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Broadening horizons in mechanisms, management, and treatment of diabetic kidney disease

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ABSTRACT

Diabetic kidney disease (DKD) is the first cause of end-stage kidney disease in patients with diabetes and its prevalence is increasing worldwide. It encompasses histological alterations that mainly affect the glomerular filtration unit, which include thickening of the basement membrane, mesangial cell proliferation, endothelial alteration, and podocyte injury. These morphological abnormalities further result in a persistent increase of urinary albumin-to-creatinine ratio and in a reduction of the estimated glomerular filtration rate. Several molecular and cellular mechanisms have been recognized, up to date, as major players in mediating such clinical and histological features and many more are being under investigation. This review summarizes the most recent advances in understanding cell death mechanisms, intracellular signaling pathways and molecular effectors that play a role in the onset and progression of diabetic kidney damage. Some of those molecular and cellular mechanisms have been already successfully targeted in preclinical models of DKD and, in some cases, strategies have been tested in clinical trials. Finally, this report sheds light on the relevance of novel pathways that may become therapeutic targets for future applications in DKD.

1. Diabetic kidney disease

Diabetic kidney disease (DKD) occurs in 20–40% of all diabetic patients [1] and is the primary cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide [2]. The probability of developing CKD in patients with diabetes, including both type 1 (T1D) and type 2 (T2D) diabetes, is estimated to be approximately 1.75 (95% CI: 1.62–1.89) [3], with a resulting mortality risk rising to 30% [4]. As a result, the percentage of the prevalent ESKD patients with diabetes increased from 19.0% in 2000 to 29.7% in 2015 worldwide, while the percentage of incident ESKD patients due to diabetes increased from 22.1% to 31.3% [5]. As the natural history of DKD develops throughout decades, several prospective studies showed that DKD occurrence is uncommon ten years from the diagnosis, whereas incidence rates of 3% per year are seen 10–20 years after diabetes onset. On the other hand, diabetic patients who do not develop DKD after 20–25 years from the

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diagnosis seem to be more resilient to exhibit any sign of kidney damage later [6,7]. Although the prevalence of DKD among diabetic patients is similar across ethnicities, the prevalence of ESKD is 1.5 times higher in Asians, 2.5 times higher in Hispanics, and nearly 4 times higher in African-Americans as compared to that observed in white Caucasians [8]. A recent cross-sectional study on 452,238 American patients with CKD analyzed whether the delivered quality of care suffered of racial and ethnic disparities. Interestingly, achievement of diabetes control, with hemoglobin A1c (HbA1c) less than 7.0%, and of blood pressure control was similar in Asian, Black, and Hispanic patients as compared to White Caucasian patients, thereby suggesting that disparities in CKD progression and ESKD prevalence among diabetic patients were not related or directly caused by a difference in medication prescription and/or in the clinical management of patients at the follow-up [9].

2. DKD diagnosis and management

2.1. Diagnosis

The diagnosis of DKD is primarily clinical, whereas the kidney biopsy is performed only to rule out other suspected causes of kidney disease [10]. The time passed from diabetes onset, the persistently high urinary albumin-to-creatinine ratio $>$ 30 mg/g, and/or the sustained reduction in estimated glomerular filtration rate (eGFR) below 60 ml/min per 1.73 m^2 significantly correlate with the diagnosis of DKD [10]. Moreover, the simultaneous presence of diabetic retinopathy in patients with persistent albuminuria is now considered strongly suggestive of DKD [11]. To efficiently approach an early diagnosis of DKD and according to the existing KDIGO guidelines, clinical and laboratory screening should be performed annually in patients with T1D starting 5 years after the diagnosis, and annually for all patients with T2D starting at the time of diagnosis [12]. However, DKD does not always follow the classic pattern of glomerular hyperfiltration that eventually leads to persistent albuminuria, hypertension, and a decline of the GFR [13]. In the United Kingdom Prospective Diabetes Study (UKPDS), after 15 years of follow-up, 60% of the patients who developed CKD did not have preceding albuminuria, and 40% of the whole cohort never developed albuminuria during the study [14]. In the Multifactorial Intervention for Patients with Type 2 Diabetes Study, among patients with microalbuminuria, 31% progressed to macroalbuminuria, 31% regressed to normoalbuminuria, and 38% remained macroalbuminuric during the 7.8 years of follow-up [15]. Furthermore, a recent autopsy study observed a higher prevalence of DKD diagnosed histologically rather than clinically, with 20% (21 of 106) of patients with diabetes never exhibiting albuminuria or eGFR lower than 60 ml/min but showing histopathologic changes typical of DKD [16]. These studies highlight the unpredictable progression of DKD and pointing out at the need for new strategies to better evaluate disease progression. Besides eGFR and albuminuria, no novel prognostic biomarkers are being used in routinary analysis nowadays in clinic or are being tested in ongoing clinical trials. Although several candidate biomarkers have been described in sporadic reports in the literature, only a few studies tested a large panel of markers that may help in identifying phases of DKD progression. More importantly, the lack of long-term studies represents a limitation in assessing the relevance of single biomarkers included in large panels in predicting the onset and progression of the disease [17]. In this regard, progresses were made when a set of 25 circulating proteins linked to the transforming growth factor-β (TGF-β) pathway and routinely measured during a 10-year follow-up in 754 Caucasian or Pima Indian individuals with T1D or T2D, was assessed to correlate with the development of DKD [18]. Notably, out of these 25 proteins, the study identified neuroblastoma suppressor of tumorigenicity 1 (NBL1) to be strongly and independently associated with progression to ESKD. Furthermore, the study showed that *in vitro* exposure to NBL1 induced apoptosis of human podocytes, thereby suggesting that NBL1 may represent a biomarker for disease progression but also a pathogenic factor directly involved in kidney damage in the context of DKD [18].

2.2. DKD management

DKD management includes lifestyle and dietary modification, intensive control of hyperglycemia and hypertension, and, in recent years, the use of new drugs able to independently slow the progression of the disease (*i.e.*, antiproteinuric and blood pressure lowering agents) has been implemented. Patients with DKD should follow a diet, with a moderate protein restriction (0.8 g protein/kg (weight)/day) and a reduced sodium intake ($<$2 g/day) [19]. Moreover, patients should undertake moderate-intensity physical activity for a cumulative duration of at least 150 min per week or to a level compatible with their cardiovascular and physical tolerance. Lipid reduction and smoking cessation are also beneficial [19]. However, the cornerstone to slowing the DKD progression towards ESKD is still represented by the strict control of hypertension and hyperglycemia. Therefore, patients with diabetes and hypertension should always be treated with renin-angiotensin-aldosterone system (RAAS) inhibitors titrated to the highest approved dose that is tolerated [12]. With regard to diabetes management, the first-line treatment is metformin, which in the case of DKD onset, should be associated with sodium-glucose-cotransporter 2 inhibitors (SGLT2-i), according to the most recent guidelines. Indeed, although mildly effective at glycemic control, SGLT2-i are very effective at reducing proteinuria, delaying the progression of DKD, and reducing cardiovascular risk [20]. If despite the use of metformin and SGLT2-i, patients do not achieve individualized glycemic targets, KDIGO guidelines recommend the use of long-acting glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which also showed beneficial effects in delaying, but to a lesser extent, the progression of DKD [21]. Whilst not mentioned in the 2020 KDIGO guidelines, recently published trials on finerenone, a new non-steroidal mineralocorticoid receptor antagonist, showed a significant improvement in both kidney and cardiovascular outcomes in patients with DKD regardless of HbA1c levels, insulin use, or SGLT2-i use [22,23]. Based on these findings and observations, finerenone might be considered a possible add-on therapy in patients at high risk for DKD progression.

3. Diabetic kidney disease and mechanisms underneath

3.1. Morphological and structural modifications at the organ level

DKD is characterized by progressive glomerulopathy that affects all the layers of the glomerular structure. Whether proteinuria is present or absent, kidney biopsies from diabetic patients show common histopathological findings, including thickening of the glomerular basement membrane (GBM), mesangial proliferation, endothelial alteration, and podocyte injury [24]. These glomerular alterations are the consequence of hyperglycemia-driven vascular and podocyte injury, which eventually result in proteinuria, glomerulosclerosis, and CKD. However, podocyte loss in patients progressing to CKD may not be fully explained by the hyperglycemia-mediated injury and other factors directly targeting podocytes should be considered [18].

3.2. Endothelial changes

Diabetes-associated microvascular and macrovascular complications often lead to organ damage and are responsible for increased mortality among diabetic patients [25,26]. Systemic endothelial cell dysfunction is a consequence of chronic hyperglycemia and inflammation, which results in increased vascular permeability, vascular stiffness, and dysregulation of vascular tone [27]. At the kidney level, microvascular changes are primary drivers of DKD, leading to increased glomerular permeability and proliferation. The increased glomerular permeability eventually leads to microalbuminuria, which is usually the first indicator of glomerular endothelial cell damage [28]. Indeed, the loss of

specific components of the negatively charged glycocalyx that covers the fenestrated endothelial barrier, such as heparan sulfate and hyaluronic acid, increases the permeability of the endothelium to negatively charged proteins, including albumin [29].

3.3. Glomerular basement membrane thickening and mesangial proliferation

Interestingly, the damaged endothelium tends to proliferate in response to inflammation and an increase in abnormal extracellular matrix deposition and secretion of pro-fibrotic factors, including TGF-β and vascular endothelial growth factor (VEGF) are both evident. TGF-β signaling further activates podocytes, which are already in a pro-fibrotic state following the exposure to the hyperglycemic and inflammatory microenvironment [30] and it promotes mesangial cell proliferation and new extracellular matrix deposition [31]. Therefore, several glomerular cells, including podocytes, endothelial and mesangial cells, contribute to an abundant extracellular matrix deposition that leads to the thickening of the GMB. This represents an early histopathological finding in DKD, which has been shown to predict the development of macroalbuminuria and ESKD, with even a better correlation as compared to microalbuminuria [32,33]. Indeed, GBM thickening could be detected as early as 1.5 years after disease onset in patients with T1D and it is followed by mesangial expansion at five years, whereas GBM changes are more heterogeneous in patients with T2D [34].

Podocytopathy Besides increased vascular permeability, segmental sclerosis, and extra capillary hypercellularity, DKD might also induce a profound podocytopathy. Indeed, cellular hypertrophy, foot process effacement, and the reduction in podocyte number strongly correlate with albuminuria and eGFR decline in diabetic patients [35]. Podocyte loss is related to the rearrangement of podocyte intracellular scaffold complex and to direct glucose or TGF-β-induced apoptosis [36], and further contributes to an increase in proteinuria and development of CKD.

3.4. Cell death

Death of cells all along the nephron plays a critical role in DKD development (Fig. 1A). Cell death modalities are multiple and include apoptosis, pyroptosis, ferroptosis and necroptosis. A pillar study,

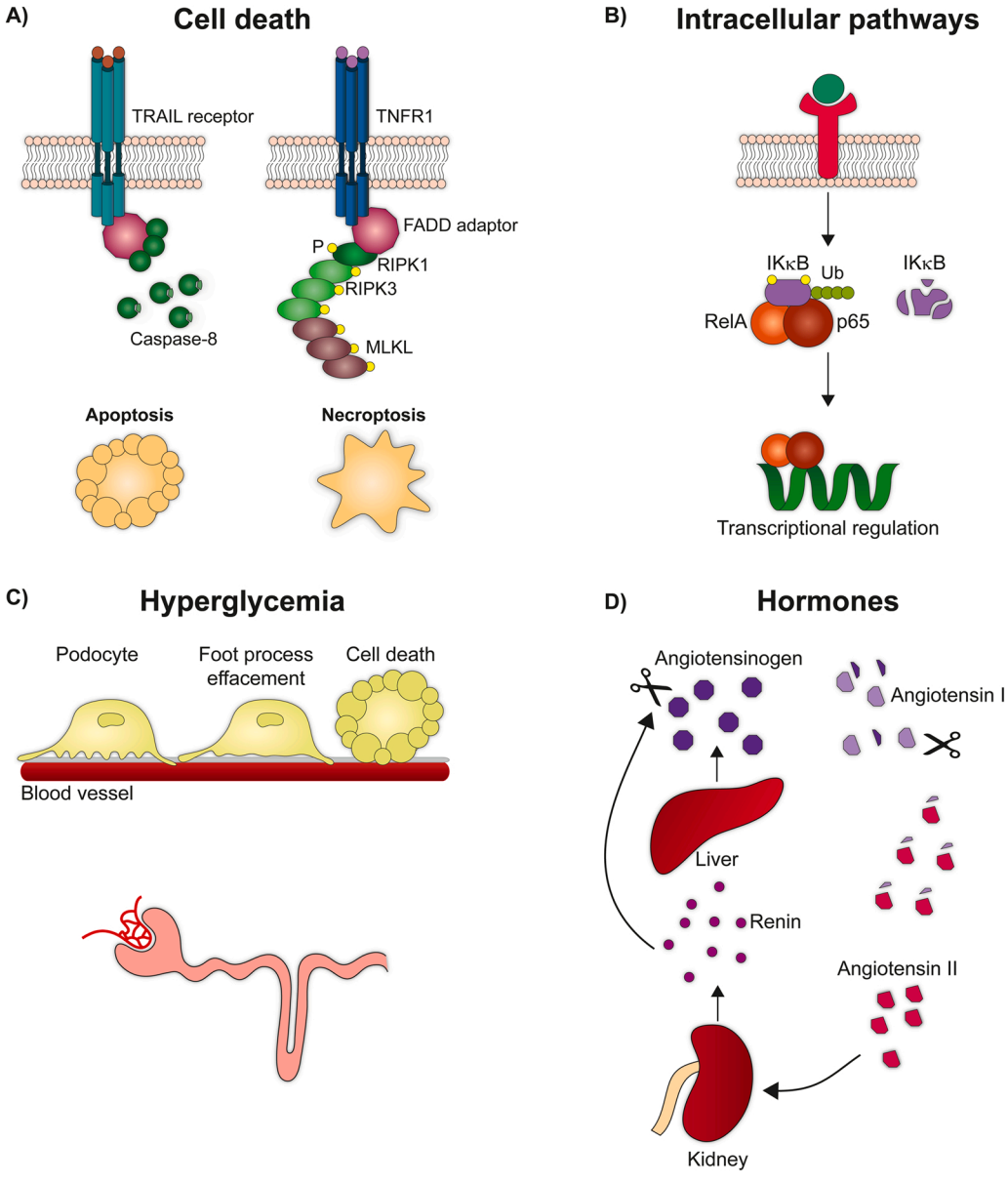

Fig. 1. Pathogenic molecular and cellular mechanisms in DKD. A) Engagement of death-inducing receptors (TRAIL or TNFR1) results in the recruitment of FADD adaptor. If caspase-8 is recruited, apoptotic cell death occurs. Alternatively, when RIPK1-RIPK3-MKLK complex forms, cells dye by necroptosis. B) Activation of NFkB pathway is pathogenic in DKD. It occurs downstream of cytokine or growth factor receptors upon phosphorylation, polyubiquitination and consequent degradation of IkB, which impedes nuclear translocation of RelA-p65 complex (classical pathway). Once IkB is degraded, RelA-p65 complex translocates to the nucleus, where it regulates gene expression. C) Hyperglycemia damages podocytes within nephrons, by inducing foot process effacement and apoptosis. D) RASS pathway. Renin, produced by juxtaglomerular cells of the kidney cut angiotensinogen, produced by the liver, in angiotensin-I. ACE or CMA1 cut angiotensin-I to angiotensin-II, which, in turn, exert many effects on the kidney in both physiological and pathological condition. **Abbreviations**: Abbreviation: FADD: Fas associated protein with death domain; IκB: inhibitor of nuclear factor kappa B; MLKL: mixed lineage kinase domain like pseudokinase; RIPK: receptor-interacting serine/threonine-protein kinase; P: phosphate; TNFR: tumor necrosis factor receptor; TRAIL: tumor-necrosis factor related apoptosis-inducing ligand; Ub: ubiquitin;.

published in 2008, described tubular cell apoptosis throughout DKD progression. Lorz et al. [37] explored the expression level of numerous cell death-inducing genes in micro dissected tubulointerstitial tissue of DKD patients and found tumor necrosis factor (TNF)-related apoptosis-inducing ligand (*TRAIL*) and its decoy receptor (osteoprotegerin, *OPG*) among the most upregulated mRNAs in DKD as compared to control subjects [37], thereby suggesting cell-extrinsic apoptosis activation in diabetic tubules. TRAIL induces cell death upon binding of TRAIL receptor (TRAIL-R)1 and TRAILR-2, which in turn activates receptor oligomerization and recruitment of Fas-associated death domain (FADD) adaptor protein and pro-caspase-8. Activated caspase-8 cleaves pro-caspase-3 and induces cell death [38]. *TRAIL* and *OPG* expression levels correlated with clinical and histopathological characteristics of DKD, such as elevated serum creatinine level and severity of disease histological score [37]. Moreover, TRAIL was strongly detected in DKD tubular sections, and its expression level paralleled the increasing tubular atrophy, interstitial fibrosis, and interstitial infiltrate. The *in vitro* model of proximal tubular epithelial cells helped to understand the mechanisms behind kidney damage. Briefly, hyperglycemia increases proinflammatory cytokine levels, which induce TRAIL expression and tubular cell death in an autocrine manner. Even though Lorz and collogues [37] focused their attention on tubules, TRAIL was also markedly expressed by glomerular cells in kidney samples of patients with DKD, thus suggesting that apoptosis of podocytes may play a role in the disease progression as well [39]. Despite apoptosis is usually considered immunologically and inflammatorily silent, DKD is frequently associated with signs of inflammation. In particular, pro-inflammatory cell death mechanisms, such as pyroptosis, have been described to contribute to DKD onset. Two polycaspase inhibitors, M-920 and CIX, have been tested to prevent pyroptosis or apoptosis in an *in vivo* model of DKD, the diabetic (db/db) mice [40]. While CIX targets caspase-3, − 6, − 7, − 8, and 10, M-920 inhibits caspase-1, − 3, − 4, − 5, − 6, − 7 and − 8. Interestingly, M-920 but not CIX reduced albuminuria and extracellular matrix deposition within glomeruli. In parallel, M-920-treated mice exhibited lower expression of interleukin (IL)− 1β and IL-18 as well as Nlpr3 in renal cortex and decreased IL-1β in the serum. Moreover, caspase-1- but not caspase-3-deficient mice were protected from experimentally induced nephropathy, thereby indicating the relevance of caspase-1 signaling in participating to cell death processes during DKD [40]. Indeed, podocytes challenged with high glucose, activated caspase-1 upregulated Nlpr3 expression, as part of the inflammasome-mediated injury process. Altogether, these observations supported that a hyperglycemia-mediated activation of inflammasome exists in podocytes and it is associated with kidney injury [40]. Beside apoptotic and pyroptotic cell death, ferroptosis and necroptosis have been demonstrated to play a role in DKD progression as well. Briefly, ferroptosis is a cell death modality induced by increased level of lipid peroxides, which further generate reactive oxygen species (ROS) in a Fe-dependent manner [41]. Intracellular pathways involved in the ferroptosis process are still under investigation. Nevertheless, the role of glutathione peroxidase 4 (GPX4) has been very well established. GPX4 reduces cytotoxic lipid peroxides and simultaneously oxidizes glutathione. Thus, genetic or pharmacologic inhibition of GPX4 activity regulates sensitivity to ferroptosis [42]. Interestingly, human proximal tubular cells decreased GPX4 expression when cultured in high glucose milieu [43]. Alternatively, TGF-β regulated GPX4 in a similar fashion in rat tubular cells [44]. Therefore, intracellular glutathione levels decreased in high-glucose condition, thus leading to lipid peroxide accumulation and death by ferroptosis. Importantly, pharmacological inhibition of ferroptosis attenuated signs of kidney injury both in the streptozotocin (STZ)-treated mice and in the db/db mice, two models extensively used to study DKD *in vivo*. Administration of ferrostatin-1, a ferroptosis selective inhibitor, reduced urinary albumin-to-creatinine ratio in STZ-treated mice and diminished lipid peroxidation both in STZ-treated and in db/db mice [44]. In addition, kidney biopsies of diabetic patients showed decreased *GPX4* mRNA expression as compared to matched controls, thereby confirming the role of ferroptosis-mediated cell death in the kidneys of patients with diabetes [44]. Activation of necroptosis follows the engagement of surface death receptors, which results in the recruitment of a protein complex constituted by receptor-interacting serine/threonine-protein kinase (RIPK) 1 and RIPK3 and mixed lineage kinase domain like pseudokinase (MLKL) [45]. Upon phosphorylation, MLKL oligomerizes and migrates to the plasma membrane where it binds phosphatidylinositol lipids, contributing to the permeabilization of the plasma membrane and cell swelling, ultimately resulting in cell death [46,47]. Of note, rat tubular cells challenged with high glucose, showed activation of RIPK1, RIPK3 and MLKL phosphorylation *in vitro* through ROS production. RIPK1, RIPK3 and MLKL were also phosphorylated in the kidney of STZ/high-fat-diet induced diabetic mice and pharmacological inhibition of necroptosis delayed the progression of renal damage [48]. Similarly, STZ administration in wild type mice induced RIPK3 activation, as well as fibrosis. However, STZ administration failed to activate surrogate markers of fibrosis in kidneys of RIPK3 knockout mice [49]. Furthermore, podocytes grown in hyperglycemic condition activated TNF receptor (TNFR) 1 and initiated necroptosis *in vitro*, while TNFR1 genetic knockdown rescued expression of lineage markers, such as Wilms' tumor (WT) 1 and synaptopodin in high glucose milieu [50]. In summary, the death of glomerular and tubular cells occurs though several pathways and manners, immunologically silent or inflammatory-mediated, which ultimately leads to major structural and morphological changes observed at the kidney level in disease conditions, including the DKD.

3.5. Intracellular pathways deregulated in DKD

Several intracellular pathways are dysfunctional in DKD, and their deregulation precedes functional and morphological changes at cell and organ level (Fig. 1B). The discovery of such dysfunctional pathways proceeded through hypothesis and attempts in the past [51]. Nowadays, whole transcriptome profiling, even at the single cell level, as well as bioinformatics tools, helped to delineate a more comprehensive view of the numerous pathways altered in DKD. Many of those high-throughput experiments confirmed previous observations and yet demonstrated the role of other pathways altered at DKD onset, as well as upstream regulators. For instance, comparison of gene expression profiles of DKD patients and control subjects allowed to identify six sets of genes, whose expression was altered in DKD, and linked to several distinct pathways, including mitogen-activated protein kinase (MAPK) and hedgehog pathways and the inositol-requiring enzyme 1 (IRE-1)-mediated unfolded protein response [52]. Interestingly, master regulator of such gene sets was found to be *RELA*, pointing to NFκB classical pathway as crucial in the damage observed in DKD [52]. NFκB activation was observed in tubular as well in glomerular cells of diabetic patients [53,54] and correlated with proteinuria and disease stage [53,55]. Then, analysis of whole transcriptome of samples obtained from patients at an early or advanced stage of the disease, based on the urinary albumin-creatinine ratio, identified the retinoic acid pathway as a potential blocker of DKD progression, with related gene expression upregulated in early stages of kidney disease but downregulated later [56]. Thanks to single nucleus RNA-sequencing, gene expression changes were observed in the thick ascending limb, late distal convoluted tubule, and principal cells that altogether coordinated to promote potassium secretion. Indeed, increased potassium levels were observed in patients with DKD, which may be the results of an early adaptive response to renal injury [57]. Very recently, Wilson and collaborators [58] went even further and integrated the gene expression profile of DKD kidney cortex, using single nucleus RNA sequencing, with single nucleus transposase-accessible chromatin sequencing data, the latter as surrogate marker of cell-specific gene expression regulation. Their effort uncovered the increased activation of glucocorticoid receptor signaling pathway in proximal tubule cells and thick ascending limb of diabetic

patients. They observed reduced chromatin accessibility of two negative regulators of the pathway (FKBP5 and HSD11B2) in DKD patients, thus leading to hyperactivation of glucocorticoid receptor downstream signaling, gluconeogenesis and insulin resistance occurring in proximal tubule cells of diabetic patients [58]. In summary, technological advances allowed the discovery of numerous intracellular pathways altered throughout DKD progression and involved in the renal damaging process, which may further serve as potential therapeutic targets in the future.

4. Intercellular communication, from diabetes to DKD

4.1. Hyperglycemia

Hyperglycemia is the primary clinical manifestation of diabetes and the principal cause of diabetic complications. Although DKD development depends on several diabetes-related factors, including hemodynamic changes and systemic inflammation, hyperglycemia has a driving role. Indeed, chronic hyperglycemia leads to direct renal cell toxicity, renal hyperfiltration, and the generation of reactive oxygen and nitrogen species, that could damage the nephrons [59]. In physiological conditions, most glucose entering the tubular system is reabsorbed along the proximal tubule. However, when chronic hyperglycemia occurs, in attempt to reestablish homeostasis, renal cells increase the expression of glucose transporters such as glucose transporter (GLUT)− 1, GLUT-2, SGLT1, and SGLT2, which are responsible for glucose uptake [60]. However, these glucose carriers do not regulate glucose entry into cells, eventually accumulating a high quantity of glucose and mediating cell glucotoxicity. Moreover, when glucose reabsorption in the proximal tubule is increased, the tubule-glomerular-feedback is inhibited, resulting in a reduction of afferent arteriolar resistance and an increase of nephrons glomerular filtration rate that further damages the hyperactivated proximal tubular cells [61]. Besides proximal tubular cells, also podocytes, endothelial cells, and mesangial cells are directly and indirectly affected by hyperglycemia [35]. In the early stages of DKD, hyperglycemia inhibits nitric oxide production by endothelial cells, increasing the afferent arteriolar resistance and reducing the GFR. This inhibition stimulates massive podocytic production of VEGF-A, which results in the growth and proliferation of mesangial and endothelial cells. In the late stages of DKD, these proliferative processes lead to collagen deposition and final glomerulosclerosis [62]. Furthermore, hyperglycemia causes cytoskeletal rearrangement of podocytes with flattening, widening, and foot processes effacement (Fig. 1C), and DKD is often associated with a reduction in the expression of nephrin, a crucial protein of the slit diaphragm [63]. Moreover, the diabetic milieu alters the activity of the Rho-GTPase molecules, which are critical regulators of actin cytoskeleton remodeling, leading to cytoskeletal rearrangement and foot process effacement [64]. Finally, the increase in oxidative stress, particularly of ROS, which upon hyperglycemia, mediate podocyte dysfunction through mitochondrial fragmentation, has been described as a potential mechanism whereby podocytes are damaged during DKD [65].

4.2. Hormones

Hyperglycemia has been largely recognized as a major driver of diabetic complications, including DKD, but, more recently, other factors, such as hormones, have been hypothesized to participate in advancing kidney damage during DKD. RAAS is a complex yet critical pathway that regulate renal function and a disruption of the RASS was proved to contribute to DKD onset (Fig. 1D). Early evidences demonstrated that RAAS was hyperactivated in patients with T1D, particularly in hyperglycemic conditions. Renal hemodynamic response to RAAS blockade therapy was greater in the hyperglycemic phase as compared to euglycemic condition, whereas response was comparable between glycemic phases after angiotensin II infusion, further suggesting a hyperglycemia-mediated RAAS activation [66]. In line with this, increased RAAS activation was evident in diabetic patients with DKD as compared to those identified as DKD resistors [67]. Later studies suggested the activation of wnt/β-catenin pathway upstream of RAAS in patients with DKD. Indeed, the wnt/β-catenin inhibitor, klotho, was downregulated in diabetic patients exhibiting kidney injury and, when administered to diabetic mice, it decreased proteinuria [68,69]. Despite the role of vasopressin in DKD etiology has not been mechanistically addressed up to date, several reports showed a positive correlation between high levels of circulating copeptin (C-terminal portion of vasopressin) and urinary albumin excretion [70]. Moreover, DKD resistors had lower levels of copeptin as compared to patients with T1D who developed kidney injury, with copeptin being positively correlated with renin levels, thereby suggesting a complex interplay between the two kidney-associated hormonal systems [71]. Finally, a cross-sectional study, which enrolled 862 patients with T2D, demonstrated that kidney failure was significantly more common among patients with lower free triiodothyronine (FT3) serum levels, with FT3 hormone appearing as a protective factor in DKD development [72]. Results were confirmed in a larger patient cohort study, but this correlation requires further investigations from a mechanistic point of view [73]. However, FT3 regulates endothelial function and administration of FT3 to db/db mice reduced collagen deposition and mesangial matrix expansion [74].

4.3. Cytokines

In 1991 the role of pro-inflammatory cytokines in DKD onset was described for the first time. Hasegawa et al. [75] proved that macrophages produced significantly more TNF-α and IL-1 when cultured with glomerular basement membranes isolated from diabetic rats than when cultured with basement membranes of nondiabetic rats. Since then, several additional evidences proved the role of pro-inflammatory cytokines as predictors and/or cause of DKD. Of note, increase in circulating IL-6 levels was observed in patients with T2D and nephropathy as compared to diabetic patients without renal complications. Moreover, IL-6 mRNA expression in glomerular cells correlated with the extent of mesangial expansion in these patients. Similarly, an increase in IL-18 and TNF-α levels in DKD was documented and further correlated with elevated urinary albumin excretion and glomerular and tubulointerstitial damage, respectively. Moreover, TNF-α had direct cytotoxic effects, partly through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, by favoring ROS production and induction of apoptosis. In a similar manner, IL-8 induced podocyte DNA damage and apoptosis *in vitro* thereby confirming the direct cytotoxic effect of pro-inflammatory cytokines in kidney tissue. Besides, the highest levels of IL-8 were found in patients with T2D and with the largest decline in glomerular filtration rate, increased albumin-to-creatine ratio and the worst renal outcome [76]. More recently, NBL1, a circulating protein of the TGF-β superfamily, gained attention due to the important correlation that levels of serum NBL1 had with progression to DKD [18]. Indeed, NBL1 serum levels were found to be strongly and independently associated to the risk of progressing to DKD. Such association was present in four independent cohort of T1D or T2D, with either early or advanced DKD, and it proved that the risk of ESKD at 10 years was significantly higher in subjects with the highest NBL1 serum levels. Moreover, NBL1 concentration in early DKD patient correlated with structural and morphological changes of glomeruli. In particular, it positively correlated with mesangial fractional volume and GBM width and it negatively correlated with podocyte number as well as fractional volume of podocyte cells per glomerulus. In fact, NBL1 had direct cytotoxic effect because it caused podocytes cell death *in vitro* [18]. In summary, plenty of molecular effectors, beside hyperglycemia, contribute to DKD onset and progression. Levels or cytotoxic activities of some effectors are strictly linked to hyperglycemia. For some others, causal link with hyperglycemia is still being investigated. Despite this, those factors may represent novel therapeutic target directed to improve disease signs or,

at least, to delay the progression to ESRD.

5. Upcoming treatments for DKD

5.1. Promising drugs in preclinic

Each of the aforementioned pathway and molecular effector has been explored and tested as potential therapeutic target for DKD. First, blockade of apoptosis ameliorated renal injury in STZ-treated mice, as demonstrated by Liu and colleagues [77]. By using wogonin to tip the balance between apoptosis and autophagy toward autophagy, the Authors obtained an important reduction in renal cell apoptosis in diabetic mice. Indeed, wogonin, as a single agent, attenuated renal inflammation and damage and improved kidney function. The molecular mechanisms behind wogonin beneficial effect in DKD, was investigated in murine podocytes; wogonin physically interacted with Bcl2 and promoted the activation of Bax, thereby preventing cytochrome c release from mitochondria and subsequent apoptosis. In parallel, wogonin inhibited Bcl2-Beclin1 binding and increased podocytes autophagy [77]. With regard to non-apoptotic cell death mechanisms, an isoflavone extracted from astragalus membranaceus, calycosin, inhibited high glucose-induced ferroptosis *in vitro* in podocytes and improved signs of kidney dysfunction *in vivo* in diabetic mice. Indeed, db/db mice experienced a dose-dependent reduction of blood urea nitrogen and serum creatinine levels after treatment with calycosin, whereas GPX4 expression and function were preserved [78]. Among targeted strategies, blockade of intracellular pathways dysregulated in DKD showed encouraging results in animal models of kidney disease. Pharmacological inhibition of the NFκB pathway with celastrol reduced signs of renal damage, such as the elevated urinary albumin excretion and mesangial expansion, as well as decreased collagen IV and TGF-β expression in renal tissues of db/db mice [79]. However, this NFκB inhibitor also lowered fasting plasma glucose, HbA1C, and increased plasma adiponectin levels, thus suggesting the relevance of NFκB transcriptional activity in numerous organs [79] and underling both the potential advantages and difficulties of targeting such pathway. Chronic administration of another NFκB inhibitor, pyrrolidine dithiocarbamate, prevented inflammation in renal tissue, without interfering with blood glucose, in rat injected with STZ. In parallel, pyrrolidine dithiocarbamate inhibited STZ-induced glomerular injury [54]. In another study, STAT3 inhibitor S3I-20, showed positive effects in STZ-treated mice, such as decrease in interstitial fibrosis, collagen IV accumulation and TGF-β production, and ultimately re-established near-normal kidney functions. Interestingly, S3I-201 also prevented overexpression of RAAS [80]. However, S3I-201 is hardly selective for inhibition of STAT3, over other STATs transcription factors. Moreover, STAT3 regulates many fundamental physiological processes, thus translation to the clinic appears limited. Multi-omics approaches revolutionized the identification of novel therapeutic targets as well as drug discovery, also in the field of DKD [58,81]. Very recently, Klein and collaborators [82] used large-scale mass spectrometry-based proteomic and bioinformatic tools to identify novel drug candidates for DKD. First, they identified a glomerular protein signature characteristic of diabetic mice exhibiting renal damage. Then, they took advantage of a drug repurposing algorithm to compare DKD-protein signature to thousands of signatures of bioactive compounds. As a result of the in-silico analysis, parthenolide, traditionally used to treat arthritis, headaches, and fever, was identified as a potential treatment for DKD [82]. The parthenolide bioavailable analog, dimethylaminoparthenolide, significantly ameliorated renal injury in Ins2Akita mice *in vivo*, with a decrease in albumin-to-creatinine ratio, glomerular stress and fibrosis [82]. Finally, as multiple factors are involved in the pathogenesis of DKD, strategies aimed at targeting in combination different pathways are emerging and obtaining encouraging results. Notably, by using the cutting-edge single-nuclei RNA sequencing, Wu and collaborators [83] demonstrated that combination of lisinopril, angiotensin-converting enzyme inhibitor (ACE-i) and JNJ39933673 (SGLT2-i) or lisinopril and rosiglitazone modified the expression of different gene networks in distinct cell types in uninephrectomized diabetic mice, overexpressing renin. Moreover, combination of ACEi and SGLT-2i or ACEi and rosiglitazone showed a synergistic effect in reducing the expression of Havcr1, a well-established marker of proximal tubular cell injury. However, reduction of albumin-to-creatinine ratio was mainly driven by ACEi and no synergism with SGLT-2i or rosiglitazone was evident in this model [83]. In conclusion, targeting pathogenic molecular mechanisms or intracellular signaling pathways obtained very promising results in preclinical model of DKD. While those models fail to fully recapitulate the human disease and despite the physiological role of the pathways targeted, hopes are high for their translation to the clinic.

5.2. Ongoing clinical trials

All phase II and III clinical trials active as August 2022 and enrolling patients with DKD are listed in Table 1, in chronological order. Among those, trials testing the effects of SGLT2-i and GLP-1 RAs, both approved for the treatment of T2D as antidiabetic drugs, represent the vast majority. SGLT2 is a low affinity glucose transport, located in the renal proximal tubule and responsible for glucose reabsorption, whose pharmacological inhibition results in increased urinary glucose excretion and output, followed by a decrease in blood pressure [84]. Glomeruli benefit from lowered blood pressure and glucose, and renal outcomes improve, with results obtained in clinical trials being promising. The DAPA-CKD (NCT03036150) trial demonstrated that the risk of a decline in the eGFR, progression to end-stage disease or death from renal cause was reduced by nearly 50% by dapagliflozin treatment. The trial was stopped because of obvious efficacy [85]. Then, the double-blind, randomized trial NCT02065791 (CREDENCE) demonstrated very promising improvements of albuminuric DKD patients after treatment with canagliflozin. The relative risk of the renal-specific composite of ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml per minute per 1.73 m2), a doubling of the creatinine level, or death from renal causes was decreased by 34% [86]. Interestingly, administration of SGLT2-i is associated with a reduction in blood glucose level, like a fasting condition, and this may activate AMP kinase pathway and inhibit mammalian target of rapamycin (mTOR) signaling, thus reprogramming energy metabolism, and showing a protective effect. GLP1RAs have been developed to mimic the glucose lowering effect of GLP1 and are primarily used for glycemic management. However, GLP1RAs also protect heart and kidney [87]. The AMPLITUDE-O study demonstrated that efpeglenatide exerted a positive effect on the progression of severe cardiovascular disease and DKD in patients with T2D and a known history of cardiovascular disease and/or CKD. In particular, treatment with efpeglenatide attenuated albuminuria and eGFR decline when compared to placebo [88]. The AWARD-7 compared GLP1RA, dulaglutide, to insulin in patients with T2D and moderate-to-severe chronic kidney disease. Glycemic control achieved by dulaglutide was comparable to that achieved by insulin but dulaglutide better prevented eGFR decline [89]. Therefore, efficient management of glycaemia is critical to arrest or delay DKD onset and progression. However, glomerular capillaries, juxtaglomerular cells, and possibly proximal tubules express GLP1 receptor and the anti-inflammatory and anti-fibrotic effect of GLP1R activation in the kidney may contribute to the beneficial effects observed with the use of GLP1RAs. A Phase IV clinical trial is now exploring the combination of SGLT2-i and GLP1RAs to achieve a synergistic effect (NCT05390892), and many other trials are now testing combinations with ACEi (NCT05373004) or aldosterone synthase inhibitor (NCT05182840) to simultaneously achieve glucose control and target RASS. Despite mechanisms other than glycemic control contribute to SGLT2-i and GLP1RAs renoprotection, both classes of drugs fail to target the molecular mechanisms underneath DKD progression. Interestingly, phase III trial NCT03550443 assessed the efficacy of bardoxolone methyl to counteract the increased oxidative stress as a major

Table 1
List of clinical trials present in Clinicaltrials.gov testing new compounds in DKD (Assessed in January 2023).

Status	Intervention	Clinical trial number	Notes	Target
Not yet recruiting	INV-202	Phase II NCT05514548		Cannabinoid receptor
Recruiting	Canagliflozin	Phase II NCT05507892	Investigation of canaglifozin mechanism of action	SGLT-2
Not yet recruiting	Tadalafil Pentoxifylline	Phase III NCT05487755		PDE5
Recruiting	Tofogliflozin Metformin	Phase II NCT05469659		SGLT-2 Gluconeogenesis
Not yet recruiting	SGLT-2 inhibitor ± GLP-1 receptor agonist	Phase IV NCT05390892	Prevention of cardiovascular and renal complications	SGLT-2 GLP-1
Not yet recruiting	Empagliflozin Enalapril Maleate	Phase II-III NCT05373004		SGLT-2 ACE
Recruiting	Montelukast	Phase III NCT05362474		Leukotriene receptors
Not yet recruiting	Dulaglutide + Insulin Degludec	Phase IV NCT05218915		GLP-1
Recruiting	BI 690517 + Empagliflozin	Phase II NCT05182840	Diabetic and non-diabetic kidney disease	aldosterone synthase SGLT-2
Not yet recruiting	Trimetazidine	Phase II NCT05147194		Long-chain 3-ketoacyl-CoA thiolase
Not yet recruiting	Sodium zirconium cyclosilicate before Irbesartan	Phase II NCT04983979		K+ Angiotensin II receptor
Recruiting	Fenofibrate	Phase II NCT04929379		PPARα
Recruiting	SER150	Phase II-III NCT04881123	Patients in treatment with RAS inhibitors	Thromboxane synthase and thromboxane receptor
Not yet recruiting	Roflumilast	Phase III NCT04755946	Addition to standard therapy	Phosphodiesterase-4
Active, not recruiting	BI 685509	Phase II NCT04750577		Guanylate cyclase
Recruiting	Semaglutide	Phase III NCT04741074		GLP1
Recruiting	Roux-en-Y gastric bypass	Phase II NCT04626323		
Recruiting	AZD9977 ± Dapagliflozin	Phase II NCT04595370		Mineralcorticoid receptor SGLT-2
Active, not recruiting	Ezetimibe	Phase III NCT04589351		Cholesterol absorption
Recruiting	Atrasentan	Phase II NCT04573920	In addition to standard treatment with RAS inhibitor and SGLT2 inhibitor	Endothelin A receptor
Recruiting	Dapagliflozin ± AZD5718	Phase II NCT04492722	Diabetic and non-diabetic kidney disease	SGLT-2 FLAP
Recruiting	CSL346	Phase II NCT04419467	In addition to standard treatment	VEGF
Recruiting	GFB-887	Phase II NCT04387448	Diabetic and non-diabetic kidney disease	TRPC5 ion channel
Recruiting	Dapagliflozin ± MEDI3506	Phase II NCT04170543	In addition to standard therapy	SGLT-2 IL-33
Recruiting	Ertugliflozin	Phase IV NCT04027530		SGLT-2
Recruiting	Pegloticase	Phase II NCT03899883	Adolescents and young adults with youth-onset T2D	Uric acid
Recruiting	Fenofibrate	Phase III NCT03869931		PPARα
Recruiting	Pentoxifylline	Phase IV NCT03625648		Phosphodiesterase
Recruiting	Vertical Sleeve Gastrectomy	Phase I-II NCT03620773		
Active, not recruiting	Bardoxolone methyl	Phase III NCT03550443		Nrf2
Recruiting	Astragalus powder	Phase II-III NCT03535935	Addition to standard of care	
Recruiting	RAAS blockers ± Spironolactone	Phase IV NCT03502031		RAAS system Mineralocorticoid receptors
Active, not recruiting	Empagliflozin + linagliptin Gliclazide	Phase IV NCT03433248		SGLT-2 DPP-4 alpha-cell depolarization
Recruiting	Fisetin	Phase II NCT03325322	Analysis of adipose tissue-derived mesenchymal stem/stromal cell function	
Active, not recruiting	Renal Autologous Cell Therapy	Phase II NCT03270956		
Active, not recruiting	Jinshuibao capsule	Phase II-III NCT03164785	Addition to standard of care	
	Renal Autologous Cell Therapy			

(*continued on next page*)

Table 1 (*continued*)

Status	Intervention	Clinical trial number	Notes	Target
Active, not recruiting		Phase II NCT02836574	Comparison of immediate *vs.* delayed treatment	
Recruiting	Allogeneic bone marrow-derived mesenchymal stromal cell therapy	Phase I-II NCT02585622		
Recruiting	Fenofibrate	Phase III NCT01320345		PPARα

Abbreviations: ACE: angiotensin-converting enzyme; DPP-4: dipeptidyl peptidase 4; FLAP: 5-lipoxygenase-activating protein; GLP-1: glucagon-like peptide 1; IL-33: interleukin 33; Nrf2: nuclear factor erythroid 2 related factor 2; PDE5: phosphodiesterase type 5; PPAR-a: peroxisome proliferator-activated receptor alpha; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium-glucose-cotransporter-2; TRP5: transient receptor protein 5; VEGF-β: vascular endothelial growth factor.

cause of kidney failure. Indeed, diabetic mice lacking Nrf2 presented with worse renal pathology [90], whereas those with enhanced Nrf2 activation were protected from renal damage [91]. Bardoxolone methyl activates Nrf2 and significantly improved the GFR, measured by inulin clearance, in a phase II trial [92] and a phase III study is ongoing. In conclusion, the majority of active Phase II and III clinical trials are testing the effect of glucose lowering drugs on renal outcomes. While it is evident that the glycemic control is beneficial and mandatory in these patients, there is still the need to develop and test more tailored therapies, which target specific mechanisms of action involved in the pathogenesis of DKD. Ideally, targeted therapies would block the molecular and/or cellular mechanisms responsible for DKD progression, ameliorate patients' symptoms and postpone the end-stage disease.

6. Conclusions

DKD is a severe complication of diabetes, which leads to a net increase in morbidity and mortality rates. The mechanisms behind the development of kidney damage are still not fully understood and may target different component of the glomerular unit, such as podocytes, mesangial cells, and endothelial cells. Inflammation, hyperglycemia, and hormonal responses are all taking part into the onset of diabetic kidney damage, but multiple factors and pathways are involved. In this complex scenario, podocytes loss represents the final event, and it may occur through different mechanisms of derangement and cell death. Such mechanisms should be ultimately unveiled and targeted to identify novel markers aimed at distinguishing both DKD progressors and resistors as well as to design selective strategies to be tested in preclinical models and in clinical studies as novel therapeutic opportunities for patients with DKD.

CRediT authorship contribution statement

Adriana Petrazzuolo and Gianmarco Sabiu writing original draft, visualization, investigation; Emma Assi, Anna Maestroni, Ida Pastore, Maria Elena Lunati, Laura Montefusco, Cristian Loretelli, Giada Rossi, Moufida Ben Nasr, Vera Usuelli, Yanan Xie, Hari Baskar Balasubramanian, Monica Zocchi draft preparation, literature search; Jun Yang and Basset El Essawy editing, Francesca D'Addio and Paolo Fiorina writing, reviewing, and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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The authors have nothing to disclose.

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