The Review of DIABETIC STUDIES

REVIEW

Improvements in the Management of Diabetic Nephropathy

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■ Abstract

The burden of diabetes mellitus is relentlessly increasing. Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) worldwide and a major cause of morbidity and mortality in patients with diabetes. The current standard therapy of diabetic nephropathy involves intensive treatment of hyperglycemia and strict blood pressure control, mainly via blockade of the renin-angiotensin system (RAS). Attention has been drawn to additional beneficial effects of oral hypoglycemic drugs and fibrates on other aspects of diabetic nephropathy. On the other hand, antiproteinuric effects of RAS combination therapy do not seem to enhance the prevention of renal disease progression, and it has been associated with an increased rate of serious adverse events. Novel agents, such as bardoxolone methyl, pentoxifylline, inhibitors of protein kinase C (PKC), sulodexide, pirfenidone, endothelin receptor antagonists, vitamin D supplements, and phosphate binders have been associated with controversial outcomes or significant side effects. Although new insights into the pathogenetic mechanisms have opened new horizons towards novel interventions, there is still a long way to go in the field of DN research. The aim of this review is to highlight the recent progress made in the field of diabetes management based on the existing evidence. The article also discusses novel targets of therapy, with a special focus on the major pathophysiologic mechanisms implicated in the initiation and progression of diabetic nephropathy.

Keywords: diabetes mellitus · albuminuria · diabetic nephropathy · end-stage renal disease · ACE inhibitors

1. Introduction

The burden of diabetes mellitus is relentlessly increasing and the global prevalence is expected to rise from 6.4% in 2010 to 7.7% by 2030 [1]. Diabetic nephropathy which affects approximately one-third of individuals with diabetes is the most common cause of end-stage renal disease (ESRD) worldwide and a major cause of morbidity and mortality in patients with diabetes. This is due to the progression to ESRD and associated cardiovascular disease, especially in patients with type 2 diabetes [2, 3].

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria (>300 mg/24 hr, or 300 mg/g creatinine), a progressive decline in glomerular filtration rate (GFR), arterial hypertension, and increased cardiovascular morbidity and mortality. It can also be defined as a spectrum of characteristic structural and functional changes, including glomerular hyperfiltration in the very early disease stage and the presence of moderately increased albuminuria. The latter is also called “microalbuminuria”, which is defined as urinary albumin excretion between 30 and 300 mg/day or albumin-to-creatinine ratio between

2 and 28 mg albumin per mmol creatinine (mg/mmol) on a random urine sample [4, 5].

The current standard therapy of diabetic nephropathy involves intensive treatment of hyperglycemia and strict blood pressure control, mainly via blockade of the renin-angiotensin system (RAS). Major attention is currently focused on ongoing experimental studies and clinical trials with novel specific agents, which target the emerging pathophysiologic mechanisms involved in the progression of diabetic nephropathy. A few agents have shown beneficial effects in the experimental studies performed to date, although data regarding their clinical impact on diabetic patients remain ambiguous.

The aim of this review article is to highlight the recent progress made in the field of management of diabetic nephropathy based on the existing evidence. The article intends to provide evidence-based guidance on treatment options with reference to novel targets of therapy, while focusing on the major pathophysiologic mechanisms implicated in the initiation and progression of diabetic nephropathy which substantially constitute the targets for therapy.

Abbreviations:
ACEI – angiotensin-converting enzyme inhibitors
AGE – advanced glycosylation end products
ARB – angiotensin II receptor blockers
CKD – chronic kidney disease
DN – diabetic nephropathy,
DPP-4 – dipeptidyl peptidase 4
ESH/ESC – European Societies of Hypertension and Cardiology
ESRD – end stage renal disease
ET-1 – endothelin 1
GFR – glomerular filtration rate
GLP-1 – glucagons-like peptide 1
JNC-8 – Eighth Joint National Committee
KDIGO – kidney disease improving global outcomes
NKF/KDOQI – National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PPAR-α – peroxisome proliferator-activated receptor alpha
PPAR-γ – peroxisome proliferator activator receptor gamma
PKC – protein kinase C
RAS – rennin-angiotensin system
SGLT-2 – sodium-glucose co-transporter-2
TZD – thiazolidinediones
UAE – urine albumin excretion
VEGF – vascular endothelial growth factor

2. Pathophysiological insights as potential therapeutic targets in diabetic nephropathy

Several pathogenetic processes are considered to be involved in diabetic nephropathy (**Figure 1**). Both intraglomerular hypertension induced by renal vasodilatation and ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli could lead to glomerulosclerosis [6]. Hyperglycemia may also directly induce mesangial expansion and injury, possibly via increased matrix production or glycation of matrix proteins [7]. Based on the observation that a decrease in cell surface heparan sulfate contributes to increased glomerular basement membrane permeability to albumin, the activation of protein kinase C and upregulation of heparanase expression may regarded as additional hyperglycemia-mediated mechanisms that are potentially pathogenic in diabetic nephropathy [8]. Activation of cytokines, profibrotic elements, inflammation, and vascular growth factors such as vascular endothelial growth factor (VEGF) may be involved in the process of matrix accumulation in diabetic nephropathy [9]. Defects in podocyte-specific insulin signaling may also contribute to the process. Therefore, the podocyte insulin receptor may provide a target for agents that prevent proteinuria and/or the development and progression of diabetic nephropathy [10].

While longitudinal studies have shown that microalbuminuria strongly predicts the development of diabetic nephropathy in type 1 diabetic patients [11, 12], there are biological mechanisms that initiate the early decline in kidney function, including oxidative, inflammatory, and fibrotic pathways [13]. These mechanisms should be considered in diagnosis and treatment besides the determination of microalbuminuria.

It has been suggested that a fraction of the microalbuminuric patients returns to normoalbuminuria. However, only treatment-induced and not spontaneous regression is associated with stable and long-lasting normalization in patients with type 1 diabetes [12]. In type 2 diabetes, moderately increased albuminuria is associated with declining kidney function, progression to severely increased albuminuria, and increased long-term mortality. Remission to normal albuminuria may occur as well [14, 15]. Additonally, microalbuminuria is a strong predictor of overall and cardiovascular mortality in diabetic patients, a finding which is valid for the general population as well [16]. Several other factors in addition to hyperglycemia are associated with microalbuminuria in diabetic patients, including arterial hypertension, obesity, heart failure, and other comorbidities [17, 18]. Until now, the exact mechanisms linking microalbu-

minuria to death from cardiovascular disease have been poorly understood. It is supposed that endothelial dysfunction resulting from endothelial-podocyte crosstalk across the glomerular filtration barrier is the underlying mechanism [19].

Finally, a subset of patients with diabetic nephropathy does not have overt proteinuria as a prerequisite to renal dysfunction. The exact pathogenetic mechanisms involved in this condition are also unknown [20].

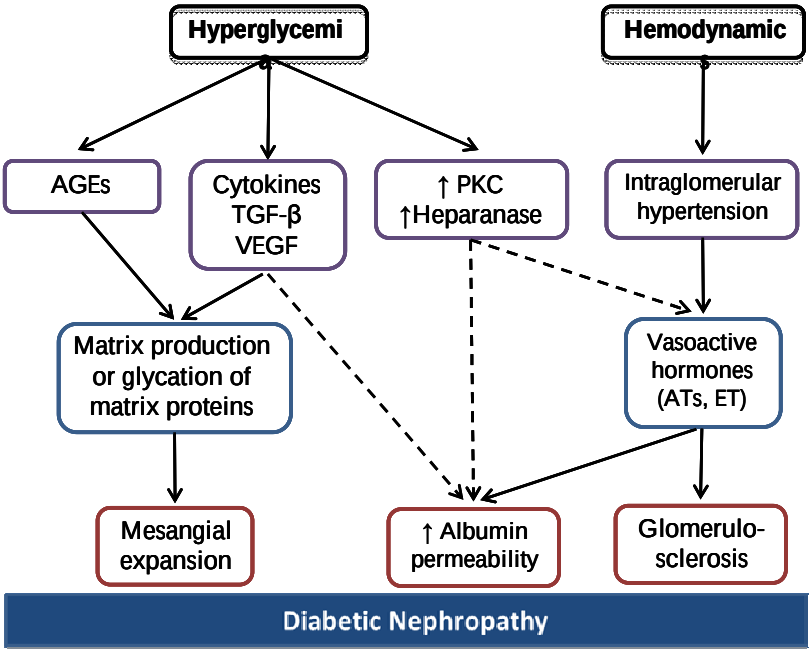

Figure 1. Proposed pathophysiological mechanisms implicated in the pathogenesis of diabetic nephropathy. Hyperglycemia may induce mesangial expansion via the stimulation of cytokines and vascular growth factors or glycation of matrix proteins. Hyperglycemia-induced activation of protein kinase C and upregulation of heparanase expression result in increased glomerular permeability. Intraglomerular hypertension and subsequent stimulation of vasoactive hormones cause glomerulosclerosis. Substantial overlap exists between these different pathways.

3. Glycemic control

Timely and effective glycemic control may have a positive effect on the prevention of diabetic nephropathy. Evidence for the impact of strict glycemic control was first provided in type 1 diabetes. Two major clinical trials involving nearly 1,500 patients with type 1 diabetes demonstrated that intensive glycemic control reduces the incidence of micro- and macroalbuminuria by 39% and 54%, respectively. Intensive glycemic control resulted in a reduction of microalbuminuria by 45% after 18 years of follow-up, enabling a protection from kidney disease [21, 22].

Another important finding was that the long-term risk of a reduced glomerular filtration rate (GFR) was significantly lower among type 1 diabetes patients treated early in the course of the disease with intensive insulin therapy (HbA1c <6.05%, use of insulin pump) than among those treated with non-intensive insulin therapy [23]. Higher HbA1c concentrations are strongly associated with risk of chronic kidney disease (CKD), but a positive association seems to exist between higher HbA1c levels and incidence of CKD as well, even in the absence of albuminuria or other microvascular complications of diabetes [24]. According to the outcomes of several studies, which included patients who underwent pancreatic transplantation, strict glycemic control deccelerates the rate of progressive renal damage even in the presence of overt proteinuria [25-30].

Regarding type 2 diabetes, the two most important trials, UKPDS and ADVANCE, demonstrated that intensive glycemic control decreases the risks of moderately increased albuminuria [31, 32], overt proteinuria, and ESRD compared with standard control [32].

Poor glycemic control (HbA1c > 9%) appears to be common among patients with early stages of CKD; it is associated with a marked decline in clinical outcome and risk of progression to kidney disease. Thus, appropriate and timely control of HbA1c levesl in patients with diabetes and CKD is an essential step towards reducing diabetic complications. However, intensive glycemic control, with HbA1c <6.5%, may be associated with increased mortality [33]. A recent meta-analysis showed that, although intensive glucose control reduces the risk for micro- and macroalbuminuria, evidence regarding the effects on progression of CKD and end-stage renal disease remains ambiguous [34]. Another recent meta-analysis investigating the effect of intensive compared with con-

ventional glycemic control on all-cause mortality showed that the HbA1c and all-cause mortality relationship in patients with type 2 diabetes is J-shaped, meaning that the relative risk for all-cause mortality increases with an increase in HbA1c above 7,5% and decreases with an increase in HbA1c below 7,5% [35]. Likewise, the ACCORD investigators found that HbA1c levels of 6.0% versus 7.0-7.9% resulted in excess mortality, thus suggesting that the benefits of intensive therapy regarding microvascular outcomes should be weighted against the increase in total and cardiovascular mortality and high risk for severe hypoglycemia [36]. Nevertheless, intensive glycemic control seemed to reduce the risk of microvascular complications in the ACCORD trail, albeit at the expense of an increased risk of hypoglycemia and higher all-cause mortality [36]. Another recent meta-analysis failed to demonstrate an all cause-mortality benefit of intensive glycemic control or a significant reduction in the rate of composite microvascular complications [37].

The current recommendation by the American Association of Clinical Endocrinologists is to target HbA1c <6.5%. In an attempt to balance out the risk of hypoglycemia with the clear benefit of renoprotection, the American Diabetes Association sets a goal of HbA1c <7% [38]. Accordingly, the recent KDIGO (Kidney Disease: Improving Global Outcomes) report on diabetic kidney disease highlights the fact that the beneficial effect of tight glycemic control on diabetic nephropathy is based almost exclusively on prevention of microalbuminuria and hindering its progression to overt albuminuria. The report suggest that the target HbA1c level may need to be adjusted upwards in patients with more advanced kidney disease, but particular attention should be paid to the augmented risk of severe hypoglycemia and death in these patients [39].

Besides glycemic control, attention has been paid to additional beneficial effects of oral hypoglycemic drugs on other aspects of diabetic nephropathy. These effects include the restoration of tubuloglomerular feedback mechanisms, lowering of glomerular hyperfiltration, and reduction of hyperglycemia-induced inflammatory and fibrotic markers by sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists are able to exert a renoprotective effect by reducing inflammation, fibrosis, and blood pressure [40]. Optimal prevention and treatment requires the implementation of therapies that interfere specifically with the pathogenesis of microvascular complications of diabetes. Therefore, glucose-lowering agents that provide renoprotection independent of their hypoglycemic effects may be considered as combined therapy. Simultaneous application of an SGLT-2 inhibitor and blockade of the renin-angiotensin-aldosterone system may be a more effective strategy to prevent the progression of diabetic nephropathy than either drug alone [40].

Abundant experimental data indicate that thiazolidinediones (TZD), a family of anti-diabetic drugs that activate the transcription factor peroxisome proliferator activator receptor gamma (PPAR-γ), have direct renoprotective effects [41-43]. These effects are most probably exerted by preventing diabetes-induced renal inflammatory processes. However, clinical studies have reported controversial outcomes, with some of them reporting significant antiproteinuric effects [44-46], and others demonstrating insignificant effects [47]. A meta-analysis of 15 studies, involving approximately 2,800 patients, showed that treatment with TZD significantly decreases urinary albumin and protein excretion [46]. A pilot study conducted in diabetic subjects with CKD showed a slower decline in renal function after initiation of TZD [48]. Another study compared the treatment with rosiglitazone, metformin, and glyburide in 4,351 recently diagnosed, drug-naïve type 2 diabetes patients. During a 5-year period after initial treatment with rosiglitazone, the increase in albuminuria was delayed (compared with metformin), renal function was preserved (compared with glyburide), and blood pressure control was improved relative to both other medications [49]. On the other hand, these agents raised some safety concerns, including an increased risk of cardiovascular disease, especially with rosiglitzone [50-52], and malignancy [53, 54]. In contrast, a recent study conducted by the Diabetes Shared Care Program (DSCP) in Taiwan showed an association between the use of TZD and reduced risk of cardiovascular events, including stroke and all-cause mortality [55].

Glomerular hyperfiltration is recognized as the first step in the progression of kidney disease in diabetic patients. At the onset of type 2 diabetes, hyperglycemia enhances proximal tubular reabsorption, thus leading to a decrease in solute load reaching the macula densa, with subsequent suppression of the tubuloglomerular feedback and increased glomerular filtration rate [56, 57]. As mentioned above, and evidenced by experimental studies, SGLT-2 inhibitors attenuate the progressive nature of diabetic nephropathy by preventing glomerular hyperfiltration independent of their

blood glucose-lowering effects [58-60]. However, clinical data about the potential role of the proximal tubule in the pathophysiology of diabetic nephropathy and the nephroprotective effects of SGLT-2 inhibitors are currently insufficient [60]. Additionally, these agents have been tried in patients with type 1 diabetes, and short-term treatment with the SGLT-2 inhibitor empagliflozin was found to attenuate renal hyperfiltration [61, 62].

Studies have shown that DPP-4 inhibitors appear to possess anti-inflammatory properties and improve endothelial function, blood pressure control, lipid metabolism, and bone marrow function [63]. Additional experimental data reported direct favorable effects of DPP-4 inhibitors on microvascular complications of diabetes. However, the evidence is insufficient to confirm the preventive effect of this drug on the progression of diabetic microangiopathy in humans, independently of the effects on improved glucose control [63, 64].

4. Renin-angiotensin system (RAS)

Solid evidence from experimental studies in diabetic animals suggests that intraglomerular hypertension and glomerular hypertrophy play important roles in the onset of diabetic nephropathy as hyperglycemia induces renal vasodilation and a rise in GFR. Subsequent loss of nephrons accelerates the increase in intraglomerular pressure through the compensatory response of remaining nephrons. RAS inhibitors, including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), are widely used to control blood pressure in diabetic patients. These drugs have been extensively studied, and are considered superior to other antihypertensive drug categories in the treatment of diabetic nephropathy because of their capacity to reduce both intraglomerular pressure and proteinuria by preferentially dilating the efferent arteriole. The degree of proteinuria in glomerular disease tends to relate directly with the intraglomerular pressure; thus a treatment-induced reduction in protein excretion causes a desirable decline in intraglomerular pressure, and as a consequence improves renal outcome. There is now consensus that a decrease in protein excretion has predictive significance for improved renal prognosis [65-68]. Additionally, RAS components seem to be altered in diabetic podocytopathy, and their modulation may modify the progression of diabetic nephropathy [69].

The efficacy of ACEI therapy in type 1 diabetic patients with moderately increased albuminuria has been evaluated in several randomized prospective trials. In addition to the reduction of albuminuria, ACEI have significant long-term benefits [70]. In a systematic review of 11 trials of normotensive type 1 diabetic patients with moderately increased albuminuria, ACEI therapy significantly reduced the risk of progression to severe albuminuria, and significantly increased the chance of regression to normoalbuminuria [71]. Additionally, the beneficial response to ACEI seen in both hypertensive and normotensive subjects is consistent with several studies suggesting that these antihypertensive agents deccelerate the progression of diabetic nephropathy [72, 73]. Moreover, in some patients with type 1 diabetes, ACEI exhibit a marked antiproteinuric effect with sustained long-term remission or regression of nephropathy or the nephrotic syndrome; such patients appear to have better renal outcomes [74, 75]. Therefore, intensive control of systemic blood pressure, in particular with ACEI, may enable recovery from diabetic nephropathy in type 1 diabetes patients with advanced renal disease. Although there are few data on the efficacy of ARB in patients with type 1 diabetes and moderately increased albuminuria, based on their proven benefit in patients with type 2 diabetes, these drugs are probably as effective in type 1 diabetes patients as ACEI.

Regarding primary prevention of moderately increased albuminuria in patients with type 1 diabetes, several clinical trials have evaluated the efficacy of ACEI or ARB. However, three randomized, placebo-controlled trials in patients with type 1 diabetes and normoalbuminuria (EUCLID, RASS, DIRECT) showed no benefit from angiotensin inhibition [76-78]. Moreover, specific histologic findings from kidney biopsies of patients with diabetic nephropathy showed that treatment with these drugs had no significantly beneficial effects compared with placebo [77].

In contrast, the renoprotective effects observed with ACEI and ARB treatment have been substantiated in type 2 diabetic patients with moderately increased albuminuria [32, 79, 80]; both groups (ACEI and ARB) appeared to be equally effective [80]. Also, a clear renoprotective benefit of ACEI and ARB has been demonstrated in patients with type 2 diabetes and overt nephropathy; a larger reduction in albuminuria was correlated with a progressively lower risk of ESRD. It should be noted that these effects were independent of the difference in blood pressure reductions among the groups [81-88]. Lowering of albuminuria early in the course of the disease correlates with a decreased subsequent cardiovascular risk [89]. Nev-

ertheless, patients with type 2 diabetes and advanced kidney disease are likely to progress to ESRD eventually, although more slowly, despite treatment with ACEI or ARBs.

Regarding primary prevention of moderately increased albuminuria, the effect of angiotensin inhibition in hypertensive patients with type 2 diabetes has been evaluated in four randomized, placebo controlled trials in patients with type 2 diabetes and normal albuminuria [90-94]. The trials suggest that ACEI and ARB are effective in preventing the new onset of moderately increased albuminuria in this group of patients. On the other hand, results from clinical trials in patients with type 2 diabetes and normal blood pressure remain controversial regarding the effectiveness of ACEI or ARB in primary prevention of moderately increased albuminuria; these results should thus be interpreted with caution [78, 94]. Therefore, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) clinical practice guidelines have not proposed the implementation of ACEI or ARB in primary prevention of diabetic nephropathy in normotensive individuals with normo-albuminuria [95].

Combination therapy with ACEI and ARB compared with ACEI or ARB monotherapy was shown to reduce proteinuria in patients with type 1 and type 2 diabetes [96, 97]. However, the antiproteinuric effects of combination therapy do not seem to be sufficient for the prevention of renal disease progression or death. Moreover, combination therapy has been associated with an increased rate of serious adverse events. The VA NEPHRON-D trial was discontinued after approximately 2 years because of safety concerns; patients experienced acute kidney injury and severe hyperkalemia, conditions that were significantly more common with combination therapy [98]. The ONTARGET trial investigated the administration of combination therapy with telmisartan and ramipril in patients with diabetic nephropathy. It appeared that the therapy was associated with a non-significantly higher incidence of dialysis initiation or doubling of serum creatinine in comparison with monotherapy, as well as higher rates of acute kidney injury, hyperkalemia, and hypotension [99, 100]. A recent meta-analysis that evaluated the efficacy and safety of combination therapy in diabetic nephropathy suggested that it may be safely applied in early stages of the disease when there are signs of proteinuria, but should be cautiously used in the setting of advanced stages of renal dysfunction [101].

Aliskiren, an oral direct renin inhibitor, has a similar degree of blood pressure-lowering properties as other agents. In the AVOID trial, aliskiren combined with losartan was associated with a significantly greater reduction in proteinuria, but no significantly greater antihypertensive effect, than losartan monotherapy [102]. On the other hand, results from the multinational, randomized ALTITUDE trial, which included type 2 diabetic patients with pre-existing renal or cardiovascular disease assigned to aliskiren or placebo, showed that more patients in the aliskiren group reached the composite primary endpoint of renal and cardiovascular events, despite a similar incidence of renal events in both groups. Additionally, hyperkalemia was significantly more frequent with aliskiren. Therefore, the trial was prematurely terminated because of the lack of evidence regarding benefits and the higher risk of side effects [103].

Aldosterone antagonists seem to possess antiproteinuric effects when used alone and in combination with ACEI or ARB in both type 1 and type 2 diabetes, but involve a risk of hyperkalemia when applied in patients with reduced GFR [104-106]. However, there is no adequate long-term evidence of beneficial effects regarding the prevention of renal impairment through aldosterone antagonists [107, 108].

5. Blood pressure goals in diabetic nephropathy

It is well established that early treatment of hypertension is particularly important in diabetic patients both to prevent cardiovascular disease and to minimize the progression of microvascular complications of diabetes. Past major guidelines recommended that the target blood pressure in diabetic patients should be less than 130/80 mmHg. The ACCORD BP trial, which enrolled type 2 diabetic patients with increased cardiovascular risk, found no significant cardiovascular benefit, except for stroke, and more drug-related side effects at a mean systolic blood pressure of 119.3 than at 133.5 mmHg [109].

A recent meta-analysis of 40 trials examined the association between antihypertensive treatment and vascular disease in type 2 diabetes in 100,354 patients, including normotensive and hypertensive subjects [110]. Compared with placebo, antihypertensive therapy significantly reduced the rate of mortality, total cardiovascular disease, myocardial infarction, and stroke. However, analyses of patients classified according to their base-

line systolic pressure level revealed that, with the exception of stroke, the benefit of antihypertensive therapy was limited to those whose initial systolic pressures were greater than 140 mmHg. Also, the different drug classes did not exhibit significant differences in their antihypertensive effects, except for stroke and heart failure [110].

The most recent major guidelines published by the eighth Joint National Committee (JNC 8) and the European Societies of Hypertension and Cardiology (ESH/ESC) recommend that all patients with diabetes should have a target blood pressure of less than 140/90 mmHg [111, 112].

6. Intensive lipid control

Intensive lipid lowering is an important part of diabetes management since diabetes is considered a coronary heart disease equivalent. In addition to promoting systemic atherosclerosis, an elevation in lipid levels may also contribute to the development of glomerulosclerosis in CKD [113]. Interventional studies suggest that anti-hyperlipidemic agents have a beneficial effect on diabetic nephropathy through improvement of albuminuria and renal function [114, 115]. Recent data show that fibrates are renoprotective, an effect independent of their antihyperlipidemic action [115, 116]. The benefits of fibrates may be associated with their anti-inflammatory properties and decreased production of type 1 collagen in the mesangium. Peroxisome proliferator-activated receptor α (PPAR-α) is expressed in several tissues including the kidney. Experimental data have suggested that fibrate-induced activation of PPAR-α, a member of a large nuclear receptor superfamily, plays a significant role in various metabolic and inflammatory signaling pathways that are involved in diabetic microvascular complications [117].

7. Novel targets in therapy

Bardoxolone methyl is an oral antioxidant. Its structure and activity profile is similar to cyclopentenone prostaglandins that exert anti-inflammatory effects by inhibiting the nuclear factor κB pathway. Experimental data of drug-induced or ischemic acute kidney injury have shown beneficial effects [118]. These positive effects were confirmed in the Bardoxolone Methyl in CKD and type 2 Diabetes (BEAM) trial, which enrolled 227 patients with type 2 diabetes and CKD stage III-IV. According to this trial, bardoxolone methyl therapy significantly increased estimated glomerular filtration rate (eGFR) at 1 year of follow-up, while placebo therapy did not have any effects on the eGFR [119].

The subsequent BEACON trial evaluated 2,185 patients with type 2 diabetes and stage 4 CKD, who were randomly assigned to bardoxolone methyl or placebo, while being under concomitant therapy with an ACEI or ARB [120]. The trial was stopped early after a median follow-up of nine months due to a significant increase in the incidence of cardiovascular events, although the primary endpoint which was a composite of end-stage renal disease and cardiovascular death was identical in both groups. Additionally, despite causing a significant rise in GFR, bardoxolone methyl significantly increased blood pressure and albuminuria, most probably via sodium and water retention [121].

Pentoxifylline is a non-specific phosphodiesterase inhibitor with anti-inflammatory properties; it has been used in patients with peripheral artery disease and alcoholic hepatitis. Several small studies including patients with diabetic nephropathy showed that pentoxifylline had anti-proteinuric effects and reduced the rate of decline in eGFR [122-125]. Additional data are needed before pentoxifylline can be recommended as treatment for diabetic nephropathy.

Although the molecular mechanism of hyperglycemia-induced tissue injury still remains unclear, oxidative stress seems to play a key role, and exerts its harmful impact via the sorbitol pathway and accumulation of advanced glycosylation end (AGE) products. In experimental diabetes, sorbitol production is markedly enhanced by the intracellular conversion of glucose to sorbitol. Accumulation of sorbitol within the cells results in a rise in cell osmolality and a decrease in intracellular myo-inositol, changes which lead to a decrease in Na-K-ATPase activity and a possible shift in the intracellular redox potential [126]. Aldose reductase inhibitors such as tolrestat were shown to improve some of the manifestations of diabetic nephropathy by reversing glomerular hyperfiltration and decreasing albuminuria, but their potential benefit remains in the initial stages of diabetic nephropathy in type 2 diabetes [127-129]. At present, aldose reductase inhibitors have shown evidence of benefit in patients with diabetic peripheral neuropathy [130].

Increased activity of protein kinase C (PKC) appears to contribute to the micro- and macrovascular complications of diabetes through changes in vascular permeability, angiogenesis, cell growth and apoptosis, vasodilation, cytokine activation, basement membrane thickening, and extracellular

matrix expansion [131]. Lowering PKC may be possible via isoform-specific PKC inhibitors such as ruboxistaurin mesylate therapy. Therapies aimed at lowering PKC may be beneficial in slowing the progression of diabetic nephropathy, as shown in animal studies. However, studies in humans have provided ambiguous results to date; much larger trials are necessary to determine the potential clinical role of this agent [132-134].

Experimental data suggest that glomerular capillary wall and mesangial alterations in diabetic nephropathy involve alterations of glycoproteins in these structures [135]. Experimental data from diabetic animals reveal that the administration of anionic glycoproteins can effectively prevent the biochemical alterations that promote albuminuria [136]. Administration of sulodexide, a purified mixture of sulfated glycosaminoglycan polysaccharides, has been associated with a reduction in albuminuria in diabetic patients [137, 138]. However, a recent multicenter, placebo-controlled, double-blinded study showed that sulodexide did not decrease UAE in patients with diabetic nephropathy and microalbuminuria [139]. Based on these controversial data, further research is needed to clarify the potentially beneficial role of sulodexide in the early stages of diabetic nephropathy.

Pirfenidone is an oral synthetic antifibrotic agent that has demonstrated benefits in animal models of diabetic nephropathy and in patients with this syndrome by preventing the progression of renal impairment. Pirfenidone is thus a promising agent for the treatment of diabetic nephropathy, and should be further investigated and advanced [140, 141].

Experimental and clinical studies have shown that vitamin D has antiproteinuric effects via both RAS-dependent and RAS-independent pathways [142]. In experimental diabetic nephropathy, vitamin D receptor activation via calcitriol and paricalcitol was shown to decrease the expression of proinfammatory mediators in podocytes and tubular cells, and to prevent glomerular infiltration by macrophages, apoptosis, and extracellular matrix deposition [143]. These effects were observed even when proteinuria was not reduced. The vitamin D Receptor Activator in Albuminuria Lowering (VITAL) study, a multinational, placebo-controlled, double-blind trial, included albuminuric, type 2 diabetic patients receiving ACEI or ARB. It was found that the addition of paricalcitol to RAS inhibition reduced residual albuminuria in patients with diabetic nephropathy [144].

Endothelin-1 (ET-1) is a potent vasoconstrictory peptide with proinflammatory and profibrotic properties that exerts its biological effects through two receptor subtypes, namely ET(A) and ET(B). ET-1 promotes diuresis and natriuresis by local production and action through ET(B) receptors in the renal medulla, whereas activation of ET(A) receptors causes vasoconstriction, mesangial-cell proliferation, extracellular matrix production, and inflammation [145]. Endothelin-receptor antagonists are a promising therapeutic tool for diabetic nephropathy. However, their benefit remains controversial since administration of non-selective endothelin antagonists has been associated with adverse cardiovascular events, including congestive heart failure and fluid overload. Selective inhibition of ET(A) receptors appears not to interfere with the natriuretic, antihypertensive, and ET-clearing effects of ET(B) [146-149]. A recent meta-analysis of five randomized controlled trials on endothelin-receptor antagonists found reduced albuminuria in patients with diabetic nephropathy, but also an increased rate of serious adverse events compared with placebo [150]. It will be necessary to perform well-controlled, adequately powered trials with a longer duration to determine and weigh the potential benefits versus risks of endothelin inhibition in diabetic nephropathy. In an attempt to realize this proposal, the SONAR study, a currently ongoing, large, randomized, clinical trial, aims to determine the efficacy of atrasentan in preventing the progression of diabetic nephropathy [151].

Finally, the phosphate binder sevelamer carbonate, a currently used phosphate binder, was shown to significantly reduce HbA1c, fibroblast growth factor 23, and lipids, and to exhibit anti-inflammatory and antioxidant properties, independently of phosphate level reduction in patients with diabetes and early kidney disease [152]. However, a recent trial did not show any benefits of sevelamer regarding reductions in HbA1c or albuminuria overall in patients with type 2 diabetes and diabetic nephropathy, except for very specific groups of patients [153]. Thus, further studies may be warranted regarding this agent.

8. Conclusions and future challenges

The clinical course of diabetic nephropathy has changed significantly due to improvements in patient diagnosis, follow-up, and treatment. The availability and implementation of major guidelines play an important role in clinical treatment

by supporting physicians to make evidence-based clinical decisions. Nowadays, the gold standard of diabetic nephropathy therapy involves intensive treatment of hyperglycemia and hypertension, mostly through RAS blockade. Additional beneficial effects on the pathophysiology of diabetic nephropathy could be ulitized by specific oral hypoglycemic drugs (such as PPAR-γ agonists, SGLT2 inhibitors, and DPP4 inhibitors) and fibrates. These agents are important therapeutic options.

Novel agents, such as bardoxolone methyl, pentoxifylline, PKC inhibitors, sulodexide, pirfenidone, endothelin receptor antagonists, vitamin D supplementation, and phosphate binders, have been associated with controversial results (**Figure 2**). Athough new insights into the pathogenetic mechanisms involved in diabetic nephropathy, including gene expression and identification of susceptibility loci, have opened new horizons towards novel intervention strategies, there is still a long way to go in the field of research into diabetic nephropathy.

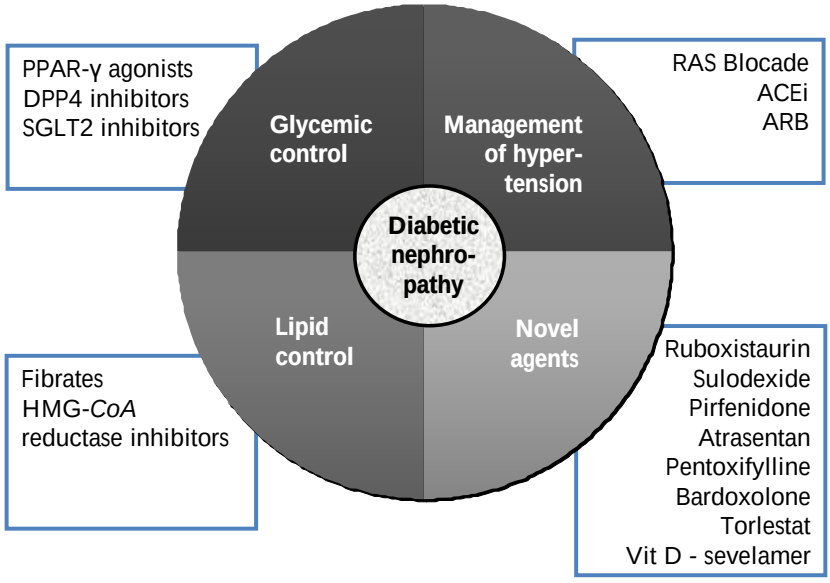

Figure 2. Key elements in the management of diabetic nephropathy with established and potential novel therapeutic agents. Specific classes of oral hypoglycemic and hypolipidemic agents are associated with renoprotective effects. RAS blockade remains the mainstay of treatment. Novel agents that target different pathophysiologic pathways in diabetic nephropathy are being investigated.

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