B pathway, thereby exacerbating renal tubular injury in DKD [134].

2.5.4 | Apoptosis

Apoptosis is likely to be the primary mechanism underlying tubular atrophy [110]. Substantial evidence indicates that elevated glucose levels modulate the expression of apoptosis-regulating genes and promote apoptosis in PTECs. During DKD progression, the pro-apoptotic protein Bax is upregulated, while the anti-apoptotic protein Bcl-2 is downregulated [135, 136]. Moreover, high glucose levels can induce the expression of p53, activated caspase-3, MALAT1, LIN28A, and Nox4, which can aggravate ROS production and inflammatory cytokine secretion, thereby giving rise to cell apoptosis [136–139]. Additionally, in DKD rat models, the expression of amine oxidase renalase is reduced and prompts PTEC apoptosis and interstitial fibrosis by activating the p38 MAPK pathway [140].

2.5.5 | Necroptosis

Necroptosis is another form of programmed cell death. High glucose and fatty acids levels are the main factors leading to proximal tubule necroptosis [141]. The level of necroptosis marker p-MLKL has been shown to be positively correlated with the severity of renal function, pathological damage, and lipid droplet accumulation in patients with DKD [141]. Studies have found that high glucose levels induce the activation of the receptor-interacting protein kinase/mixed lineage kinase domain-like (RIPK1/RIPK3/MLKL) signalling pathway, which leads to proximal tubular necroptosis in patients with DKD [141, 142].

2.5.6 | Pyroptosis

Pyroptosis has been considered a novel pattern of cell death during DKD progression in recent years [143]. The canonical pathway induced by caspase-1 and the non-canonical pathway activated by caspase-4/5/11 have been implicated in pyroptosis-mediated cell death. Furthermore, the caspase-3/8 signalling cascade can also trigger cell pyroptosis [144, 145]. Research reveals that Gasdermin D (GSDMD), a vital biomarker of pyroptosis, is upregulated in the proximal tubules of patients with DKD [83, 146]. Both the TLR4/NF-κB and ALPK1/NF-κB pathways initiate the canonical caspase-1-GSDMD pyroptosis pathway, contributing to renal tubular injury and interstitial inflammation in DKD [83, 146]. Meanwhile, signalling pathways involving ROS/TXNIP/NLRP3, lncRNA-related, and the AMPK/SIRT1/NF-κB inflammasome, among other pyroptosis-related inflammasome signalling pathways, may also significantly contribute to DKD development [145].

2.5.7 | Ferroptosis

Ferroptosis, a non-apoptotic mode of cell death, is characterised by lethal levels of iron-dependent lipid peroxides. Recent research has indicated that ferroptosis is involved in renal tubular injury in DKD [147, 148], and that this process may be mediated via the HIF-1α/HO-1 pathway [149]. Additionally, the protein arginine methyltransferase 6 (PRMT6)/signal transducer and activator of transcription 1 (STAT1)/acyl-CoA synthetase long-chain family member 1 (ACSL1) axis also plays a role in this process. Specifically, studies have found that PRMT6 and STAT1 synergistically regulate ACSL1 transcription, enhancing phospholip-polyunsaturated fatty acid synthesis and thereby driving ferroptosis in DKD [150].

2.6 | Crosstalk of Tubules and Other Cells

Crosstalk between tubules and other cells plays a pivotal role in tubular injury during the progression of DKD. On one hand, the crosstalk between TECs and glomerular endothelial cells (GECs) is crucial for DKD. During DKD development, abnormal secretion of vascular endothelial growth factor (VEGF) and inflammatory cytokines leads to GEC injury. Subsequently, injured GECs release a cascade of factors, including hepatocyte growth factor, insulin-like growth factor binding proteins, extracellular vesicles (EVs), and Kruppel-like factors, which can also act on TECs, causing varying degrees of structural and functional alterations in TECs [151]. In addition, high glucose levels stimulate GECs to secrete EVs carrying TGF-β and miRNA, promoting Smad3 pathway activation in TECs and contributing to EMT [151]. On the other hand, TEC-to-macrophage communication via EVs establishes a negative feedback loop, promoting renal inflammation and apoptosis in DKD [152]. Briefly, in DKD mouse models, lipotoxic TEC-derived EVs can activate macrophage inflammation and trigger the release of macrophage-derived EVs, which in turn can induce apoptosis in lipotoxic TECs [152].

In summary, as illustrated in Figure 1, the diabetic milieu, comprising hyperglycemia, lipid accumulation, AGEs, and other contributing factors, induces oxidative stress, hypoxia, ER stress, immune inflammation, and RAAS activation. These interconnected pathophysiological mechanisms collectively promote EMT and various forms of programmed cell death, thereby facilitating the development of tubulointerstitial fibrosis and the progression of DKD to ESRD. Notably, while renal tubular injury in DKD shares several pathophysiological pathways (such as oxidative stress, immune inflammation, and activation of the RAAS) with other kidney diseases, its distinguishing feature is the occurrence and persistence of such damage within the unique metabolic milieu of chronic hyperglycemia. This context dictates the specific mechanisms involved, the early appearance of certain biomarkers, and the rationale for employing novel, metabolism-targeting therapies.

3 | Biomarkers of Renal Tubule Injury

Previously, the indicators used to assess the presence and progression of DKD included blood urea nitrogen, serum creatinine, glomerular filtration rate (GFR), and albuminuria [153, 154]. Nevertheless, these markers lack sensitivity to minor changes in kidney function; consequently, there is a need for more sensitive and specific markers to evaluate renal injury. Tubular injury markers may be used to assess initial tubular dysfunction or damage in the early stages of DKD (Table 1).

3.1 | Traditional Biomarkers

Recently, a number of biomarkers of renal tubular injury have been discovered, which have clinical significance as markers of the occurrence and progression of DKD, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, liver fatty acid-binding protein (L-FABP), MCP-1, N-acetyl-beta-glucosidase (NAG), and retinol-binding protein (RBP) [155, 171, 190–193].

3.1.1 | KIM-1

Urinary KIM-1 may be a promising biomarker. It is a type I cell membrane glycoprotein that is almost not expressed in the normal kidneys. However, its concentration in urine increases rapidly after renal tubular injury and is positively correlated with the degree of renal tubular injury [155, 156]. KIM-1 has been found to mediate the proximal tubular uptake of palmitic acid-bound albumin, leading to DNA damage, cell cycle arrest, interstitial inflammation, and fibrosis [157]. Furthermore, a clinical study found that patients with diabetes and microalbuminuria had the highest urinary levels of IL-6, CXCL10, NAG, and KIM-1. These results suggest that KIM-1 can be used as a biomarker for renal tubular injury in DKD [158]. KIM-1 demonstrates high specificity and sensitivity for detecting renal tubular injury in DKD, identifying potential damage even before renal function decline. It has the ability for early detection, is non-invasive, reflects the extent of renal tubule damage, and can be used as a prognostic indicator. These characteristics suggest that KMI-1 plays a significant role in the early diagnosis and treatment of tubular injury in DKD [194–196].

3.1.2 | NGAL

NGAL is a 24-kDa secretory glycoprotein that is mainly expressed in the renal tubular epithelium and is significantly upregulated after renal tubular injury [159]. A large number of previous studies have shown that NGAL can be detected before the increase in serum creatinine and may be an early urinary biomarker of acute kidney injury [160–162]. During DKD progression, urinary NGAL significantly increases [163] and acts as an independent risk factor for DKD progression [164]. A clinical trial found that the uNGAL/creatinine ratio (uNCR) could serve as a potential tool for identifying clinically suspected cases of DKD. Patients with DKD exhibiting elevated uNCR were found to have a higher risk of proteinuria and a poorer prognosis [197]. In addition, NGAL levels are elevated in the early stages of DKD renal injury, which has high clinical feasibility, early diagnostic value, and potential diagnostic value for normoalbuminuric nephropathy. However, further prospective studies are required to elucidate its role in the diagnosis and risk stratification of patients with DKD [198].

3.1.3 | Cystatin C

Cystatin C is an endogenous inhibitor of cysteine protease. A previous meta-analysis reported that serum cystatin C was significantly superior to serum creatinine as a marker of GFR [199]. In a clinical trial involving 303 patients with type 2 diabetes, it was found that the ratio of the urinary tubular biomarker cystatin C to creatinine was significantly elevated in patients with DKD and was positively correlated with the degree of albuminuria [165].

3.1.4 | L-FABP

L-FABP is a 14 kDa protein which is primarily expressed in the liver. L-FABP is a promising biomarker of renal tubular injury in DKD. In a meta-analysis of DKD, urinary L-FABP concentrations were significantly higher in the macroalbuminuric diabetic group than in the microalbuminuria and current normal albuminuria groups [166]. Moreover, in a cross-sectional and longitudinal study involving 140 patients with type 2 diabetes and 412 healthy control subjects, it was observed that urinary L-FABP levels were elevated in patients with normal proteinuria and increased progressively with the degree of proteinuria. These findings indicate that urinary L-FABP levels not only reflect the severity of DKD but also serve as an independent risk factor for its progression [167]. Therefore, urinary L-FABP may be considered a promising biomarker for the early diagnosis of DKD.

3.1.5 | MCP-1

MCP-1, a member of the chemokine family, is a major factor affecting macrophage aggregation. It is expressed by both native

TABLE 1 | Biomarkers of renal tubular injury.

Traditional biomarkers			
Biomarkers	**Source cell & detection**	**Findings/main results**	**References**
Kidney injury molecule-1 (KIM-1)	Proximal tubular cells (urine)	Increased in response to tubulointerstitial injury and positively correlated with the degree of renal tubular injury	[155–157]
		KIM-1 levels were the highest in diabetic patients with microalbuminuria	[158]
Neutrophil gelatinase-associated lipocalin (NGAL)	Neutrophil/renal tubular cells (serum/urine)	Increased substantially after renal tubular injury during the progression of DKD	[159–163]
		An independent risk factor for DKD progression	[164]
Cystatin-C	Nucleated cells/proximal tubular cells (serum/urine)	Increased in response to tubular injury and positively correlated with the degree of proteinuria	[165]
Liver fatty acid-binding protein (L-FABP)	Proximal tubular cells (urine)	Urinary L-FABP concentrations were significantly higher in the macroalbuminuria group	[166]
		Increased when proximal tubular cells injury, positively correlated with proteinuria, and was a risk factor for the deterioration of DKD	[167]
Monocyte chemoattractant protein-1 (MCP-1)	Macrophages, glomerular and tubular cells (urine)	The increase of MCP-1 is associated with renal tubulointerstitial injury in DKD patients	[168]
Nacetyl-beta-D-glucosaminidase (NAG)	Proximal tubular cells (urine)	Sensitive and reliable indicator of renal tubular injury, significantly correlated with DKD duration and proteinuria	[169, 170]
Retinol binding protein (RBP)	Hepatocyte (urine)	RBP was significantly associated with DKD progression at any albuminuria levels	[171]
Promising biomarkers			
Biomarkers of inflammation			
Carnosinase-1(CN-1)	Hepatocyte, proximal tubular cells (serum/urine)	Urine CN-1 correlates with eGFR and tubular injury indicator Cystatin-C and RBP. Serum CN-1 is positively correlated with inflammatory markers	[172]
Immune-related gene SERPINA3	Hepatocyte, proximal tubular cells (serum)	Upregulate in DKD renal tubules	[173]
C-X-C motif ligand 16 (CXCL16)	Macrophages, endothelial cells, proximal tubular cells (urine)	Significantly increased when renal function decreased, reflected interstitial fibrosis and tubular atrophy severity, and predicted the renal prognosis of DKD patients	[174]
Endostatin			
Biomarkers of oxidative stress			
P66Shc	Peripheral blood monocytes, proximal tubular cells (serum)	Increased in kidney tissues of DKD patients, and acted as a crucial predictor for renal tubular damage severity	[175, 176]

(Continues)

TABLE 1 | (Continued)

Traditional biomarkers			
Biomarkers	**Source cell & detection**	**Findings/main results**	**References**
8-hydroxydeoxyguanosine (8-OHdG)	Renal tubular cells (serum/urine)	Elevated serum/urinary 8-OHdG levels in diabetics correlate with the severity of DKD	[177–179]
		Patients with higher urinary 8-OHdG excretion exhibited significantly more advanced DKD compared to those with moderate or low levels	[180]
Myo-inositol oxygenase (MIOX)	Renal tubular cells (serum/urine)	Significantly increased in DKD patients, and is positively correlated with UACR, tubulointerstitial lesions and ROS production	[181]
Autophagy-related biomarkers			
Prolyl 4-hydroxylase subunit beta (P4HB)	Hepatocyte, macrophages, renal tubular epithelial cells (−)	The expression of P4HB in renal tubules is related to renal function and is increased in high glucose-induced renal tubular epithelial cells	[182, 183]
Senescence-related biomarkers			
Urinary decoy receptor 2 (uDcR2)	Renal proximal tubular cells (urine)	Positively correlated with UACR, SCr, and IFTA, negatively correlated with eGFR	[184]
		Virtually all tubular DcR2 was co-expressed with senescent markers p16 and p21, and nearly over half of tubular DcR2 was positive for SA-β-gal	[185]
Others			
Urinary extracellular vesicles	Renal tubular epithelial cells, podocytes, endothelial cells (urine)	As proximal tubular cells are injured, a large number of microvesicles are released into the urine, and it can reflect the severity of renal tubular injury	[186, 187]
Urine cathepsin D	Renal tubular epithelial cells, podocytes (urine)	Urine cathepsin D correlated with tubulointerstitial injury, and its expression in tubulointerstitium was linked to an augmented cortical interstitial fractional volume	[188]
Urinary lactate	Renal tubular epithelial cells (urine)	Specifically upregulated in the proximal tubules, and accompanied with enhanced expression of oxidative stress	[189]

Abbreviations: 8-OHdG, 8-hydroxydeoxyguanosine; CN-1, carnosinase-1; CXCL16, C-X-C motif ligand 16; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; IFTA, interstitial fibrosis and tubular atrophy; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; MCP-1, monocyte chemoattractant protein-1; MIOX, myo-inositol oxygenase; NAG, N-acetyl-beta-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; P4HB, prolyl 4-hydroxylase subunit beta; P66Shc, 66-kilodalton Src homology and collagen protein; RBP, retinol binding protein; ROS, reactive oxidative species; SA-β-gal, senescence-associated β-galactosidase; SCr, serum creatinine; UACR, urine albumin–creatinine ratio; uDcR2, urinary decoy receptor 2.

and infiltrating cells during renal inflammation [200]. In a study conducted on subjects with type 1 diabetes, normal blood pressure, and normal urinary albumin excretion rates, the results indicated that MCP-1 was not associated with glomerular lesions. However, in female patients with type 1 diabetes, an increase in urinary MCP-1 concentration prior to the onset of clinical DKD was found to correlate with changes in renal interstitial volume. This suggests that inflammatory processes may be involved in the early pathogenesis of interstitial changes in DKD [168].

3.1.6 | NAG

NAG is a hydrolytic lysosomal enzyme that is mainly present in the proximal convoluted tubules. The measurement of urinary NAG provides a very sensitive and reliable indicator of renal injury [169]. A regression analysis showed that urinary NAG excretion was significantly associated with diabetes mellitus duration and proteinuria [170]. Furthermore, in a cohort of 400 patients with diabetes, the only biomarker significantly associated with the estimated glomerular filtration rate (eGFR) was NAG [171]. Generally, NAG is a useful marker of renal tubular damage under various conditions of renal injury or dysfunction.

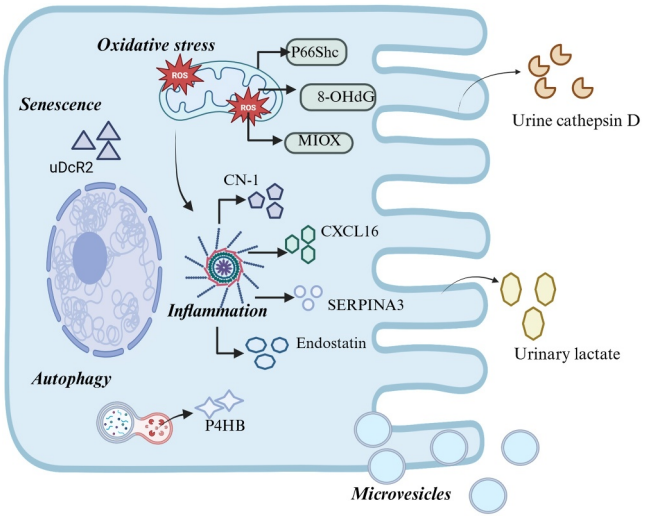

FIGURE 2 | Promising biomarkers of renal tubular injury in DKD. 8-OHdG, 8-hydroxydeoxyguanosine; CN-1, carnosinase-1; CXCL16, C-X-C motif ligand 16; MIOX, myo-inositol oxygenase; P4HB, prolyl 4-hydroxylase subunit beta; P66Shc, 66-kilodalton Src homology and collagen protein; ROS, reactive oxidative species; uDcR2, urinary decoy receptor 2.

3.1.7 | RBP

RBP is a low-molecular-weight protein belonging to the lipid carrier protein family. It is freely filtered in the glomeruli and is almost completely reabsorbed in the proximal renal tubules. In a study of patients with diabetes using a single baseline urinary biomarker test, RBP was significantly associated with DKD progression at any albuminuria level [171]. Elevated urinary RBP may be a useful marker of renal injury in early DKD [201].

3.2 | Promising Biomarkers

To improve the prediction of renal tubular injury in DKD, recent studies have focused on identifying novel biomarkers that are superior to the existing ones. In addition to the above conventional biomarker for tubular injury in DKD, emerging biomarkers associated with inflammation, oxidative stress, autophagy, and senescence have demonstrated significant potential in reflecting tubular injury. These biomarkers can capture the underlying cellular and molecular processes in DKD, allowing earlier, more accurate detection and improving clinical diagnosis and management (Figure 2).

3.2.1 | Biomarkers of Inflammation

Inflammatory biomarkers, including C-reactive protein, IL-6, soluble intercellular adhesion molecule, and secreted phospholipase A2, are associated with mortality and serve as composite endpoints in patients with DKD [202]. Moreover, carnosinase-1 (CN-1) demonstrates a strong correlation with impaired renal function in patients with diabetes. Specifically, in diabetic mice, urinary CN-1 correlates with eGFR and tubular injury indicators cystatin C and RBP, whereas serum CN-1 shows a positive association with inflammatory indicators such as neutrophils and lymphocytes [172]. However, the mechanism underlying this correlation remains unclear, necessitating further studies to clarify the role of CN-1 in diabetes and low-grade inflammation. Additionally, a study comparing differentially expressed genes in the renal tubules of patients with DKD, based on the analysis of three RNA-seq datasets obtained from the Gene Expression Omnibus (GEO) database, revealed that the immune-related gene SERPINA3, an inhibitor of mast cell chymase, was upregulated in the renal tubules of patients with DKD. This upregulation has been linked to renal tubular injury, suggesting that it may serve as a potential inflammatory biomarker for renal tubular damage in DKD [173]. However, further investigation using additional animal models and human samples is necessary to validate this preliminary finding. Additionally, a study measuring urinary inflammatory markers in patients with DKD revealed a high correlation between CXCL16 and endostatin with interstitial fibrosis and tubular atrophy scores, indicating their effectiveness in assessing renal tubular injury. Both CXCL16 and endostatin have been identified as independent risk factors for adverse renal function and play important roles in clinical prognosis. Their detection enables early identification of renal tubular injury in patients with DKD, enhances the understanding of the pathological mechanisms of the disease, particularly regarding inflammation and fibrosis, and provides potential targets for developing new therapeutic strategies to regulate inflammation and reduce renal tubular injury [174]. However, its clinical practicality and predictive value still need to be verified by larger-scale prospective studies.

3.2.2 | Biomarkers of Oxidative Stress

Oxidative stress is a key pathogenic factor in renal tubular injury during DKD progression [29]. P66Shc, functioning as a redox regulatory protein, mediates high glucose-induced mitochondrial fragmentation and pro-apoptotic signal transduction. Numerous studies have identified p66Shc as a crucial predictor for renal tubular injury severity [175, 176]. Significantly elevated expression of both p66Shc and its phosphorylated form, p-p66Shc, have been observed in peripheral blood mononuclear cells and renal tissue from patients with DKD, positively correlating with β-NAG, urine albumin-to-creatinine ratio (UACR), and glucose levels [175]. This implicates p66Shc as a novel biomarker for renal tubular oxidative damage in DKD [175, 176]. Moreover, 8-hydroxydeoxyguanosine (8-OHdG) is an oxidised nucleoside in nuclear and mitochondrial DNA. Substantial evidence suggests that 8-OHdG levels are biomarkers of cellular oxidative stress. Elevated serum or urinary 8-OHdG levels in patients with diabetes correlate with the severity of DKD [177–179]. A prospective longitudinal study indicated that patients with higher urinary 8-OHdG excretion showed significantly more advanced DKD over 5 years, suggesting its potential as a clinical biomarker for predicting DKD in patients with diabetes [180]. Except the above, the expression of myo-inositol oxygenase (MIOX) is significantly elevated in the renal tissue of patients with T2D, and rises progressively with increasing UACR. It is positively associated with renal ROS production and tubulointerstitial lesions, indicating its potential as a novel biomarker for the early detection of tubular injury in DKD [181]. P66Shc, 8-OHdG, and MIOX may serve as novel biomarkers that can provide early indications of tubular damage in the initial stages of DKD. These markers directly reflect oxidative stress levels, which is a key pathological mechanism in DKD progression. Their direct correlation enhances our understanding and monitoring of the pathological processes in DKD, showing significant novelty and advantages over existing markers. However, further studies are required to assess their feasibility and diagnostic value in clinical settings.

3.2.3 | Autophagy-Related Biomarkers

Proximal tubular autophagy is pivotal to the pathogenesis of DKD. Prolyl 4-hydroxylase subunit beta (P4HB) is an autophagy-related gene. Studies have shown that in DKD patients or HK-2 cells, the expression of P4HB in renal tubules is related to renal function is increased in high glucose-induced renal tubular epithelial cells; hence, this is a new autophagy-related biomarker related to renal tubulointerstitial injury in DKD [182, 183]. However, more standardised detection methods and clinical trials need to be developed to detect and validate the potential of P4HB in urine or serum as a promising new biomarker for DKD.

3.2.4 | Senescence-Related Biomarkers

Urinary decoy receptor 2 (uDcR2) is a potential novel biomarker for assessing renal tubulointerstitial injury in DKD, primarily expressed in the proximal renal tubules and mirroring the senescence of renal proximal tubules. In an analysis involving 153 patients with biopsy-proven DKD, elevated uDcR2 levels were found to be positively correlated with UACR, serum creatinine (SCr), and interstitial fibrosis and tubular atrophy (IFTA), while exhibiting a negative correlation with eGFR [185]. Through immunohistochemistry and double staining, virtually all tubular DcR2 was co-expressed with senescent markers p16 and p21, and nearly over half of tubular DcR2 was positive for senescence-associated β-galactosidase (SA-β-gal), mainly in the collagen I- and IV-positive regions of DKD [184]. These findings suggest that uDcR2 not only reflects the senescence of renal tubules but also serves as an early warning indicator for assessing the severity and progression of tubulointerstitial injury. Thus, it holds promise as a potential biomarker for enhancing the diagnosis, evaluation, and treatment of DKD.

3.2.5 | Others

Urinary exosome-like extracellular vesicles may be a new source of biomarkers for the early detection of renal tubular injury in DKD [186]. As proximal tubular cells are injured under high-glucose conditions, a large number of microvesicles are released into the urine, which can reflect the severity of renal tubular injury [187]. This provides a new method for early diagnosis, indicating a potential technological breakthrough. Moreover, urine cathepsin D is associated with a rapid decline in eGFR in T1D and reflects kidney tubulointerstitial injury. Specifically, its expression in the tubulointerstitium is linked to an augmented cortical interstitial fractional volume [188]. Finally, urinary lactate levels are specifically upregulated in the proximal tubules, accompanied by an enhanced expression of oxidative stress [189].

These novel biomarkers show comprehensive advantages in the early detection and monitoring of renal tubular injury, covering multiple mechanisms such as inflammation, oxidative stress, autophagy, and senescence-related, compensating for the shortcomings of existing studies. Unlike traditional biomarkers, these new biomarkers provide a more holistic perspective by integrating information from various pathophysiological pathways, enabling more accurate and timely identification of renal tubular injury in the early stages of DKD. However, their current clinical applicability is limited by the need for specialised assays. Furthermore, the discovery of these novel biomarkers may have important implications not only for diagnosis but also for understanding the underlying mechanisms associated with DKD progression. By elucidating these mechanisms, potential targets for developing targeted therapies can be identified, which could revolutionise the treatment landscape for DKD by offering more personalised and effective treatment options.

While the biomarkers discussed here are capable of early detection of tubular injury associated with DKD. However, it is important to acknowledge a key limitation. Although it is known that these biomarkers (e.g., KIM-1, NGAL) rise before microalbuminuria, the current evidence lacks to define a precise temporal sequence of their appearance. There is a need for large-scale, longitudinal studies that serially assess a panel of these biomarkers from the normoalbuminuric stage onward to determine whether certain markers consistently precede others.

Establishing such a chronology would further refine their clinical utility, allowing for staged intervention based on specific biomarker profiles. Thus, elucidating the exact temporal dynamics of these biomarkers remains an important goal for future research.

4 | Treatments Targeting Tubular Injury

DKD is a severe complication of diabetes, with tubulointerstitial fibrosis being the characteristic pathology underlying diabetic tubulopathy and ESRD. Therefore, there is an imperative need to investigate novel strategies to safeguard against tubulopathy in DKD. This review examines the renoprotective effects of hypoglycemic agents on renal tubules and highlights emerging therapeutic approaches for renal tubular protection, including anti-oxidative stress, anti-inflammatory, anti-cell death, and stem cell therapies (Table 2 and Figure 3).

The tubular injury mechanisms in DKD can help design interventions. Basically, we can categorise the interventions broadly into: (1) Repurposed established drugs with serendipitous tubular benefits; (2) Novel agents in advanced clinical development; and (3) Preclinical experimental strategies targeting emerging pathways.

4.1 | Hypoglycemic and Lipid-Lowering Agents

Blood glucose control improves the primary renal outcomes in patients with DKD and significantly reduces the risk of ESRD [203]. Intensive glucose control mitigates the risk of albuminuria and its progression [204].

Metformin, an oral hypoglycemic agent initially derived from galegine (isoamylene guanidine), is an FDA-approved drug for treating type 2 diabetes mellitus (T2DM), acting via indirect activation of 5′ Adenosine monophosphate-activated Protein Kinase (AMPK) [205]. Experimental studies demonstrate that metformin attenuates DKD by suppressing renal inflammation, oxidative stress, and fibrosis [205–207]. Specifically, AMPK agonist metformin alleviates oxidative stress and renal tubulointerstitial fibrosis by activating mitophagy through a AMPK-Pink1-Parkin pathway and reduce mitochondrial damage and ROS generation, as shown in high fat diet (HFD) and streptozotocin (STZ)-induced type 2 diabetic mice model and HK-2 cells [208]. Meanwhile, preclinical studies in diabetic mice or rats model show that metformin also alleviates oxidative stress and enhances renal autophagy through the AMPK/SIRT1/FoxO1 pathway, while suppressing partial EMT in proximal tubular epithelial cells and reducing tubulointerstitial fibrosis during early stages of DKD [206, 209, 210]. Additionally, metformin alleviates inflammation and fibrosis in DKD by mediating the tenascin-C (TNC)/TLR4/NF-κB/miR-155-5p inflammatory regulatory axis. Specifically, it reduces TNC-mediated activation of TLR4/NF-κB signalling, thereby suppressing downstream miR-155-5p expression and attenuating inflammation (via NF-κB) and fibrosis [211]. Consequently, metformin has the potential to mitigate inflammation and oxidative stress in renal tubular cells, modulate autophagy, and alleviate renal tubulointerstitial injury through multifaceted mechanisms. However, clinical data do not always align with preclinical findings; some clinical investigations have reported either negligible or detrimental effects of metformin on T2DM patients with kidney diseases. Most importantly, metformin-associated lactic acidosis (MALA) poses a significant challenge that limits the use of metformin [205, 212].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (FDA-approved for type 2 diabetes) have been shown to slow down the progression of DKD [213, 214]. Constituting a novel class of antidiabetic drugs, they lower blood glucose by curtailing glucose reabsorption in renal tubules. These inhibitors also regulate renal cell remodelling, thereby delaying DKD advancement [215]. Recent evidence underscores the significance of tubule-glomerular crosstalk in mediating these protective effects. SGLT2 inhibitors reduce glomerular hypertension and hyperfiltration, alleviating stress on the filtration barrier, decreasing albuminuria, and lowering tubular oxygen demand, thus preserving tubular function and GFR. These inhibitors enhance tubuloglomerular feedback by increasing sodium delivery to the macula densa, which, through adenosine, constricts afferent arterioles and protects glomeruli from elevated intraglomerular pressure [216, 217]. Furthermore, beyond their glucose-lowering effects, SGLT2 inhibitors improve tubular oxygenation, metabolism, and alleviate renal inflammation and fibrosis. Specifically, SGLT2 inhibitors significantly reduce inflammation in tubulointerstitium by inhibiting the activation of ICAM-1 and NF-κB pathways [218, 219]. For example, empagliflozin effectively decreases IL-1β secretion and attenuates NLRP3 inflammasome activation in patients with T2D [220], while also inhibiting renal expression of MCP-1, TGF-β, NF-κB, and IL-6 in DKD animal models [221]. Similarly, dapagliflozin directly targets renal tubular cells and macrophages to diminish renal inflammation, unaffected by glucose levels [222]. A clinical trial (NCT00968812) demonstrated that canagliflozin, compared to glimepiride, lowers pro-inflammatory markers such as TNF receptor 1, IL-6, matrix metalloproteinase 7, and fibronectin 1, thereby contributing to decreased inflammation in DKD [223].

Not only that, they can alleviate mitochondrial fission. For instance, empagliflozin has been shown to delay the progression of diabetic renal tubular damage in a diabetic mouse model and HK-2 cells by attenuating high glucose-induced mitochondrial fission, specifically by modulating the AMPK/SP1/PGAM5 pathway [224]. Moreover, empagliflozin can reduce the high glucose-induced cellular apoptosis and improve tubular mitochondrial functions by restoring mitochondrial ROS production, mitochondrial membrane potential, and ATP generation in HK-2 cells, which may be one of the novel mechanisms explaining the benefits demonstrated in EMPA-REG OUTCOME trial [225]. Additionally, SGLT2 inhibitors mediate ferroptosis in tubular cells. In preclinical studies involving DKD mice and HK-2 cells under hyperglycaemic conditions, empagliflozin significantly decreased ferroptotic damage by promoting AMPK-mediated NF-erythroid 2-related factor 2 (NRF2) activation [226]. Overall, SGLT2 inhibitors exhibit multiple mechanisms that contribute to their renoprotective effects in DKD.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are FDA-approved for T2D and have been demonstrated to lower blood glucose, stimulate endogenous insulin secretion, decrease

TABLE 2 | Treatments targeting tubular injury.

Hypoglycemic and lipid-lowering agent			
Agents	**Preclinical/ clinical**	**Key mechanisms of action**	**Reference**
Metformin	Clinical	Alleviate oxidative stress and tubulointerstitial fibrosis by activating mitosis via the AMPK-Pink1-Parkin pathway and reduce mitochondrial damage and ROS generation	[208]
		Alleviates oxidative stress and enhances renal autophagy through the AMPK/SIRT1/FoxO1 pathway, suppresses EMT and reduces tubulointerstitial fibrosis	[206, 209, 210]
		Alleviate inflammation and fibrosis in DKD through mediating TNC/TLR4/NF-kB/miR-155-5p inflammatory regulatory axis	[211]
SGLT2 inhibitors e.g., Empagliflozin Dapagliflozin Canagliflozin	Clinical	SGLT2 inhibitors reduce inflammation in tubulointerstitium by inhibiting the activation of ICAM-1 and NF-κB pathway	[218, 219]
		Empagliflozin decreases IL-1β secretion and attenuate NLRP3 inflammasome activation, inhibits MCP-1, TGF-β, NF-κB, and IL-6 expression	[220, 221]
		Dapagliflozin directly targets renal tubular cells and macrophages to diminish renal inflammation	[222]
		Canagliflozin lowers TNF receptor 1, IL-6, matrix metalloproteinase 7, and fibronectin 1 levels, thereby reducing inflammation in DKD	[223] (NCT00968812)
		Empagliflozin alleviates high glucose-induced mitochondrial fission through modulating AMPK/SP1/PGAM5 pathway	[224]
		Empagliflozin reduces apoptosis and ameliorate tubular mitochondrial damage by restoring excessive ROSs and energy production	[225]
		Empagliflozin decreases ferroptosis damage through the promotion of AMPK-mediated NRF2 activation	[226]
GLP-1R agonists e.g., Liraglutide Semaglutide	Clinical	Liraglutide reduces glycated haemoglobin (HbA1c) levels, lower rates of hypoglycemia, and less weight gain	[229] (NCT01919489)
		Alleviates oxidative stress and promote autophagy in proximal tubules	[230, 231]
DPP-4 inhibitors e.g., Linagliptin Gemigliptin Sitagliptin	Clinical	Linagliptin reduced the risk of renal disease events by 16% (HR, 0.84; 95% CI, 0.72–0.97; $p = 0.02$) in T2D patients	[234]
		Gemigliptin improves the expression of renal tubular injury biomarkers, including urinary NGAL/Cr and L-FABP/Cr	[235] (NCT04705506)
		Sitagliptin alleviate mitochondrial dysfunction of renal tubules by modulating the SDF-1α/CXCR4/STAT3 pathway	[236]

(Continues)

TABLE 2 | (Continued)

Hypoglycemic and lipid-lowering agent			
Agents	**Preclinical/ clinical**	**Key mechanisms of action**	**Reference**
Other agents e.g., Probucol Berberine	Preclinical	Probucol alleviates renal oxidative damage and fibrosis in diabetic mice	[237]
		Berberine not only alleviates oxidative stress and inflammatory indicators but also impedes excessive lipid accumulation and fatty acid oxidation	[238]
The antioxidative stress therapies			
HIF-PHI e.g., Roxadustat (FG-4592) Enarodustat (JTZ-951)	Preclinical	Roxadustat alleviates renal anaemia in CKD patients by enhancing erythropoiesis	[241] (NCT02652819)
		Enarodustat can help counteract the metabolic changes in early diabetic kidney and alleviate oxidative stress in renal tissue	[244] (Japic CTI-183870)
Melatonin	Preclinical	Orchestrate mitochondrial homoeostasis and enhance antioxidative defenses via mediating AMPK-PINK1-macrophage axis	[245]
		Impede STAT3 phosphorylation, lower the levels of senescence proteins p53 and p21, and attenuate apoptotic proteins	[246]
Bardoxolone	Preclinical	Bardoxolone ameliorates tubular injury by improving redox balance, reducing mitochondrial ROS, and suppressing pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1, as well as fibrosis	[252–255]
		Bardoxolone significantly increased eGFR in patients with advanced DKD	[256] (NCT01351675)
		Improve renal function without severe adverse effects in early-stage DKD	[257]
NOX inhibitors e.g., GKT136901 GKT137831 Chloroquine and amodiaquine	Preclinical	GKT136901 attenuates ERK1/2 phosphorylation and oxidative damage in mouse models of Type 2 diabetes	[258]
		GKT137831 suppresses ROS generation, and inhibits pro-inflammatory and pro-fibrotic indicators	[259–261]
		Chloroquine and amodiaquine inhibit mitochondrial Nox4 activation and reduce ER stress in proximal tubular epithelial cells	[263]
Other drugs e.g., MitoQ Alpha lipoamide Formononetin	Preclinical	MitoQ reduces excessive mitochondrial ROS and restores mitophagy in patients with DKD or animal models by inhibiting NLRP3 inflammasome activation and IL-1β maturation	[13, 41]
		Alpha lipoamide improves mitochondrial dysfunction by regulating the CDX2/CFTR/β-catenin signalling axis	[264]
		Formononetin reduces mitochondrial fragmentation, and protects against renal tubular injury via regulating Sirt1/PGC-1α pathway	[265]

(Continues)

TABLE 2 | (Continued)

Hypoglycemic and lipid-lowering agent			
Agents	**Preclinical/ clinical**	**Key mechanisms of action**	**Reference**
Targeting ER stress			
Adiponectin receptor agonist e.g., AdipoRon	Preclinical	Alleviate proximal tubular injury by inhibiting ER stress mediated by AdipoR1/p-AMPK pathway	[266]
Natural polyphenolic compound e.g., (+)-Catechin	Preclinical	Inhibit ER stress by down-regulating GRP78, CHOP, ATF6 and XBP1 in diabetic mice and HK-2 cells	[267]
MAM resident protein e.g., PACS-2	Preclinical	Alleviate mitochondria-associated endoplasmic reticulum membrane disruption, ER stress, and mitochondrial dysfunction	[268, 269]
Anti-inflammation therapeutics			
IL inhibitors e.g., Fc-gp130	Preclinical	Reduce immune cell infiltration and pro-fibrotic factor expression in diabetic mouse models	[270]
Monoclonal antibody neutralising Il-1β e.g., Canakinumab	Preclinical	Reduce CRP, IL-6, fibrinogen expression and inflammatory response	[271] (NCT00900146)
JAK1/2 inhibitor e.g., Baricitinib	Preclinical	Effectively reduce inflammatory molecules production	[272] (NCT01683409)
Anti-inflammatory cytokine e.g., CTRP9	Preclinical	Inhibit glycogen accumulation and reduce oxidative stress in diabetic db/db mice, thereby ameliorating tubular apoptosis and fibrosis	[274]
Inhibition of NLRP3 inflammasome e.g., CY-09	Preclinical	CY-09 binds to the ATP-binding motif of NLRP3 NACHT domain and inhibit NLRP3 inflammasome assembly and activation	[275]
CAY10603		CAY10603 reduces macrophage infiltration, inhibits NLRP3 inflammasome activation in tubular cells, and effectively alleviate renal tubular injury and interstitial fibrosis in DKD	[276]
TLR4 inhibition e.g., CRX-526	Preclinical	Diminish HMGN1expression, subsequently reduce KIM-1, MCP-1 and macrophage infiltration, thereby mitigating renal inflammation activation and tubular epithelial cell injury	[67]
Polysaccharides from Grifola frondosa		Alleviate renal macrophage infiltration and tubulointerstitial injury by suppressing NF-κB and TGF-β	[277]

(Continues)

TABLE 2 | (Continued)

Hypoglycemic and lipid-lowering agent			
Agents	**Preclinical/ clinical**	**Key mechanisms of action**	**Reference**
		Alleviate the inflammatory response and apoptosis of renal tubular epithelial cells by blocking the TLR4/NF-κB pathway	[278]
T cell co-stimulation modulators e.g., Belatacept Abatacept (CTLA4-Ig)	Preclinical	T cell co-stimulation modulators can effectively alleviate immune-mediated inflammatory responses and reduce tissue damage by blocking the key co-stimulation pathways for T-cell activation (B7/CD28 and CD40/CD40L)	[279]
		Abatacept (CTLA4-Ig) restores podocyte structure/function under hyperglycemia and attenuates inflammation, potentially delaying proteinuria onset	[280, 281]
Others e.g., MiR-20a Wogonin	Preclinical	Inhibit inflammatory response and cell apoptosis by mediating CXCL6 and JAK/STAT3 pathway	[287]
		Mitigate renal tubular epithelial cell injury and interstitial fibrosis by regulating autophagy and inflammation	[288]
Inhibition of the RAAS system			
RAAS antagonists	Clinical	Reduce inflammation and tubulointerstitial fibrosis in DKD by inhibiting the expression of NF-kB and MCP-1 genes, as well as macrophage infiltration	[289]
Mineralocorticoid receptor antagonists e.g., Finerenone	Clinical	Restore mitosis as well as reduce oxidative stress, mitochondrial fragmentation, and apoptosis	[292]
		Reduce UACR and cardiovascular events of DKD patients, improving DKD prognosis	[293–297] (NCT02545049) (NCT02540993)
Therapy to regulate programed cell death			
TXNIP inhibitor e.g., Verapamil	Preclinical	Suppress apoptosis and fibrosis in proximal tubular epithelial cells	[298]
Astragalosides IV	Preclinical	Reduce the expression of apoptosis-related proteins (cleaved caspase-3, Bax/Bcl-2 ratio) and ER stress-related proteins, alleviating renal tubular epithelial cells apoptosis in type 2 DKD rat	[299]
		Inhibit ferroptosis in proximal tubules via down-regulating the HIF-1α/HMOX1 pathway	[306]

(Continues)

TABLE 2 | (Continued)

Hypoglycemic and lipid-lowering agent			
Agents	**Preclinical/ clinical**	**Key mechanisms of action**	**Reference**
RIPK1 inhibitors e.g., Necrostatin-1 RIPA-56	Preclinical	Reduce oxidative stress and ultimately inhibit tubular necroptosis by downregulating the RIPK1/RIPK3/MLKL pathway	[142]
		Reduce necroinflammation, lipid droplet accumulation, and necroptosis pathway activation	[141]
Hirudin	Preclinical	Regulate GSDMD-mediated pyroptosis in proximal tubules by inhibiting interferon regulatory factor 2	[303]
Vitamin D receptor agonist e.g., Paricalcitol	Preclinical	Reduces tubular ferroptosis by upregulating the Nrf2/HO-1 signalling pathway	[304]
		Enhance Klotho via suppressing P53, then lessen ROS stress and lipid peroxidation accumulation, ultimately reduce ferroptosis	[305]
Quercetin	Preclinical	Hinder ferroptosis by activating the Nrf2/HO-1 signalling pathway	[147]
Stem cell therapies			
Mesenchymal stem cells e.g., Bone marrow-derived mesenchymal stem cells Umbilical cord mesenchymal stem cells	Preclinical	Reduced ROS production, ER stress, inflammation, and even P53 levels, decreasing tubular apoptosis in preclinical models	[311, 312]
		MSCs treatment significantly reduced the rate of eGFR decline in patients within 18 months, possibly slowing down the deterioration of renal function	[313]
Others			
Klotho e.g., Sulodexide	Preclinical	Suppress TGF-β1-mediated EMT, consequently mitigating renal tubulointerstitial fibrosis	[323–327]
		Reduce oxidative stress and inflammation	[87, 328, 329]
		Ameliorate oxidative stress-induced renal tubulointerstitial injury by upregulating klotho expression	[332]
RAAS blocker e.g., Valsartan	Clinical	Enhance soluble klotho levels, conferring renal protection in DKD individuals	[333] (NCT00171561) (NCT00001715)
Endothelin A receptor antagonists e.g., Atrasentan	Preclinical	Attenuate albuminuria by maintaining the integrity of the glomerular endothelial glycocalyx structure	[336, 337]
		Downregulate miR-199b-5p, augmenting klotho levels and mitigating tubular damage	[338, 339]
The inhibition of TGF-β e.g., Astragaloside I (ASI)	Preclinical	Reduce renal fibrosis markers, and inhibit the TGF-β1/Smad2/3 pathway. Downregulate HDAC3 expression, upregulate klotho expression and enhance klotho release	[343]

(Continues)

TABLE 2 | (Continued)

Hypoglycemic and lipid-lowering agent			
Agents	**Preclinical/clinical**	**Key mechanisms of action**	**Reference**
Traditional Chinese medicine (TCM) e.g., Qidan Tangshen Granule	Preclinical	Inhibit inflammatory cytokines and various growth factor expressions, reduce blood glucose, and has significant effects on insulin resistance, lipid metabolism, and improve renal function Reduce HbA1c and UACR levels, improve renal function, and exerted antioxidative effects in DKD patients	[344] [347]

Abbreviations: 3-NT, 3-nitrotyrosine; 8-OHdG, 8-hydroxydeoxyguanosine; AdipoR1, adiponectin receptor 1; AMPK, adenosine monophosphate activated protein kinase; ASI, Astragaloside I; ATF6, activating transcription factor 6; CDX2, caudal-type homoeobox transcription factor 2; CFTR, cystic fibrosis transmembrane conductance regulator; CHOP, C/EBP homologous protein; CTRP9, tumour necrosis factor-related protein-9; CXCL, C-X-C motif chemokine ligand; CXCR4, C-X-C chemokine receptor type 4; DKD, diabetic kidney disease; DPP-4, Dipeptidyl peptidase-4; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FoxO1, forkhead box protein O1; GLP-1R, glucagon-like peptide-1 receptor; GRP78, glucose-regulated protein 78; GSDMD, gasdermin D; HbA1c, glycosylated haemoglobin; HDAC6, histone deacetylase 6; HIF, hypoxia-inducible factor; HIF-1α, hypoxia-inducible factor 1a; HMOX1, heme oxygenase 1; HO-1, hemeoxygenase-1; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; JAK, janus kinase; MAM, mitochondria-associated endoplasmic reticulum membrane; MCP-1, monocyte chemoattractant protein-1; MLKL, mixed lineage kinase domain-like; NF-κB, nuclear factor-kappa-B; NLRP3, NOD-like receptor protein 3; NOX, nicotinamide adenine dinucleotide phosphate oxidases; Nrf2, nuclear factor erythroid-2 related factor 2; PACS-2, phosphofurin acidic cluster sorting protein 2; p-AMPK, phosphorylated AMP-activated protein kinase; PGAM5, phosphoglycerate mutase family member 5; PGC-1α, peroxisome proliferator activated receptor gamma coactivator 1alpha; PHI, prolyl hydroxylase inhibitor; PINK1, PTEN-induced putative kinase 1; RAAS, renin-angiotensin-aldosterone system; RAAS, renin-angiotensin-aldosterone system; RIPK1, receptor-interacting protein kinase 1; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1; SGLT2, sodium-glucose co-transporter 2; SIRT1, Sirtuin 1; SIRT1, sirtuin-1; SP1, specificityprotein1; STAT3, signal transducer and activator of transcription 3; TCM, Traditional Chinese medicine; TGF-β, transforming growth factor-beta; TLR, toll-like receptor; TNC, tenascin-C; TNF, tumour necrosis factor; TXNIP, thioredoxin-interacting protein; UACR, urine albumin–creatinine ratio; XBP1, X-box binding protein 1.

plasma glucagon levels, inhibit gastric emptying, reduce food intake and reduce glucagon release [227]. Additionally, GLP-1 receptors are extensively present in proximal tubules both in vitro and in vivo, with their activation notably mitigating renal tubular injury in DKD mouse models [228]. A clinical trial (NCT01919489) comparing liraglutide, a GLP-1 analogue, with insulin glargine therapy revealed that liraglutide offers superior benefits, including comparable reduction in glycated haemoglobin (HbA1c) levels, lower rates of hypoglycemia, and less weight gain, although it is associated with a higher incidence of gastrointestinal adverse events in T2D patients [229]. Importantly, preclinical studies indicate that GLP-1 drugs such as liraglutide not only regulate blood glucose but also promote autophagy and reduce oxidative stress, thereby providing renal protective effects in a DKD rat model. The underlying mechanism involves the GLP-1R-AMPK-mTOR-autophagy-ROS signalling axis, and reversing the nuclear transport of the antioxidant factor NRF2 [230, 231]. Furthermore, GLP-1RA also protects renal tubules in diabetes by suppressing ferroptosis through enhancing AMPK-fatty acid metabolic signalling [232]. These findings suggest that GLP-1RAs are expected to serve as a novel therapeutic strategy for the prevention and treatment of DKD, with a mechanism independent of blood glucose control.

Dipeptidyl peptidase-4 (*DPP-4*) *inhibitors* are a class of anti-hyperglycaemic drugs that effectively lower postprandial glucose levels by preserving GLP-1 activity and promoting the natriuretic effect of distal renal tubules [233]. These inhibitors not only improve glycaemic control but also safeguard the kidney under high glucose conditions. A clinical study assessing the renal safety of DPP-4 inhibitors revealed that linagliptin treatment reduced the risk of renal disease events by 16% (HR, 0.84; 95% CI, 0.72–0.97; $p = 0.02$) in T2D patients, and did not increase the occurrence of kidney-related adverse events [234]. Furthermore, a clinical trial (NCT04705506) involving 201 DKD patients demonstrated that gemigliptin significantly improved the expression of renal tubular injury biomarkers, including urinary NGAL/Cr and L-FABP/Cr, supporting its potential for mitigating tubular injury [235]. In human proximal tubular cells (HK-2) and diabetic mice, studies have found that the DPP4 inhibitor sitagliptin alleviates mitochondrial dysfunction of renal tubules by modulating the SDF-1α/CXCR4/STAT3 pathway [236]. While DPP-4 inhibitors are not yet FDA-approved for DKD-specific indications, their renal benefits warrant further validation in dedicated DKD trials.

Other therapies, such as lipid-lowering medications, are effective in mitigating tubular damage in DKD supported by preclinical evidence. Probucol, an antihyperlipidemic drug and potent antioxidant, has been shown to suppress p66Shc expression via the AMPK/SIRT1/AcH3 pathway, and reduce renal oxidative damage and fibrosis in diabetic mice, and ultimately amelioraings renal damage in DKD [237]. Another drug, berberine, acts as a primary bioactive component in Coptis Chinensis Franch, commonly used for diabetes therapy, and not only alleviates oxidative stress and inflammatory indicators but also impedes excessive lipid accumulation and fatty acid oxidation in animal models of DKD [238]. Thus, berberine may be employed to treat tubular damage in DKD.

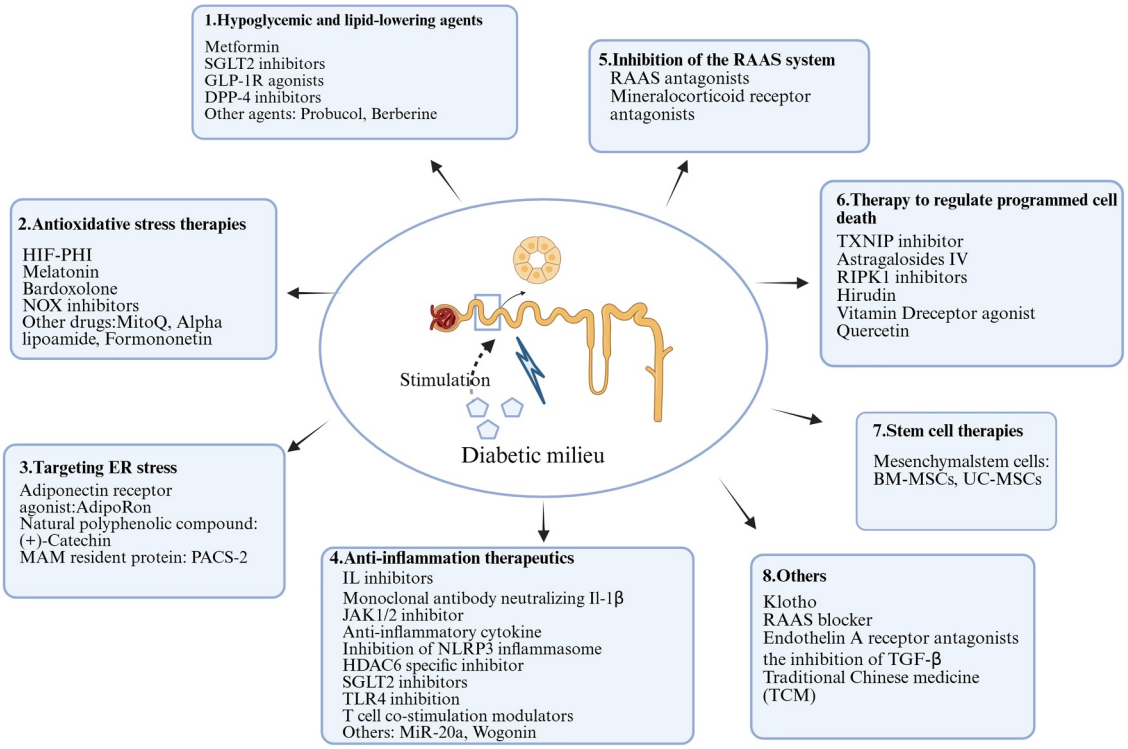

FIGURE 3 | Treatments targeting tubular injury in DKD. BM-MSCs, bone marrow-derived mesenchymal stem cells; DPP-4, Dipeptidyl peptidase-4; ER, endoplasmic reticulum; GLP-1R, glucagon-like peptide-1 receptor; HDAC6, histone deacetylase 6; HIF, hypoxia-inducible factor; IL, interleukin; JAK, janus kinase; NLRP3, NOD-like receptor protein 3; NOX, nicotinamide adenine dinucleotide phosphate oxidases; PACS-2, phosphofurin acidic cluster sorting protein 2; PHI, prolyl hydroxylase inhibitor; RAAS, renin-angiotensin-aldosterone system; RIPK1, receptor-interacting protein kinase 1; SGLT2, sodium-glucose co-transporter 2; TCM, Traditional Chinese medicine; TGF-β, transforming growth factor-beta; TLR, toll-like receptor; TXNIP, thioredoxin-interacting protein; UC-MSCs, Umbilical cord mesenchymal stem cells.

4.2 | Anti-Oxidative Stress Therapies

In addition to controlling blood glucose levels, renal tubular injury is correlated with increased oxidative stress levels. Consequently, therapies targeting the suppression of oxidative stress are promising for the management of DKD.

HIF-1, a heterodimer, exerts protective effects via modulation of mitochondrial dynamics during DKD progression [239]. HIF-1α-Parkin/PINK1-mediated mitophagy can reduce tubular apoptosis and ROS production [240]. Prolyl hydroxylase inhibitors (PHIs) are a class of drugs that act as a HIF-1α stabilizer. Clinical trials have shown that PHIs can enhance HIF activity, which has the potential to alleviate renal hypoxia induced by diabetes [241, 242]. Similarly, Roxadustat (FG-4592), an oral HIF-PHI, promotes erythropoiesis and enhances iron metabolism. A Phase 3 trial (NCT02652819) demonstrated Roxadustat's efficacy in alleviating renal anaemia in CKD patients by enhancing erythropoiesis [241]. However, its direct renal protective effects in DKD remain under investigation. A randomized controlled trial demonstrated that this drug class may decelerate renal fibrosis progress by decreasing ferroptosis via Akt/GSK-3β-mediated Nrf2 activation [243]. Enarodustat (JTZ-951) is another HIF stabilizer. Transcriptome analysis has revealed that enarodustat can help counteract metabolic changes in early diabetic kidneys and alleviate oxidative stress in renal tissues (Japic CTI-183870) [244].

Melatonin, a hormone associated with circadian rhythms and a potent antioxidant, is a tryptophan derivative present in all organisms. Preclinical studies in diabetic mice model or HK-2 cells show that it can orchestrate mitochondrial homoeostasis and enhance anti-oxidative defenses by mediating the AMPK/PINK1/macrophage axis [245]. Moreover, melatonin also impedes STAT3 phosphorylation, lowers the levels of the senescence proteins p53 and p21, and attenuates apoptotic proteins, collectively contributing to its protective role in DKD [246]. Agomelatine, with its selective melatonin receptor agonism, potently reduces oxidative stress and inflammation in STZ-induced DKD [247].

Bardoxolone methyl, a synthetic triterpenoid and potent activator of the nuclear factor erythroid 2-related factor 2 (Nrf2), has emerged as a novel therapeutic agent targeting oxidative stress in DKD [30, 84, 248, 249]. Nrf2 serves as a master regulator of antioxidant response elements (ARE) and is central to cellular redox balance, orchestrating glutathione, thioredoxin, and NADPH metabolism while controlling mitochondrial and NADPH oxidase-derived ROS generation, which collectively mitigate oxidative damage [250, 251]. Preclinical studies demonstrate that in a murine model of DKD, Bardoxolone ameliorates tubular injury by improving redox balance, reducing mitochondrial ROS, and suppressing pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1, as well as fibrosis [252–255]. Clinical trials have demonstrated that Bardoxolone methyl can

significantly improve renal function in patients with DKD. The BEACON trial (NCT01351675) revealed that Bardoxolone significantly increased eGFR in patients with advanced DKD; however, safety concerns regarding fluid overload and cardiovascular events led to trial termination [256]. Subsequent trials, such as TSUBAKI, have focused on optimizing dosing regimens and patient selection, demonstrating promising improvements in renal function without severe adverse effects in early-stage DKD [257]. In summary, these findings underscore bardoxolone's potential to delay DKD progression by enhancing endogenous antioxidant defenses. Future studies should prioritise the optimisation of dosing regimens and the assurance of long-term safety to fully harness its potential benefits.

The nicotinamide adenine dinucleotide phosphate oxidases (NOX) inhibitors exhibit a capacity to alleviate oxidative stress during DKD development. Specifically, GKT136901 is a Nox1/4 inhibitor that can protect against DKD by attenuating ERK1/2 phosphorylation and oxidative damage in mouse models of T2D [258]. Similarly, another inhibitor of Nox1/4, GKT137831, also suppresses ROS generation and inhibits pro-inflammatory and pro-fibrotic indicators, conferring renal protection in diabetes models [259–261]. Furthermore, APX-115, a novel pan-NOX-inhibitor, demonstrates potential for equal or superior protection against DKD relative to targeted Nox1/Nox4 inhibitors [262]. Beyond these, preclinical studies showed chloroquine and amodiaquine inhibit mitochondrial Nox4 activation and reduce ER stress in PTECs, collectively demonstrating therapeutic potential to alleviate renal tubular injury in DKD [263].

Other drugs that have anti-oxidative stress effects and improve mitochondrial function are also in the preclinical research stage. For instance, MitoQ, a targeted antioxidant for mitochondria, potentially reduces excessive mitochondrial ROS and restores mitophagy in patients with DKD or animal models [13] by inhibiting NLRP3 inflammasome activation and IL-1β maturation [41]. Alpha lipoamide (ALM) improves mitochondrial dysfunction in DKD by regulating the CDX2/CFTR/β-catenin signalling axis [264]. Additionally, formononetin (FMN) is a new drug isolated from astragalus membranaceus that reduces mitochondrial fragmentation and protects against renal tubular injury by regulating the SIRT1/PGC-1α pathway [265]. Notably, none of the above-mentioned drugs have been approved by the FDA for the treatment of DKD, and their efficacy and safety require further clinical research validation.

4.3 | Targeting ER Stress

ER stress is associated with the progression of renal tubular injury in DKD. Therefore, targeted ER stress therapy has emerged as a potential strategy for mitigating renal tubular injury in DKD. AdipoRon, a newly developed adiponectin receptor agonist, alleviates proximal tubular injury in diabetic mice by inhibiting ER stress mediated by the AdipoR1/p-AMPK pathway [266]. (+)-Catechin is a natural polyphenolic compound found in green tea that possesses some health benefits. Preclinical studies found that on diabetic mice and HK-2 cells, it can inhibit ER stress by down-regulating GRP78, PEAK, CHOP, ATF6, and XBP1, thereby significantly improving renal tubular injury in DKD [267]. PACS-2, a critical regulator of mitochondria-associated ER membrane formation, demonstrates significantly reduced expression in the renal tubules of patients with DKD, correlating inversely with the severity of tubulointerstitial lesions [268]. Research reveals that the absence of PACS-2 in proximal tubules facilitates mitochondria-associated ER membrane disruption, ER stress, and mitochondrial dysfunction, culminating in tubular injury and interstitial fibrosis [268, 269]. Preclinical data underscore ER stress as a promising target for DKD, but clinical translation requires development of druggable candidates and validation in human trials.

4.4 | Anti-Inflammation Therapeutics

Inflammation plays a crucial role in renal tubular injury during DKD progression. Therefore, drugs targeting inflammatory pathways have important therapeutic implications for renal protection.

4.4.1 | IL Inhibitors

Interleukins (ILs), a family of pro-inflammatory cytokines, are important mediators of immune responses and tissue injury in DKD. IL inhibitors exert protective effects against DKD. Fc-gp130, a specific inhibitor of IL-6, reduces renal immune cell infiltration and pro-fibrotic factor expression in diabetic mouse models [270]. In a double-blind, multinational phase IIb trial (NCT00900146) of 556 men and women with well-controlled diabetes mellitus and high cardiovascular risk, Canakinumab, a human monoclonal antibody neutralising IL-1β, significantly reduces CRP, IL-6, fibrinogen expression, and inflammatory response [271]. Additionally, baricitinib, as a JAK1/2 inhibitor, can effectively reduce inflammatory molecule production including urine CXCL10, urine CCL2, plasma soluble TNF receptors 1 and 2, ICAM1, and serum amyloid A in patients with DKD (NCT01683409) [272]. However, whether it can reduce the progression of DKD needs further study.

4.4.2 | Inhibition of the NLRP3 Inflammasome

NLR family members assemble inflammasomes that induce the maturation and secretion of caspase-1 and pro-inflammatory cytokines (IL-1β, IL-18), amplifying inflammatory cascades [61]. Consequently, inhibition of the NLRP3 inflammasome has emerged as a promising novel strategy for treating numerous inflammatory diseases [273]. TNF-related protein-9 (CTRP9), an anti-inflammatory and antioxidant cytokine, can inhibit glycogen accumulation and reduce oxidative stress in renal tubules in diabetic db/db mice, thereby ameliorating tubular apoptosis and fibrosis [274]. CY-09, a small-molecule inhibitor of NLRP3, directly binds to the ATP-binding motif of NLRP3 NACHT domain and inhibits NLRP3 inflammasome assembly and activation, demonstrating significant therapeutic potential in DKD [275]. Additionally, CAY10603 is a specific inhibitor of histone deacetylase 6 (HDAC6), which can reduce macrophage infiltration, inhibit NLRP3 inflammasome activation in tubular cells, and effectively alleviate renal tubular injury and

interstitial fibrosis in both early- and late-onset diabetic mice, exhibiting therapeutic potential for DKD [276]. Consequently, inhibiting inflammasomes holds promise as a therapeutic approach for DKD. However, compounds that directly and specifically target NLRP3 and have renoprotective potential in patients with DKD remain unexplored in clinical trials.

4.4.3 | Inhibition of TLR2/TLR4

As discussed earlier, TLR2/TLR4 activation by DAMPs such as HMGB1 and HMGN1 drives sterile inflammation and tubular injury in DKD. Targeting these receptors offers a promising therapeutic approach. Specifically, TLR4 inhibition diminished HMGN1 expression, subsequently reducing KIM-1, MCP-1, and macrophage infiltration, thereby mitigating renal inflammation and TEC injury [67], offering a prospective therapeutic approach. CRX-526, a TLR4 antagonist, alleviates renal macrophage infiltration and tubulointerstitial injury in diabetic mice with advanced DKD through suppression of NF-κB and TGF-β [277]. Furthermore, preclinical studies have shown that Polysaccharides from Grifola frondosa (PGF) can reduce the high glucose-induced inflammatory response and apoptosis of renal tubular epithelial cells in STZ-induced DKD mice, mechanistically alleviating the development of DKD by inhibiting the expression of TLR4 and blocking the TLR4/NF-κB signalling pathway [278].

4.4.4 | T Cell Co-Stimulation Modulators

In addition to the aforementioned anti-inflammatory strategies, T cell co-stimulation modulators have also been proven to potentially exert anti-inflammatory effects in DKD. It has been verified in numerous organ transplantation experimental models that T cell co-stimulation modulators can effectively alleviate immune-mediated inflammatory responses, prevent transplant rejection, and reduce tissue damage by blocking the key co-stimulation pathways for T-cell activation (B7/CD28 and CD40/CD40L) [279]. Notably, belatacept, a cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (CTLA4-Ig) fusion protein, has demonstrated the potential to prevent acute rejection and improve renal function in multiple animal and clinical models [279].

However, the expression and role of B7-1 in DKD remain controversial. While early studies implicated B7-1 in glomerular filtration barrier disruption and proposed it as a therapeutic target [280, 281], subsequent research failed to consistently detect significant B7-1 expression in human or experimental DKD models [282–284]. Nevertheless, preclinical and clinical data suggest that abatacept (CTLA4-Ig), a B7-1-targeted co-stimulation modulator, may have potential in alleviating proteinuria and renal injury in DKD [280, 284, 285]. Mechanistically, animal models and in vitro studies have shown that abatacept restores podocyte structure and function under hyperglycemia and attenuates inflammation, potentially delaying proteinuria onset [280, 281]. Despite unresolved controversies regarding B7-1's pathophysiological relevance and insufficient evidence from large-scale trials, abatacept's immunomodulatory specificity positions it as a promising candidate for DKD therapy.

4.4.5 | Others

An alternative approach to targeting inflammatory therapies in DKD targets miRNAs [286]. MiR-20a is an upstream regulatory miRNA of CXCL6, which inhibits inflammatory responses and cell apoptosis in DKD by mediating the CXCL6 and JAK/STAT3 pathway [287]. Furthermore, Wogonin, a flavonoid compound with anti-inflammatory, anti-oxidative, and antifibrotic properties as well as other pharmacological effects, mitigates renal TEC injury and interstitial fibrosis by regulating autophagy and inflammation via the PI3K/Akt/NF-κB pathway [288].

4.5 | Inhibition of the RAAS System

4.5.1 | RAAS Antagonists

RAAS antagonists can reduce proteinuria and tubulointerstitial fibrosis in DKD by inhibiting the expression of NF-kB and MCP-1 genes as well as macrophage infiltration, thereby exerting their anti-inflammatory effect [289]. Multiple clinical studies have shown that drugs that block the RAAS are the foundation of the treatment for DKD, and they can slow down the progression of the disease. This effect is especially pronounced in patients with proteinuria exceeding 300 mg per day [290].

4.5.2 | Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid receptor (MR) activation plays an important role in DKD pathogenesis. MRAs induce diverse conformational alterations in MRs, which inhibit aldosterone binding and subsequently suppress downstream signalling, thereby inhibiting the RAAS [291]. Finerenone (FIN) is a novel nonsteroidal MRA FDA-approved for DKD that reduces renal inflammation and fibrosis in DKD. In vivo and in vitro, FIN treatment restored mitosis and reduced oxidative stress, mitochondrial fragmentation, and apoptosis by regulating the PI3K/Akt/eNOS signalling pathway, alleviating renal tubular damage during DKD treatment [292]. Phase 3 clinical trials (FIDELIO-DKD [NCT02540993], FIGARO-DKD [NCT02545049]) confirm FIN significantly lowers UACR, improves DKD prognosis [293–295], and reduces cardiovascular events in patients with DKD [296, 297].

4.6 | Therapy to Regulate Programmed Cell Death

Programmed cell death (PCD) involves apoptosis, autophagy, pyroptosis, and ferroptosis, and is a naturally occurring process of cellular self-destruction. A growing number of studies have reported that multiform PCDs occur in the proximal tubules during DKD progression. Recently, new therapeutic strategies have been studied.

Thioredoxin-interacting protein (TXNIP), an endogenous inhibitor of thioredoxin, promotes DKD progression. Verapamil, which functions as a calcium channel blocker and a confirmed TXNIP inhibitor, has been shown to suppress apoptosis and fibrosis in PTECs of diabetic kidneys, indicating its potential as a therapeutic agent for DKD prevention and treatment [298].

Astragaloside IV (AS-IV), a bioactive saponin from Astragalus membranaceus, reduces the expression of apoptosis-related proteins (cleaved caspase-3, Bax/Bcl-2 ratio) and ER stress-related proteins, alleviating renal tubular epithelial cells apoptosis in type 2 DKD rats and providing mechanistic insights for DKD therapy [299].

Necrostatin-1 (Nec-1), a key inhibitor of RIPK1 in the necroptosis pathway, can effectively downregulate the RIPK1/RIPK3/MLKL pathway, thereby reducing oxidative stress and ultimately inhibiting tubular necroptosis in DKD [142]. Moreover, the RIPK1 inhibitor RIPA-56 can reduce necroinflammation, lipid droplet accumulation, and necroptosis pathway activation, effectively alleviating renal injury in db/db mice [141]. Therefore, RIPK1 may be a therapeutic target for the treatment of DKD.

Hirudin, a natural component of the salivary glands of blood-sucking leeches, has thrombolytic and anticoagulant activities. Historically, hirudin has been used to accelerate blood circulation in traditional Chinese medicine (TCM), and preclinical studies has revealed its potential for treating DKD [300–302]. By inhibiting interferon regulatory factor 2, hirudin regulates GSDMD-mediated pyroptosis in the proximal tubules during DKD [303].

Ferroptosis-triggered renal tubular injury has also been reported to occur during the development of DKD. On one hand, vitamin D receptor (VDR) activation upregulates the Nrf2/HO-1 signalling pathway, thereby inhibiting ferroptosis in PTECs. The VDR agonist, paricalcitol, reduces tubular ferroptosis and shields against renal dysfunction in DKD [304]. In addition, vitamin D enhances Klotho by suppressing P53, then lessening ROS stress and lipid peroxidation accumulation, ultimately curbing hyperglycemia-induced ferroptosis during DKD progression [305]. On the other hand, quercetin increases Nrf2 and HO-1 levels, subsequently activating the Nrf2/HO-1 signalling pathway to hinder ferroptosis in DKD mice and high glucose-induced renal TECs [147]. Moreover, AS-IV can also inhibit ferroptosis in proximal tubules by down-regulating the HIF-1α/HMOX1 pathway [306], suggesting that it may be a promising strategy for DKD treatment.

Current strategies targeting programmed cell death pathways remain preclinical, offering novel therapeutic perspectives for DKD. While these approaches expand treatment options, clinical translation requires validation in human trials.

4.7 | Stem Cell Therapies

Stem cell are multipotent, self-renewing cells with tissue-repair capacities. With the continuous development of technology, stem cell-based therapy may become a viable therapeutic option for the treatment of DKD. Mesenchymal stem cells (MSCs) represent an innovative therapeutic strategy; their advantage is that they have multiple therapeutic effects in DKD [307–309]. MSCs can significantly lower blood sugar, serum creatinine, blood urea nitrogen, and urinary protein levels. In addition, MSCs alleviate kidney fibrosis [310]. Therefore, MSCs constitute a promising therapeutic strategy for alleviating DKD. A study revealed that treatment with bone marrow-derived mesenchymal stem cells (BM-MSCs) reduced ER stress, inflammation, and even P53 levels, decreasing tubular apoptosis in preclinical models [311]. Specifically, these cells facilitate the transfer of their mitochondria to damaged renal tubular cells, thereby inhibiting apoptosis by augmenting the expression of mitochondrial superoxide dismutase 2 and Bcl-2, while suppressing ROS production [312]. However, clinical translation remains limited. A Phase 1b/2a trial (NCT02585622) in 16 DKD patients reported MSCs treatment significantly reduced the rate of eGFR decline in patients within 18 months, possibly slowing down the deterioration of renal function and demonstrating good safety and tolerability [313], but larger clinical trials are needed to confirm these findings. As a novel and effective treatment strategy for DKD, umbilical cord mesenchymal stem cells (UC-MSCs) can significantly improve 24-h urinary protein levels, creatinine clearance, serum creatinine, and urea nitrogen of DKD rats. UC-MSCs were also shown to markedly decrease the production of pro-inflammatory cytokines (IL-6, IL-1β) and pro-fibrotic factors (TGF-β) in renal PETs, and simultaneously secreting various growth factors to promote tissue repair [307]. These findings indicate that UC-MSCs represent a promising strategy for the treatment of DKD.

Stem cell delivery strategies for kidney repair include systemic and localised approaches. Systemic delivery methods, such as intravenous (IV) injection, enable least-invasive delivery via circulation but suffer from pulmonary sequestration, limiting the number of cells reaching the kidneys. Intra-arterial infusion improves renal targeting through direct vascular access but requires invasive catheterisation [314]. Alternatively, localised delivery methods, such as intraparenchymal injection, can be employed. Direct injection into the renal parenchyma or perirenal space can deliver stem cells precisely to the target site. This method maximises the local concentration of stem cells but poses procedural risks including bleeding or infection [314]. Emerging strategies also utilise biomaterial scaffolds or hydrogels to encapsulate MSCs, enhancing retention and survival at the injury site, though clinical validation remains limited [314–316]. Additionally, cell-free approaches like MSC-derived exosomes (MSC-Exo), are being investigated to bypass cell delivery challenges while retaining therapeutic benefits, including anti-inflammatory effects and alleviation of renal fibrosis [317, 318].

In conclusion, as a novel treatment for DKD, stem cell therapies provide a new perspective and potential mechanisms, effects, and clinical applications, which are expected to change the traditional treatment model of DKD. The use of MSCs from various sources offers diverse treatment options, enabling the development of suitable therapies for patients. Moreover, the regenerative capacity and long-lasting effects of stem cells outperform those of traditional treatments, thereby potentially slowing DKD progression and improving patient prognosis [313, 319–321]. However, no MSC products are FDA/EMA-approved for DKD, all remain in Phase I-II trials. While stem cells redefine DKD therapeutic paradigms, their real-world application demands rigorous validation of efficacy, standardized production, regulatory alignment to bridge the translational gap, and evaluation of long-term safety and efficacy in large-scale clinical trials.

4.8 | Others

The mechanisms underlying the renal tubular injury in DKD are multifaceted. Klotho, an anti-ageing protein, exhibits significantly reduced expression in DKD [322]. This protein holds therapeutic potential due to its influence on diverse pathways [322], such as suppressing TGF-β1-mediated EMT by inhibiting both ERK1/2 and RhoA/ROCK signalling, consequently mitigating renal tubulointerstitial fibrosis [323–327]. Additionally, Klotho inhibits NF-κB activation, enhances AMPK/PGC1α expression, and blocks the Wnt/β-catenin pathway, conferring anti-inflammatory and antioxidant effects [87, 328, 329]. It also promotes autophagy in proximal renal tubular cells [330, 331]. Furthermore, sulodexide has been found to ameliorate oxidative stress-induced renal tubulointerstitial injury by upregulating Klotho expression [332]. Similarly, a randomized controlled trial demonstrated that treatment with the RAAS blocker valsartan significantly enhances soluble Klotho levels, conferring renal protection in patients with DKD (NCT00171561) (NCT00001715) [333]. While Klotho-targeted therapies remain preclinical, enhancing Klotho through repurposed drugs (e.g., valsartan) or novel agents represents a promising but unproven strategy for DKD. Further clinical validation is required to assess safety and efficacy in dedicated DKD cohorts.

Endothelin (ET), a powerful regulator of renal haemodynamics and ion balance, influences renal function via ET-1, which triggers inflammation and fibrosis, contributing to DKD progression [334, 335]. Atrasentan, a selective endothelin A receptor antagonist, demonstrates efficacy in DKD by maintaining the integrity of the glomerular endothelial glycocalyx structure, thereby attenuating albuminuria [336, 337]. Notably, its mechanism extends to the molecular level, in high glucose-exposed HK-2 cells and diabetic mice, atrasentan downregulates miR-199b-5p, enhances Klotho expression, and mitigates tubular injury [338, 339]. Despite these promising findings, additional studies are imperative to fully elucidate the therapeutic potential of atrasentan against renal tubular injury in DKD.

Osteopontin (OPN), a multifunctional protein and pro-inflammatory cytokine, is upregulated in the kidneys of diabetic animals and DKD patients. It is believed to play a key role in the pathogenesis of DKD [340]. OPN expression is upregulated in DKD mouse models. Preclinical data suggest epigenetic modulation of OPN (e.g., histone mark alterations) as a therapeutic target to mitigate glucose-induced renal injury [341]. Moreover, OPN may serve as a crucial therapeutic target for treating renal tubulointerstitial inflammation in DKD [340, 342]. However, no OPN-targeted therapies have entered clinical trials for DKD, highlighting a critical translational gap.

We have elucidated EMT as a core pathological mechanism of renal tubulointerstitial fibrosis in the progression of DKD, and TGF-β as a key cytokine inducing EMT. Consequently, the inhibition of TGF-β may be a potential therapeutic target for DKD. Astragaloside I (ASI) is a bioactive saponin isolated from Anaplasma membranaceus. One study found that ASI can reduce renal fibrosis markers and inhibit the TGF-β1/Smad2/3 pathway. Moreover, it downregulates HDAC3 expression, upregulates Klotho expression, and enhances Klotho release [343]. However, more clinical trials are needed to evaluate the clinical efficacy of TGF-β antagonists in the treatment of DKD.

In recent decades, numerous studies have explored the mechanisms of traditional Chinese medicine (TCM) in the prevention and treatment of DKD, confirming its unique multi-target, multi-combination, and multi-level treatment advantages. It has shown efficacy in improving clinical symptoms, reducing proteinuria, protecting renal function, and delaying DKD progression [344–346]. Specifically, TCM intervention has the potential to inhibit inflammatory cytokines and various growth factor expressions, reduce blood glucose, and affect insulin resistance, lipid metabolism, and renal function improvement [344]. Notably, compared with Western medicine alone, the combination of TCM and Western medicine more significantly improves renal function indicators (such as serum creatinine and BUN) in patients with DKD [345]. Combining TCM with conventional therapies (such as ACEI, ARB, SGLT2i) in patients with DKD can improve their renoprotective effects and superiority, with ACEI plus TCM potentially being the most effective treatment option for DKD treatment [346]. For instance, a prospective, randomized, controlled clinical trial found that the Qidan Tangshen Granule treatment significantly reduced haemoglobin A1c (HbA1c) and UACR levels, improved renal function, and exerted antioxidative effects in DKD patients [347]. TCM involves customised treatment plans based on patient characteristics to optimise efficacy. However, no TCM formulations are FDA-approved for DKD. Heterogeneity in TCM formulations, small sample sizes, and lack of mechanistic rigour limit global adoption. In the future, efforts should be made to actively promote more rigorous and comprehensive clinical and basic research on the mechanisms of TCM in DKD treatment [348].

5 | Conclusion

In this review, we discuss the potential mechanisms underlying renal tubular injury in DKD, including hyperglycemia, oxidative stress, ER stress, immune inflammation, RAAS, programmed cell death, and related signalling pathways. Our study also integrated biomarkers of tubular injury, including KIM-1, NGAL, Cystatin C, L-FABP, MCP-1, NAG, and RBP as potential strategies for the early diagnosis of damaged tubules. Concurrently, we reviewed early intervention approaches for DKD tubular injury, such as hypoglycemic agents, anti-oxidative stress, anti-inflammatory treatments, anti-cell death, and stem cell therapies. These interventions demonstrate promise in mitigating renal tubular damage and potentially slowing DKD progression. It would be beneficial to outline specific steps to validate the long-term efficacy of stem cell therapies and other novel treatments to mitigate DKD progression. Additionally, the clinical feasibility and diagnostic utility of novel biomarkers, such as KIM-1 and NGAL, should be emphasised. Further studies are required to elucidate the pathogenesis of renal tubular injury in DKD. Moreover, it is essential to evaluate the diagnostic value and clinical feasibility of new biomarkers and to develop targeted therapies to prevent and delay renal tubular injury in DKD. These efforts will not only enhance our fundamental understanding of DKD but will also translate into more effective patient care. By focusing on these key areas, we hope to improve

the outcomes of patients with DKD and reduce the burden on individuals, families, and the global healthcare system. This comprehensive approach promises to transform the management of DKD and provide new hope for patients affected by this complex disease.

Author Contributions

Y.L., C.Y., Z.L., H.J., and Y.W. conceived and drafted the manuscript. J.Y., H.C., and C.Z. discussed the concepts of the manuscript. Y.L., C.Y., H.J., and Y.W. drew the figures and drafted the tables. H.J. and Y.W. revised the manuscript. All the authors have read and approved this manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

Peer Review

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