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Time to Prevent the Development of Diabetic Nephropathy

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Abstract

The consistent increase in the incidence of diabetes and its complications represents an obsession of health care providers worldwide. Diabetic nephropathy is responsible for nearly half of the chronic kidney diseases. The morbidity and mortality rates of diabetes patients admitted to dialysis is much higher than non-diabetic cases. These facts are behind the tremendous efforts undertaken to understand the pathogenesis and therapeutic modalities of this disease. Over the last four years, a plethora of data has evolved to revive the hope not only to slow the rate of progression of this disease but possibly to prevent its evolution. In this review, we are going to discuss the most relevant and novel pathogenic mechanisms of diabetic nephropathy and the most suitable approach to prevent its development.
Keywords: Type 1 diabetes, type 2 diabetes, diabetic nephropathy, novel markers, DPP4 inhibitors, SGLT2 inhibitors, GLP1Ras, nrf2 agonists

INTRODUCTION

In 2014, diabetes mellitus was diagnosed in 430 million people worldwide, compared with 108 million in 1980 (1). The most common cause of end-stage renal disease (ESRD) is diabetes. One-third of patients with type 1 diabetes mellitus (T1DM) develop ESRD, whereas only 10%-20% with type 2 diabetes mellitus (T2DM) progress to ESRD (2, 3). The evolution of diabetic nephropathy (DN) is responsible for a six-fold increase in the overall 10-year mortality among diabetes patients compared with healthy age matched non-diabetic individuals (4). Endothelial dysfunction is a common underlying pathogenic mechanism of diabetic complications (5). Endothelial dysfunction is a sequel to many metabolic changes encountered in patients with hyperglycemia. These metabolic changes include increased oxidative stress (6), hyperuricemia (7), stimulation of sodium hydrogen exchangers (NHE) (5), and stimulation of renal sodium glucose transporters (SGLT) (8).

During the last 16 years, three novel hypoglycemic groups were introduced to improve glycemic control in patients with T2DM, namely glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase 4 inhibitors (DPP4Is), and sodium glucose co-transporter-2 inhibitors (SGLT2Is). These three groups carry unique features, namely a minimal chance to develop significant hypoglycemia and a neutral effect on body weight in case of DPP4Is and body weight reduction in case of GLP-1RA and SGLT2Is (9, 10). Compared to older hypoglycemic agents, these newer groups carry potential favorable protective effects on endothelium and can significantly reduce adverse cardiovascular events and are renoprotective. SGLT2Is may also prevent or hamper diabetic retinal complications (11). Few months ago, DECLARE-TIMI 58 trial has shown that treatment with the SGLT2I dapagliflozin for median duration of 4.2 years was associated with significant reduction in the chance to develop renal end points even among patients with normal glomerular filtration rate (GFR) and normal urine protein excretion (12). In this

Sharaf El Din et al. Diabetic Nephropathy Prevention

Turk J Nephrol 2020; 29(2): 161-73

Figure 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 m².
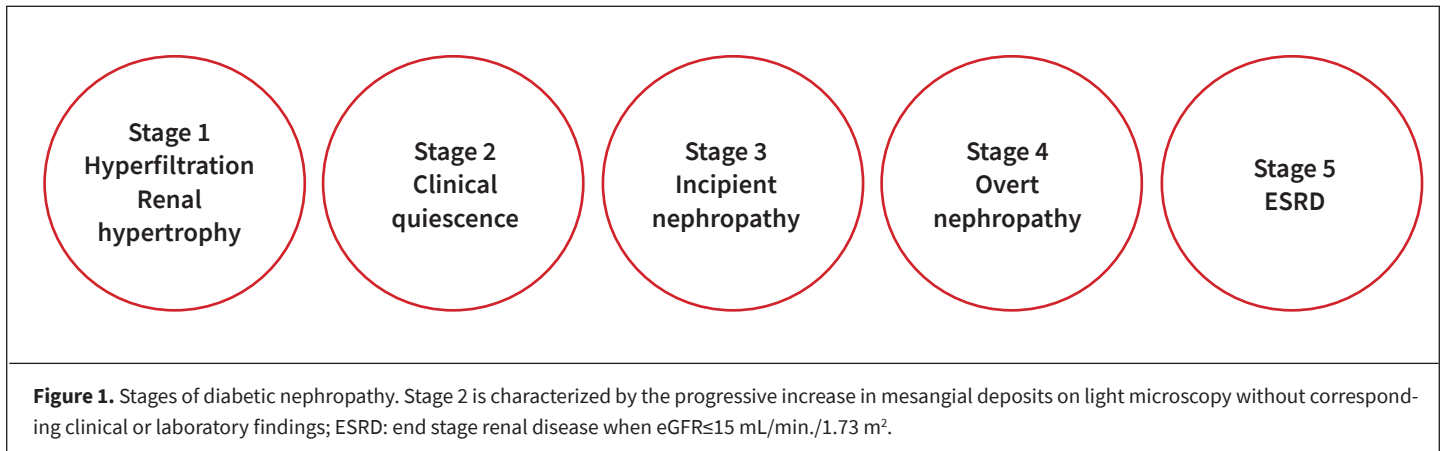
review of literature, we are going to demonstrate how it is feasible to abort the development of DN.

Evolution of Diabetic Nephropathy
Renal hyperfunction and hypertrophy represents the earliest stage of DN (13). Persistent increase in urine albumin excretion (UAE) develops a few years later when UAE becomes more than 30 mg/day, more than 20 µg/minute, or albumin-creatinine ratio (ACR) more than 30 mg/g of creatinine. When patients develop these features, they are considered to be in stage 3 DN that is also called the stage of incipient nephropathy. Initially, persistent increase in UAE is associated with increased GFR. Later on, GFR consistently declines and becomes pronounced with the continuous increase of UAE above 300 mg/day, 200 µg/minute, or when ACR exceeds 300 mg/g (Figure 1) (14). These renal changes are usually associated with progressive increase in blood pressure. Keen et al. (15) first described increased UAE in the early sixties of the twentieth century. Twenty years later, the term "microalbuminuria" became popular after the results of a 14-year longitudinal study showed microalbuminuria as a predictor of renal disease and mortality in T1DM (16). Similar re-

sults were also reported in T2DM (17). These observations led to the use of renin-angiotensin system (RAS) blockers in patients with incipient nephropathy (18, 19). However, the predictive significance of microalbuminuria was not confirmed by later studies (20, 21). Furthermore, progression of microalbuminuria to overt proteinuria was not observed in one-third of patients with T1DM that develop advanced renal disease (22). These observations then led to the reluctance to use RAS blockers in incipient nephropathy and to restrict their use to patients with overt nephropathy (23).
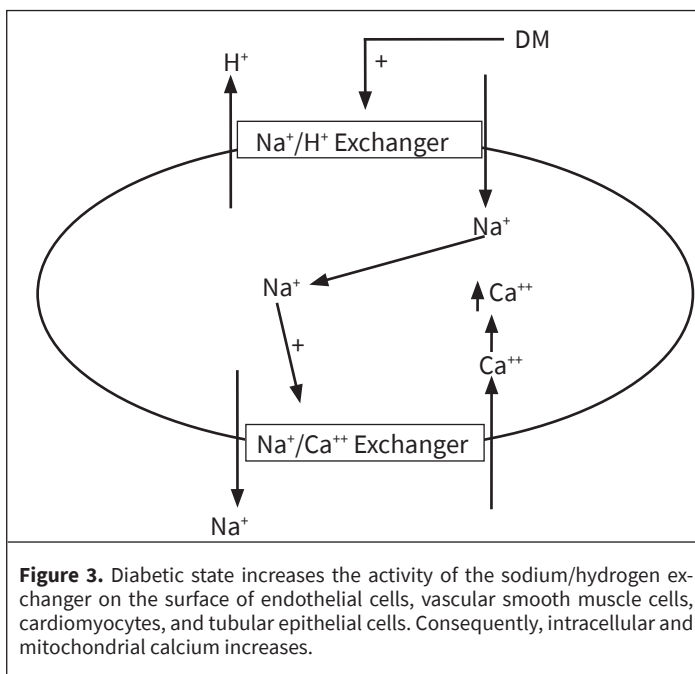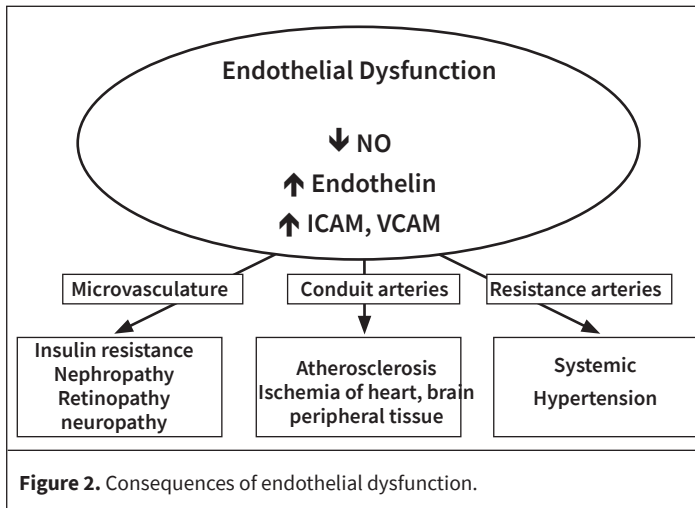
The Endothelium
The role of the endothelium as a regulator of the local vascular tone was first highlighted in 1980 (24). Endothelial dysfunction is an eminent feature in diabetes patients and in patients suffering from obesity or metabolic syndrome. Decreased synthesis of nitric oxide (NO), also known as endothelial derived relaxing factor (EDRF), is the salient feature of endothelial dysfunction. By decreasing insulin access to target cells, decreased NO underlies insulin resistance (25). Insulin also crosses the endothelial cells to reach the target cells (26, 27). Hyperglycemia leads to increased production of reactive oxygen species (ROS) in many cells including endothelium (28). Increased endothelial ROS is associated with increased breakdown of NO (29). Endothelial dysfunction is associated with development and progression of nephropathy (30) (Figure 2). In two separate studies, endothelial nitric-oxide synthase (eNOS) deficient mice consistently developed diabetic nephropathy (31, 32).

Sodium Hydrogen Exchangers
The sodium hydrogen exchangers (NHE) are responsible for intracellular pH regulation. NHE exist in nine isoforms (33, 34). NHE1 is encountered on the surface of endothelial cells, vascular smooth muscle cells (VSMCs), cardiomyocytes, and platelets, whereas NHE3 is encountered on renal tubular and intestinal epithelium. Activation of the NHE1 within endothelium, VSMCs, and cardiomyocytes may underlie microvascular and macrovascular complications of diabetes. It can also have a role in insulin resistance and systemic hypertension. These exchangers cause increased sodium influx that stimulates sodium-calcium

162

Main Points

- This review was written to emphasize the importance of use of SGLT2 inhibitors, DPP4 inhibitors and GLP1 receptor agonist to prevent the development of diabetic nephropathy in both type 1 and type 2 diabetes mellitus.
- The patients of both types of diabetes that are prone to develop diabetic nephropathy can be suspected using serum mannose binding lectin, serum adiponectin and serum fibrinogen levels as very early predictors.
- The patients suspected to develop diabetic nephropathy according to these tests should start using SGLTIs. In order to get the maximum benefit, at least a small dose of either an ACEI or ARB should be added.
- In patients of type 2 diabetes not well controlled by Metformin and the maximum dose of SGLT2I, sequential addition of DPP4I and GLP1RA would improve glycemic control and reinforce the preventive action of SGLT2I-RAS blocker combination.

Turk J Nephrol 2020; 29(2): 161-73

Sharaf El Din et al. Diabetic Nephropathy Prevention

Figure 2. Consequences of endothelial dysfunction.

Figure 3. Diabetic state increases the activity of the sodium/hydrogen exchanger on the surface of endothelial cells, vascular smooth muscle cells, cardiomyocytes, and tubular epithelial cells. Consequently, intracellular and mitochondrial calcium increases.

Figure 4. Consequences of NHE1 activation.
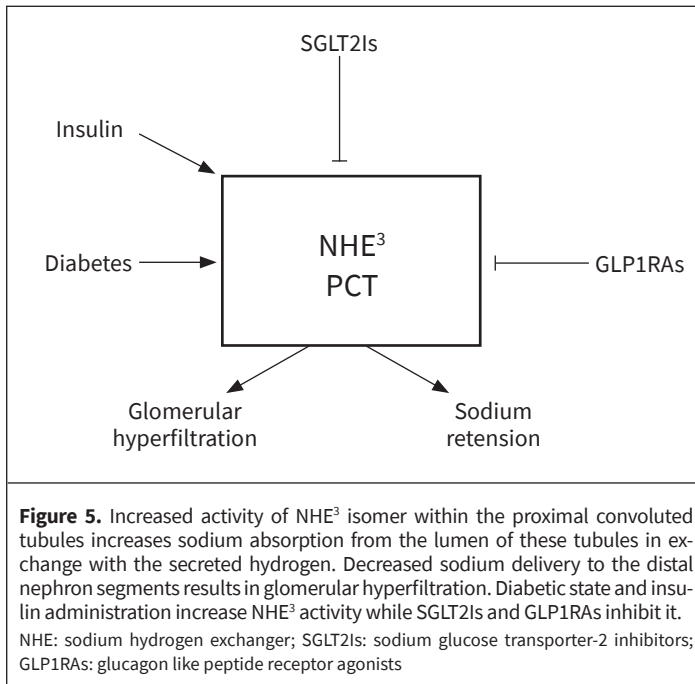NO: nitric oxide; VSMCs: vascular smooth muscle cells; PR: peripheral resistance

exchanger with consequent increase of intracellular calcium. Within endothelium, increased cytoplasmic calcium inhibits eNOS and thus decreases NO synthesis (Figure 3, 4). Increased intracellular calcium is also associated with increased intracellular and mitochondrial activity of calpain, the cysteine protease that can damage the inner mitochondrial membrane, a process that ends with cell apoptosis (35). Inhibition of endothelial NHE1 using cariporide increased eNOS activity and NO release. Enhancement of eNOS activity simultaneously inhibited ROS production, nuclear factor- κB (NF-κB) activation, and tumor necrosis factor-α and intercellular adhesion molecule-1 production (36). Within the myocardium, increased cellular calcium induced by NHE1 leads to cardiac hypertrophy. Peripheral coronary ischemia consequent to endothelial dysfunction can further activate cardiac NHE1. Increased intracellular calcium stimulates calpain enzyme activity within cardiomyocytes leading to degeneration, apoptosis, and fibrosis of myocardium (5) (Figure 4). Proximal convoluted tubular (PCT) and ascending loop of Henle have NHE3. When NHE3 is activated, excess sodium retention occurs and contributes to systemic hypertension in diabetes patients (5, 37) (Figure 5). NHE1 plays a significant role in platelet activation. This effect is mediated through increased intracellular calcium and can contribute to the pro-coagulant state in diabetes (38). Accordingly, it seems that activation of NHE1 and NHE3 plays a distinguished role in the pathogenesis of heart failure and ESRD in patients with diabetes and that inhibition of these exchangers might have an important influence in their management.

163

Oxidative Stress
Increased oxidative stress is one of the metabolic disorders encountered in diabetes. Diabetes patients overproduce free oxygen radicals. Increased production of free oxygen radicals is the sequel to increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (39, 40), cyclo-oxygenase (41), and lipoxygenase (42) enzymes in response to hyperglycemia. Proximal convoluted tubular epithelium (PCT) has SGLT2 within its brush border. SGLT2 is another pathway for overproduction of free oxygen radicals. Increased intracellular concentration of uric acid (UA) induces NADPH oxidase (43). Mitochondrial damage results in impaired antioxidant defense (44). Increased free oxygen radicals activate NF-κB (45). Translocation of NF-κB from the cytoplasm to the nucleus occurs when it gets rid of its inhibitor. Within the nucleus, NF-κB triggers the genes encoding transforming growth factor-β1 (TGF-β1), monocyte chemoattractant protein-1 (MCP-1), and intercellular adhesion molecule 1 (ICAM1) (46-48). ROS stimulates overproduction of protein kinase C (PKC) and mitogen-activated protein (MAP) kinase within mesangial cells (MCs) and pericytes with consequent overproduction of extracellular matrix proteins (49).

Uric Acid
High serum UA is indicated as a strong predictor for proteinuria in T1DM patients. The risk for development of proteinuria increases by 80% with every 1 mg/dL increase in UA (50). There is

Sharaf El Din et al. Diabetic Nephropathy Prevention

Turk J Nephrol 2020; 29(2): 161-73

Figure 5. Increased activity of NHE³ isomer within the proximal convoluted tubules increases sodium absorption from the lumen of these tubules in exchange with the secreted hydrogen. Decreased sodium delivery to the distal nephron segments results in glomerular hyperfiltration. Diabetic state and insulin administration increase NHE³ activity while SGLT2Is and GLP1RAs inhibit it.

NHE: sodium hydrogen exchanger; SGLT2Is: sodium glucose transporter-2 inhibitors; GLP1RAs: glucagon like peptide receptor agonists

a 2.4-fold risk of decline of GFR in T1DM patients with serum UA >6.6 mg/dL when compared with patients with lower UA level (51). When T1DM patients were followed up for more than 18 years, UA was an independent predictor of overt proteinuria (52); 68% of the hyperuricemic T2DM patients versus 41.5% with normal UA had DN (53). The increased risk for the development of albuminuria and accelerated decline of GFR in hyperuricemic T2DM patients is confirmed by two prospective studies (54, 55). In T2DM patients that have the disease for 15 years or more, UA >7 mg/dL in males and >6 mg/dL in females is associated with a higher rate of DN progression and overall mortality (56). Treatment of T2DM patients suffering from DN and high serum UA with allopurinol decreased UAE and serum creatinine significantly and significantly increased GFR over three years of follow-up (57). In a meta-analysis of 19 randomized controlled trials enrolling 992 patients, the significant favorable effect of urate-lowering therapy on the rate of GFR decline was confirmed (58).

Increased level of UA is associated with endothelial dysfunction. In a recent *in vitro* study, high UA concentration inhibited eNOS expression and NO production in human umbilical vein endothelial cells (HUVECs), activated NF-κB, and increased the level of inflammatory cytokines (59). High UA significantly predicts systemic hypertension (60).

Role of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA)
Glucagon-like peptide-1 (GLP-1) is a polypeptide hormone. Small intestinal mucosal neuro-endocrine cells secrete GLP-1 to activate pancreatic insulin secretion, inhibit glucagon secretion by pancreatic α cells, slow gastric emptying, and control appetite (61). Dipeptidyl peptidase-4 enzyme breakdown of GLP-1 is responsible for the very short plasma half-life of this hormone.

Continuous intravenous infusion is thus needed if this agent is used therapeutically (62). GLP-1RA are exogenous GLP-1 analogues with variable sequence similarity to the human GLP-1 (63). This variability involves mainly two sites in the GLP-1 molecule susceptible to cleavage by DPP4; namely, alanine and lysine at positions 8 and 34 respectively. These changes, beside other modifications, have helped to discover many peptides that simulate GLP-1 action but with longer half-life (62). GLP-1RAs can control blood sugar and decrease body weight without increasing the risk of hypoglycemia (64). GLP-1RAs can lower systolic, and to a minor degree, diastolic blood pressure (65). In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide use significantly decreased mortality from any cause and cardiovascular events in patients with T2DM at high risk for cardiovascular events. This benefit is more pronounced in patients with eGFR <60 mL/min/1.73 m² and in patients 50 years or more. The chance of development of diabetic nephropathy was significantly lower in patients treated with liraglutide (66). Similarly, SUSTAIN-6 trial showed a significant decrease in the incidence and progression of nephropathy in T2DM patients using semaglutide. However, a higher percentage of patients in the semaglutide group developed retinopathy. Semaglutide was also associated with a 26% reduction in the hazard of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke (67).

GLP-1RAs can promote natriuresis and diuresis through inhibition of renal NHE3. Additional effects include inhibition of the intrarenal renin-angiotensin system, inflammation, and apoptosis. These effects might be related to the antioxidant and anti-apoptotic activities of GLP-1RAs (68) (Figure 6).

A major drawback of GLP-1RA is the need for frequent injections. Recently, oral semaglutide proved to be as efficacious as parenteral formula in glycemic and body weight control (69). However, the cardiovascular and renal effects of this oral formula are not yet established.

Role of Dipeptidyl Peptidase 4 (DPP4) Inhibitors
The non-enzymatic functions for DPP4 within the kidney attracted attention for the renoprotective action of DPP4Is especially after reporting the anti-proteinuric effect of saxagliptin in T2DM patients in the "Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53" (SAVOR-TIMI 53) trial (70, 71). In addition, animal models of acute and chronic kidney disease have demonstrated that pharmacologic and genetic inhibition of DPP4 can prevent progressive renal damage (72, 73).

DPP4Is inhibit the breakdown of endogenous GLP and glucose-dependent insulinotropic peptide (GIP) and hence improve the response of pancreatic β cells to glucose (74).

Within the kidney, DPP4 exists on the surface of S1-S3 segments of the PCT and plays a role in salt and water retention through
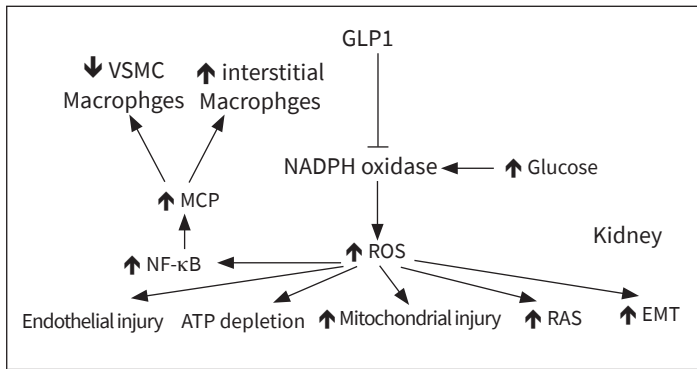
Turk J Nephrol 2020; 29(2): 161-73

Sharaf El Din et al. Diabetic Nephropathy Prevention

Figure 6. Hyperglycemia stimulates NADPH oxidase enzyme within different organs including the kidney. Consequent increased production of free oxygen radicals results in increased cascade of degenerative and inflammatory processes that underlie pathology of the diabetic kidney. Glucagon like peptides inhibit NADPH oxidase and thus can muffle development or progression of diabetic nephropathy.

GLP1: glucagon like peptides; NADPH: nicotinamide adenine phosphate; ROS: reactive oxygen species; NF-κB: nuclear factor kappa B; MCP1: macrophage chemoattractant fpeptide; VSMCs: vascular smooth muscle cells; ATP: adenosine triphosphate; RAS: renin-angiotensin system; EMT: epithelial mesenchymal transition
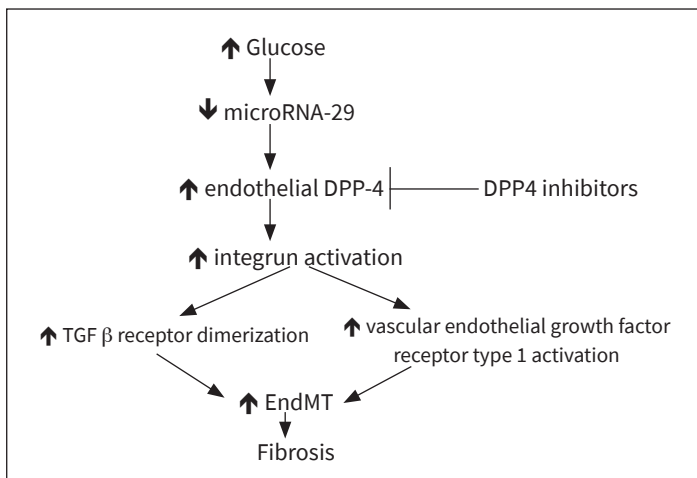

Figure 7. MicroRNA-29 is a natural inhibitor of endothelial DPP-4 within renal vasculature. Hyperglycemia inhibits microRNA-29 and thus stimulates endothelial DPP-4.

DPP-4: dipeptidyl peptidase; TGF: transforming growth factor; EndMT: endothelial mesenchymal transition

stimulation of NHE3 (75). Angiotensin II inhibits megalin receptor and thus can increase proteinuria. This process is reversed by DPP4Is (76). Treatment with DPP4Is thus reverse reduced uptake of albumin and other low molecular weight proteins by PCT (77). DPP4 was also discovered on the glomerular endothelium and the base of the foot processes of podocytes (78). DPP4 is expressed on T-cells, B-cells, macrophages, and dendritic cells in the kidney (79). Stimulation of DPP4 on the surface of different immune and inflammatory cells is claimed to induce inflammation within the diabetic kidney and DPP4Is can decrease this inflammation (80).

The anti-proteinuric effect DPP4Is in T2DM patients was observed in three randomized controlled studies. In all these trials, urine protein excretion was not a prespecified end point.

Moreover, DPP4Is failed to have a significant impact on doubling of serum creatinine, change in GFR, or ESRD in any of these trials (81-83). In contrast, MARLINA-T2D trial that specifically looked for the anti-proteinuric effect of linagliptin failed to find any significant impact (84) contrary to a previous trial done by the same authors who demonstrated that the co-administration of linagliptin to T2DM patients that had renal dysfunction and were prescribed angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) has led to additive significant reduction in albuminuria (85).

In normal situations, microRNA-29 (miR29) suppresses DPP4 gene. In diabetic state, this suppression is lost. As a consequence, DPP4 activity increases (86). In diabetic mice, activated endothelial DPP4 induces phosphorylation of adjacent integrin β1 on the surface of the endothelium. The activated DPP4, together with the phosphorylated integrin β1, form a complex that up-regulates TGF β receptor and activates the surface vascular endothelial growth factor receptor type 1(VEGFR1). Upregulated TGF β receptor and VEGFR1 stimulate endothelial-mesenchymal transition (EndMT) that increases transition to fibroblasts with subsequent increased fibrogenesis (87) (Figure 7). However, human studies performed so far cast doubts on their anti-fibrosis impact in humans.

The effect of DPP4Is treatment on the retina is debatable. While some investigators reported an increase in retinal endothelial leakage and vascularity (88), others have reported a significant reduction in the risk of diabetic retinopathy progression (89).

The potentiation of the stem cell chemokine, stromal cell-derived factor-1 (SDF-1) by DDP4Is can partially explain the lack of the expected favorable effect of these agents on the diabetic microvascular and macrovascular complications in spite of proven molecular and experimental mechanisms. SDF-1 promotes inflammation, proliferation and neovascularization (90). It can also enhance atheromatous plaque growth and instability, cardiac inflammation, and fibrosis (91). Potentiation of SDF-1 within the renal tissue leads to podocyte injury and glomerulosclerosis. SDF-1 also induces natriuresis in the distal tubules, contrary to SGLT2Is and NHE3 inhibitors that act on PCT. The adverse effects of SDF-1 on the kidney would muffle the experimental favorable effects of DPP4Is observed in animal studies and can explain the need of co-administration of RAS blockers to gain the additive anti-proteinuric effect of DPP4Is (90, 92) (Figure 8).

Role of Sodium Glucose Co-Transporters Inhibitors (SGLT2Is)
SGLT2Is constitute the most recently introduced group that is insulin independent. Three members of this group, namely empagliflozin, canagliflozin, and dapagliflozin are now used worldwide after the food and drug administration (FDA) approval. They inhibit the upregulated SGLT2 co-transporters of the PCT S1 segment brush border, and thus reduce the renal threshold for plasma glucose from 196 to 22 mg/dL and
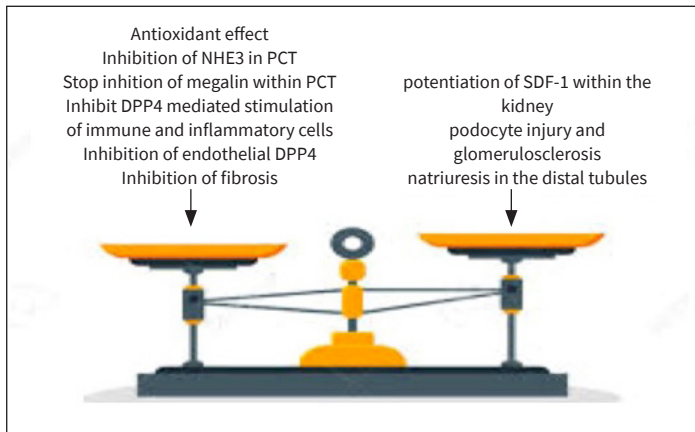
Sharaf El Din et al. Diabetic Nephropathy Prevention

Turk J Nephrol 2020; 29(2): 161-73

Figure 8. The beneficial effects of DPP4Is on the kidney are muffled by the bad effect induced by stromal cells derived factor 1(SDF-1).

DPP-4: dipeptidyl peptidase; TGF: transforming growth factor; EndMT: endothelial mesenchymal transition
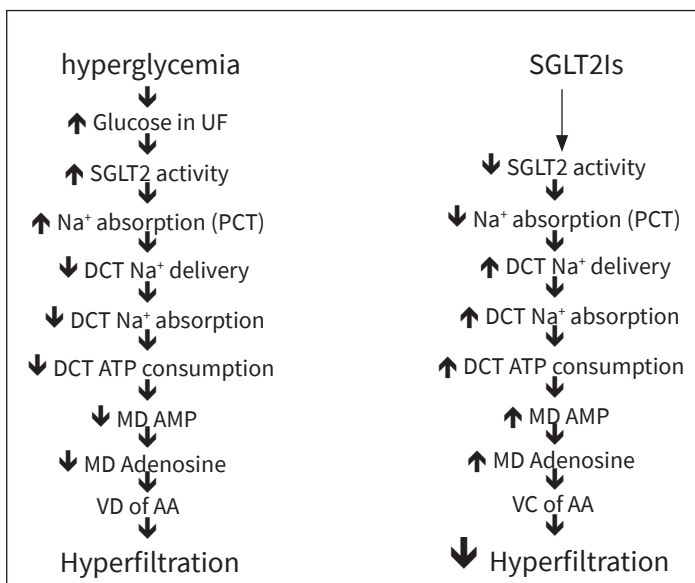
166

Figure 9. Mechanism of hyperfitration induced by hyperglycemia and how do SGLT2Is control it.

UF: ultrafiltrate; SGLT: sodium glucose transporter; Na+: sodium; PCT: proximal convoluted tubules; DCT: distal convoluted tubules; ATP: adenosine triphosphate; MD: macula densa; AMP: adenosine monophosphate; VD: vasodilatation; AA: afferent arteriole; VC: vaso-constriction
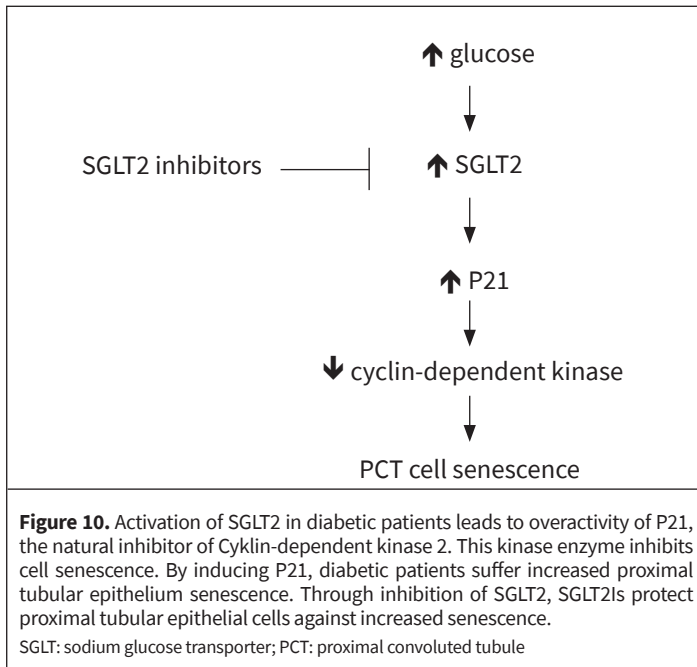
enhance the urinary excretion of glucose (93). Inhibition of PCT absorption of sodium is attributed to inhibition of SGLT2 and NHE3 within PCT and NHE within the loop of Henle. This leads to increase in distal sodium delivery and distal tubular sodium absorption. Increased adenosine triphosphate (ATP) consumption during sodium absorption causes increase of adenosine production. Afferent arteriolar vasoconstriction consequent to excess adenosine leads to a fall in renal blood flow, reversal of hyperfiltration, and reduces renal injury (Figure 9). SGLT2Is exert additional beneficial effects, including body weight reduction, decrease of UA, and blood pressure (94). GLUT9 within the S3 segment of the PCT is a surface urate transporter that is triggered by excess glucose to excrete UA

in exchange with glucose (95). The antihypertensive effect of SGLT2Is is mediated by volume depletion, loss of body weight, inhibition of endothelial NHE1 and renal NHE3, and reduction in serum UA (60).

SGLT2Is can also decrease PCT intracellular fructose metabolism and UA synthesis (96). Contrary to extracellular UA, intracellular UA is pro-oxidant. It stimulates NADPH oxidase enzyme activity and increases ROS production. Excess free oxygen radicals within tubular cells leads to premature senescence of these cells, activation of the renin-angiotensin system, epithelial-mesenchymal transition, and activation of NF-κB (97-99) (Figure 6). Cyclin-dependent kinase (CDK) inhibits cell senescence. P21 is an inhibitor of CDK and thus promotes cell senescence. Hyperglycemia induces P21, whereas SGLT2Is inhibit this factor within PCT cells (100, 101) (Figure 10). SGLT2Is can dampen the renal parenchymal Toll-like receptor-4 expression, the binding of activator protein 1 to nuclear DNA, prohibit increased collagen IV expression as well as interleukin-6 secretion, and macrophage infiltration to the interstitium induced by hyperglycemia (102). Moreover, SGLT2Is suppress the fibrotic and inflammatory genes within the diabetic kidney (103, 104).

By suppressing the intracellular UA production, SGLT2Is can inhibit renal gluconeogenesis. UA induces adenosine monophosphate dehydrogenase (AMPD) enzyme and suppresses adenosine monophosphate kinase (AMPK) enzyme activities. Intracellular AMPD stimulates, whereas AMPK inhibits, gluconeogenesis (105). In healthy individuals, the kidneys participate in endogenous glucose production. In the fasting state, 20%-25% of endogenous glucose production takes place through renal gluconeogenesis. In T2DM, renal gluconeogenesis increases three-fold (106).

In EMPA-REG study, empagliflozin achieved 55% reduction in the incidence of ESRD in T2DM patients with established cardiovascular disease having eGFR >30 mL/min/1.73m^2 over a median duration of 3.1 years (107). In RENAAL trial, losartan treatment of a similar population having DN led to a 28% delay in the onset of ESRD over a mean follow-up of 3.4 years (108). In addition, empagliflozin caused a 39% reduction of incident or worsening nephropathy, a 38% reduction in progression to overt albuminuria, and a 44% reduction in doubling of serum creatinine (109). The favorable outcome of SGLT2Is is attributable to their effect on glomerular hyperfiltration, blood pressure, body weight, and serum UA in diabetic patients (109-111). SGLT2Is also inhibit NHEs on the surface of cardiomyocytes, endothelial cells, and renal tubular epithelial cells. NHE inhibition can explain the distinguished cardioprotective and renoprotective actions of SGLT2Is (112-114). Decreased renal blood flow induced by SGLT2Is is related to tubuloglomerular feedback and not related to the RAS blockade. Empagliflozin and dapagliflozin increase plasma aldosterone and angiotensin II (115, 116), together with increased activity of urinary angiotensin converting enzyme and angiotensin converting enzyme2 (117).

Figure 10. Activation of SGLT2 in diabetic patients leads to overactivity of P21, the natural inhibitor of Cyklin-dependent kinase 2. This kinase enzyme inhibits cell senescence. By inducing P21, diabetic patients suffer increased proximal tubular epithelium senescence. Through inhibition of SGLT2, SGLT2Is protect proximal tubular epithelial cells against increased senescence.

SGLT: sodium glucose transporter; PCT: proximal convoluted tubule

When T2DM patients (total of 1,450 cases) already on metformin were treated for 2 years with either once-daily canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride titrated to 6-8 mg, the eGFR declined by 0.5, 0.9, and 3.3 mL/min/1.73 m^2/year respectively (p<0.01 for each canagliflozin group versus glimepiride) in spite of comparable reductions in HbA1c. Compared to glimepiride, UAE declined more with canagliflozin 100 mg or canagliflozin 300 mg. These results reinforce the renoprotective effect of SGLT2Is independent of their glycemic effect (118). Contrary to DPP4Is and sulfonylureas that are significantly associated with increased risk of diabetic retinopathy, SGLT2Is were not associated with a higher risk of diabetic retinopathy than placebo among 100,928 patients with T2DM included in 37 independent randomized controlled trials with 1,806 diabetic retinopathy events (119). Canagliflozin Cardiovascular Assessment Study (CANVAS) recruited 10 142 T2DM patients. These patients were assigned to either canagliflozin 100 mg daily, canagliflozin 300 mg daily or placebo in 1:1:1 ratio. 34% of the patients had ≥2 risk factors for cardiovascular events but had no history of previous cardiovascular event (primary prevention cohort), whereas the remaining 66% had a positive history of cardiovascular event (secondary prevention cohort). After treatment for a mean of 3.6 years, the primary endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) has occurred less frequently with canagliflozin compared with placebo (26.9 versus 31.5/1000 patient-years; p=0.02). There was no statistical evidence of heterogeneity between the primary and secondary prevention cohorts. Renal outcomes were reduced by 40% and heart failure hospitalization was reduced by 33% in patients treated with canagliflozin (120, 121). In the DECLARE-TIMI 58 trial, 17,160 T2DM patients, including 6,974 with atherosclerotic cardiovascular disease, were assigned for 10 mg dapagliflozin or placebo in 1:1 ratio and were followed for a median of 4.2

years. Dapagliflozin decreased the composite of cardiovascular death or hospitalizations for heart failure in those with established atherosclerotic cardiovascular disease (ASCVD) and those with only multiple risk factors (122). When patients with previous myocardial infarction (n= 3,584) were specifically looked at, adverse cardiovascular events were 16% less in the dapagliflozin arm (123). According to these studies, SGLT2Is should be prescribed aiming at cardiovascular protection in patients with T2DM and ASCVD (124). In addition, the renal outcome results of the DECLARE-TIMI 58 have supported the favorable renoprotective effects of SGLT2Is. 47.6% of the patients in this trial had GFR >90, 45.1% had GFR between 60 and 90, whereas only 7.4% of the patients had GFR <60 mL/min/1.73m^2. More than two-thirds of the recruited patients had normal urine albumin excretion.

In the CREDENCE trial, T2DM patients suffering chronic kidney disease (CKD) and albuminuria (4,400 patients) were randomly assigned to receive canagliflozin 100 mg daily or placebo in 1:1 ratio. All the patients had an eGFR of 30 to <90 mL/minute/1.73 m^2 and albuminuria (urine albumin/creatinine ratio >300 to 5,000 mg/g) that were receiving RAS blockers. The primary outcome was a composite of ESRD (dialysis, transplantation, or a sustained eGFR of <15 mL/ min / 1.73 m^2), a doubling of the serum creatinine, or death from renal or cardiovascular causes. The projected duration of the study was 5.5 years. Investigators of this study prematurely terminated the trial after a planned interim analysis on the recommendation of the data and safety monitoring committee. This analysis has shown a highly significant reduction of the primary composite endpoint by 34% in patients treated with canagliflozin after 2.6 years of treatment. Patients in the canagliflozin group also had a lower risk of ESRD, hospitalization for heart failure (HF), and the composite of CV death, myocardial infarction, or stroke. These results indicate that canagliflozin is an effective treatment for renal and cardiovascular protection in T2DM patients suffering CKD (125). The observed benefits were obtained mainly in patients whose basal eGFR was between 30 and <60 mL/min/1.73 m^2. The hypoglycemic effect of SGLT2Is is almost lost when eGFR is lower than 45 mL/min/1.73 m^2. In addition, these findings were observed despite very modest differences in blood sugar, weight, and blood pressure between the placebo and the active treatment groups. This suggests that the benefits obtained are independent of glycemic control and are likely related to the reduction in single nephron hyperfiltration mediated by NHE3 inhibition.

Contrary to CREDENCE trial patients where all patients were prescribed RAS blockers, only 81.3% of DECLARE study patients were on RAS blockers. The prespecified composite cardio-renal endpoints (≥40% decrease in estimated glomerular filtration rate to <60 mL per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) were significantly reduced by 24% in the dapagliflozin group, whereas the prespecified composite renal endpoints decreased by 47%, and the chance to develop ESRD decreased by 56% in the dapagliflozin group. The significant impact of dapagliflozin

167

Sharaf El Din et al. Diabetic Nephropathy Prevention

Turk J Nephrol 2020; 29(2): 161-73

was encountered in patients having baseline GFR >90, in cases with GFR between 60 and 90, in normo-albuminuric patients, in patients with microalbuminuria, and in those with overt proteinuria. These favorable effects were only observed in patients already maintained on either ACE inhibitors or ARBs (12).

Role of Free Oxygen Radicals Scavengers

Many preclinical studies have underlined the role of ROS in the pathogenesis of diabetic complications. However, the less favorable outcomes of different antioxidants to prohibit the development or progression of diabetic complications in large clinical trials have dampened the enthusiasm for the use of antioxidant agents in diabetes (126). Clinical studies using vitamin A, C, and E as antioxidant agents in pre-diabetic and T2DM patients were disappointing.

Recommendations of Diabetes Associations

In October 2018, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) issued an updated consensus on management of T2DM patients. In this consensus, patients with clinical CV disease should receive one of SGLT2Is or GLP-1RAs, whereas in patients with CKD or clinical HF and ASCVD, SGLT2Is should be considered (127). The choice of diabetes therapies as recommended by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) must be individualized on the basis of many attributes including the risk reduction in heart and kidney disease (128).

Novel Markers of Diabetic Complications

Mannose-binding lectin (MBL), a recognized protein of the innate immune system is independently associated with HbA1c in diabetic patients (129). MBL is a possible independent predictor of DR, DN and other vascular complications in type 1 and type 2 diabetes (130-134).

In 297 newly diagnosed T2DM patients, serum fibrinogen was a strong predictor for DN (135). Serum adiponectin was proved as a strong predictor of DN in both type 1 and type 2 diabetic patients according to a recent meta-analysis of 13 studies of more than 5,000 cases (136).

CONCLUSION

SGLT2Is, GLP1RAs, and DPP4Is represent a new hope in preventing or slowing down the rate of progression of DN. Their favorable effect on body weight and the decreased likelihood of hypoglycemia promote their use even in T1DM. The rapidly accumulating evidence of the significant renal and cardiac protective effects of SGLT2Is and GLP-1RAs has enforced the ADA, EASD, ACE, and AACE to recommend their use as second-line treatment in T2DM patients with cardiovascular disease or CKD (127, 128, 137). However, all the available evidence has supported the impact of these agents in secondary prevention. The lack of similar significant evidence on the impact of these agents in primary prevention is likely due to the relatively short duration of the available trials.

United Kingdom Prospective diabetes study (UKPDS) is the most famous primary prevention trial in T2DM patients. The results of this study failed to show any significant impact of the tight sugar control on the cardiovascular endpoints at the end of the study. Ten more years after the end of the study were needed to get significant differences in acute myocardial infarction and overall mortality (138). The planned duration of the CREDENCE trial was 5.5 years. This study was then prematurely terminated when a significant difference in the composite endpoints between the two arms in the whole group became evident (125). This shortened duration could explain why patients with eGFR ≥60 mL/min/1.73 m^2 and patients with UAE ≤1,000 mg/gm creatinine failed to get the expected benefit. The most recent DECLARE-TIMI 58 study has supported this view. This last study continued for 4.2 years and showed the significant impact of dapagliflozin in patients having baseline GFR >90, those with GFR between 60 and 90, and even in normoalbuminuric patients (12). The pronounced effects in patients of DECLARE study are likely due to the relatively longer duration of follow-up. Based on these facts, it seems that more lengthy primary preventive studies are needed. Such studies should recruit newly diagnosed T2DM patients who have laboratory markers suggesting the likelihood to develop DN. The very high cost is main obstacle for these studies as the duration needed to get enough endpoints for adequate statistical analysis is very long. Given the documented safety and superiority of SGLT2Is, GLP1RAs, and DPP4Is, we suggest a more reproducible approach to manage T2DM patients. Routine tests for novel predictors screening for the likelihood to develop DN should be done in all T1DM and T2DM patients. Serum MBL, fibrinogen, or adiponectin can help to select patients prone to develop DN. These patients should be prescribed SGLT2Is aiming at prevention instead of waiting until signs of renal involvement develop. This primary prevention approach will supposedly abort the development of DN instead of the current secondary prevention approach that only postpones ESRD for few months or years. The primary prevention should be extended to involve T1DM patients but with great attention to insulin treatment in order to avoid diabetic ketoacidosis. Although this preventive approach caries some risk especially in T1DM, the benefits obtained will definitely outweigh the drawbacks. Development of ESRD in diabetic patients is a real nightmare for nephrologists. Morbidity and mortality are significantly higher among diabetic patients starting dialysis compared with non-diabetic patients (139, 140). In one series none of the diabetic patients survived for five years on dialysis in comparison to over 50% in non-diabetic patients (140).

Turk J Nephrol 2020; 29(2): 161-73

Sharaf El Din et al. Diabetic Nephropathy Prevention

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169

Sharaf El Din et al. Diabetic Nephropathy Prevention

Turk J Nephrol 2020; 29(2): 161-73

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171

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Turk J Nephrol 2020; 29(2): 161-73

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Turk J Nephrol 2020; 29(2): 161-73

Sharaf El Din et al. Diabetic Nephropathy Prevention

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