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Recent Advances in Management of Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is not only the most common cause of end-stage renal disease world-wide but also increases the risk of mortality up to fourteen times compared to normoalbuminuric diabetic patients. After a long time of inertia, recent advances in the management of diabetes have added a valuable share to the effort of prevention and slowing the progression of DN. Beyond their hypoglycemic effects, dipeptidyl peptidase-4 inhibitors, and sodium glucose transporter 2 inhibitors have shown unique renoprotective mechanisms in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM). Advances in this field included, in addition, the introduction of many anti-oxidant and anti-inflammatory agents that proved in experimental and in vitro studies to add significant impact on development and progression of DN. Most of these agents are still waiting for clinical studies to confirm their safety and efficacy. Beside their role in improving plans of management, the new discoveries have improved our understanding of the pathogenesis of DN. This review will cover the updates in established and potential therapeutic modalities that would improve the management of DN after discussing the pathogenic pathways that help in understanding the mechanism of action of these different treatments.

Keywords: Type 1 diabetes, Type 2 diabetes, Diabetic nephropathy, Dipeptidyl peptidase-4 inhibitors, Sodium glucose transporter 2 inhibitors, Hyperfiltration

Abbreviations: DN: Diabetic Nephropathy; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; GFR: Glomerular Filtration Rate; UAE: Urine Albumin Excretion; ACR: Albumin:Creatinine Ratio; BP: Blood Pressure; RAS: Renin-Angiotensin System; ROS: Reactive Oxygen Species; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; SGLT2: Sodium Glucose Transporter 2; PCT: Proximal Convoluted Tubules; ATP: Adenosine Triphosphate; EMT: Epithelial-Mesenchyme Transition; NF-κB: Nuclear Factor-κB; TGF- β: Transforming Growth Factor- β; CCL2: Chemokine Ligand 2; MCP-1: Chemoattractant Protein-1; ICAM1: Intercellular Adhesion Molecule 1; PKC: Protein Kinase C; MAP: Mitogen-Activated Protein; MCs: Mesangial Cells; mTOR: mammalian target of Rapamycin; PI3K: Phosphatidylinosiol-3 Kinase; AKT: Protein Kinase B; CTGF: Connective Tissue Growth Factor; AII: Angiotensin II; ICN1: Notch1 Intracellular Domain; AT1R: Angiotensin Receptors1; AMP: adenosine monophosphate; CDK: Cyclin-Dependent Kinase; DPP-4: Dipeptidyl Peptidase-4; CD26: Cluster Of Differentiation 26; miR29: MicroRNA-29; VEGFR1: vascular endothelial growth factor receptor type 1; EndMT: Endothelial-Mesenchymal Transition; FGF23: Fibroblast Growth Factor 23; VDRs: Vitamin D Receptors; CKD: Chronic Kidney Disease; ET-1: Endothelin-1; nrf2: Nuclear Factor Erythroid 2-Related Factor 2; IL-1: Interleukin-1; TNF α: Tumor Necrosis Factor-α; Keap1: Kelch-Like ECH-Associated Protein 1; JAK/STAT: Janus Kinase/Signal Transducers And Activators Of Transcription; ACE: Angiotensin-Converting Enzyme; ESRD: End-Stage Renal Disease; ARB: Angiotensin II Type 1 Receptor Blocker; UKPDS: United Kingdom Prospective Diabetes Study; GLP-1: Glucagon Like Peptide-1; AMPK: Adenosine Monophosphate Kinase; MET: Mesenchymal to Epithelial Transition; PPARγ: Peroxisomal Proliferator-Activated Receptor γ; PKA: Protein Kinase A; BMI: Body Mass Index; SIRT1: Silent Information Regulator T1; SOCS1: Suppressor Of Cytokine Signaling-1

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Introduction

In its earliest stage, diabetic nephropathy (DN) manifests by renal hyper-perfusion and hypertrophy [1]. This stage starts with the onset of diabetes in T1DM before insulin treatment. This is called stage 1 and is followed few years later by stage 2 characterized by clinical silence and morphologic changes characteristic of diabetic glomerulosclerosis. Glomerular filtration rate (GFR) is still higher than normal during this stage. Some diabetic patients continue in this stage throughout their lives. Increased urine albumin excretion (UAE) was first described by Keen and Chlouverakis [2] in 1963. However, microalbuminuria became popular twenty years later after the results of fourteen years longitudinal study that disclosed the predictive value of increased UAE were published [3]. Microalbuminuria is the salient feature of stage 3 DN, also called the stage of incipient nephropathy, and is defined as UAE >30 mg/d, >20 µg/min, or albumin:creatinine ratio (ACR) >30 mg/g creatinine. This stage is initially associated with increased GFR. However, GFR starts a consistent decline that becomes more evident with the continuous increase of UAE above 300 mg/d, 200 µg/min, or when ACR exceeds 300 mg/g. This is the stage of overt nephropathy, also called stage 4 DN **(Figure 1)** [1,4]. Progressive increase in blood pressure (BP) is usually associated with these renal changes. After the introduction of the different renin-angiotensin system (RAS) blockers in the management of DN, little was added to improve the management of this disease. Moreover, RAS blockers were ineffective in the primary prevention of DN in T1DM and T2DM [5-8]. Additional studies failed to demonstrate a renal protective effect of RAS blockers when used in diabetic patients without overt nephropathy [9]. These results have criticized the use of RAS blockers in incipient nephropathy. RAS blockers were then limited to patients with overt nephropathy [10,11].

The risk of DN is strongly linked to poor glycemic control in both T1DM and T2DM [12,13]. In addition, there is strong evidence that tight blood sugar control has a significant impact on primary prevention of DN [14,15]. However, tight glycemic control is not always an easy task.

After a long time of inertia, many novel agents were introduced as potential additions to the standard of care treatment of DN. These agents have also improved our understanding of the pathogenesis of DN. Moreover, the introduction of some of these agents will change the strategy of management from being postponed to stage 4 DN to a much earlier stage, namely, stage 1DN. This hypothesis needs verification and assessment of cost effectiveness.

In this review, we will concentrate on the different novel therapeutic tools highlighting their impact on the prevention and withhold of the progression of DN.

Pathogenesis

The overproduction of reactive oxygen species (ROS) is one of the hallmarks of diabetic kidney. ROS overproduction is the main cause of DN [16]. Hyperglycemia induces nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme activity and is responsible for ROS overproduction [17]. Up-regulation of sodium glucose transporter 2 (SGLT2) in the brush border of proximal convoluted tubules (PCT) is another pathway of ROS overproduction. SGLT2 up-regulation causes uric acid (UA) overproduction with consequent NADPH oxidase-ROS induction [18]. Excess ROS mediates podocyte apoptosis and alteration in the slit diaphragm podocin protein **(Figure 2)** [19], increases intracellular oxidative stress, mitochondrial injury, adenosine triphosphate (ATP) depletion [20,21], endothelial injury, RAS activation and increased epithelial-mesenchyme transition (EMT) with consequent fibrosis [22]. ROS overproduction activates the nuclear factor-κB (NF-κB) within the kidney [23]. NF-κB translocates to the nucleus to trigger several genes like those encoding transforming growth factor-β (TGF-β), chemokine ligand 2 (CCL2) also known as monocyte chemoattractant protein-1 (MCP-1) and intercellular Adhesion Molecule 1 (ICAM1) [24-27]. This leads to macrophage recruitment and excess collagen deposition within the diabetic kidney **(Figure 3)**. Beside activation of NF-κB, ROS activates protein kinase C (PKC) and mitogen-activated protein (MAP) kinase within mesangial cells (MCs). All these factors stimulate overproduction of extracellular matrix proteins **(Figure 4)** [27].

Activation of mammalian target of Rapamycin (mTOR) is another feature of DN. Hyperglycemia stimulates phosphatidylinosiol-3 kinase (PI3K) and protein kinase B (AKT) pathways, with subsequent activation of mTOR. Activated mTOR is responsible for basement membrane thickening, mesangial matrix expansion [28], and renal fibrosis. The mTOR induced renal fibrosis is a consequence of fibroblast proliferation, EMT and the expression

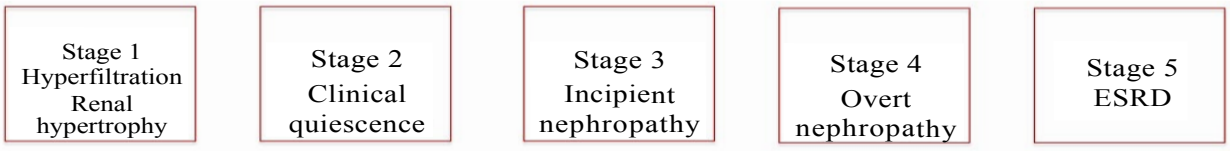

Figure 1 Stages of Diabetic nephropathy. Stage 2 is characterised by the progressive increase in mesangial deposits on light microscopy without corresponding clinical or laboratory findings; ESRD= end stage renal disease when eGFR≤15 mL/min/1.73 m^2.

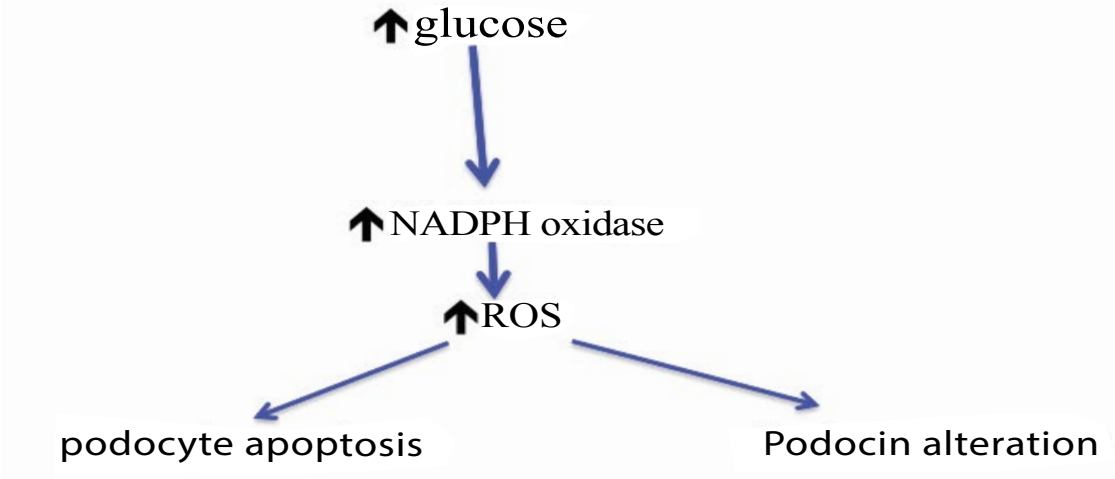

Figure 2 Reactive oxygen species mediated podocyte injury and podocin protein alteration. NADP= Nicotinamide adenine dinucleotide phosphate; ROS= Reactive oxygen species.

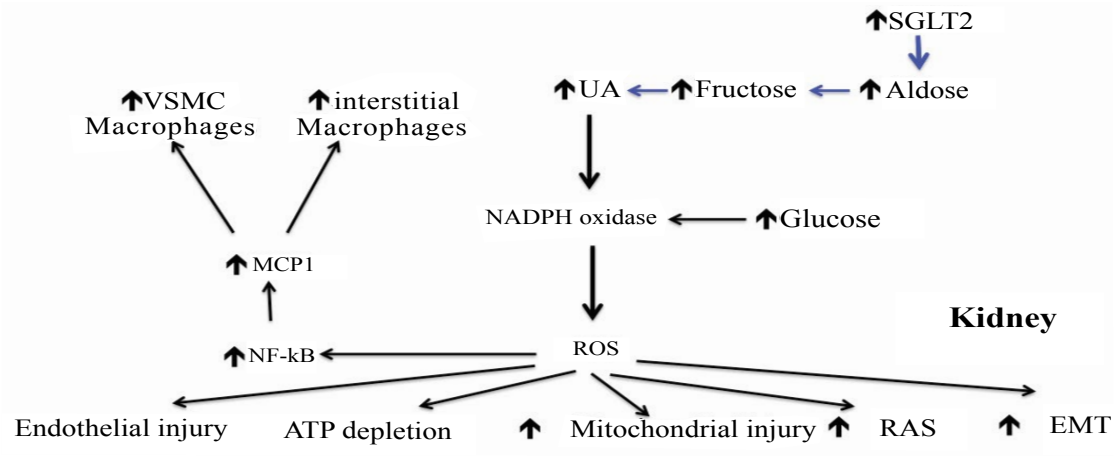

Figure 3 Different pathogenic mechanisms of kidney injury possibly induced by uric acid. UA= uric acid; ROS= reactive oxygen species; NF-κB= Nuclear Factor kappa B; MCP1= Macrophage Chemoattractant protein-1; RAS= Renin angiotensin system; EMT= Epithelium mesenchyme transition; VSMC= Vascular smooth muscle cells.

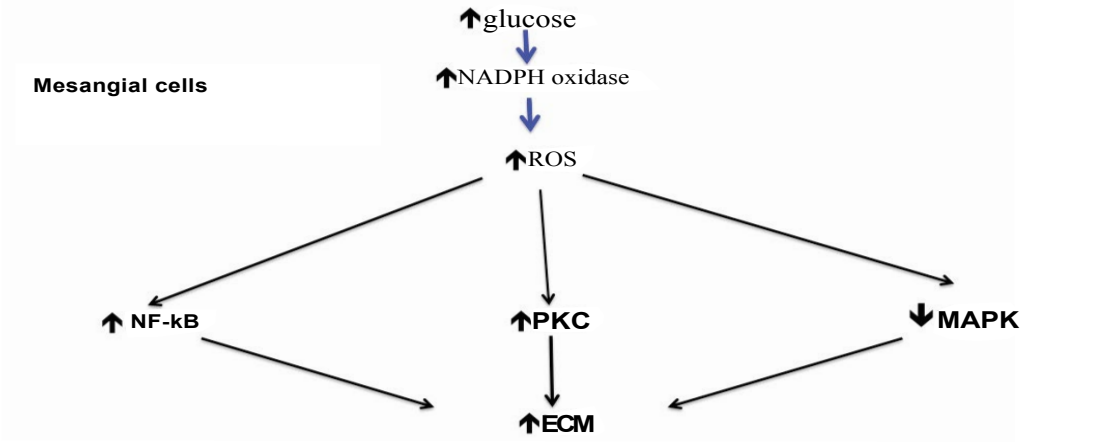

Figure 4 Hyperglycemia induced mesangial expansion. NADP= Nicotinamide adenine dinucleotide phosphate; ROS= Reactive oxygen species; NF-κB= Nuclear Factor kappa B; PKC= Protein kinase C; MAPK= Mitogen-activated protein kinase; ECM= Extracellular matrix.

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of TGF-β and connective tissue growth factor (CTGF, CCN2) [29,30]. Stimulation of MCP1 by mTOR leads to increased macrophage recruitment within the interstitium of the kidney [30]. In addition, increased mTOR activity can aggravate tubular epithelial damage and apoptosis **(Figure 5)** [31].

CCN2 is the newer alternative name of CTGF. It has an eminent role in DN [32]. Within the diabetic kidney, CCN2 is detected in almost all cell types [33]. When exposed to high glucose, the glomeruli of diabetic rats and human MCs express a high activity of CCN2 [34]. In the diabetic kidney, CCN2 expression is stimulated by TGF-β1, AGE, and angiotensin II (AII). The CCN2 stimulates EMT, fibroblast proliferation, and extracellular matrix accumulation **(Figure 6)** [32].

Nephrin and podocin are slit diaphragm proteins synthesized by podocytes. They are essential for the maintenance of the sieving properties of the glomerular basement membrane [35]. The addition of AII to cultured podocytes causes in vitro loss of nephrin [36]. Moreover, infusion of AII in the renal artery of rat kidney results in effacement of foot processes of podocytes with an increase in proteinuria [37]. In diabetic rats, AII synthesis blockers preserve the nephrin within the slit diaphragm and decrease UAE [38]. AII down-regulates nephrin through a transmembrane receptor called Notch1. Notch1 plays a role in cell differentiation and renal development. When Notch1 receptor is activated, it leads to the release of the active Notch1 intracellular domain (ICN1). ICN1 translocates to the nucleus. Additionally, notch 1 triggers another transcription factor called the snail that exists within the cytoplasm of podocytes. Upon signaling of notch1 by AII, both ICN1 and snail translocate to the nucleus and share in repression of nephrin expression, stimulation of apoptosis, podocyte loss and consequent increase of UAE **(Figure 7)** [38,39]. Inhibition of Notch1 signaling pathway in human and animal podocytes was associated with restored

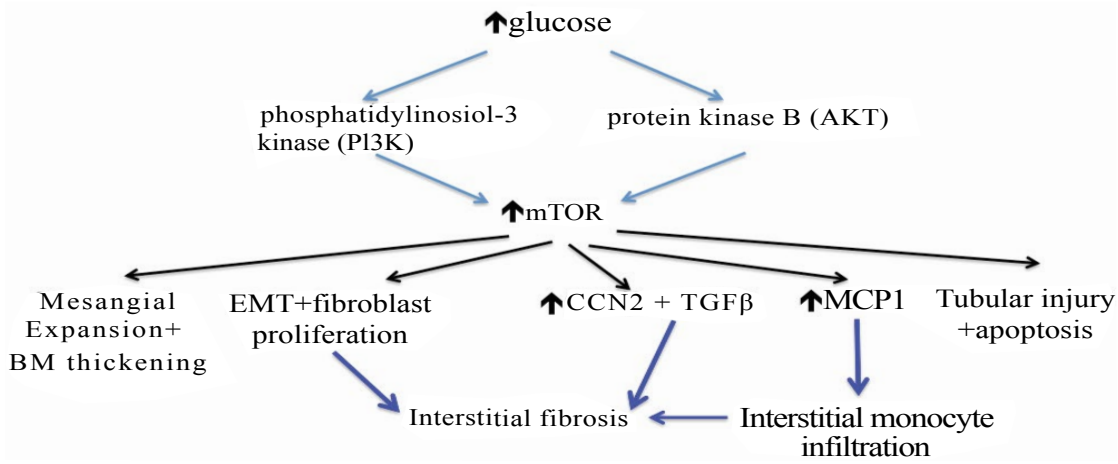

Figure 5 Consequences of mTOR activation induced by hyperglycemia. mTOR= mammalian target of rapamycin; BM= basement membrane; EMT= Epithelium mesenchyme transition; CCN2= Connective tissue growth factor; TGFβ= Transforming Growth Factor β; MCP1= Macrophage chemoattractant protein.

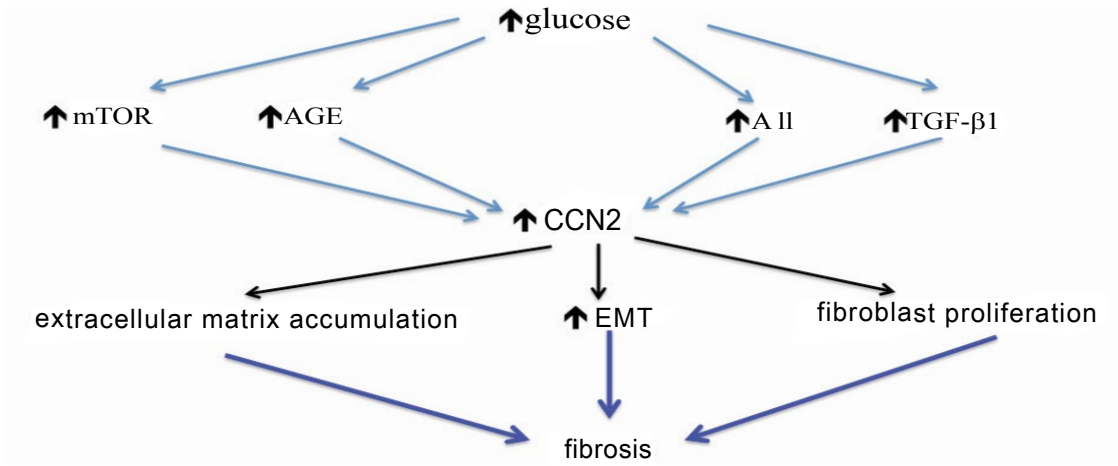

Figure 6 CCN2 mediated glomerular and interstitial fibrosis. mTOR= Mammalian target of rapamycin; AGE= Advanced glycation endproducts; A II= Angiutensin II; TGFβ= Transforming Growth Factor β; CCN2= Connective tissue growth factor; EMT= Epithelium mesenchyme transition.

nephrin protein, decreased podocyte apoptosis, and attenuated UAE [40]. As mentioned before, ROS induced by hyperglycemia mediates alteration of podocin **(Figure 2)** [19].

The expression of RAS genes is induced in diabetes [41]. Angiotensin receptors1 (AT1R) are up-regulated in diabetic rat kidneys, while AT2R are down-regulated [42]. In streptozotocin-induced diabetes rats, increased intraglomerular capillary pressure is the initiating early event. Increased mechanical strain increases AII production and up-regulates AT1R. This increase in AII maintains and aggravates glomerular hypertension [43,44].

Glomerular hyperperfusion and hyperfiltration are the earliest manifestations of diabetic kidney. These glomerular hemodynamic changes are due to afferent and to less extent efferent arteriolar vasodilatation as a consequence of changes in various biochemical factors, including nitrous oxide, atrial natriuretic factor, adenosine, glucagon, and insulin [45]. Increased glucose in the glomerular ultra-filtrate stimulates SGLT2 gene with consequent increased proximal tubular absorption of filtered sodium and glucose. Distal sodium delivery will consequently diminish. Sodium reabsorption by the macula densa would accordingly diminish. Hence, ATP consumption and adenosine monophosphate (AMP) production diminish. Adenosine, the byproduct of AMP, is a potent vasoconstrictor. Decreased availability of adenosine results in afferent arteriolar vasodilatation **(Figure 8)** [46,47]. This tubuloglomerular feedback would start glomerular hyperperfusion and hyperfiltration. These hemodynamic changes trigger AII that maintains these changes.

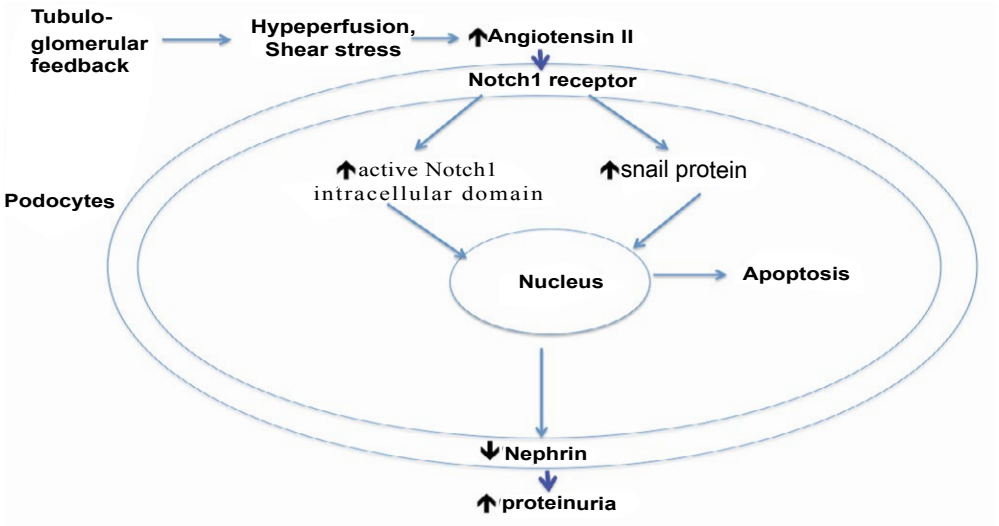

Figure 7 Mechanism of podocyte injury and proteinuria induced by angiotensin II.

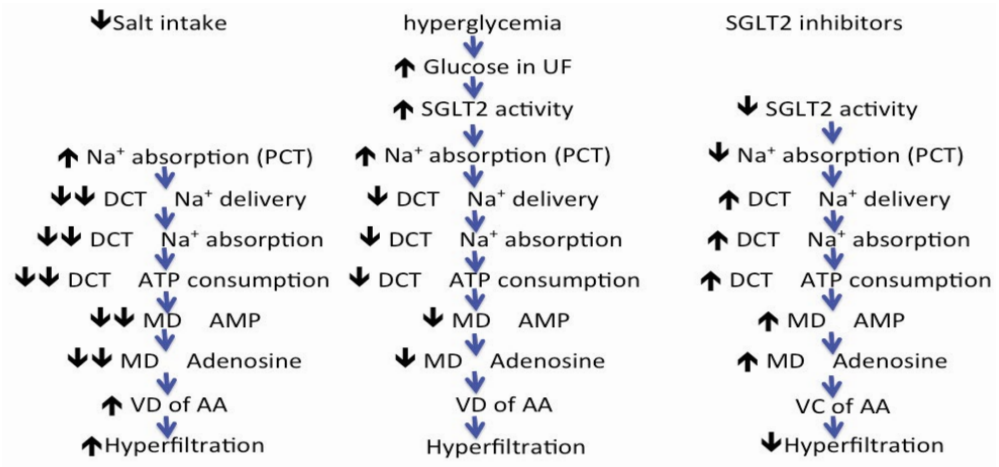

Figure 8 Tubuloglomerular feedback: impact of low salt intake and SGLT2 inhibitors. UF= glomerular ultrafiltrate; SGLT= Sodium glucose transporter; PCT=proximal convoluted tubules; DCT= distal convoluted tubule; MD=Macula densa; AMP= adenosine monophosphate; VD= Vasodilation; AA= Afferent arteriole.

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In addition, SGLT2 contributes to hyperglycemia-induced PCT cell senescence. Knocking down of SGLT2 can abort in vitro induction of P21 in PCT when exposed to hyperglycemia. P21 inhibits cyclin-dependent kinase (CDK). CDK is an inhibitor of cell senescence **(Figure 9)** [48,49].

Dipeptidyl peptidase-4 (DPP-4) is a cell surface enzyme that was originally characterized as a T cell cluster of differentiation 26 (CD26). DPP-4 degrades incretins secreted by the gut. It is also found in the endothelial cells in multiple organs including the kidney [50]. The soluble circulating form of DPP-4 is responsible for DPP-4 activity in human serum and is originally shed from cell membranes [51]. MicroRNA-29 (miR29) suppresses DPP-4 gene in normoglycemic status. This suppression is lost in hyperglycemic state with consequent increase of cell surface DPP-4 activity [52]. DN is characterized by increased expression of surface DPP-4 on endothelial and tubular epithelial cells. Activated DPP-4 induces phosphorylation of integrin β1. Activated DPP-4 phosphorylated integrin β1 complex up-regulates TGF β receptor dimerization and activates the vascular endothelial growth factor receptor type 1(VEGFR1). Up-regulated TGF β receptor and VEGFR1 stimulate endothelial-mesenchymal transition (EndMT). These changes enhance fibrogenesis **(Figure 10)** [53].

The serum level of fibroblast growth factor 23 (FGF23), the phosphatonin responsible for renal phosphate elimination, is higher in T2DM [54]. Although the kidneys of normal rats do not express FGF23 mRNA, it appears in the kidneys of diabetic rats 4 mo after onset of diabetes and increases thereafter [55]. FGF23 suppresses 1-α hydroxylase gene. This leads to decreased calcitriol synthesis. An inverse relation between serum calcitriol and serum renin activity was encountered in a large cohort study [56], a finding that discloses the cross talk between FGF23 and the RAS **(Figure 11)**. Vitamin D receptors (VDRs) suppress activation of NF-κB and MCP1 induced by hyperglycemia [57]. Stimulation of VDRs by 1-α,25-dihydroxyvitamin D3 suppresses activation

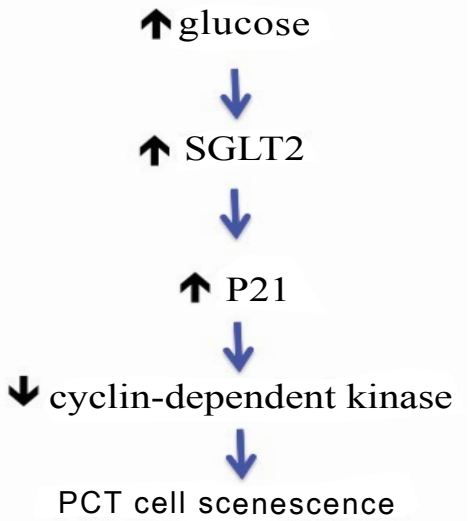

Figure 9 SGLT2 mediated PCT cell senescence. SGLT= Sodium glucose transporter; PCT= Proximal convoluted tubules.

of RAS and TGF-β induced by hyperglycemia in MCs [58]. After adjustment for GFR, and parathyroid hormone, FGF23 was found as an independent predictor of DN progression [59]. Klotho acts as a co-receptor to enhance FGF23 binding to its ubiquitous FGF receptors. Deficient Klotho is one of the causes of increasing level of FGF23 in chronic kidney disease (CKD) [60]. Plasma α-klotho level negatively correlates with UAE in T2DM patients [61]. In patients with T2DM, systemic hypertension, and albuminuria, the RAS blockers stimulate α-klotho production [62,63].

Another feature of diabetic patients is the persistent elevation of endothelin level. Endothelin-1 (ET-1) is a powerful vasoconstrictor agent with additional pro-inflammatory and pro-fibrogenic activities. ET-1 is incriminated in DN progression [64]. ET1 has 2 receptor named ETA and ETB. Stimulation of ETA causes vasoconstriction, cell proliferation, and extracellular matrix accumulation while ETB mediates vasodilatation [65]. Increased ET-1 in the kidney of T2DM db/db mice positively correlated with collagen deposition within their kidneys [66].

In the last 2 decades, inflammation has evolved as an important pathogenic mechanism of DN. The identification of transcription factors, cytokines, chemokines, adhesion molecules, and nuclear receptors would lead to the development of new therapeutic strategies [23]. NF-kB is the pivotal transcription factor involved in DN. NF-κB activators includes hyperglycemia, free oxygen radicals, and proteinuria [67]. Beside its role in macrophage recruitment and excess collagen deposition, activated NF-κB triggers PKC [68], RAS [69], advanced glycation end product proteins (AGEs) accumulation [70], and oxidative stress [71]. NF-κB activation can be offset by thiazolidinediones [72], 1,25-dihydroxyvitamin D3 [73], and Nuclear factor erythroid 2-related factor 2 (nrf2) agonists [74]. Interleukin-1 (IL-1), IL-6, IL-18, and tumor necrosis factor-α (TNF α) have distinguished role in the pathogenesis of DN [75]. Nrf2 regulates the synthesis of antioxidants and cytoprotective factors that can muffle the oxidative stress and the pro-inflammatory signals [76]. It does not exist free in the cytoplasm, but rather as an inactive complex bound to Kelch-like ECH-associated protein 1 (Keap1) [77]. Keap1 has many sensors of the intracellular redox state. On modifying these sensors, ROS can dissociate Nrf2 from Keap1/Nrf2 complex [78]. The dissociated Nrf2 translocates to the nucleus where it triggers the genes encoding the antioxidant and detoxifying molecules, thus activating their transcription. In addition, Nrf2 inhibits transcription of NF-kB [79]. Nrf2 is adaptively activated in diabetic status but is not activated enough to resist the oxidative stress provoked by hyperglycemia [80]. The association between oxidative stress and inflammation stimulated planning of studies looking for efficiency of Nrf2/Keap1 activators as potential renoprotective agents [81].

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway evidently mediate the contribution of hyperglycemia to proliferation, inflammation, and fibrosis encountered in DN [82]. Exposure of cultured glomerular MCs to both high levels of glucose and A2 activates JAK/STAT signaling [83]. A significant increase of JAK2 protein in glomerular and tubulointerstitial compartments is encountered

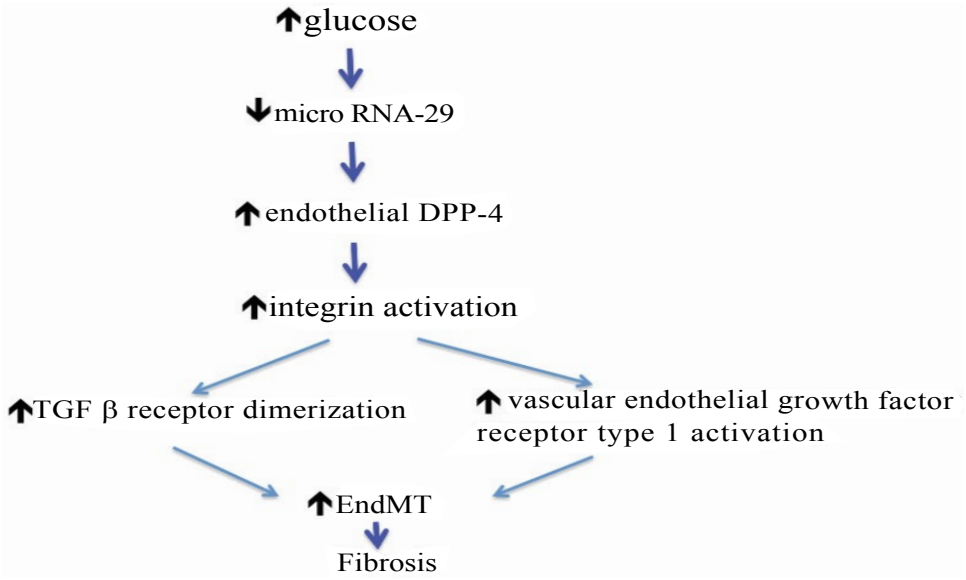

Figure 10 DPP-4 mediated renal fibrosis. DPP4= Dipeptyl peptidase-4; TGFβ= Transforming Growth Factor β; EndMT= Endothelial-mesenchymal transition.

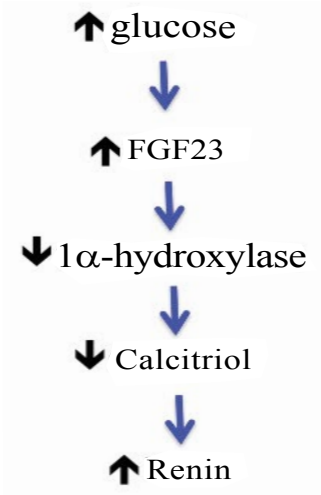

Figure 11 FGF23 mediated increased renin activity in diabetic patients. FGF23= Fibroblast growth factor 23.

in patients with DN, with a negative correlation between JAK2 mRNA levels and GFR [82].

Diagnosis of DN

The pathologic changes of DN include mesangial expansion, diffuse glomerular basement membrane thickening, diffuse glomerulosclerosis, nodular glomerulosclerosis, afferent and efferent arteriolar hyalinosis, interstitial mononuclear cell infiltrate, tubular atrophy, and interstitial fibrosis [84]. Moreover, diabetic patients can develop non-diabetic renal disease with a prevalence that varies from 10% to 85% in different studies [85-88]. Frequently, diabetic patients do not require kidney biopsy when they develop proteinuria unless non-diabetic kidney disease is suspected [89]. This suspicion is raised when duration of diabetes is less than 5 years, BP is normal, microscopic or frank hematuria is detected, or when diabetic retinopathy is absent in T1DM [89]. However, the presence of microscopic hematuria does not preclude DN. T2DM patients can develop DN without antecedent diabetic retinopathy in contrast to T1DM [90].

Management of DN

Therapeutic interventions that are clinically approved are going to be discussed under the heading “approved interventions”. Other modalities that are not yet clinically approved will be discussed under “potential therapeutic modalities”.

Approved interventions (Table 1)

These interventions include control of BP, control of blood sugar, use of hypolipidemic agents, quitting smoking, diet control, managing hyperuricemia, hyperphosphatemia and metabolic acidosis, use of pentoxifylline, sarpogrelate and use of vitamin D receptor agonists.

Control of BP: Control of BP significantly muffles GFR decline in pre-dialysis DN patients [91]. Target BP in DN patients is 130/80 mmHg [92]. In DN patients with proteinuria, RAS blockers are the 1st anti-hypertensive agents of choice thanks to their significant impact on GFR decline [93,94]. They achieve their favorable effect through many mechanisms including the reduction of glomerular tuft pressure [95], the inhibition of cytokine overproduction [96-98], the increase of serum and tissue angiotensin1-7 [99] and the stimulation of Klotho gene expression. Klotho gene suppression might mediate RAS-induced renal damage, a mechanism that clarifies the renal protective effects of these agents [61-63]. However, RAS blockers are not able to fully attenuate hyperfiltration in T1DM patients. This failure was still observed even with dual RAS inhibition using angiotensin-converting

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Table 1: Approved interventions that can prevent development and progression of DN.

Drug class	On-target action	Off-target actions	Remarks	Ref.
Antihypertensive RAS blockers	Blood pressure control	UAE↓, GTP↓, K^+ ↑, AT1-7↑, cytokines↓, Klotho↑	Failed to prevent DN, can accelerate progression in advanced CKD & old age	[7,8,10,11, 61-63, 91-103]
Blood Sugar control	Normalize blood sugar	UAE↓, incident CKD↓, CKD progression ↓	Hypoglycemia increases morbidity & mortality risk esp with SU & insulin	[105-109]
• Metformin	"	AMPK↑, mTOR↓	↓ dose by 50% if GFR<60 mL/min, stop if GFR<30	[111-119]
• Pioglitazone	"	UAE↓, NF-κB↓, CKD progression ↓	Salt and water retension, osteopenia, BW↑	[120-124]
• GLP-1 agonists	"	BW↓, UAE↓, ROS↓, TGF-β1↓, CCN2↓	Nausea, vomiting, stop if GFR<30	[125-127]
• DPP-4 inhibitors	"	UAE↓, ROS↓, CCN2↓,EndMT↓, CKD progression ↓	Hypoglycemia less likely, dose adjustment with CKD progression except Linagliptin	[128-140]
• SGLT2 inhibitors	"	Hyperfiltration ↓, BW↓, BP↓,UA↓, ROS↓.	stop if GFR<30	[141-157]
Statins	↓Serum Cholesterol	↓CVD	No effect on stroke, CKD progession or mortality	[158-160]
Quitting smoking		↓DN progress		[161-163]
Diet control				
• salt restriction	↓BP, ↓UAE,	↓DN progress	Salt paradox in very low salt	[164-169]
• ptn restriction	↓DN progress		Of value only in T1DM	[170-176]
Hypouricemic agents	↓UA	↓UAE, ↓DN progress		[178-188]
Phosphate handling				
• ↓P intake +sevelamer	↓Serum P	↓DN progress, ↓mortality		[189,199]
HCO3 supplement	Treat acidosis	↓DN progress	May↑BP, may ↑edema	[200-202]
Pentoxifylline	RBCs rheology	↓UAE, ↓DN progress	1200 mg/day	[203,204]
Sarpogrelate	↓thromboxane A2	↓UAE, ↓MCP1		[205,206
Paricalcitol	↓PTH	↓UAE		[207]

enzyme (ACE) and direct renin inhibitors [7,8]. Moreover, RAS blockers failed to fully prevent the progression of renal injury in T1DM [100]. In addition, the efficacy of ACE inhibitors in reducing the incidence of overt nephropathy was not encountered in 2 studies in T2DM with incipient nephropathy [101,102]. Moreover, the incidence of end-stage renal disease (ESRD) was not significantly decreased using either ACE inhibitors [103] or an angiotensin II type 1 receptor blocker (ARB) [104]. RAS blockers prescription became limited to diabetic patients with overt nephropathy [10,11].

Control of blood sugar: In order to appreciate the impact of optimized blood sugar control on the course of DN, Fioretto et al. [105], looked at kidney pathologic changes in DN of T1DM patients after undergoing Pancreas transplantation. Repeated kidney biopsies demonstrated that by 10 years post-transplant, normoglycemia was associated with the reversal of glomerulopathy, interstitial fibrosis and tubular atrophy initially encountered [105]. In the United Kingdom Prospective Diabetes Study (UKPDS), blood sugar control for 12 years was associated with 33% reduction in the relative risk of progression from normoalbuminuria to microalbuminuria or from micro to overt proteinuria [106]. In the tight glycemic control group, the chance of doubling of serum creatinine was also significantly reduced. Control of blood glucose might also delay CKD progression and postpones the need for dialysis [107,108]. In a recent study of 891 670 US diabetic veterans with estimated GFR >60 mL/min per 1.73 m^2, HbA1c >7.0% was associated with worse risk of all-cause mortality and incident CKD in all systolic BP categories [109]. On the other hand, a meta-analysis of 5 mega-trials that randomly assigned 27159 T2DM patients showed that intensive glycemic control (mean HbA1c=6.6%) compared to those on convention care (mean HbA1c=7.4%) did not improve overall or cardiovascular mortality or ESRD [110].

Metformin, thiazolidinediones, glucagon like peptide-1 (GLP-1) agonists, DPP-4 inhibitors, and SGLT2 inhibitors have additional favorable effects in DN patients beyond their hypoglycemic effects.

Metformin activates adenosine monophosphate kinase (AMPK) pathway [111,112]. AMPK activation leads to inhibition of mTOR [113]. Metformin is also able to inhibit mTOR independent of AMPK [114]. Metformin inhibits hyperglycemia-induced podocyte apoptosis, an effect mediated by AMPK activation and mTOR signaling inhibition [115] and through the restoration of expression of nephrin [116]. In addition, metformin can promote mesenchymal to epithelial transition (MET), a consequence of up-regulation of the epithelial marker cadherin [117]. In T2DM rats, metformin suppresses inflammatory, oxidative and profibrotic renal damage markers and thus improves renal damage [118]. The kidney excretes metformin, thus it can accumulate with the continuous decrease of kidney function. In order to avoid adverse effects, the dose of metformin should be reduced by 50% if GFR goes below 45 mL/min and should be stopped if GFR becomes below 30 mL/min [119].

Peroxisomal proliferator-activated receptor γ (PPARγ) is expressed in different renal cells that include MCs, tubular cells, and renal medullary interstitial cells [120]. The thiazolidinedione, pioglitazone hydrochloride, is one of PPARγ agonists that have anti proteinuric effect in animal models of T1DM and T2DM through amelioration of glucose-induced oxidative stress, and down-regulation of MCP1, ICAM1, NF-κB, and TGF β [23]. In order to explore the possible renoprotective mechanisms of pioglitazone hydrochloride, its effect on urinary podocalyxin and MCP-1 excretion were studied in T2DM. After 12 weeks of pioglitazone treatment, there was a significant decline in systolic and diastolic BP, UAE, and urinary podocalyxin excretion. The podocyte-protective capacity of pioglitazone was partly attributed to its effective suppression of local renal inflammation induced by diabetes [121]. The antiproteinuric effect of pioglitazone was still evident after its administration to T2DM patients already treated with RAS blockers [122]. In T2DM patients at stages 3 and 4 of CKD treated with losartan and pioglitazone, the declines in GFR below baseline measurements were significantly slower compared with those treated with losartan alone [123]. After 12 wk of pioglitazone treatment, urinary TGF- β 1 excretion decreases significantly [124]. Pioglitazone use is associated with increased body weight together with salt and water retention. Precaution is therefore needed to avoid these undesirable adverse effects.

GLP-1 receptors deficient Rats develop up-regulation of renal NADPH oxidase, increased glomerular ROS, reduced renal cAMP and protein kinase A (PKA) activity, increased UAE, and advanced mesangial expansion [125]. These changes could be explained by the antioxidative properties of GLP-1. The GLP-1 agonist exendin inhibited expression of TGF- β 1 and CCN2 by human mesangial cells cultured in high glucose medium [126]. Liraglutide suppressed the progression of DN as demonstrated by decreased levels of renal NADPH oxidase, decreased levels of glomerular ROS, elevated renal cAMP, elevated renal PKA activity, reduced UAE and mesangial expansion in diabetic mice [121]. We still lack clinical studies of GLP-1 agonists in patients with T2DM and moderate-to-severe CKD [127].

DPP-4 inhibitors were reported as beneficial renoprotective agents against DN in both experimental and clinical studies. In clinical practice, two types of DPP-4 inhibitors are used: Vildagliptin, sitagliptin, and saxagliptin are dipeptide mimetics while linagliptin and alogliptin are nonpeptidomimetics. In addition to their hypoglycemic effect, DPP-4 inhibitors are protective against kidney fibrosis [52]. Vildagliptin treatment significantly decreased UAE, improved GFR, and dose-dependently inhibited interstitial expansion, glomerulosclerosis, and the thickening of the glomerular basement membrane and significantly decreased renal tissue expression of T GF- β1 in T1DM rats with DN [128]. When T2DM patients were treated by vildagliptin for 8 weeks in a single-arm clinical study, UAE significantly decreased by 44.6% [129]. On the other hand, treatment of T2DM rats with sitagliptin did not significantly affect kidney size, mesangial expansion, glomerular atrophy, glomerular basement membrane thickening, tubular degeneration, tubular atrophy, or interstitial fibrosis while significantly reduced global glomerulosclerosis and vascular glomerular pole hyalinosis [130]. Sitagliptin was able to significantly decrease UAE in normoalbuminuric, microalbuminuric, and overt proteinuric patients in a small-uncontrolled clinical trial on thirty-six T2DM patients [131]. In comparison to other oral hypoglycemic agents that achieved a comparable decrease in HbA1c, sitagliptin significantly reduced UAE in an open-labeled, prospective, randomized study in T2DM [132]. However, a more recent and larger uncontrolled trial of sitagliptin in T2DM patients failed to show a consistent favorable effect on UAE. While two-thirds showed a reduction, one-third of the patients experienced an exacerbation of UAE. Reduction of UAE was likely related to reduction of BP and eGFR [133]. Because of its non-renal route of excretion, linagliptin, in contrast to other DPP-4 inhibitors, does not need dose adjustment with GFR decline. A pooled analysis of four clinical studies of 217 T2DM patients with increased UAE that are receiving stable doses of RAS inhibitors, patients were randomized to either linagliptin 5 mg/d (n=162) or placebo (n=55). After 24 wk of treatment, UAE decreased significantly in the linagliptin group (-32% *vs* -6% in placebo group) [134]. Linagliptin directly inhibits DPP-4- integrin - β1 interaction, and thus blunts pathological TGF- β signaling and restores the physiological balance of VEGF receptors. Consequently, EndMT and subsequent renal fibrosis are inhibited [53]. Over five thousands of inadequately controlled T2DM patients were recruited to 13 phase 2 or phase 3 randomized, double-blind, placebo-controlled, clinical trials of linagliptin, out of them 3505 received linagliptin, and the remaining cases received placebo. The primary composite outcome included the switch to a higher grade of albuminuria, the increase of serum creatinine above 250 μmol/L, the reduction of eGFR by 50%, the development of acute kidney injury, or death from any cause. The primary composite outcome was significantly lower in the linagliptin group (12.8% in linagliptin versus 15.6% in the placebo group) [135]. The renoprotective effect of linagliptin possibly extends beyond DN. In comparison to telmisartan, linagliptin significantly decreased interstitial fibrosis in 5/6 nephrectomized rats. UAE reduction was comparable to telmisartan in these animals [136]. Saxagliptin add-on treatment in a rat model of T1DM has limited renal hypertrophy, TGF-β upregulation, NF-κB-mediated macrophage infiltration, and histological markers of tubulointerstitial fibrosis in spite of the lack of change in UAE [137]. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, the renal outcomes of 16492 T2DM patients, randomized to saxagliptin versus placebo and followed for a median of 25 months were evaluated. Saxagliptin decreased UAE but had no effect on eGFR, an effect that was independent of baseline renal function [138] and the glycemic effect of saxagliptin [139]. In order to assess if alogliptin has a renoprotective effect, a crossover study with sitagliptin and alogliptin in 12 incipient nephropathy T2DM patients taking ARBs was performed. The study design consisted of three treatment periods: the first period of 4 wk using sitagliptin 50 mg/d followed by the second period using alogliptin 25 mg/d for 4 wk instead, and lastly the third period of 4 wk reusing sitagliptin 50 mg/d. The three treatment periods showed no significant changes in

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body mass index (BMI), BP, serum lipids, serum creatinine, eGFR, and HbA1c. After the switch from sitagliptin to alogliptin, the studied candidates experienced reduced UAE and 8-hydroxy-2'-deoxyguanosine (an oxidative stress marker). These observations have led to the conclusion that the use of alogliptin on top of ARB would offer additional protection against the early-stage of DN beyond that attributed to glycemic control via reduction of renal oxidative stress [140].

SGLT2 inhibitors, the members of a new class of hypoglycemic agents, succeeded to slow progression of DN. SGLT2 inhibition increases distal sodium delivery, increased distal tubular sodium absorption and hence increases adenosine production, causing afferent arteriolar vasoconstriction with fall in renal blood flow, decreased hyperfiltration and reduced renal injury. In RENAAL trial, losartan treatment of T2DM patients having DN was associated with the delay in the onset of ESRD by 28% during a mean follow-up of 3.4 years [141]. On the other hand, empagliflozin in EMPA-REG trial in T2DM patients with DN achieved 55% reduction of the chance of ESRD over a median observation time of 3.1 years [142]. Empagliflozin was also associated with a significant reduction in incident or worsening nephropathy by 39%, progression to overt albuminuria by 38% and doubling of serum creatinine by 44% [142]. The significant favorable outcome of SGLT2 inhibitors is attributed to their effect on hyperfiltration, BP, body weight and serum UA in both T1DM and T2DM [143-145]. We would like to emphasize that the effect of SGLT2 inhibitors on renal blood flow is not related to RAS blockade as empagliflozin and dapagliflozin do increase plasma aldosterone and A2 [146,147], as well as urinary ACE and ACE2 [148].

One thousand four hundred and fifty T2DM patients receiving metformin were randomly assigned to either once-daily canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride titrated to 6-8 mg for 2 years. In glimepiride, canagliflozin 100 mg, and canagliflozine 300 mg groups, eGFR declined by 3.3, 0.5, and 0.9 mL/min per 1.73 m^2 per year respectively ($P<0.01$ for each canagliflozin group versus glimepiride) in spite of comparable reductions in HbA1c. UAE declined more with canagliflozin 100 mg or canagliflozin 300 mg than with glimepiride. These results support the renoprotective effect of canagliflozin compared with glimepiride independent of the glycemic effect [149]. SGLT2 inhibitors muffle hyperglycemia-induced expression of toll-like receptor-4, increased nuclear DNA binding for NF-kB and activator protein 1, increased collagen IV expression as well as IL-6 secretion within renal parenchyma [150]. They can also inhibit high glucose- induced oxidative stress and interstitial macrophage infiltration. SGLT2 antagonists also suppress fibrotic and inflammatory genes [151,152]. Tofogliflozin, ipragliflozin and luseogliflozin are other members that showed similar renoprotective effects in animal studies [153-155], but lack clinical trials. The body weight and BP lowering effects of SGLT2 inhibitors are still observed in T2DM patients in stage 3a and stage 3b CKD [156]. However, the ability of these agents to decrease renal glucose reabsorption fades with declining GFR. Compared with normal or mildly impaired kidney function patients, urinary glucose excretion becomes 50% lower in T2DM patients with CKD stage 3 when treated with dapagliflozin [157]. This poses a negative impact on the hypoglycemic efficacy of these agents beyond stage 3 CKD.

Hypolipidemic treatment: All DN patients should be treated with statins [158,159]. In spite of the significant impact of statin treatment on the risk of atherosclerotic cardiovascular disease in CKD patients, they have a minimal effect, if any, on CKD progression [160]. Statins did not significantly affect either all-cause mortality or stroke in diabetic adults with CKD when compared to placebo [158,159]. Fenofibrate treatment increased the switch of microalbuminuria to normoalbuminuria in DN patients compared to placebo [110].

Quitting smoking: A three years prospective observation study of three hundred T1DM patients that have overt proteinuria (178 were smokers) concluded that smokers did not have a worse decline of GFR [161]. On the other hand, a more recent and larger study of 3613 T1DM patients has reported that the 12-year cumulative risks of microalbuminuria, overt proteinuria and ESRD were significantly higher in current and ex-smokers compared to non-smokers. This risk increased in heavy smokers [162]. Quitting smoking is mandatory in T1DM and T2DM. Smoking is an important factor for DN progression in T2DM [163].

Diet control: Dietary salt restriction to less than 100 mmol (5-6 g)/d significantly reduces BP in T1DM and T2DM [164]. Salt restriction should be advised very early in the course of diabetes mellitus. The reduction of salt intake leads to fall in BP and UAE in individuals with diet-controlled T2DM or with impaired glucose tolerance [165]. In stage 4 CKD T2DM patients, salt intake is an independent factor that affects the annual rate of decline of GFR [166]. On the other hand, the effect of sodium intake on the clinical outcome is more complicated in T1DM. As an index of dietary sodium intake, urinary sodium excretion was associated non-linearly with overall mortality in T1DM. Patients at high and low extremes of urinary sodium excretion had reduced survival. Moreover, the lowest urinary sodium excretion had the highest risk of ESRD [167]. Decreased salt intake can exaggerate glomerular hyper filtration in the hyperglycemic state **(Figure 8)** [168]. This salt paradox was characterized in T1DM. However, clinical observations suggest its existence in T2DM as well [169].

The impact of protein restriction on CKD progression in DN is debatable. In 1996, a meta-analysis showed that dietary protein restriction effectively slows the progression of DN [170]. In 2000, a new meta-analysis showed similar results in T1DM patients with DN [171]. However, a more recent meta-analysis appeared in 2007 announcing the lack of a significant impact of protein restriction on DN progression in either T1DM or T2DM [172]. The last meta-analysis was performed in 2015 to report a significant impact of protein restriction on the rate of CKD progression only in T1DM [173]. The 2013 KDOQI clinical practice guidelines update on diabetes and CKD endorsed its KDOQI 2007 guidelines regarding the role of protein nutrition in diabetic kidney disease (DKD). For CKD stages 1 and 2, a daily protein intake of 0.8 g/kg is recommended, while in stages 3 and 4 the allowance should decline to 0.6-0.8 g/kg [158]. The source of dietary protein should also be considered. Switching to a predominantly vegetarian diet is associated with significant decrease of UAE in T1DM patients

with DN [174]. Similar results were observed in DN complicating T2DM [175]. Essential amino acids content of the vegetarian diet is usually sufficient for optimal nutrition [176].

The potential protective value of polyunsaturated fatty acids in diabetic patients is limited to the cardiovascular system, otherwise, no appreciable benefits could be traced in relation to DKD [177].

Treatment of hyperuricemia: In T1DM patients with normal UAE, serum UA is a strong predictor for the increased UAE. Every 1 mg/dL increase in serum UA increases the risk of development of albuminuria by 80% [178]. In T1DM patients with serum UA >6.6 mg/dL, the unadjusted risk of eGFR loss increases 2.4 folds in comparison to those with lower level [179]. In addition, serum UA was a significant independent predictor of overt proteinuria after 18 years follow-up of 263 newly diagnosed T1DM patients [180]. In a cross-sectional study of 3212 T2DM patients, 68% of the hyperuricemic T2DM patients had DN versus 41.5% of T2DM that have normal serum UA [181]. In a longitudinal study of more than twenty thousand T2DM patients having eGFR > 60 mL/min and normal UAE, the incidence of eGFR <60 mL/min., increased UAE or both over 4 years of follow-up was 7.9%, 14.1%, and 2% respectively. The highest relative risk of eGFR decline was encountered in the highest serum UA quintile. There was a significant association of serum UA and UAE in the cases that developed eGFR decline [182]. A more recent Japanese study has reinforced these findings [183]. In a prospective study of 422 T2DM patients with a disease duration for more than fifteen years that were followed for up to 77 mo, serum UA >7 mg/dL in males and >6 mg/dL in females had a significantly higher rate of DN progression, and overall mortality [184]. Compared to diabetic control mice, T2DM hyperuricemic mice treated with allopurinol experienced smaller increases in UAE. In addition, allopurinol attenuated the activation of TGF-β 1-induced Smad pathway in tubular epithelial cells [185]. When T2DM patients suffering DN were treated with allopurinol for three years, they experienced a significant decrease of UAE and serum creatinine and a significant increase of GFR [186]. Furthermore, 6 months' treatment of asymptomatic hyperuricemic stage 3-4 CKD patients (44% of them had T2DM) with febuxostat significantly slowed the decline of GFR compared to placebo [187]. In a recent meta-analysis of 19 randomized controlled trials that enrolled 992 participants proved a significant favorable effect of urate-lowering medications on the rate of GFR decline [188].

Phosphate handling: Hyperphosphatemia, a consequence of impaired excretion by the failing kidney, is a potential risk factor for the perpetuation of the rapid decline in renal function [189]. Renal phosphate excretion is FGF23 dependent. Serum level of FGF23 is higher in T2DM [54] and is an independent predictor of DN progression [59]. FGF23 was able to induce *TNF α* and *TGF β* genes within the mouse kidney [190]. Moreover, FGF23 stimulates hepatic secretion of IL6 and CRP [191]. According to these findings, control of FGF23 as soon as its level starts to raise in the very early days of stage 2 CKD is a mandate [192,193]. Intestinal phosphate absorption is the most modifiable target for FGF23 control. Non calcium-based phosphate binders can suppress FGF23, a finding that can explain their anti-inflammatory action and their role in overall mortality [194-197]. Sevelamer carbonate administered to patients with T2DM and early kidney disease, significantly reduced FGF 23, lipids, and markers of inflammation and oxidative stress, and markedly increased antioxidant markers [198]. It also reduced cellular and circulating AGEs [193]. Combining dietary phosphate restriction and sevelamer in predialysis CKD patients (24% of them were diabetic) resulted in a significant decrease in overall mortality and progression to dialysis [199].

Control of chronic metabolic acidosis: Metabolic acidosis is an independent risk factor for CKD progression [200]. Sodium bicarbonate supplementation significantly slowed the rate of decline of GFR and improved nutritional status in stage 4 CKD patients (27.5% of them were diabetic) [201]. Comparable to sodium bicarbonate, base-producing fruits and vegetables can correct metabolic acidosis without appreciable increase in serum potassium [202]. Long-term prospective placebo-controlled studies are still needed to highlight the potential benefits of alkali therapy, the ideal type of alkali supplements, and the optimal serum bicarbonate level.

Pentoxifylline: Low-dose pentoxifylline (400 mg/d) was tried in T2DM patients already maintained on losartan plus enalapril to control proteinuria. A significant decrease of UAE from a baseline of 616 mg/d to 192 mg/d was noticed after 6 mo of pentoxifylline [203]. A higher dose of pentoxifylline (1200 mg/d) added to maximum RAS blockade was associated with a slower rate of GFR loss and a significant reduction in UAE in stage 4 DN T2DM patients [204].

Sarpogrelate: Sarpogrelate, a 5-hydroxy tryptamine receptor antagonist, is used as an anti-platelet agent. It inhibits thromboxane A2 production [205]. A significant decrease of UAE and MCP1 in serum and urine follow Sarpogrelate treatment of DN patients [206]. We still lack long-term studies.

Vitamin D receptor agonists: In T2DM patients with overt nephropathy, paricalcitol in a dose of 2 μg/d showed a significant reduction of UAE [207].

Potential therapeutic modalities (Table 2)

Nuclear factor erythroid 2-related factor 2 activation: Nrf2 is adaptively activated in diabetic patients. However, this degree of activation is not sufficient to combat the oxidative stress aggravated by hyperglycemia [81]. Excess ROS generation is considered the main cause of the development of DN. Nrf2 is emerging as a potential therapeutic target for DN [208]. Non-toxic natural compounds can activate Nrf2. Sulforaphane (present in cruciferous vegetables), resveratrol (found in grapes), rutin (found in buckwheat, black tea, citrus fruits, and apple peels), cinnamic aldehyde (present in cinnamon essential oil), curcumin (found in turmeric), berberine (found in Berberis Mahonia plant), actinidia callosa (found in kiwi fruits), Sinomenine (found in the root of the climbing plant Sinomenium acutum), garlic, and Bitter Melon are natural Nrf2 activators [209-212]. Nrf2 activation

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Table 2: The Potential therapeutic modalities.

Drug class	On-target action	Off-target actions	Remarks	Ref.
Nrf2 activator	↓ROS	↓NF-κB, ↓EMT		
• Curcumin	"	↓UAE, ↓inflam.	No long term trials	[215]
• Resveratrol	"	↓EMT	No clinical trials	[218-220]
• Bardoxolone	"	↓GFR	UAE↑, BP↑, HF↑, mortality↑, nausea, wt loss, muscle spasm	[229-230]
Inhibitors of leucocyte recruitment				
• Emapticap Pegol	↓MCP1	↓UAE	I.V administration	[236-239]
• CCX140-B	CCR2 antagonist	UAE↓, GFR+	Oral administration	[240]
• JAK/STAT signaling inhibition	↓WBCs recruitmment	↓UAE, GFR+	Only animal trial	[241]
Exogenous klotho	↓EMT, ↓TGF-β	↓Fibrosis		[242,244]
Low dose IL-17A	↓MCP1	↓UAE, ↓kidney size, ↓mes. matrix, ↓IF, ↓urine IP10, ↓TNFα, ↓IL-6, and ↓S urea	No clinical trials	[245]
Aldose reductase inhibitors	↓IC sorbitol, ↓IC fructose	↓UAE	No adequate RCTs	[246]
Ruboxistaurin	↓PKC	UAE +, TGF-β+		[247,248]
Sulodexide		UAE +		[249-251]
Atrasentan	Endothelin receptor antagonist	↓UAE	Serious side effects postponed approval	[252,253]

suppressed the expression of TGF β, extracellular matrix proteins accumulation, and p21 activation in streptozotocin-induced DN [213]. In streptozotocin-induced T1DM rats, sulforaphane was able to prevent renal inflammation and fibrosis [214]. In T2DM patients with DN, curcumin at the dose of 500 mg/d orally for 15-30 d caused a significant decrease of UAE, and malondialdehyde (a measure of lipid oxidation index), beside suppression of inflammatory markers [215]. Hyperglycemia-induced glomerular hyperpermeability and a decrease in the junction protein occludin are significantly in vitro corrected by the Nrf2 agonist Rutin when added to the human renal glomerular endothelial cells [216]. Sodium butyrate is another member that activates Nrf2 transcription probably through inhibition of histone deacetylase activity at the nucleus. Consequently, sodium butyrate was able to ameliorate DN pathological changes and UAE in streptozotocin-induced diabetic mice. These effects were completely abolished after deletion of the *Nrf2* gene [217]. Resveratrol exerts its cytoprotective effect through two mechanisms, antioxidant activity and *Sirtuin 1* gene (silent information regulator T1, SIRT1) activation [218,219]. The antioxidant activity of resveratrol is mediated by either activation of Nrf2 or directly by scavenging different ROS [220]. The SIRT1 cytoprotective action occurs through its anti-oxidative, anti-inflammatory, and anti-apoptotic mechanisms and the regulation of mitochondrial metabolism and autophagy in response to the cell energy and redox status. Among many other diseases, resveratrol can prevent kidney diseases, and cardiovascular disease through SIRT1 activation [218,221,222]. In vitro high glucose-induced mesangial cell proliferation and NF-κB activation are attenuated by resveratrol [222]. Resveratrol increases AMPK phosphorylation and eliminates the suppressive effect of hyperglycemia on AMPK phosphorylation with consequent activation of NADPH oxidase [220]. The inhibitory effect of resveratrol on excess ROS production in the hyperglycemic environment would explain the significant attenuation of renal fibrosis in db/db mice when treated with resveratrol [223]. Similarly, resveratrol alleviates EMT [224] and glomerulosclerosis through suppression of TGF-β/smad activation [225]. Additionally, Reservatrol increases serum adiponectin and its receptors AdipoR1 and AdipoR2 within the kidney. Through activation of AMPK–SIRT1–PPARγ axis and PPARγ, adiponectin prevented human glomerular endothelial cells oxidative stress and apoptosis [226]. Two-week treatment of streptozotocin-diabetic rats with resveratrol improved UAE and GFR [219]. Resveratrol treatment may also weaken diabetes induced increased expression of VEGF [227]. There's ongoing clinical trial looking for the effect of resveratrol on UAE and serum creatinine in T2DM. Bardoxolone is Nrf2 activator that was first tried as a radiation protection agent [228]. BEAM study is a phase 2 double-blind randomized placebo-controlled trial of bardoxolone in adult patients with T2DM and CKD (eGFR of 20 to 45 mL/min per 1.73 m^2). Two hundred and twenty-seven adults were assigned to receive placebo or bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily for 1 year. At 6 mo onwards of treatment, Bardoxolone methyl significantly increased eGFR [229]. A significant increase of UAE, a trend of higher systolic BP, nausea, weight loss, and muscle spasm represent the most important adverse effects of bardoxolone in this study. Twenty-five percent of patients experienced nausea. While normal BMI patients lost a mean of 3 kg over the year of study, this loss reached 10 kg in high BMI patients. 63% of patients on 75 mg of bardoxolone experienced a muscle spasm. Hypomagnesemia was also encountered among bardoxolone group. This study was followed by a larger study, the BEACON study, of 2185 T2DM DN patients in stage 4CKD (eGFR of 15-30 mL/kg per 1.73 m^2). The study was designed to continue for 24 mo using 20 mg of bardoxolone methyl as a single daily dose in the treatment group [230]. At an average follow-up of 9 mo, the study was prematurely terminated thanks to the frequent cases of heart failure and mortality in the active treatment group in comparison to the placebo group. The increased incidence of

cardiovascular events is probably unrelated to bardoxolone methyl. Increased excretion of RAS blockers in the bardoxolone methyl group might have deprived these patients the cardioprotective, nephroprotective, and antihypertensive effects of RAS blockers [231]. Endothelial dysfunction as a possible consequence of hypomagnesemia may be another explanation for increased proteinuria, heart failure, increased mortality and muscle spasm [232]. Chromium picolinate, chromium histidinate [233], polydatin (a glucoside of resveratrol) [234], and the tetracycline antibiotic minocycline [235] are other Nrf2 activators that have favorable results in experimental studies. However, long-term prospective randomized placebo-controlled trials that would prove the long-term safety and efficacy of these agents are still needed.

Inhibitors of renal leukocyte recruitment: Membrane receptors on the surface of leukocytes have evolved as a therapeutic target to interrupt their renal recruitment [236]. A mirror-image (Spiegelmer) of MCP-1(CCL2), the pro-inflammatory chemokine capable for renal leukocytes recruitment in DN [237], was in vitro built-up using non-natural nucleotides. This spiegelmer is called Emapticap Pegol. It is an oligonucleotide that binds and neutralizes MCP-1[238]. In the study of safety and efficacy of Emapticap Pegol in stage 4 DN, statistically significant reduction in UAE showed up after 12 wk of Emapticap Pegol use as 3 times weekly subcutaneous injections[239]. Oral CCX140-B is another CCR2 antagonist that was tried in T2DM DN patients. In a dose of 5 mg/d on top of the standard of care treatment, CCX140-B caused a significant reduction of UAE and the rate of GFR decline. The significant impact on GFR was not supported in phase 3 study of CCX140-B [240].

A third agent capable of inhibition of renal interstitial leucocyte recruitment by suppressing JAK/STAT signaling was tried in diabetic rats at either early or advanced stages of diabetes. This cell-permeable peptide mimicking the kinase-inhibitory region of suppressor of cytokine signaling-1 (SOCS1) regulatory protein was found to reduce serum creatinine level, UAE, and renal histologic changes in all treated rats [241].

Exogenous klotho: This anti-senescence protein favors epithelial regeneration and inhibits fibroblast phenotype transformation during EMT [242]. Exogenous klotho was capable of attenuation of TGF-β bioactivity, type II TGF-β receptor protein expression, TGF- β Smad 2/3 signaling, and fibronectin expression in high glucose cultured renal interstitial fibroblasts [243]. Intravenous klotho gene administration was able to prevent the progression of renal hypertrophy and fibrosis in diabetic rats [244].

IL-17: Plasma and urine IL-17A levels are reduced in patients with advanced DN. T1DM mice genetically deficient in IL-17A developed more severe nephropathy. Treatment of T1DM and T2DM mice with low doses of IL-17A reversed the pathologic stigmata of DN in these mice. Low doses of IL-17A significantly decreased kidney size, mesangial matrix expansion, interstitial fibrosis, UAE, urine MCP1, IP10, TNF α, IL-6, and serum urea level in comparison to control animals [245].

Aldose reductase inhibitors: The potential role of aldose reductase inhibitors in the treatment and management of the major complications of diabetes like cataract, retinopathy, neuropathy, and cardiovascular disease has achieved appreciable advances. However, their use in DN is still unsatisfactory [246].

Protein kinase C inhibitors: One-year treatment of T2DM patients using ruboxistaurin mesylate significantly reduced UAE and maintained eGFR [247]. On the other hand, a more recent trial failed to disclose a significant value of ruboxistaurin on urine TGF-β or UAE [248]. This discrepancy will postpone the use of this agent till further trials can settle this controversy.

Sulodexide: Sulodexide, a purified mixture of sulfated glycosaminoglycan polysaccharides, was assessed in 2 clinical studies looking for its potential antiproteinuric effect. In early DN patients with T1DM and T2DM, sulodexide was associated with significant reduction of UAE [249]. In the second trial, reduction of UAE was not statistically significant in T2DM patients [250]. A more recent multicenter double-blind placebo-controlled study failed to demonstrate a significant decrease of UAE in T2DM with incipient nephropathy after use of sulodexide [251].

Endothelin receptor antagonists: The use of endothelin receptor antagonists is associated with serious adverse events in spite of their favorable effect on UAE in DN patients. A meta-analysis of five randomized controlled trials has confirmed this impression [252]. The SONAR is an ongoing hard outcome trial in T2DM patients with DN to evaluate atrasentan. Results of this trial will hopefully settle the possible role of this agent [253].

Intensified Multifactorial Intervention

STENO-2 is an open parallel trial that randomly allocated T2DM patients with incipient nephropathy to either standard treatment (n=80) or intensive treatment (n=80). Patient recruitment occurred during 1992-1993. The intensive treatment group had optimized diet regimen, 30 min exercise program 3-5 times/wk, avoided smoking, got vitamin C, vitamin E, and oral hypoglycemic treatment if diet alone failed to keep HbA1c <6.5%, had statin treatment for hypercholesterolemic and fibrate treatment for hypertriglyceridemic patients. For overweight, oral hypoglycemic agents were metformin and for lean patients, gliclazide was used. If HbA1c did not reach the target with a single agent, a combination of both agents was prescribed. If oral treatment failed to achieve the target, insulin was added. Seventy-one patients in the intensive treatment group received antihypertensive treatment versus only 48 in the standard group thanks to lower BP target in the intensive treatment group. Out of these sixty-nine had ACE inhibitor in the intensive treatment versus thirty-eight in the standard treatment. After 7.8 years, all the patients were subsequently offered intensified multifactorial treatment according to the original protocol due to the marked risk reductions encountered with intensive treatment. In spite of the significant impact on survival and cardiovascular outcome, there was no significant difference in the incidence of ESRD between the 2 groups after a median observation time of 21.2 years [103,254].

Perspectives

In spite of the disappointing finding of the STENO-2 study, the recent developments in the field of management of DN

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give a big hope of better prevention and management of this progressive distressing disease. These new discoveries mandate the change of management plan. Control of blood sugar to the target often fails. The use of RAS blockers offers, at the best, partial protection. These agents were advised when diabetic patients proceed to stage 4 DN. RAS blockers failed to completely reverse the hemodynamic change encountered since the very early days of diabetes mellitus even with dual blockade of the RAS system. The early introduction of SGLT2 inhibitors to T1DM and T2DM offers a new addition to hyperfiltration control. The co-administration of RAS blocker and SGLT2 inhibitor deserves a long-term prospective trial in both types of diabetic patients with the use of both agents starting in the very early days of stage 1 of DN. This co-administration would avoid RAS system activation triggered by SGLT2 inhibitors. The anti-fibrotic effect of the DPP-4 inhibitors linagliptin and saxagliptin deserves their use as the favorable hypoglycemic agents in patients with DN. Diabetic patients in early stages of DN expectedly would get a maximal benefit after the triple treatment with RAS blocker, SGLT2 inhibitor, and either saxagliptin or linagliptin. In spite of the favorable impact of pioglitazone, its salt and water retaining effect limits its use in DN. With CKD progression to stage 4, Metformin and GLP-1 agonists should be avoided. However, their use in the earlier stages adds to the favorable effect of other agents. Once the DN patient has overt proteinuria, pentoxifylline should be added to the prescribed treatment. Although the chance of hyperuricemia is expectedly lower in patients already kept on SGLT2 inhibitor, serum uric acid should be monitored and hypouricemic treatment must be added if serum UA is above 6.5 mg/dL. A strong evidence of safety and efficacy of the long-term use of Nrf2 agonists, leucocyte recruitment inhibitors, IL17 and klotho is still needed before allowing them to the approved list. Control of hyperphosphatemia and correction of metabolic acidosis are necessary once the patient proceeds to stage 4 CKD. Finally, we should emphasize that metformin, pioglitazone, DPP-4 inhibitors, and SGLT2 inhibitors can be used in T1DM. Their use might decrease the chance of development and progression of DN.

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