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Review

Diabetic nephropathy: Time to withhold development and progression - A review

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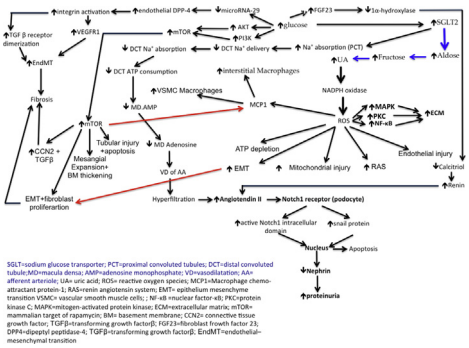
GRAPHICAL ABSTRACT



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ABSTRACT

The recent discoveries in the fields of pathogenesis and management of diabetic nephropathy have revolutionized the knowledge about this disease. Little was added to the management of diabetic nephropathy after the introduction of renin angiotensin system blockers. The ineffective role of the renin- angiotensin system blockers in primary prevention of diabetic nephropathy in type 1 diabetes mellitus necessitated the search for other early therapeutic interventions that target alternative pathogenic mechanisms. Among the different classes of oral hypoglycemic agents, recent studies highlighted the distinguished mechanisms of sodium glucose transporter 2 blockers and dipeptidyl peptidase-4 inhibitors that settle their renoprotective actions beyond the hypoglycemic effects. The introduction of antioxidant and anti-inflammatory agents to this field had also added wealth of knowledge. However, many of these agents are still waiting well-designed clinical studies in order to prove their beneficial therapeutic role. The aim of this review of literature is to highlight the recent advances in understanding the pathogenesis, diagnosis, the established and the potential renoprotective therapeutic agents that would prevent the development or the progression of diabetic nephropathy.

Introduction

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) in most of the countries worldwide. One third of type 1 diabetes mellitus (T1DM) patients develop

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ESRD, while only 10–20% of type 2 diabetes mellitus (T2DM) patients progress to ESRD [1,2]. DN increases the overall 10-year mortality among diabetic patients at least 6 folds compared to healthy age matched non-diabetic individuals [3]. The earliest stage of DN is characterized by renal hyperfunction and hypertrophy [4]. Few years later, persistent increase in urine albumin excretion (UAE) develops. This stage is called the stage of incipient nephropathy characterized by UAE > 30 mg/day, >20 μg/min, or urine albumin:creatinine ratio (ACR) > 30 mg/g of creatinine. The persistent increase in UAE is initially associated with increased glomerular filtration rate (GFR). However, GFR shows consistent decline that becomes pronounced with the continuous increase of UAE above 300 mg/day, 200 μg/min, or when urine ACR exceeds 300 mg/g (Fig. 1)[5]. Progressive increase in blood pressure is usually associated with these renal changes. The 1st description of increased UAE was by Keen and Chlouverakis in 1963 [6]. The term "microalbuminuria" has gained popularity in 1982 after the publication of a 14-year longitudinal study that showed microalbuminuria as a predictor of increased risk of renal disease and mortality in T1DM [7]. The predictive value of microalbuminuria for renal and cardiovascular disease morbidity and mortality was later confirmed in T2DM [8]. These observations encouraged the use of renin angiotensin system blockers (RAS blockers) in patients with DN if they have incipient nephropathy [9]. However, a later study failed to demonstrate the predictive significance of microalbuminuria in DN progression [10]. Another study showed that in one third of T1DM patients that develop advanced renal disease, progression of microalbuminuria to overt proteinuria was not required for kidney disease progression [11]. These observations have lead to less enthusiasm to use RAS blockers in incipient nephropathy and to limit this mode of therapy to patients with overt nephropathy [12]. This trend was reflected in the attitude of many authorities to redefine DN as development of UAE > 300 mg/day in diabetic patients overlooking the earlier 3 stages. Consequently, treatment with RAS blockers became advised when the patients proceed to stage 4 DN. According to the new discoveries in experimental and clinical trials, a new strategy of DN treatment should be implemented. In this review, an updated approach to prevent, and control the progression of DN will be highlighted.

Methodology

In order to create this review, the authors looked for all the available literature concerned with this topic in pubmed, Ovid, Web of Science, Sciencedirect, Scopus, Cochrane Library, and Google Scholar beside the data they were collecting over the last 35 years during their attendance to meetings and workshops and during preparing their lectures in this piece of knowledge. In addition, clinicaltrials.gov website was frequently visited to look for running or just finished studies of the different therapeutic agents that have potential impact on the course of DN.

Pathogenesis of diabetic nephropathy

The effect of hyperglycemia is generally mediated through hemodynamic and multiple metabolic pathways. A stress upon the different pathogenic mechanisms that have therapeutic implications will be accomplished.

The glomerular hyperperfusion and hyperfiltration are owed to the decrease of the afferent arteriolar resistance. Increased glucose in glomerular ultrafiltrate stimulates sodium glucose transporter-2 (SGLT2) gene with consequent increased proximal tubular absorption of filtered sodium and glucose. SGLT2 in the apical membrane of the proximal tubular epithelial (PCT) cells is responsible for absorption of 90% of the glucose in the ultrafiltrate [13]. As a result, distal tubular sodium delivery decreases and hence distal tubular macula densa pays less energy in sodium absorption. Decreased energy expenditure decreases adenosine activity with consequent vasodilatation of afferent arterioles (Fig. 2) [14]. The increased glucose absorption raises intracellular glucose availability with consequent increased activity of polyol pathway that leads to increased fructose synthesis. Fructose metabolism leads to increased intracellular uric acid (UA) synthesis [15]. UA stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme causing increased intracellular oxidative stress, mitochondrial injury, adenosine triphosphate (ATP) depletion [16], endothelial injury, RAS activation and increased epithelial- mesenchyme transition (EMT). Excess fibroblasts infiltrate the interstitium with consequent progressive interstitial fibrosis (Fig. 3)[17].

Human glomerular mesangial cells (MCs) express NADPH oxidase [18]. ROS activates protein kinase C (PKC), mitogen-activated protein (MAP) kinase, and nuclear factor-κB (NF-κB) which eventually results in overproduction of extracellular matrix proteins (Fig. 4)[19].

Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates the synthesis of many antioxidising and cytoprotective factors that can antagonize the oxidative stress and pro-inflammatory signals [20]. Nrf2 exists in the cytoplasm as an inactive complex bound to a repressor protein called Kelch-like ECH-associated protein 1 (Keap1). The free Nrf2 translocates to the nucleus where it binds to the promoter regions of genes encoding the antioxidant and phase 2 detoxifying molecules, activating their transcription. In addition, Nrf2 suppresses transcription of NF-kB [21]. Nrf2 is adaptively activated in diabetes but is not efficient enough to resist the oxidative stress provoked by hyperglycemia. The association between oxidative stress and inflammation with progression of DN directed attention towards Nrf2/Keap1 activators, as potential renoprotective agents.

Intrarenal RAS genes expression is induced in diabetes [22]. Mechanical strain increases angiotensin II (A2) production and up-regulates AT1R in podocytes [23]. Increased A2 maintains and aggravates glomerular hypertension. A2 caused *in vitro* loss of nephrin, the protein component of the slit diaphragm, in cultured podocytes [24]. Notch1 couples A2 with nephrin down regulation. Notch1 is a transmembrane receptor that plays a role in cell differentiation and renal development. Activation of Notch1 receptor

Fig. 1. Stages of Diabetic nephropathy. Stage 2 is characterized 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.

leads to the release of the active Notch1 intracellular domain (ICN1). Another transcription factor within the cytoplasm is triggered by notch 1 receptor signaling. This factor is called the snail. Upon notch1 signaling both ICN1 and snail translocate to the nucleus and share in repression of nephrin expression and podocyte apoptosis (Fig. 5) [25].

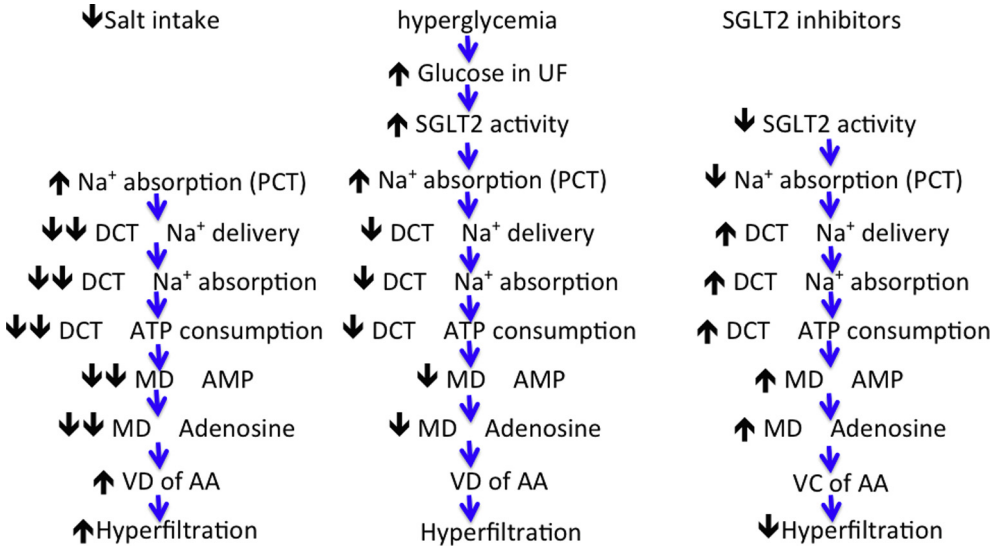

Fig. 2. Tubuloglomerular feedback:impact of low salt intake and SGLT2 inhibitors. UF = glomerular ultrafiltrate; SGLT = sodium glucose transporter; PCT = proximal convoluted tubules; DCT = distal convoluted tubule; MD = macula densa; AMP = adenosine monophosphate; VD = vasodilation; AA = afferent arteriole.

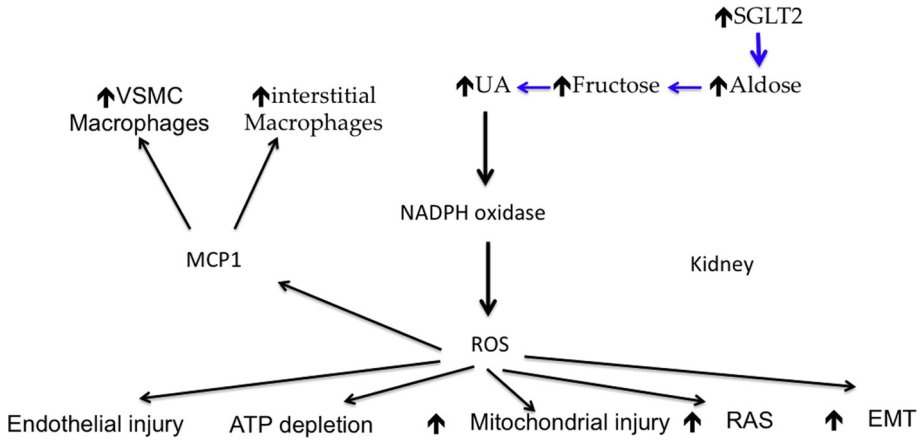

Fig. 3. Different pathogenic mechanisms of kidney injury possibly induced by uric acid. UA = acid; ROS = reactive oxygen species; MCP1 = Maacrophage chemo-attractant protein-1; RAS = renin angiotensin system; EMT = epithelium mesenchyme transition VSMC = vascular smooth muscle cells.

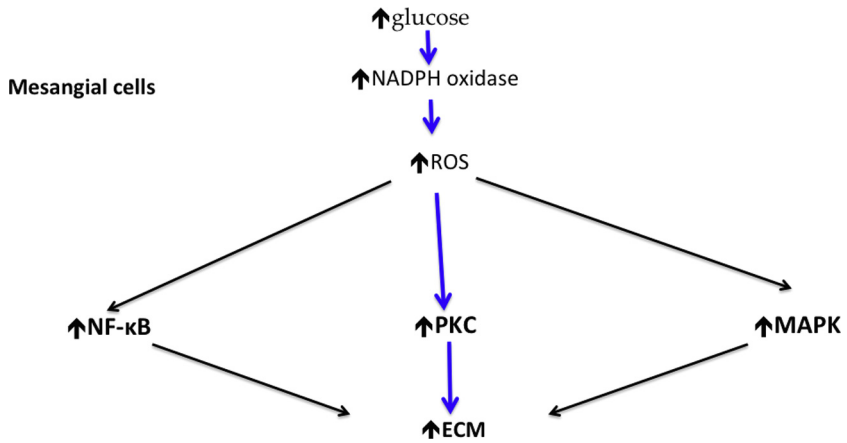

Fig. 4. Hyperglycemia induced mesangial expansion. NADp = Nicotinamide adenine dinucleotide phosphate; ROS = reactive oxygen species; NF-kB = nuclear factor-kB; PKC = protein kinase C; MAPK = mitogen-activated protein kinase; ECM = extracellular matrix.

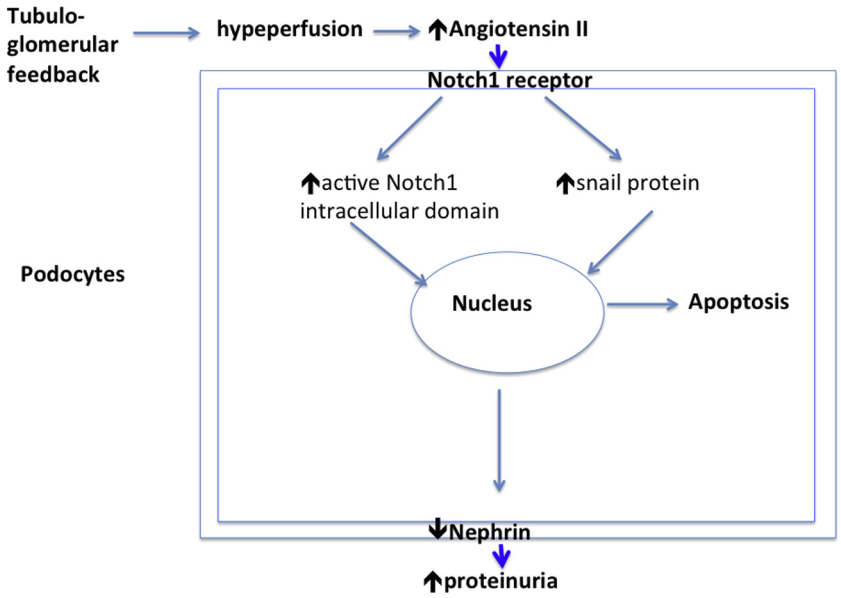

Fig. 5. Mechanism of podocyte injury and proteinuria induced by angiotensin II.

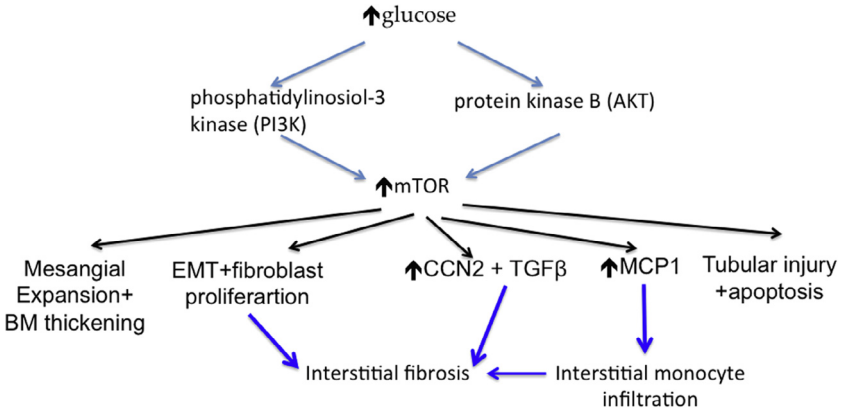

Fig. 6. Consequences of mTOR activation induced by hyperglycemia. mTOR = mammalian target of rapamycin; BM = basement membrane; EMT = epithelium mesenchyme transition tissue growth factor; TGFβ = transforming growth factorβ; MCP1 = macrophage chemoattractant protein.

Many studies have demonstrated that hyperglycemia can trigger the activation of phosphatidylinosiol-3 kinase (PI3K) and protein kinase B (AKT) pathways, which subsequently lead to the activation of mammalian target of Rapamycin (mTOR). Activated mTOR induces the synthesis of matrix proteins responsible for basement membrane thickening and mesangial matrix accumulation. In addition, mTOR is incriminated in renal fibrosis. In addition, mTOR stimulates infiltration of the kidney interstitium by macrophages through monocyte chemoattractant protein-1 (MCP-1) upgrading (Fig. 6) [26].

Fibroblast growth factor 23 (FGF23) is a phosphatonin responsible for renal phosphate elimination. FGF23 mRNA is not detected in the kidneys of normal rats but starts to appear in the kidneys of diabetic rats at 4 months and increases thereafter [27]. FGF23 inhibits 1-α hydroxylase gene with consequent decreased calcitriol synthesis. An inverse relationship between calcitriol and renin levels was displayed [28]. These findings disclose the cross talk between FGF23 and the RAS (Fig. 7).

Elevated endothelin level is a constant feature of diabetic patients. Endothelin-1 (ET-1) is implicated in the progression of DN [29]. Increased expression of ET-1 in the kidney of type

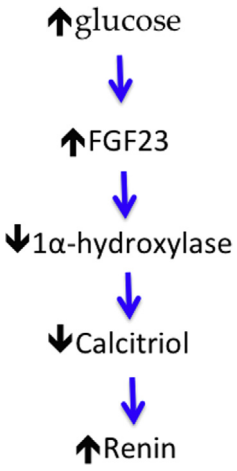

Fig. 7. FGF23 mediated increased renin activity in diabetic patients. FGF23 = fibroblast frowth factor 23.

2 diabetic db/db mice correlated with collagen deposition [30].

Accumulating evidence suggests that the JAK/STAT pathway plays a central role through which hyperglycaemia contributes to proliferation, inflammation, and fibrosis encountered in DN [31].

Dipeptidyl petidase-4 (DPP-4) is a cell surface aminopeptidase enzyme that degrades incretins secreted by the gut. DPP-4 is found in many cell types, including the endothelial cells in multiple organs including the kidney [32]. In normoglycemic status, microRNA-29 (miR29) controls membrane DPP-4 through suppression of its gene. Such effect is lost when miR29 levels decrease in hyperglycemic environment [33]. DN is associated with increased expression of surface DPP-4, predominantly on endothelial and tubular epithelial cells. This increased expression and activity targets a broad range of peptides within its vicinity. Activated DPP-4 interacts with integrin β1 and induces its phosphorylation. Activated DPP-4 phosphorylated integrin β1 complex triggers TGF β receptor dimerization and activation of vascular endothelial growth factor receptor type 1(VEGFR1). Enhanced TGF β receptor and VEGFR1 stimulate endothelial– mesenchymal transition (EndMT) with consequent increased fibrogenesis (Fig. 8) [33].

In the last 2 decades, many investigators are convinced with the crucial role of inflammation in the pathogenesis of DN. The identification of new inflammatory molecules acts as a link to the development of new therapeutic strategies. NF-kB is the most important transcription factor involved in DN. NF-κB is activated within the diabetic kidney by hyperglycemia, free oxygen radicals, and proteinuria. Activated NF-κB binds within the nucleus to the promoter regions of several genes that mediate the pathogenesis of DN like those encoding TGF-β1, chemokine ligand 2 (CCL2) also known as MCP-1 and intercellular adhesion molecule 1(ICAM1) [34]. As a consequence, the diabetic kidney would be the site of macrophage recruitment and excess collagen deposition.

Diagnosis of diabetic nephropathy

The pathologic changes encountered in DN include mesangial expansion, diffuse glomerular basement membrane thickening, diffuse glomerulosclerosis, nodular glomerulosclerosis, afferent and efferent arteriolar hyalinosis, interstitial mononuclear cell infiltrate, and interstitial fibrosis together with tubular atrophy [35]. The prevalence of non-diabetic renal disease among diabetic patients varies from 10% to 85% in different reports [36–39]. Non-diabetic renal disease should be suspected in patients with persistent proteinuria if the duration of diabetes is less than 5 years, if the blood pressure is normal, if there is microscopic or frank hematuria, and if diabetic retinopathy is absent in T1DM [40]. However, the presence of microscopic hematuria can be encountered in some cases of DN. Contrary to T1DM, T2DM patients can develop DN without diabetic retinopathy [41].

Management of diabetic nephropathy

Many of the therapeutic modalities are already approved by clinical trials that proved safety and efficacy of these modalities. Others are still waiting this approval. These 2 categories will be discussed under "Approved treatment" and "Potential therapeutic modalities" respectively.

Approved treatment

Control of blood pressure

Control of BP decreases the rate of decline in GFR in pre-dialysis DN patients significantly. RAS blockers should be used to control BP in DN patients with increased UAE. These agents have a significant impact on the rate of decline of GFR in DN patients with proteinuria. They decrease glomerular tuft pressure, inhibit cytokine overproduction, increase serum and tissue angiotensin1-7 and stimulate Klotho gene expression in DN patients. Klotho gene manipulation might mediate renal damage induced by RAS. According to Kidney disease improved global outcome guidelines, BP target in DN patients is 130/80 mmHg [42]. RAS blockade remains the most accepted renoprotection tool for diabetic nephropathy and diabetic CKD progression. However, RAS blockade failed to fully prevent progressive renal injury in T1DM [43]. In addition, RAS blockers may cause accelerated progression of renal disease in patients with advanced CKD or in old aged patients. Discontinuation of RAS blockers has delayed the onset of RRT in the majority of the studied cases [44–46].

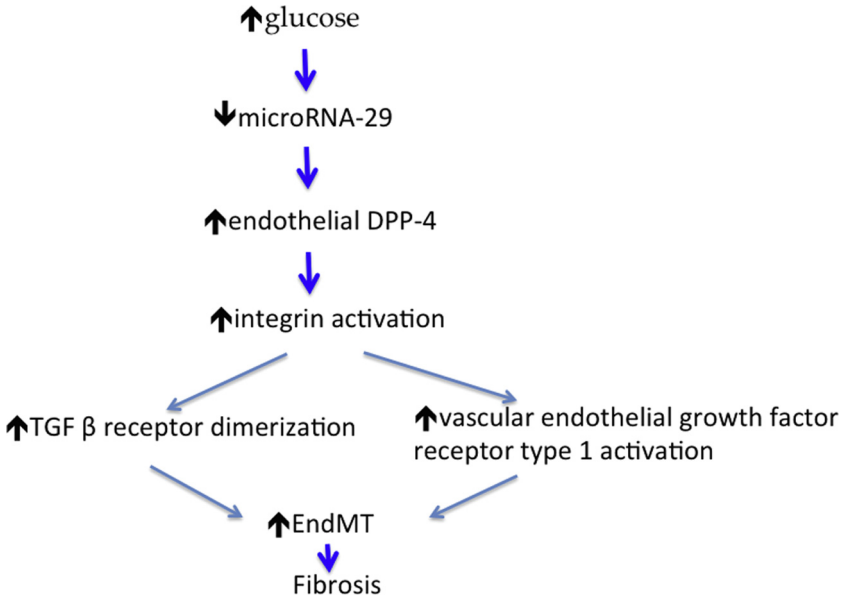

Fig. 8. DPP-4 mediated renel fibrosis. DPP4 = dipeptyl peptidase-4; TGFβ = transforming growth factorβ; EndMT = endothelial-mesenchymal transition.

Control of blood sugar

In UKPDS, blood sugar control was associated with 33% reduction in the relative risk of progression from normoalbuminuria to microalbuminuria or from micro to overt proteinuria at 12 years [47]. The chance of doubling of serum creatinine was also significantly reduced in the tight glycemic control group. On the other hand, the impact of tight blood sugar control on the rate of progression of CKD was the subject of controversy in sequential studies. In the most recent study of 891 670 US diabetic veterans that have 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, coronary heart disease, and stroke in all systolic BP categories [48]. Beyond their hypoglycemic effects, metformin, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, and GLP-1 agonists have favorable effects in DN patients.

Metformin

Metformin elicits its therapeutic effects through many mechanisms including activation of AMPK pathway. The beneficial effects of metformin in patients with DN are partly mediated through AMPK activation. Metformin-mediated AMPK activation leads to inhibition of mTOR . Metformin inhibits podocyte apoptosis induced by hyperglycemia. This effect is mediated by activation of AMPK and inhibition of mTOR signaling [49].

Thiazolidinediones

The effects of the thiazolidinedione, pioglitazone hydrochloride, on urinary podocalyxin and MCP-1 excretion were studied in T2DM to explore its possible renoprotective mechanisms. Beside the significant decline in both systolic and diastolic BP, both UAE and urinary podocalyxin excretion decreased significantly after 12 weeks of pioglitazone. These results highlight a podocyte-protective capacity of pioglitazone that was partly attributed to its effective suppression of diabetes induced local renal inflammation. The declines in GFR below baseline measurements at stages 3 and 4 of CKD were significantly slower for T2DM treated with losartan and pioglitazone compared with those treated with losartan alone [50].

Glucagon like peptide-1 agonists

GLP-1 has antioxidative properties. Rats deficient in GLP-1 receptors develop increased UAE, increased glomerular ROS, upregulated renal NADPH oxidase, and advanced mesangial expansion [51]. GLP-1 agonists inhibit expression of TGF-β1 and CCN2 in human mesangial cells [52]. So far, there are no clinical studies of GLP-1 agonists in T2DM patients with DN.

Dipeptidyl peptidase-4 inhibitors

In a single-arm clinical study in T2DM for 8 weeks, vildagliptin significantly decreased UAE by 44.6% [53]. In an open-labeled, prospective, randomized study in T2DM, sitagliptin significantly reduced UAE in comparison to other oral hypoglycemic agents that achieved comparable decrease in HbA1c. These results dictate that the effect on UAE was not due to glycemic control. Reduction in eGFR was comparable in the 2 groups [54]. Among DPP-4 inhibitors, linagliptin is unique, because it does not need dose adjustment with GFR decline. A pooled analysis of four clinical studies including 217 T2DM with increased UAE while receiving stable doses of RAAS inhibitors, patients were randomized to either linagliptin 5 mg/day (n = 162) or placebo (n = 55). By 24 weeks of treatment, UAE decreased significantly in the linagliptin group (32% vs 6% reduction in placebo group) [55]. Through direct inhibition of DPP-4 –integrin- β1 interaction, linagliptin blunts pathological TGF-β signaling and restores the physiological balance of VEGF receptors. These favorable responses inhibit EndMT and subsequent renal fibrosis [56]. In rat model of T1DM, saxagliptin add-on treatment 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 [57]. The renal outcomes of 16,492 T2DM patients randomized to saxagliptin versus placebo and followed for a median of 25 months in the SAVOR-TIMI 53 Trial, saxagliptin decreased UAE without affecting eGFR [58]. To assess the renoprotective effect of alogliptin, a crossover study with sitagliptin and alogliptin in 12 T2DM patients with incipient nephropathy taking angiotensin II type 1 receptor blocker (ARBs) was performed. Reduced UAE was observed after the switch from sitagliptin to alogliptin [59].

Sodium glucose transporter-2 inhibitors

The new class of hypoglycemic agents, SGLT2 inhibitors succeeded to slow progression of DN. SGLT2 inhibition expectedly increases distal sodium delivery, hence increases adenosine production, causing afferent vasoconstriction with fall in renal blood flow, decreased hyperfiltration and reduced renal injury (Fig. 2). While losartan reduced the chance of ESRD in T2DM patients by 28% during a mean follow up of 3.4 years [60], empagliflozin achieved 55% reduction of the chance of ESRD over a median observation time of 3.1 years. In addition, empagliflozin reduced the incident or worsening of nephropathy by 39%, the progression to overt albuminuria by 38% and the doubling of serum creatinine by 44%. The favorable effects of SGLT2 inhibitors could also be due to reduction of body weight, BP, and serum UA level [61].

Hypolipidemic treatment

Treatment of all DN patients with statins is recommended [42]. Statins decrease the risk of atherosclerotic cardiovascular disease in CKD patients. However, they have a minimal effect on CKD progression [62]. Statins did not decrease all-cause mortality or stroke in adults with diabetes and CKD compared to placebo.

Quitting smoking

A recent study of 3613 T1DM patients showed that the 12-year cumulative risks of microalbuminuria, overt proteinuria and ESRD were significantly higher in current and ex-smokers compared to non-smokers and the risk increases with increasing the dose of smoking [63]. Quitting smoking is mandatory not only in T1DM but also in T2DM. Smoking is one of the important factors responsible for DN progression in T2DM [64].

Diet control

Dietary salt restriction to less than 5–6 g (100 m mol)/day significantly reduces BP in T1DM and T2DM. It seems that salt restriction should be advised very early in the course of diabetes mellitus. This reduction in salt intake leads to fall in BP and UAE in individuals with diet-controlled T2DM or impaired glucose tolerance. Salt intake is an independent factor that affects the annual creatinine clearance decline in T2DM in stage 4 CKD [65]. The association between dietary sodium intake and clinical outcome is more complicated in T1DM. Patients with the highest, as well as the lowest, daily urinary sodium excretion, had reduced survival. Patients with the lowest urinary sodium excretion had the highest risk of ESRD [66]. Decreased salt intake can lead to exaggeration of glomerular hyperfilteration in hyperglycemic state (Fig. 2). This salt paradox was explained in T1DM. Although the tubuloglomerular feedback has not been well evaluated in T2DM, clinical observations support that the tubuloglomerular feedback is also true in T2DM.

There is controversy regarding the impact of protein restriction on CKD progression in DN. The most recent meta-analysis reported a significant impact only in T1DM [67]. For CKD stages 1 and 2, a protein intake of 0.8 g/kg is recommended, while in stages 3 and 4 the allowance should be 0.6–0.8 g/kg [68].

In spite of the established cardiovascular favorable effects of polyunsaturated fatty acids' consumption in diabetic patients, they do not seem to attenuate glomerular dysfunction in DN patients [69].

Treatment of hyperuricemia

Three years treatment of T2DM patients suffering DN with allopurinol significantly decreased UAE and serum creatinine and significantly increased GFR [70]. In addition, treatment of asymptomatic hyperuricemic stage 3–4 CKD patients (44% of them had T2DM) with febuxostat for 6 months significantly slowed the decline of GFR compared to placebo [71]. A recent meta-analysis of 19 randomized controlled trials enrolling 992 participants showed a significant favorable effect of allopurinol on the rate of GFR decline [72].

Phosphate handling

Hyperphosphatemia is suggested as a potential risk factor for the rapid decline in renal function in CKD patients [73]. Combining dietary phosphate restriction and sevelamer in non-dialysis CKD patients (24% of them were diabetic) led to a significant decrease of overall mortality and progression to dialysis [74].

Control of chronic metabolic acidosis

Low serum bicarbonate level is an independent risk factor for CKD progression. Sodium bicarbonate supplementation in stage 4 CKD patients (27.5% of them were diabetic) succeeded to significantly slow the rate of decline of renal function and to improve nutritional status [75].

Pentoxifylline

Pentoxifylline added to maximized RAS blockade had a significant positive impact on renal disease progression in T2DM patients in stage 4 DN. The dose of Pentoxifylline in this trial was 1200 mg/-day. Pentoxifylline was associated with a slower rate of GFR loss and a significant reduction in UAE [76].

Sarpogrelate

Sarpogrelate is a 5-hydroxy tryptamine receptor antagonist. It is used as anti-platelet agent as it inhibits thromboxane A2 production. Sarpogrelate treatment causes a significant decrease of UAE and MCP1 in serum and urine of DN patients [77].

Vitamin D receptor agonists

Paricalcitol in a dose of 2 μg /day showed a significant effect on UAE in T2DM patients with overt nephropathy [78]. (See Tables 1 and 2)

Potential therapeutic modalities

Protein kinase C inhibitors

A recent trial failed to find out a significant impact of ruboxistaurin on urine TGF-β or UAE [79].

Sulodexide

In a recent multicenter double-blind placebo controlled study in T2DM with incipient nephropathy, sulodexide failed to decrease UAE [80].

Endothelin receptor antagonists

In spite of the favorable effect of endothelin receptor antagonists on UAE in DN patients, a meta-analysis of five randomized controlled studies that included 2034 patients disclosed that their use is complicated by serious adverse events in comparison to pla-

Table 1
Approved treatment Modalities to prevent or withhold progression of DN.

Drug class	On-target action	Off-target actions	Remarks	Ref.
Antihypertensive RAS blockers	BP↓	UAE↓, GTP↓, K+ ↑, AT1-7↑, cytokines↓, Klotho↑	Failed to fully prevent DN, may accelerate progression in advanced CKD and old age	[42–46]
Blood Sugar control	Blood sugar ↓	UAE↓, incident CKD↓, CKD progression ↓	Hypoglycemia increases morbidity and mortality risk esp with SU and insulin	[47,48]
Metformin	Blood sugar ↓	AMPK↑, mTOR↓	↓ dose by 50% if GFR < 60 mL/min, stop if GFR < 30	[49]
Pioglitazone	Blood sugar ↓	UAE↓, NF-κB↓, CKD progression ↓	Salt and water retension, osteopenia, BW↑	[50]
GLP-1 agonists	Blood sugar ↓	BW↓, UAE↓, ROS↓, TGF-β1↓, CCN2↓	Nausea, vomiting, stop if GFR < 30	[51,52]
DPP-4 inhibitors	Blood sugar ↓	UAE↓, ROS↓, CCN2↓,EndM T↓, CKD progression ↓	Hypoglycemia less likely, dose adjustment with CKD progression except Linagliptin	[53–59]
SGLT2 inhibitors	Blood sugar ↓	Hyperfiltration ↓, BW↓, BP↓,UA↓, ROS↓.	Stop if GFR < 30	[61]
Statins	Serum Cholesterol↓	CVD↓	No effect on stroke, CKD progression or mortality	[42,62]
Quitting smoking		DN progress↓		[63,64]
Diet control				
salt restriction	BP↓, UAE↓,	DN progress↓	Salt paradox in very low salt	[65,66]
ptn restriction	DN progress↓		Of value only in T1DM	[67]
Hypouricemic agents	UA↓	UAE↓, DN progress↓		[70–72]
Phosphate handling				
↓P intake + sevelamer	Serum P ↓	DN progress↓, mortality ↓		[73,74]
HCO3 supplement	Treat acidosis	DN progress↓	May↑BP, may ↑edema	[75]
Pentoxifylline	RBCs rheology↑	UAE↓, DN progress↓	1200 mg/day	[76]
Sarpogrelate	Thromboxane A2↓	UAE↓, MCP1↓		[77]
Paricalcitol	PTH↓	UAE↓		[78]

RAS = renin angiotensin system; BP = blood pressure; UAE = urine albumin excretion; GTP = glomerular tuft pressure; K = potassium; AT1-7 = angiotensin1-7; DN = diabetic nephropathy; CKD = chronic kidney disease; SU = sulphonylurea; AMPK = adenosine monophosphate kinase; mTOR = mammalian target of rapamycin; GFR = glomerular filtration rate; NF-κB = nuclear factor kappa B; GLP = glucagon like peptide; BW = body weight; ROS = reactive oxygen species; TGF-β1 = transforming growth factor; CCN2 = connective tissue growth factor; DPP = dipeptidyl peptidase; EndM T = endothelial mesenchymal transition; SGLT = sodium glucose co-transporter; UA = uric acid; CVD = cardiovascular disease; T1DM = type1 diabetes mellitus; P = phosphate; HCO3 = bicarbonate; RBCs = red blood corpuscles; MCP = macrophage chemoattractant protein; PTH = parathormone.

Table 2
Potential therapeutic modalities to prevent or withhold progression of DN.

Drug class	On-target action	Off-target actions	Remarks	Ref.
Ruboxistaurin	PKC↓	UAE ±, TGF-β±		[79]
Sulodexide		UAE ±		[80]
Atrasentan	Endothelin receptor antagonist	UAE↓	Serious side effects postponed approval	[81]
Aldose reductase inhibitors	IC sorbitol↓, IC fructose ↓	UAE↓	No adequate RCTs	[82]
Nrf2 activator	ROS↓	NF-κB↓, EMT↓		
Curcumin	ROS↓	UAE↓, inflam. ↓	No long term trials	[83]
Resveratrol	ROS↓	EMT↓	No clinical trials	[84]
Bardoxolone	ROS↓	GFR↑	UAE↑, BP↑, HF↑, mortality↑, nausea, wt loss, muscle spasm	[85,86]
Empaticap Pegol	MCP1↓	UAE↓	I.V administration	[89]
CCX140-B	CCR2 antagonist	UAE↓, GFR±	Oral administration	[90]
Exogenous klotho	EMT↓, TGF-β↓	Fibrosis↓		[91–93]
Low dose IL-17A	MCP1↓	UAE↓, kidney size↓, mes. matrix↓, IF↓, urine IP10↓, TNFα↓, IL-6↓, and S ureai	No clinical trials	[94]

PKC = protein kinase C; UAE = urine albumin excretion; TGF-β1 = transforming growth factor; IC = intracellular; RCTs = randomized controlled trials; ROS = reactive oxygen species; NF-κB = nuclear factor kappa B; EMT = epithelial mesenchymal transition; inflame. = inflammation; GFR = glomerular filtration rate; BP = blood pressure; HF = heart failure; wt = weight; MCP = macrophage chemoattractant protein; I.V = intravenous; CCR2 = C—C motif chemokine receptor2; mes. = mesangial; IF = interstitial fibrosis; IP10 = Interferon-γ inducible protein 10; TNF = tumour necrosis factor; IL = interleukin; S = serum.

cebo. These findings necessitate further trials of larger sample size and of longer duration for proper evaluation. An ongoing hard outcome trial, the SONAR, in T2DM patients with DN to evaluate atrasentan might settle this issue [81].

Aldose reductase inhibitors

Advances were achieved on the potential role of aldose reductase inhibitors in the treatment and management of the major complications of diabetes like cataract, retinopathy, neuropathy, nephropathy and cardiovascular disease. However, their use in DN is limited to early stage [82].

Nuclear factor erythroid 2-related factor 2 activation

Nrf2 is an emerging potential therapeutic target for DN. Nrf2 could be activated by natural compounds with low toxicity including sulforaphane (present in cruciferous vegetables), cinnamic aldehyde (present in cinnamon essential oil), curcumin (found in turmeric), resveratrol (found in grapes), actinidia callosa (found in kiwi fruits), Sinomenine (found in the root of the climbing plant Sinomenium acutum), rutin (found in buckwheat, black tea, citrus fruits, and apple peels), berberin (found in Berberis Mahonia plant), garlic, Bitter Melon - Momordica charantia, and others. Administration of curcumin at the dose of 500 mg/day orally for a period of 15–30 days in T2DM patients with DN caused significant decrease of UAE, and the lipid oxidation index, malondialdehyde, beside suppression of inflammatory markers [83]. By scavenging different ROS, resveratrol exerts its direct antioxidant activity while its indirect activity is mediated by activation of Nrf2. Resveratrol increases AMPK phosphorylation and abolishes high glucose-induced reductions in the AMPK phosphorylation with consequent activation of NADPH oxidase, increases release of ROS, fibroblast proliferation and activation. Furthermore, resveratrol alleviates EMT induced by NADPH oxidase activation [84]. In spite of the frequent Clinical trials of resveratrol in neurological and cardiovascular diseases, no single clinical trial of this agent in DN is encountered. In a phase 2 double-blind randomized placebo-controlled trial, 227 adults with T2DM and CKD (eGFR of 20 to 45 mL/min/1.73 m^2) were assigned to receive placebo or bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily for 52 weeks. At 24 weeks of treatment, Bardoxolone methyl significantly increased eGFR. This increase was maintained throughout 1 year of treatment. Potential adverse effects included a significant increase of UAE, a trend of higher systolic BP, nausea, weight loss, and muscle spasm. Nausea occurred in 25% of patients. Weight loss over the year of treatment was significant (mean of 10 kgs in high and 3 kgs in normal body mass index patients). Muscle spasm occurred in 63% of 75 mg group. Hypomagnesemia was also observed [85]. This study was followed by larger study (2185 patients) of T2DM DN patients in stage 4CKD (eGFR of 15–30 mL/kg/1.73 m^2) that was designed to continue for 2 years using 20 mg of bardoxolone methyl as a single daily dose in the treatment group [86]. Unfortunately, the study was prematurely terminated at an average follow up of 9 months because of the frequent cases of heart failure and mortality in the active treatment group in comparison to the placebo group. This increased risk of cardiovascular events may not be due to direct cardiovascular effect of bardoxolone methyl. Reduced cardioprotective, nephroprotective, and antihypertensive effects of RAS blockers because of their increased excretion in the bardoxolone methyl group may be responsible for the increased cardiovascular events [87]. Endothelial dysfunction, a possible sequence of hypomagnesemia, might be another explanation for increased proteinuria, heart failure, increased mortality and muscle spasm [88].

Inhibitors of renal leukocyte recruitment

Therapeutic interventions targeting the membrane receptors on the surface of leukocytes can interrupt their renal recruitment. MCP-1 (CCL2) is a pro-inflammatory chemokine that is able to play an important role in leukocytes renal recruitment in DN. Using non-natural nucleotides, a mirror image (Spiegelmer) of MCP-1 was *in vitro* built-up. Emapticap Pegol binds and neutralizes MCP-1. In a phase IIa study, intravenous Emapticap Pegol administration for 12 weeks significantly reduced UAE in T2DM patients with DN [89]. Another CCR2 antagonist (CCX140-B) was tried in DN T2DM patients. Oral CCX140-B in a dose 5 mg/day on top of the standard of care treatment caused a significant reduction of UAE. This was associated with improvement in rate of GFR decline. However, phase 3 study of CCX140-B did not support the significant impact on GFR but confirmed the anti-proteinuric outcome reported in the earlier study [90].

Exogenous klotho

Klotho is an anti-senescence protein that favors epithelial regeneration and inhibits fibroblast phenotype transformation during EMT [91]. In high glucose cultured renal interstitial fibroblasts, exogenous klotho attenuated TGF-β bioactivity, type II TGF-β

receptor protein expression, TGF-β Smad2/3 signaling, and fibronectin expression induced by high glucose [92]. When intravenously delivered to diabetic rats, klotho gene was able to prevent the progression of renal hypertrophy and fibrosis [93].

Interleukin 17

Treatment of diabetic mice with low doses of IL-17A reversed DN in these mice. Treatment with low doses of IL-17A significantly decreased UAE, kidney size, mesangial matrix expansion, interstitial fibrosis, urine MCP1, IP10, TNFα, IL-6, and serum urea level in comparison to control animals [94].

Intensified multifactorial intervention

In an open parallel trial (Steno-2), T2DM patients with incipient nephropathy were randomly allocated to either standard treatment (n = 80) or intensive treatment (n = 80). All patients were recruited during 1992–93. The intensive treatment arm were kept on optimized diet regimen, 30 min exercise 3–5 times/week, no smoking, vitamin C, vitamin E, oral hypoglycemic treatment if diet alone failed to keep HbA1c < 6.5%, statin treatment for hypercholesrolemic and fibrate treatment for hypertriglycridemic patients. Oral hypoglycemic agents were metformin for overweight and gliclazide for lean patients. Combination of both agents was prescribed if HbA1c did not reach the target with a single agent. This was followed by adding insulin if oral treatment failed to achieve the target. Due to lower blood pressure target in the intensive treatment group, 71 patients in the intensive treatment group received antihypertensive treatment versus only 48 in the standard group. Out of these 69 had ACE inhibitor in the intensive treatment versus only 38 in the standard treatment. Due to the marked risk reductions encountered with intensive therapy after 7.8 years, all the patients were subsequently offered intensified multifactorial treatment according to the original protocol. After a median observation time of 21.2 years, there was no significant difference in the incidence of ESRD between the 2 groups in spite of the significant impact on survival and cardiovascular outcome [95,96].

Conclusions and future perspectives

According to the accumulating evidence, a change in the plan of managing diabetic patients to prevent the development and progression of DN became a mandate. Control of blood sugar to the target is often very tedious. The use of RAS blockers offers, at the best, partial protection. In addition, these agents were advised only when diabetic patients proceed to stage 4 DN. In spite of the favorable effect of RAS blockers on glomerular hyperfiltration, these agents failed to completely reverse this hemodynamic change even with dual blockade of RAS system [97,98]. SGLT2 inhibitors offer a new addition to hyperfiltration control. This effect is encountered even in T1DM [99] and is not related to RAS blockade [100]. These findings deserve the co-administration of both agents starting in the very early days of stage 1 of DN. This hypothesis deserves confirmation by randomized prospective trials in both T1DM and T2DM. This co-administration would also avoid the potential increased activity of the RAS system triggered by SGLT2 inhibitors likely related to their diuretic effect. However, co-administration of SGLT2 inhibitor and RAS blockers should be used very cautiously and better avoided if GFR is below 45 ml/min to avoid the potential risk of acute kidney injury. The best chance of SGLT2 inhibitors is in the very early stages of DN. Once GFR approaches 30 mL/min/1.73 m^2, these agents loose their therapeutic capabilities. In addition, the unique anti-fibrotic effect of the DPP-4 inhibitors especially linagliptin and saxagliptin deserves their use as the favorable hypoglycemic agents in patients with DN. A maximal benefit after the triple treatment with RAS blocker, SGLT2 inhibitor and either saxagliptin, or linagliptin is expected. The later does not require dose adjustment with progressive renal disease. The salt and water retaining effect of pioglitazone limits its use in DN. Metformin and GLP-1 agonists should be avoided with CKD progression to late stage 4 and in stage 5 of DN. Pentoxifylline should be added to the prescribed treatment once the patient has overt proteinuria. Control of hyperuricemia is a mandate. Nrf2 agonists should be postponed till a strong evidence of long term safety and efficacy is achieved. The same is applicable to renal leucocyte recruitment inhibitors, IL17 and klotho. Control of hyperphosphatemia and correction of metabolic acidosis are necessary once the patient proceeds to stage 4 CKD. Finally, it should be emphasized that the oral hypoglycemic agents, namely, Metformin, pioglitazone, DPP-4 inhibitors, and SGLT2 inhibitors can be used in T1DM patients when develop DN.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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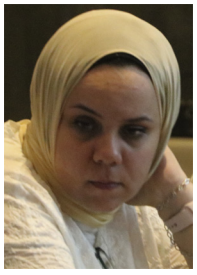

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