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REVIEW

Diabetic Nephropathy: From Bench to Bedside

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List of abbreviations
ESRD: End-stage renal disease
GFR: Glomerular filtration rate
DN: Diabetic nephropathy
AGEs: Advanced glycation end products
ACE: Angiotensin-converting enzyme
ARBs: Angiotensin receptor blockers
ACR: Albumin to creatinine ratio
FGF-23: Fibroblast Growth Factor-23
SGLT-2 Inhibitors: Sodium Glucose Co-transporters 2 Inhibitors

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ABSTRACT

Diabetes mellitus together with arterial hypertension are the most common causes of chronic kidney disease. Notably, diabetic kidney disease remains a major and independent risk for premature mortality. Therefore, continuous and accurate control of risk factors for the development of diabetic nephropathy is mandatory. Measurement of serum creatinine levels and calculation of estimated glomerular filtration rate according to CKD-EPI equation must be performed annually. Also, measurement of urine albumin and calculation of the urine albumin to creatinine ratio rate is recommended to be performed annually, too, as ratio >30 mg/g creatinine is considered to be a continuous risk factor for cardiovascular disease. Equally important is good glycemic control, as determined by glycated hemoglobin levels of <7%, as well as control of hypertension, often with more than three anti-hypertensive drugs needed to achieve this goal. Inhibition of the renin-angiotensin-aldosterone system is not only effective in managing hypertension, but seems to reduce albuminuria levels among patients with diabetic nephropathy. Other antihypertensive drugs which decrease albuminuria levels are the newer dihydropyridines calcium blockers manidipine and the latest b-blockers (carvedilol). Dyslipidemia parameters should be improved, too, especially the serum LDL-cholesterol levels <100 mg/dl. Vitamin D analogues have been shown to decrease albuminuria if glomerular filtration rate <60 ml/min/1.73 cm^2. Besides, sodium glucose co-transporter 2 inhibitors, which produce glucosuria seem to possess nephroprotective properties among type 2 diabetic patients. In particular, the EMPAREG study has documented that empagliflozin reduces the relative risk of serum creatinine doubling by 44%, while the relative risk of introducing hemoperfusion has been decreased by 55% within four years. It seems likely that atrasentan, a selective antagonist of the receptor of endothelin A also reduces albuminuria by approximately 35%. Moreover, the significance of substances with anti-inflammatory properties, such as oxidase inhibitors, pentoxyfilline, and N-acetyl-cysteine remains to be elucidated. It is noteworthy that weight loss together with dietary consultation, not only are implicated in better glycemic control and dyslipidemia management, but also in improving diabetic nephropathy per se.

INTRODUCTION

Diabetic kidney disease or diabetic nephropathy is the most common cause of chronic kidney disease, leading to end-stage renal disease (ESRD) and death, both

in the developed and developing countries, as well. Of note, the excess risk of death from any cause among patients with diabetes is mainly associated with the presence of kidney disease. In the absence of diabetic nephropathy, the risk of death among persons with diabetes type 1 or type 2 is similar to that in the general population.[1,2] The main alterations that occur in the initiation of diabetic nephropathy (DN) are increase of mesangial matrix, thickening of glomerular basement membrane, hyperfiltration and increase of Glomerular Filtration Rate (GFR).[1,2]

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

These alterations are related to changes such as increased production of adipocytokines and reactive oxygen species along with accumulation of advanced glycation end products (AGEs), which lead to deposition of mesangial matrix, glomerular sclerosis, and tubulointerstitial fibrosis. In this complex process growth factors, such as TGF-β (Transforming Growth Factor-β) and VEGF (Vascular Endothelial Growth Factor) along with proinflammatory cytokines, such as IL-1, IL-6 and TNF-a play a key-role. Also, oxidative stress is implicated in the mesangial cell proliferation and podocytopathy, which leads to mesangial expansion and glomerular basal membrane thickening.[3,4]

On the other hand, hemodynamic changes result in hyperfiltration, an early event in the course of type 2 diabetes, which usually precedes the diagnosis of diabetes.[5,6] Hyperfiltration is documented to be followed by a progressive decrease in glomerular filtration rate (GFR). Specifically, hyperfiltration leads to early glomerular death. In diabetes mellitus, glomerular hyperfiltration is suggested to be due to glomerular hemodynamic changes as well as glomerular-tubular feedback mechanisms.[5,6]

Hyperglycemia-induced dysregulation of the glomerular afferent and efferent arteriole tone, which leads to higher decrease in the afferent arteriolar tone compared with the efferent arteriolar tone is mostly driven by local upregulation of angiotensin II. The hemodynamic mechanism behind this dysregulation is complex, but it is noteworthy that the efferent glomerular arteriole is 10 – 100 times more sensitive to the vasoconstrictive properties of angiotensin II than the afferent arteriole, and this might account for the consequent higher intraglomerular capillary pressure, which is believed to be the cornerstone of diabetic nephropathy.[7]

In normal subjects, the tubuloglomerular feedback autoregulates glomerular filtration by changing the tone of the afferent glomerular arteriole. In particular, an enhancement in distal sodium concentrations results in increased vasoconstriction of the afferent glomerular arteriole by the macula densa, while a decrease in sodium concentrations in the distal tubuli, leads to vasodilation of the afferent glomerular arteriole. In patients with type 2 diabetes mellitus, upregulation of glucose and sodium reabsorption by sodium glucose co-transporter 2 (SGLT-2) in the S1 and S2 segments of the proximal tubule, accounts for a local decrease in sodium levels and subsequent vasodilation of the afferent glomerular arteriole thereby resulting in enhanced filtration.[8,9]

TREATMENT OPTIONS FOR DIABETIC KIDNEY DISEASE

The management of diabetic nephropathy focuses on the treatment of hyperglycemia and hypertension, with the inhibition of the renin-angiotensin-aldosterone system being the cornerstone of treatment.[10] Regarding hyperglycemia, intensifying the management of glycemia to lower glycated hemoglobin targets in older people with type 2 diabetes (ie. glycated hemoglobin, <6.0 to 6.5% in persons typically >60 years of age, depending on the study) has been shown to produce small decreases in the risk of albuminuria onset or progression, but has been associated with more frequent episodes of severe hypoglycemia than conventional glycemic management. Moreover, these targets have not reduced the risk of death, cardiovascular disease, or ESRD.[10] Therefore, glycated hemoglobin at the levels of <7% should be aimed as usually recommended.[10]

Regarding hypertension, drugs inhibiting the renin-angiotensin-aldosterone system remain the gold standard of treatment, as they have been documented to reduce urinary albumin excretion rates and thereby mitigating progression to ESRD.[11] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce intra-glomerular pressure by inhibiting angiotensin II mediated efferent arteriolar vasoconstriction. Thus, apart from their anti-hypertensive properties they possess anti-proteinuric potential, too. Urine albumin at concentrations >30 mg/g creatinine (ACR) is a strong predictor of cardiovascular adverse events. Therefore, annually determination of ACR together with serum creatinine levels and calculation of GFR using the CKD-EPI calculator is mandatory. Whether the goal of treatment of systolic blood pressure <140 mmHg -which is still our aiming- will prove to be efficacious among patients with diabetes and nephropathy remains to be elucidated. Another disappointing feature has been maximal inhibition of the renin- angiotensin-aldosterone system. Dual-blockade strategies (an angiotensin-converting-enzyme inhibitor plus an angiotensin-receptor blocker or one of those agents plus a renin inhibitor) have lowered the risk of albuminuria, but have increased the risk of adverse events (hyperkalemia, hypotension and acute kidney injury), without reducing the risk of ESRD.[12-14] Apart from the inhibition of the renin-angiotensin-aldosterone system, other antihypertensive drugs that seem to reduce albuminuria are dihydropyridine

calcium antagonists, such as manidipine, non-dihydropyridine calcium antagonists, such as diltiazem and verapamil, as well as newer b-blockers, such as carvedilol.[15,16]

Furthermore, fighting hyperlipidemia with hypolipidemic agents, such as statins and/or ezetimibe or the newer category of PCSK9 inhibitors seems to be fundamental, too.[17] It seems likely that dyslipidemia is involved in oxidative stress and the production of proinflammatory cytokines, as has been mentioned above.[3,4,18]

Patients with chronic kidney disease have a very high prevalence of deficiency of 25-hydroxyvitamin D. Although the endocrine effects of vitamin D are widely recognized, somewhat less appreciated is that vitamin D may possess paracrine functions through local activation by 1-α-hydroxylase and thus maintain immunity, vascular function, cardiomyocyte health, and diminish inflammation and insulin resistance. In the kidney, vitamin D may be important for maintaining podocyte health, preventing epithelial-to-mesenchymal transformation, and suppressing renin gene expression and inflammation. Replacement with pharmacologic dosages of vitamin D analogues in animal models of kidney disease have consistently shown reductions in albuminuria and minimization of glomerulosclerosis and glomerular inflammation. Emerging evidence in patients with chronic kidney disease has documented that vitamin D can reduce proteinuria or albuminuria even in the presence of angiotensin-converting enzyme inhibition. In addition to reducing proteinuria, Vitamin D analogues may reduce insulin resistance, blood pressure and inflammation and may preserve podocyte loss; thus, providing biologic plausibility to the notion that the use of these agents may exert favorable outcomes in patients with diabetic nephropathy. Moreover, vitamin D analogues have been shown to decrease albuminuria, probably through i) inhibition of the renin-angiotensin-aldosterone system ii) immune and anti-inflammatory potential and iii) inhibition of mesangial fibrosis by affecting FGF-23 (Fibroblast Growth Factor-23) in the diabetic kidney. In particular, in a study enrolling >100.000 participants a six-fold incidence of hypertension has been recorded among participants with serum 25(OH)D levels <15 ng/ml, in comparison with those that have had serum 25(OH)D levels ≥30 ng/ml.[19-20]

In the EMPA-REG Study (Empagliflozin Cardiovascular Outcome Event Trial) among 7,928 type 2 diabetic patients with increased cardiovascular risk, the relative risk of serum creatinine doubling has been reduced by 44%, while the relative risk of starting hemoperfusion has been reduced by 55% at four years of monitoring those patients.[21] This study has introduced the SGLT-2 Inhibitors (Sodium Glucose Co-transporters 2 Inhibitors) at the heart of the management of type 2 diabetes not only because of their cardioprotective properties, but due to their nephroprotective potential, as well.[22]

Among dipeptidyl-dipeptidase-4 inhibitors, linagliptin has been documented to lower albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction.[23] Regarding patients with type 2 diabetes, linagliptin has been shown to ameliorate albuminuria, probably by means of combating oxidative stress as well as by interfering with the formation of advanced glycation end products.[23]

As endothelin plays a pivotal role in vasoconstriction and thus is involved in increasing the intraglomerular pressure, it seems likely that endothelin inhibition could prevent the progression of diabetic nephropathy. Atrasentan is a highly specific inhibitor of endothelin A receptors in the kidney. It has been shown to reduce albuminuria by 35% among 211 patients with type 2 diabetes. Also, a decrease in systolic and diastolic blood pressure as well as LDL-cholesterol and triglycerides has been documented after the administration of atrasentan. Fluid retention and anemia are the most common adverse effects that have been associated with atrasentan, but have been mitigated with the withdrawal of this agent.[24]

Last but not least, are the dietary habits that diabetic patients have to follow, in order to fight the obesity epidemic that keeps rising. GFR has been documented to decrease after

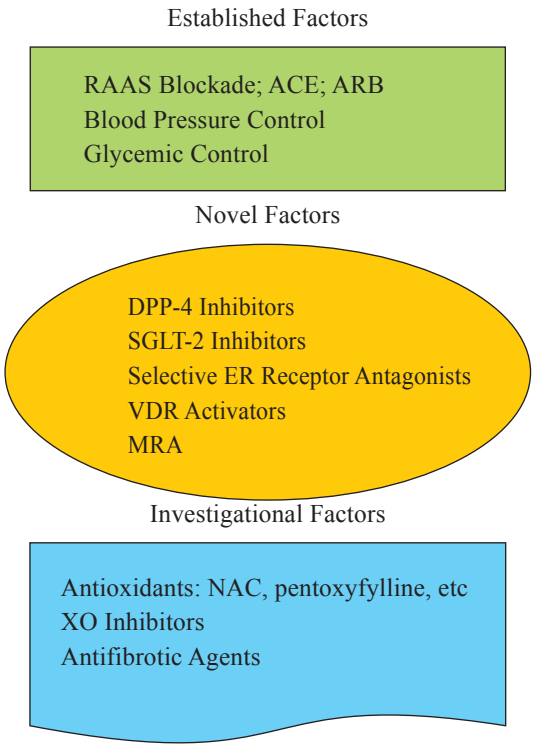

TABLE 1. Agents that have established efficacy in preventing diabetic nephropathy, novel therapeutic interventions and agents under investigation. (NAC: N-acetyl-cysteine; XO inhibitors: Xanthino-oxidase inhibitors; DPP-4 inhibitors: dipeptyl-peptidase-4 inhibitors; ET: Endothelin; VDR activators: Vitamin D Receptor activators; MRA: Mineralocorticoid receptor antagonists; RAS: Renin-angiotensin system; ACEI: Angiotensin convertor enzyme inhibitors; ARB: Angiotensin II receptor blockers).

body weight loss among patients with obesity.[25] Obesity is related to ESRD, in part due to its relationship to diabetes and hypertension. However, obesity per se seems to be associated with a 1.2 to 1.6 increase in relative risk for chronic kidney disease. Therefore, weight loss of even 5 kilos is fundamental in preventing diabetic nephropathy. Referral to dieticians who are involved in diets regarding diabetes is essential for the management of the diabetic patient. Also, among patients with diabetic nephropathy a diet including 0.8 protein/Kgr seems to be a prudent diet for the prevention of malnutrition, which is another problem of ESRD.[25]

CONCLUSION

In order to minimize the risk of diabetic nephropathy among patients with type 1 or type 2 diabetes, combating hyperglycemia, hypertension, dyslipidemia and obesity all play a pivotal role. Among type 2 diabetic patients, the newer class of SGLT-2 Inhibitors together with the dipeptidyl-dipeptidase inhibitor-4 linagliptin seem to be very promising. Furthermore, vitamin D analogues together with agents that possess antioxidant and anti-inflammatory properties, such as allopurinol, febuxostat, MCP-1, pentoxyphylline and N-acetyl-cysteine are still under investigation (Fig. 1). Further research is warranted in order to decrease the rates of diabetic nephropathy, which keep rising together with the diabetes epidemic.

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