Advance Research on Endocrinology & Metabolism
AREM, 1(1): 11-29
www.scitcentral.com

Review Article: Open Access

Management of New Onset Diabetes: Time to Change Therapeutic Strategies

Usama A Sharaf El-Din[1*], Mona M Salem[2] and Dina O Abdulazim[3]

*[*1]Nephrology Unit, Internal Medicine Department, School of Medicine, Cairo University, Nasr City, Cairo, Egypt*

[2]Endocrinology Unit, Internal Medicine Department, School of Medicine, Cairo University Nasr City, Cairo, Egypt

[3]Rheumatology and Rehabilitation Department, School of Medicine, Cairo University Nasr City, Cairo, Egypt.

Received April 27, 2019; Accepted May 16, 2019; Published October 11, 2019

ABSTRACT

The tight blood sugar control among type 1 (T1DM) and type 2 (T2DM) diabetes mellitus patients is recommended by different specialists concerned with this disease aiming at avoidance of long term complications of diabetes. In spite of the significant impact of this approach on decreasing of these complications, still these complications are still frequently encountered. This weak success is partly explained by the frequent failure to achieve glycemic targets. In addition, the conventional hypoglycemic agents do not properly control the underlying pathogenic mechanisms of these complications. The last decade has witnessed the evolution of new hypoglycemic and antioxidant agents the carry additional features enabling them to adequately fight these pathogenic mechanisms. In this review, we are going to thoroughly discuss these mechanisms and highlight the therapeutic value of initiating treatment of new onset diabetes using these agents instead of the long standing traditional approach.

Keywords: Type 1 diabetes, Type 2 diabetes, Microvascular complications, Macrovascular complications, DPP4Is, SGLT2Is, NRF2 agonists

INTRODUCTION

Diabetes mellitus is a pandemic disease that affected 108 million persons worldwide in 1980 [1]. This figure is exponentially increasing to approach 430 million persons in 2014 [1]. In spite of the increased awareness about this disease and the worldwide efforts to follow guidelines in management, 3.7 million persons lost their lives in 2012 because of diabetes and its complications [2]. The hazard ratio of cardiovascular mortality among diabetic patients is 2.3 folds that in non-diabetic personnel [3]. The average life span of the diabetic patients is 10-15 years shorter than non-diabetic subjects [4]. Beside this increased mortality, diabetes is the cause of many disabling morbidities. Diabetic retinopathy is the leading cause of blindness among working-age adults worldwide in spite of the energetic treatment of the established cases of retinopathy that can reduce the risk of visual loss by 60% [5]. Diabetes is the leading cause of non-traumatic lower-extremity amputation [6]. Diabetic peripheral neuropathy (PN) is the most prevalent cause of sensory neuropathy [7]. Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD). One third of T1DM develop ESRD, while only 10-20% of type 2 diabetes mellitus (T2DM) patients progress to ESRD [8,9]. The prevalence of congestive heart failure (CHF) among diabetic patients aged 55 to 64 years is 5.5 folds the prevalence among non-diabetic personnel of the same age [10]. Diabetes is an independent risk factor for the development of ischemic heart disease (IHD). CHF and IHD are the main causes of death in T1DM and T2DM patients [11]. Diabetes mellitus confers a greater risk of cerebrovascular stroke [12]. Endothelial dysfunction is a common pathology underlying the etiopathogenic mechanism of all these complications [13]. This endothelial dysfunction is a sequel of many metabolic changes that are usually encountered in hyperglycemic personnel. These metabolic changes include increased oxidative stress [14], hyperuricemia [15], stimulation of sodium hydrogen exchangers (NHE) [13] and stimulation of renal sodium

Corresponding author: Professor Usama AA Sharaf El-Din, Nephrology Unit, Internal Medicine Department, School of Medicine, Cairo University, Nasr City, Post Code: 11759, Cairo, Egypt, Tel: +201111333800; Fax: +20222753890; E-mail: usamaaas@gmail.com

Citation: El-Din UAS, Salem MM & Abdulazim DO. (2019) Effects of Mobile Phone Radiation and Exercise on Testicular Function in Male Wistar Rats. Adv Res Endocrinol Metab, 1(1): 11-29.

hydrogen exchangers (NHE) [13] and stimulation of renal sodium glucose transporters (SGLT) [16].

25 years ago, the Diabetes Control and Complications Trial (DCCT) research group announced the significant impact of tight blood sugar control on development of micro-vascular complications among T1DM [17]. Five years later, the United Kingdom Prospective Diabetes Study (UKPDS) group announced similar findings among T2DM patients [18]. However, reduction of micro-vascular complications in the intensive insulin treatment group was by 50% compared to poorly controlled cases in DCCT trial. In addition, the tight blood sugar control only has a marginal impact on cardiovascular disease and all-cause mortality among diabetic patients [19]. On the other hand, the tight blood sugar control using sulphonyl urea compounds and insulin is associated with increased risk of severe hypoglycemia and/or weight gain [17,18]. IN UKPDS study, T2DM patients allocated to metformin had 32% reduction for any diabetes-related endpoint, 42% for diabetes-related death and 36% for all-cause mortality when compared with patients allocated to sulphonyl urea or insulin [20]. These favorable effects of metformin were suggested as consequence of the impact of this agent on body weight and hypoglycemic attacks. According to these results and others, the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinology (AACE) recommend that the choice of anti-diabetic therapies must be based on many attributes that include anti-hyperglycemic efficacy, risk of inducing hypoglycemia and risk of weight gain [21]. The last 15 years have witnessed the introduction of three new hypoglycemic agents, namely, glucagon like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase 4 inhibitors (DPP4Is) and sodium glucose co-transporter-2 inhibitors (SGLT2Is). These 3 agents carry common features, namely, the minimal incidence of hypoglycemic events and the favorable impact on body weight. GLP-1RA and SGLT2Is are associated with body weight reduction while DPP4Is are weight neutral [22,23]. Compared to older hypoglycemic agents, these newer groups carry potential favorable protective effects on endothelium, and can significantly reduce adverse cardiovascular events of diabetes in case of SGLT2Is and GLP-1RA and are reno-protective. In addition, SGLT2Is could prevent or withhold diabetic retinal complications [24]. This review will highlight the possible new strategy to prevent the development and/or progression of diabetic complications, the main target of this disease management.

THE ENDOTHELIUM IN DIABETES

The role of the endothelium as an important regulator of local vascular tone was first reported in 1980 [25]. The vascular endothelium is an important component of diabetic complications. Endothelial dysfunction is eminent not only in diabetic patients, but also in patients suffering obesity or metabolic syndrome. Decreased synthesis of nitric oxide (NO), a potent vasodilator, is the eminent feature of endothelial dysfunction. Decreased NO underlies insulin resistance by reducing insulin access to tissue [26]. Beside the blood flow effect, insulin has to cross endothelial cells to reach target tissues [27,28]. In addition, hyperglycemia is associated with endothelial mitochondrial fragmentation with increased production of reactive oxygen species (ROS) [29]. Increased endothelial ROS is associated with increased breakdown of NO [30]. Impaired endothelial function was demonstrated within visceral fat [31], cardiac and skeletal muscles [32]. Endothelial dysfunction is associated with accelerated atherosclerosis in an animal model [33], diabetic retinopathy [34], nephropathy [35], neuropathy [36] and cerebral dysfunction [37]. In order to affirm the role of endothelial dysfunction in development of diabetic nephropathy, 2 separate studies have disclosed that endothelial nitric-oxide synthase (eNOS) deficient mice robustly develop diabetic nephropathy [38,39].

SODIUM HYDROGEN EXCHANGERS

The sodium hydrogen exchangers (NHE) are trans-membrane ion channels that are responsible for intracellular pH regulation through extrusion of hydrogen ion in exchange with sodium influx **(Figure 1)**. NHE exist in nine isoforms [40,41]. NHE1 is present on the surface of endothelium, vascular smooth muscle cells (VSMCs), cardiomyocytes and platelets, while the isoform encountered on the surface of renal tubular and intestinal epithelium is NHE3. Activation of the NHE1 within endothelium, VSMCs and cardiomyocytes may underlie micro-vascular and macro-vascular 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 exchanger with consequent increase of intracellular calcium. Within endothelium, increased cytoplasmic calcium inhibits eNOS with consequent decrease of NO synthesis **(Figure 2)**. In addition increased intracellular calcium is associated with increased intracellular and mitochondrial activity of calpain, a cysteine protease that can damage the inner mitochondrial membrane, a process that ends with cell apoptosis [42]. Activation of NHE1 in diabetic patients is a consequence of high blood glucose, insulin, angiotensin or adipokines [43]. Endothelial NHE1 activation leads to increased influx of calcium into the cytoplasm and mitochondria associated with increased calpain enzyme activity. These changes lead to endothelial dysfunction and senescence. The development of systemic hypertension, increased insulin resistance, diabetic retinopathy, nephropathy and neuropathy are consequences of decreased eNOS activity and accelerated endothelial senescence. It can also explain the increased frequency of vascular calcification, peripheral vascular disease and diabetic cerebrovascular dysfunction [44]. Mitochondrial injury is associated with impaired antioxidant defense [45]. Inhibition of NHE1 using cariporide was associated with increased NO release, eNOS activity simultaneously

decreased ROS production, decreased nuclear factor-κB (NF-κB) activation and decreased production of tumor necrosis factor-α and intercellular adhesion molecule-1 [46]. Increased intracellular calcium induced by NHE1 isoform on the surface of cardiomyocytes leads to cardiac hypertrophy. Peripheral coronary ischemia secondary to endothelial dysfunction can further activate cardiac NHE1. In addition active NHE1 increases intracellular and intra-mitochondrial calpain that contributes to degeneration, apoptosis and fibrosis of myocardium **(Figure 3)** [43]. NHE3 is the isoform within the cytoplasmic membrane of the renal proximal tubular epithelium and ascending limb of loop of Henle. Activation of renal NHE3 causes sodium retention and can thus contribute to development of systemic hypertension in diabetic patients **(Figure 4)** [43,47]. Activation of NHE1 on the surface of platelets 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 [48]. Accordingly, activation of NHE1 on the surface of endothelial cells, VSMCs, platelets and cardiomyocytes beside the activation of renal NHE3 share in the pathogenesis of systemic hypertension, microvascular complications and macrovascular complications of diabetes that finally result in heart failure and end stage renal disease.

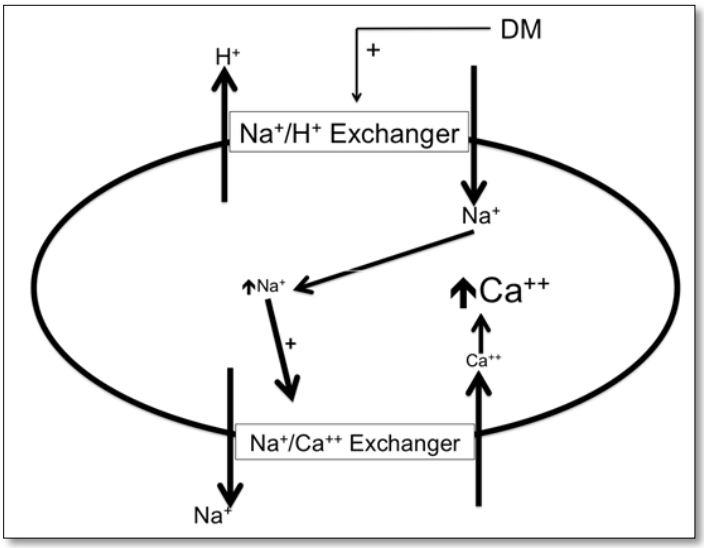

Figure 1. Diabetic state increases the activity of the sodium/hydrogen exchanger on the surface of endothelial cells, vascular smooth muscle cells, cardiomyocytes and tubular epithelial cells. Consequently, intracellular and mitochondrial calcium.

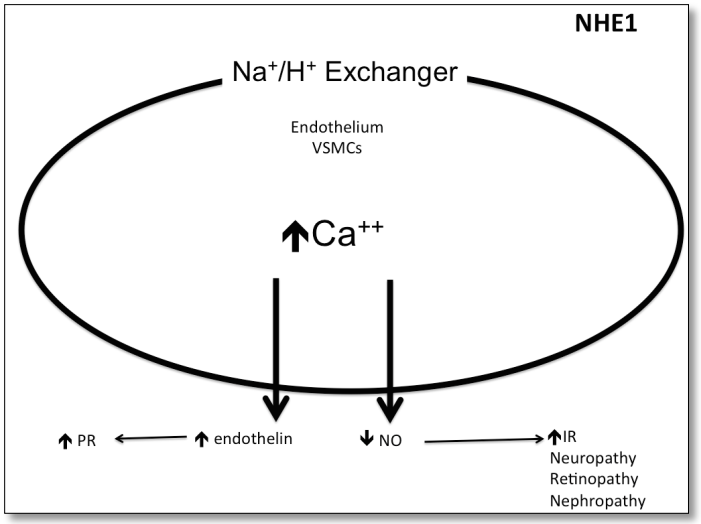

Figure 2. Increased cytosolic calcium leads to decreased nitric oxide synthesis and increased secretion of endothelin. Increased vascular smooth muscle tone leads to increased peripheral resistance and decreased tissue perfusion. This leads to decreased insulin delivery. Endothelial damage induced by calcium can also decrease permeability of the endothelium to the delivered insulin. Decrease nitric oxide production has a role in pathogenesis of neuropathy, retinopathy and nephropathy.
PR: Peripheral Resistance; IR: Insulin Resistance

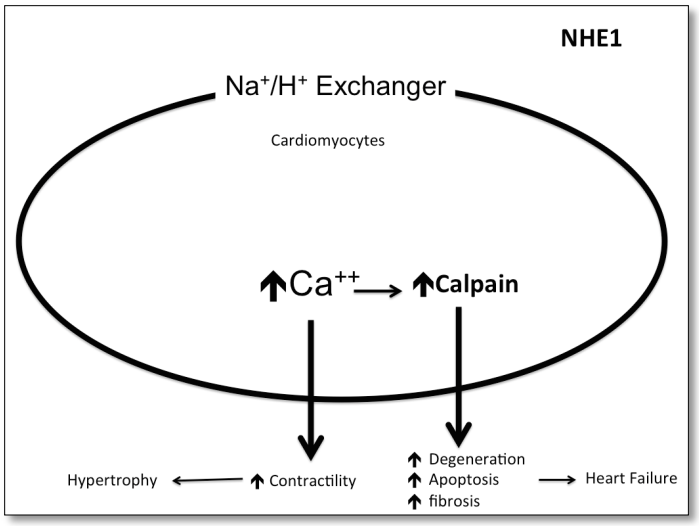

Figure 3. Increased cytosolic calcium within the cardiomyocytes leads to ventricular hypertrophy and increased activity of the digestive enzyme calpain. This lysolethicin digests mitochondrial membranes and results in myocardial damage that finally leads to heart failure.

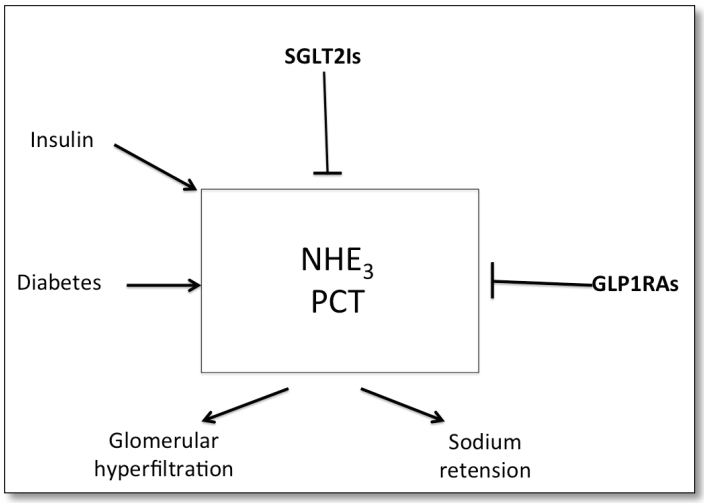

Figure 4. Increased activity of NHE3 isomer within the proximal convoluted tubules increases sodium absorption from the lumen of these tubules in exchange with the secreted hydrogen. Decreased sodium delivery to the distal nephron segments results in glomerular hyperfiltration. Diabetic state and insulin 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

OXIDATIVE STRESS

Increased oxidative stress is one of the metabolic derangements encountered in diabetes. Diabetic patients have increased production of free oxygen radicals and decreased wash out of these radicals. Increased production of free oxygen radicals is attributed to increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [49,50], cyclo-oxygenase [51] and lipoxygenase [52] enzymes. All these enzymes are induced by hyperglycemia. Sodium-glucose cotransporter 2 (SGLT2) within the brush border of proximal convoluted tubular epithelium (PCT) is another pathway of free oxygen radicals' overproduction. Increased intracellular uric acid (UA) induces NADPH oxidase [53]. Mitochondrial damage results in impaired antioxidant defense [45]. Increased free oxygen radicals activate NF-κB [54]. When NF-κB is free from its inhibitor, it translocate from the cytoplasm to the nucleus where it triggers the genes encoding transforming growth factor-β1 (TGF-β1) and monocyte chemo-attractant protein-1 (MCP-1) and intercellular adhesion molecule 1 (ICAM1) [55-57]. Reactive oxygen species (ROS) stimulate overproduction of protein kinase C (PKC) and mitogen-activated protein (MAP) kinase within mesangial cells

(MCs) and pericytes. All these factors stimulate overproduction of extracellular matrix proteins [58].

URIC ACID

Serum uric acid (SUA) is a strong predictor for development of proteinuria in T1DM patients. The risk for proteinuria increases by 80% with every 1 mg/dL rise in SUA [59]. In addition, the risk of decline of glomerular filtration rate (GFR) is significantly higher (2.4 folds) in T1DM patients with SUA>6.6 mg/dL when compared with candidates with lower level [60]. In T1DM patients followed-up for more than 18 years, SUA was an independent predictor of overt proteinuria [61]. In T2DM patients, 68% of the hyperuricemic versus 41.5% with normal SUA had diabetic nephropathy (DN) [62]. Further prospective studies confirmed the increased risk of development of proteinuria and decline of GFR among T2DM with high SUA [63,64]. SUA>7 mg/dL in males and >6 mg/dL in females were associated with higher rate of DN progression and overall mortality among T2DM patients that have the disease for fifteen years or more [65]. Treatment of T2DM patients suffering DN and high SUA with allopurinol was associated with a significant decrease of urine albumin excretion (UAE) and serum creatinine and a significant increase of GFR over three years of follow-up [66]. The significant favorable effect of urate-lowering therapy on the rate of GFR decline has been confirmed in a recent meta-analysis of 19 randomized controlled trials that enrolled 992 patients [67].

Increased level of SUA is associated with endothelial dysfunction. High mobility group box chromosomal protein 1 (HMGB1) is a pro-inflammatory mediator synthesized and secreted by activated phagocytes or monocytes. When secreted extracellular, HMGB1 can interact with the receptor for advanced glycation end products (RAGE), inducing the production of multiple cytokines, and the induction of vascular adhesion molecules [68]. In a recent in vitro study, high UA concentration inhibited eNOS expression and NO production in human umbilical vein endothelial cells (HUVECs), increased extracellular HMGB1 secretion, up-regulated RAGE expression, activated NF-κB and increased the level of inflammatory cytokines. Blocking RAGE significantly suppressed the DNA binding activity of NF-κB and the levels of inflammatory cytokines [69]. In addition, high SUA is a significant predictor of systemic hypertension [122].

ROLE OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1RA)

Glucagon like peptide-1 (GLP-1) is a peptide hormone secreted by the neuro-endocrine cells within the mucosa of the small intestine [70]. In healthy individuals, GLP-1 activates insulin secretion, inhibits glucagon secretion and slows gastric emptying and increases sense of satiety [70]. The susceptibility of this peptide hormone to enzyme breakdown by the dipeptidyl peptidase-4 enzyme (DPP-4) is responsible for the very short plasma half-life of GLP-1. It cannot be used therapeutically except as continuous intravenous infusion [71]. GLP-1RA is exogenous GLP-1 analogues with variable sequence similarity to the human GLP-1 [72]. The variability involved mainly two sites in the GLP-1 molecule susceptible to cleavage by DPP4, namely, alanine at position 8 and lysine at position 34. These changes beside other modifications have helped to find out many peptides that simulate GLP-1 action but with longer half-life [71]. GLP-1RAs were found to decrease body weight and some cardiovascular morbidity, without increasing the risk of hypoglycemia [73]. Robust indications for GLP-1RAs in T2DM patients not responding to metformin monotherapy, dual therapy, or insulin include overweight, inability to control appetite, high risk of cardiovascular disease, and the need of high doses of insulin [71]. Several clinical studies have shown that the use of GLP-1 RAs is associated with reduction in systolic and to a minor degree, diastolic blood pressure [74]. However, long term use of GLP-1 RAs was frequently reported to be associated with increased heart rate [74,75]. In addition, the current evidence does not support any beneficial effect of GLP-1RAs in patients with heart failure and/or impaired ventricular function [76,77]. The evaluation of lixisenatide in acute coronary syndrome (ELIXA) trial was the first cardiovascular outcome trial (CVOT) of GLP-1RAs in T2DM. Based on this trial, treatment with lixisenatide in addition to conventional therapy had no impact on the cardiovascular risk in patients with T2DM and recent acute coronary syndrome [78]. In the liraglutide effect and action in diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, which was finalized in December 2015, liraglutide was significantly associated with reduced rate of death from any cause and cardiovascular events in patients with T2DM at high risk for cardiovascular events. In addition, patients with eGFR<60 ml/min/1.73 m2 and patients aged 50 years or more may have greater benefit of liraglutide treatment. On the other hand, hospitalizations for heart failure were not different between liraglutide and placebo groups [79]. Although the incidence of retinopathy was similar in this trial, the chance of development of nephropathy was significantly lower in patients treated with liraglutide [79]. In SUSTAIN-6 trial, semaglutide was associated with significantly less incidence and progression of nephropathy. On the other hand, higher percentage of patients in semaglutide group developed retinopathy. Semaglutide was also associated with 26% reduction in the hazard of cardiovascular mortality, non-fatal myocardial infarction or non-fatal stroke [80]. In EXSCEL trial, extended release exenatide failed to significantly decrease the incidence of cardiovascular events [81]. This result could be due to the broader T2DM population studied in EXSCEL trial as regard to age and cardiovascular risk, the shorter follow-up period, the lower HbA1c levels and the concomitant hypoglycemic treatment (SGLT2Is were frequently used in

the placebo group) [82]. A meta-analysis including nine randomized trials with dulaglutide in 6010 T2DM patients has shown that 0.67% of patients treated with dulaglutide vs. 1.18% of the placebo group developed one of the end points. This difference was not significant [83].

Other glucose-independent effects of GLP-1RAs include decrease in blood pressure, dyslipidemia, inflammation and fibrosis. Through inhibition of renal NHE3, GLP-1RAs can promote natriuresis and diuresis. Additional effects include inhibition of the intrarenal renin angiotensin system, inflammation, and apoptosis. The mechanism of these effects remains to be established. Recent studies suggest important antioxidant and anti-apoptotic activities of GLP-1RAs **(Figure 5)** [84].

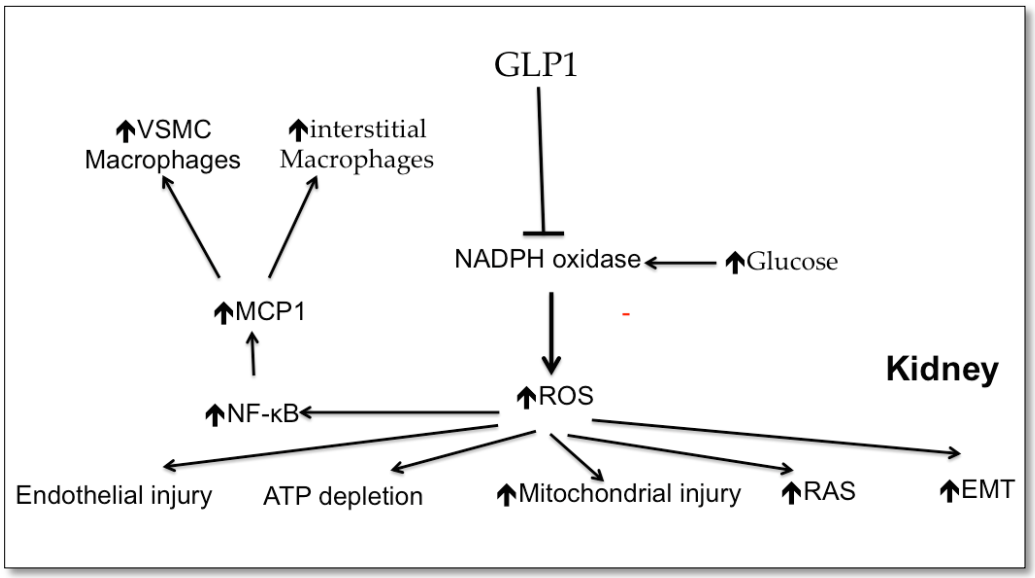

Figure 5. Hyperglycemia stimulates NADPH oxidase enzyme within different organs including the kidney. Consequent increased production of free oxygen radicals results in increased cascade of degenerative and inflammatory processes that underlie pathology of the diabetic kidney. Glucagon like peptides inhibits 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 Peptide; VSMCs: Vascular Smooth Muscle Cells; ATP: Adenosine Triphosphate; RAS: Renin-Angiotensin System; EMT: Epithelial Mesenchymal Transition

DIPEPTIDYL PEPTIDASE 4 INHIBITORS

The discovery of non-enzymatic functions for DPP4 within the kidney has attracted the attention for the reno-protective functions of this hypoglycemic agent especially after disclosure of the anti-proteinuric effect of saxagliptin in T2DM patients during "Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53" (SAVOR-TIMI 53) trial [85-89]. In addition experimental pharmacologic and genetic inhibition of DPP4 had proven efficacy in preventing progressive renal damage in animal models of acute and chronic kidney disease [90,91].

The glucose lowering action of DPP4Is is through inhibition of breakdown of endogenous GLP and glucose-dependent insulinotropic peptide (GIP). These incretins improve sensitivity of pancreatic β cells to glucose [92]. DPP4 exists in 2 forms, membrane bound form and soluble form [93]. Membrane bound DPP4 was encountered on the cell membrane of epithelial cells in the kidneys, lungs, and small intestine. It also exists on endothelial cells, and immune cells [94-96]. DPP4 on the surface of immune cells was initially recognized as cluster of differentiation 26 (CD26) [95,96]. The soluble form (sDPP4) is the consequence of shedding of the membrane bound form. sDPP4 level increases in obese subjects and in T2DM patients and may participated in increased insulin resistance in these cases [97]. Membrane bound DPP4 expression is induced under conditions of hypoxia as well as its' shedding [98,99].

Within the kidney, DPP4 in S1-S3 segments of the proximal convoluted tubules (PCT) are linked to NHE3 and plays a role in salt and water retention through stimulation of this exchanger, NHE3 activity decreases on inhibition of angiotensin II synthesis by captopril [100] or inhibition of DPP4 [101]. Angiotensin II inhibits megalin receptor endocytosis protein expression. This process is reversed by DPP4Is [102]. Treatment with DPP4 inhibitors may reverse reduced uptake of albumin and other low molecular weight proteins by PCT [103]. DPP4 was also localized on the glomerular endothelium and the base of the foot processes of podocytes [104]. DPP4 is expressed on T-cells, B-cells, macrophages and dendritic cells in the kidney [96].

Stimulation of DPP4 on the surface of different immune and inflammatory cells may mediate inflammatory response within the kidney in diabetic patients. Inflammation as a common feature in diabetes is reduced with DPP4Is. This finding highly suggests inflammation as a major player in DPP4-mediated kidney injury [105].

However, in spite of the reduction in urine albumin excretion observed in 3 randomized controlled studies (RCT) in T2DM patients treated with DPP4Is [106-108], the only study that specifically looked for the anti-proteinuric effect of linagliptin failed to find a significant impact [109]. Moreover, DPP4Is failed to have a significant impact on doubling of serum creatinine, change in GFR or ESRD [106-108]. On the other hand, administration of linagliptin to T2DM patients that had renal dysfunction and were already treated with ACE inhibitors or ARBs has led to further significant reduction in albuminuria [110].

In normoglycemic milieu, microRNA-29 (miR29) suppresses DPP4 gene. In hyperglycemic state, this suppression is lost. As a consequence, cell surface DPP4 activity increases [111]. 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). Up-regulated TGF β receptor and VEGFR1 stimulate endothelial-mesenchymal transition (EndMT) that increases transition to fibroblasts with consequent increased fibrogenesis **(Figure 6)** [112]. However, the lack of significant impact of DPP4Is on rate of decline of GFR in human studies would cast doubts on their favorable effect on renal fibrosis in humans.

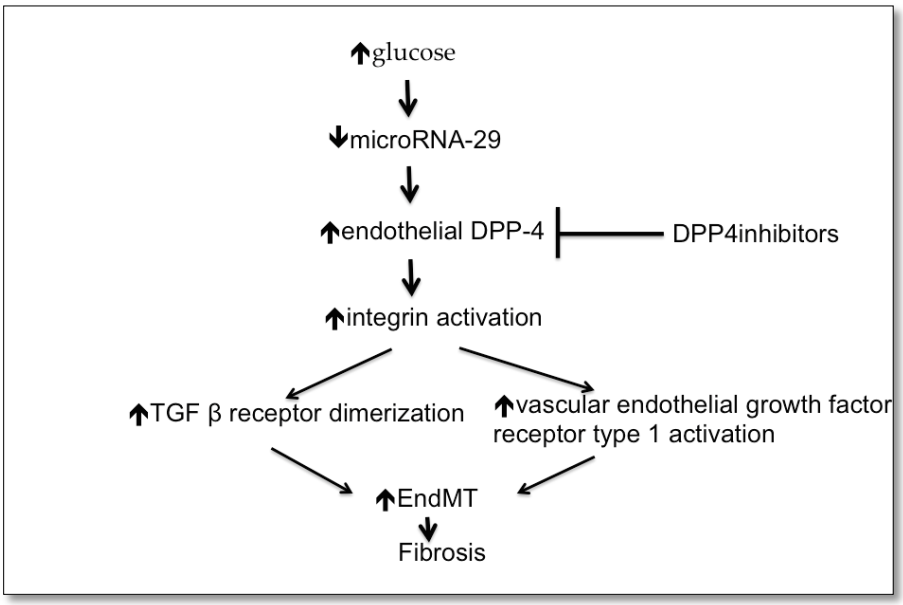

Figure 6. microRNA-29 is a natural inhibitor of endothelial DPP-4 within renal vasculature. Hyperglycemia inhibits microRNA-29 and thus stimulates endothelial DPP-4.
DPP-4: Dipeptidyl Peptidase; TGF: Transforming Growth Factor; EndMT: Endothelial Mesenchymal Transition

In addition, the impact of DPP4Is on the retina is debatable. While some investigators reported an increase in retinal endothelial leakage and vascularity [113], others have reported a significant reduction in the risk of diabetic retinopathy progression [114].

The lack of strong favorable effect of DDP4Is on diabetic microvascular and macrovascular complications of diabetes in spite of the attractive and favorable molecular and experimental mechanisms can be attributed to potentiation of the stem cell chemokine, stromal cell-derived factor-1 (SDF-1), which promotes inflammation, proliferation and neovascularization [115]. SDF-1 enhances atheromatous plaque growth and instability, and promotes cardiac inflammation and fibrosis [116]. The renal effects of DPP4Is are mainly through potentiation of SDF-1which in turn can promote podocyte injury and glomerulosclerosis. In addition, SDF-1 induces natriuresis in the distal tubules, contrary to SGLT2Is and NHE3 inhibitors that act on PCT. Hence, SDF-1 cannot utilize tubuloglomerular feedback to modulate the glomerular hyper filtration **(Figure 7)** [115,117]. SDF-1 may also aggravate both retinopathy and neuropathy [115,118].

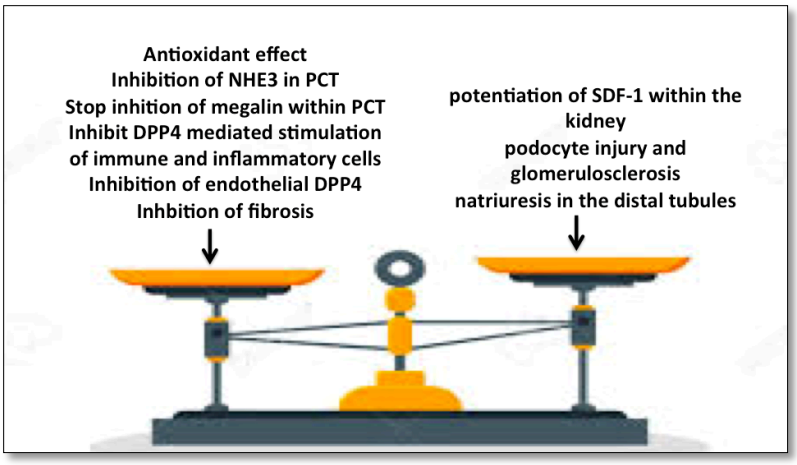

Figure 7. The beneficial effects of DPP4Is on the kidney are muffled by the bad effect induced by stromal cells derived factor 1 (SDF-1).
DPP-4: Dipeptidyl Peptidase; TGF: Transforming Growth Factor; EndMT: Endothelial Mesenchymal Transition

SODIUM GLUCOSE CO-TRANSPORTERS INHIBITORS

SGLT2Is constitute a recently introduced group that has insulin independent hypoglycemic effect. Three members of this group, namely empagliflozin, canagliflozin and dapagliflozin are FDA approved and are used in USA and Europe. By inhibiting the upregulated SGLT2 co-transporters in the brush border of S1 segment of the PCT, SGLT2Is can reduce the renal threshold for plasma glucose from 196 to 22 mg/dL, thereby enhancing urinary excretion of glucose [119]. They also increase distal sodium delivery and hence distal tubular sodium absorption. Increased adenosine triphosphate (ATP) consumption during sodium absorption with a consequent increase of adenosine production causes afferent arteriolar vasoconstriction and fall in renal blood flow, reversal of hyper filtration and accordingly reduces renal injury **(Figure 8)**. In addition, SGLT2Is exert other beneficial effects, including reductions in body weight, SUA and blood pressure [120]. Excess glucose within the tubular lumen triggers the uric acid transporter GLUT9 within S3 segment of the PCT and in the collecting duct to excrete UA in exchange with glucose [121]. The antihypertensive effect of SGLT2Is is related to volume depletion, loss of body weight, inhibition of endothelial NHE1 and renal NHE3 and reduction in SUA.

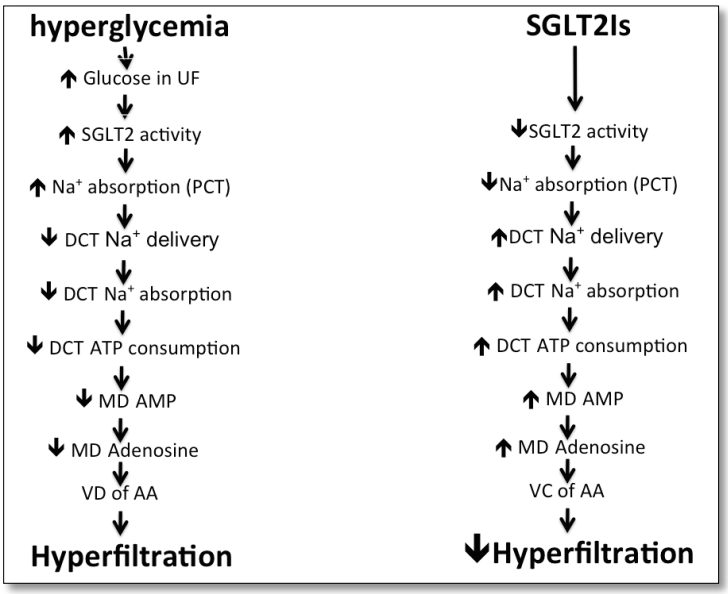

Figure 8. Mechanism of hyperfitration induced by hyperglycemia and how do SGLT2Is control it.
UF: Ultrafiltrate; SGLT: Sodium Glucose Transporter; Na+: Sodium; PCT: Proximal Convoluted Tubules; DCT: Distal Convoluted Tubules; ATP: Adenosine Triphosphate; MD: Macula Densa; AMP: Adenosine Monophosphate; VD: Vasodilatation; AA: Afferent Arteriole; VC: Vaso-Constriction

SGLT2Is not only decrease SUA, but through inhibition of the aldose reductase activity, they can decrease intracellular fructose metabolism and UA synthesis in PCT epithelium [123]. Intracellular UA is pro-oxidant. NADPH oxidase is thus activated with increased production of ROS, this leads to premature senescence of these cells, activation of renin angiotensin system, epithelial mesenchymal transition, and activation of inflammatory cascade through activation of NF-κB **(Figure 5)** [124-126]. Cyclin-dependent kinase (CDK) inhibits cell senescence. P21 is an inhibitor of CDK and thus promote cell senescence. Hyperglycemia induces P21 while SGLT2Is inhibit this factor within PCT cells **(Figure 9)** [127,128]. In addition, SGLT2Is muffle the expression of toll-like receptor-4, the binding of nuclear DNA for activator protein 1, the increased collagen IV expression as well as the increase in interleukin-6 secretion and interstitial macrophage infiltration induced by hyperglycemia within the renal parenchyma [129]. Moreover, fibrotic and inflammatory genes are suppressed within the diabetic kidney by SGLT2Is [130,131].

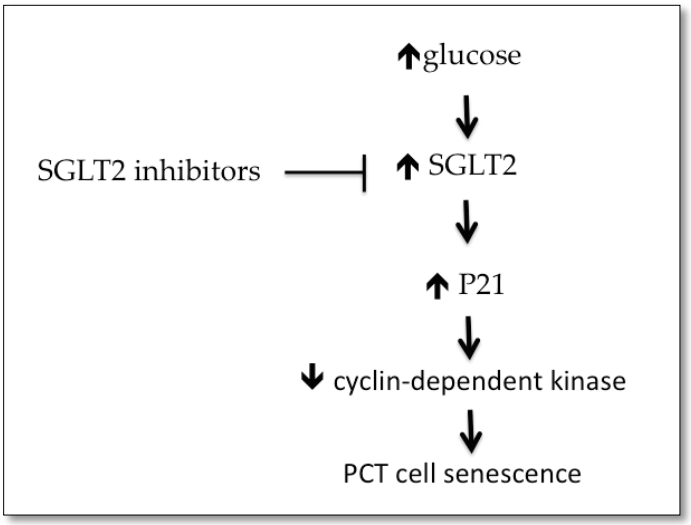

Figure 9. Activation of SGLT2 in diabetic patients leads to overactivity of P21, the natural inhibitor of Cyklin-dependent kinase 2. This kinase enzyme inhibits cell senescence. By inducing P21, diabetic patients suffer increased proximal tubular epithelium senescence. Through inhibition of SGLT2, SGLT2Is ptotect proximal tubular epithelial cells against increased senescence.

SGLT: Sodium Glucose Transporter; PCT: Proximal Convoluted Tubule

Through suppression of intracellular UA production, SGLT2Is inhibits renal gluconeogenesis. Intracellular UA stimulates adenosine monophosphate dehydrogenase (AMPD) enzyme and inhibits adenosine monophosphate kinase (AMPK) enzyme activities. Intracellular AMPD stimulates while AMPK inhibits gluconeogenesis [132]. In healthy personnel, 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 threefold [133].

Over a median observation time of 3.1 years, empagliflozin in EMPA-REG trial achieved 55% reduction of the chance of ESRD in T2DM patients with established cardiovascular disease and an eGFR>30 mL/min/1.73m^2 [134]. In comparison, losartan treatment of similar population having DN was associated with 28% delay in the onset of ESRD during a mean follow-up of 3.4 years [135]. In addition, empagliflozin was associated with 39% reduction in incident or worsening nephropathy, 38% reduction in progression to overt albuminuria and 44% reduction in doubling of serum creatinine [134]. The significant favorable outcome of SGLT2Is is attributable to their effect on glomerular hyper filtration, blood pressure, body weight and serum UA in diabetic patients [136-138]. In addition, SGLT2Is inhibit NHEs on surface of cardiomyocytes, endothelial cells and renal tubular epithelial cells. NHE inhibition can explain the unique cardioprotective and renoprotective actions of SGLT2Is [139-141]. Decreased renal blood flow induced by SGLT2Is is related to tubuloglomerular feedback and not related to RAS blockade. Empagliflozin and dapagliflozin increase plasma aldosterone and angiotensin II [142,143], together with urinary angiotensin converting enzyme and angiotensin converting enzyme [144].

When T2DM patients (total of 1450 cases) receiving metformin were randomly assigned to either once-daily canagliflozin 100 mg, canagliflozin 300 mg or glimepiride titrated to 6-8 mg for 2 years, eGFR declined by 3.3, 0.5 and 0.9 ml/min/1.73 m^2/year in glimepiride, canagliflozin 100 mg and canagliflozine 300 mg groups respectively (P<0.01 for each canagliflozin group versus glimepiride) in spite of comparable reductions in HbA1c. In addition, UAE declined more with canagliflozin 100 mg or canagliflozin 300 mg than with glimepiride. These results further support that the

renoprotective effect of SGLT2Is is independent of their glycemic effect [145]. 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 1806 diabetic retinopathy events [146].

FREE OXYGEN RADICALS SCAVENGERS

The role of reactive oxygen species (ROS) in the pathogenesis of diabetic complications is overwhelmed by many preclinical studies. 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 [147]. Clinical studies using vitamin A, C and E as antioxidant agents in pre-diabetic and T2DM patients were disappointing. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that protects and restores cell homeostasis upon activation. Although Nrf2 is adaptively activated in hyperglycemic status, this activation does not reach the sufficient level capable to combat the oxidative stress fueled by hyperglycemia [148]. Insufficient Nrf2 activity is often associated with the pathogenesis of diabetes and its complications [149]. Natural products can activate Nrf2, as a potential therapeutic target to control diabetic complications [149,150]. Cruciferous vegetables are rich source of sulforaphane, resveratrol is present in grapes, rutin is found in buckwheat, black tea, citrus fruits, and apple peels, cinnamic aldehyde is found in cinnamon essential oil, curcumin is found in turmeric, berberine in Berberis mahonia plant, actinidia callosa in kiwi fruits, Sinomenine in the root of the climbing plant Sinomenium acutum, garlic and bitter melon. All these agents are natural Nrf2 activators [151-154].

Consumption of 10 g of broccoli sprouts powder, a rich source of sulforaphane, daily for four weeks was associated with significant improvement in insulin resistance in sixty three T2DM patients [155]. In a double blind trial in T2DM patients, the study candidates consumed oral 2 × 5 mg resveratrol (resveratrol group) or a placebo (control group) for four weeks. Resveratrol significantly decreased insulin resistance, urine ortho-tyrosine/creatinine ratio as an index of ROS production and platelets' phosphorylated protein kinase B (pAkt):protein kinase B (Akt) ratio. These results indicated that resveratrol improves insulin sensitivity in humans, propably due to decreased oxidative stress with consequent more efficient insulin signaling via the Akt pathway [156]. A more recent study of ten T2DM subjects, 12 week daily consumption of 3 g of resveratrol increased skeletal muscle Sirtuin1 and adenosine monophosphate kinase enzymes expression. These findings can further support the insulin sensitizing effect of resveratrol [157]. On the other hand, resveratrol supplementation over five weeks in fourteen T2DM diet controlled patients did not have significant effect on glycemic control [158].

In seventy-five patients undergoing primary cardiovascular disease prevention including diabetic patients, resveratrol-rich grape supplement significantly decreased high-sensitivity C-reactive protein, tumor necrosis factor-α, plasminogen activator inhibitor type 1 and increased anti-inflammatory interleukin-10. The authors concluded that 1 year consumption of a resveratrol-rich grape supplement improved the inflammatory and fibrinolytic status in high cardiovascular risk and diabetic patients [159]. The beneficial anti-inflammatory effect of resveratrol-rich grape supplement was further supported in a later study of 35 T2DM male patients. One year consumption of resveratrol-rich grape supplement down-regulated the expression of pro-inflammatory cytokines in circulating mononuclear cells [160]. However, a more recent and larger study failed to prove a significant impact of low dose (40 mg/day) and higher dose (500 mg/day) used for 6 months on fasting blood sugar, glycated hemoglobin or c-reactive protein [161]. When 36 dementia-free, T2DM 49-78 years old patients consumed single doses of synthetic trans-resveratrol (75, 150 and 300 mg) at weekly intervals, trans-cranial Doppler ultrasound both before and 45 min after treatment had shown that only the 75 mg dose was efficacious to improve the cerebral vasodilator responsiveness in both middle and posterior cerebral arteries [162]. In addition, a single 75 mg dose of resveratrol was found to improve neurovascular coupling and cognitive performance in 36 T2DM adults aged 40-80 years [163]. A more recent study has shown that a daily 100 mg resveratrol supplementation for 12 weeks in 50 T2DM patients was associated with a significant decrease of arterial stiffness estimated by cardio-ankle vascular index [164].

When endothelial function was assessed using digital volume plethysmography to measure change in reflective index, oral intake of curcumin 150 mg twice daily for eight weeks has led to significant improvement in endothelial function [165]. Supplementation of twenty T2DM patients suffering overt proteinuria with 22 mg of curcumin three times daily for 2 months significantly decreased urinary protein excretion and urine IL-8 beside serum levels of TGF-β and IL-8 [166]. Curcumin in a dose of 500 mg administered three times daily for 9 months in 120 pre-diabetic patients significantly improved insulin resistance and beta cell function with consequent prevention of diabetes [167]. Further studies supported the favorable anti-diabetic effect of curcumin [168-170].

RECOMMENDATIONS OF DIABETES ASSOCIATIONS

In October 2018, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) have issued an updated consensus statement on

management of hyperglycemia in type 2 diabetes patients. This consensus was published during the annual meeting of EASD in Berlin, Germany. In this consensus, patients with clinical cardiovascular disease should receive one of SGLT2Is or GLP-1RAs, while in patients with chronic kidney disease (CKD) or clinical heart failure and atherosclerotic cardiovascular disease (ASCVD), SGLT2Is should be considered [171]. The choice of diabetes therapies as recommended by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) must be individualized based on many attributes including the risk reduction in heart and kidney disease [172].

NOVEL MARKERS OF DIABETIC COMPLICATIONS

Mannose-binding lectin (MBL) is a recognized protein of the innate immune system. It is composed of a lectin (carbohydrate-binding) moiety attached to a collagenous moiety. MBL binds to a wide range of sugars that permits MBL permits to interact with a wide range of viruses, bacteria, yeasts, fungi and protozoa containing such sugars within their cell walls or membranes. When bound to its target sugar moiety, MBL can activate the complement system in the classic pathway or in C1-independent manner [173]. MBL is independently associated with HbA1c among diabetic patients [174]. MBL is involved in complement activation within the diabetic kidney [175] and was discovered as a possible independent predictor of DR, DN and other vascular complications in type 1 and type 2 diabetes [176-181].

In 297 newly diagnosed type 2 diabetic patients, serum fibrinogen was a strong predictor for DN [182]. Serum Adiponectin was proved as strong predictor of DN in both type 1 and type 2 diabetic patients according to a recent meta-analysis of 13 studies including more than five thousand cases [183].

DISCUSSION

The annual mortality rate secondary to kidney disease has risen over the last decade to above 5 million worldwide. This alarming rate is mainly attributed to the increased rate of obesity with consequent increase in the rate of type 2 diabetes, hypertension and cardiovascular disease [184]. Diabetic complications pose a huge public health and economic burden. Before the last 2 decades, the medical community has witnessed long term inertia in the available therapeutic tools that can prevent or delay progression of these complications. The introduction of GLP1RAs, DPP4Is and SGLT2Is has revived the hope to effectively prevent or slow the rate of progression of these complications. Beside their efficiency to control blood sugar, these agents have a favorable effect on body weight with decreased likelihood to experience hypoglycemia. In view of these valuable effects, the American diabetes association considered SGLT2Is as second- or third-line anti-hyperglycemic treatment [185]. In addition, the updated consensus statement on management of hyperglycemia in type 2 diabetes issued by EASD and ADA has recommended the early introduction of SGLT2Is and GLP1RAs to diabetic patients with clinical cardiovascular disease and SGLT2Is to patients with CKD or clinical heart failure and ASCVD. The results of CREDENCE trial that appeared couple of days ago have supported the significant cardioprotective and renoprotective of SGLT2Is in diabetic CKD patients. Canagliflozine 100 mg daily succeeded to convince the investigators to prematurely terminate the trial prematurely 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 end point by 34% after 2.6 years of treatment. All patients in this study had albuminuria >300 mg/day and had eGFR between 60 and 30 ml/min/1.73m^2. These data highly suggest that the beneficial effect of SGLT2Is is not likely related to the anti-hyperglycemic effect of these agents [186].

In view of these results and according to the accumulating evidence, more energetic primary preventive approach should be tailored. Routine screening of diabetic patients for likelihood to develop diabetic nephropathy using the early predictors like serum MBL, fibrinogen or adiponectin can help researchers to select patients prone to develop diabetic nephropathy. These patients should be studied looking for the capability of SGLT2Is to prevent the development of the disease instead of waiting till they develop albuminuria. Similar studies should be designed to study the possible impact of administration of GLP1RA, SGLT2Is and/or DPP4Is on the rate of development of different cardiovascular events in selected high risk diabetic population.

FUNDS

This study did not receive funds.

REFERENCES

1. Hu FB, Satija A, Manson JE (2015) Curbing the diabetes pandemic: The need for global policy solutions. JAMA 313: 2319-2320.
2. World Health Organization (2016) Diabetes mellitus - Epidemiology: Global report on diabetes.
3. Rao KSS, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, et al. (2011) Diabetes mellitus, fasting glucose and risk of cause-specific death. N Engl J Med 364: 829-841.
4. Loukine L, Waters C, Choi BC, Ellison J (2012) Impact of diabetes mellitus on life expectancy and health-adjusted life expectancy in Canada. Popul Health Metr 10: 7.

5. Zheng Y, He M, Congdon N (2012) The worldwide epidemic of diabetic retinopathy. Indian J Ophthalmol 60: 428-431.

6. Deshpande AD, Harris-Hayes M, Schootman M (2008) Epidemiology of diabetes and diabetes-related complications. Phys Ther 88: 1254-1264.

7. Candrilli SD, Davis KL, Kan HJ, Lucero MA, Rousculp MD (2007) Prevalence and the associated burden of illness of symptoms of diabetic peripheral neuropathy and diabetic retinopathy. J Diabetes Complications 21: 306-314.

8. Humphry LL, Ballard DJ, Frohnert PP, Chu CP, O'Fallon WM, et al. (1989) Chronic renal failure in non-insulin dependent diabetes mellitus. A population-based study in Rochester, Minnesota. Ann Intern Med 111: 788-796.

9. DeFronzo RA (1995) Diabetic nephropathy: Etiologic and therapeutic considerations. Diabetes Rev 3: 510-564.

10. Nichols GA, Hillier TA, Erbey JR, Brown JB (2001) Congestive heart failure in type 2 diabetes: Prevalence, incidence and risk factors. Diabetes Care 24: 1614-1619.

11. Zeadin MG, Petlura CI, Werstuck GH (2013) Molecular mechanisms linking diabetes to the accelerated development of atherosclerosis. Can J Diabetes 37: 345-350.

12. Chen R, Ovbiagele B, Feng W (2016) Diabetes and stroke: Epidemiology, pathophysiology, pharmaceuticals and outcomes. Am J Med Sci 351: 380-386.

13. Packer M (2017) activation and inhibition of sodium-hydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. Circulation 136: 1548-1559.

14. Maiese K (2015) New insights for oxidative stress and diabetes mellitus. Oxid Med Cell Longev 2015: 875961.

15. Cai W, Duan XM, Liu Y, Yu J, Tang YL, et al. (2017) uric acid induces endothelial dysfunction by activating the HMGB1/RAGE signaling pathway. Biomed Res Int 2017: 4391920.

16. List JF, Whaley JM (2011) Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. Kidney Int Suppl 120: 20-27.

17. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329: 977-986.

18. UK Prospective Diabetes Study (UKPDS) Group (1998). Intensive blood-glucose control with sulphonyl ureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes (UKPDS 33). Lancet 352: 837-853.

19. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, et al. (2009) Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: A meta-analysis of randomised controlled trials. Lancet 373: 1765-1772.

20. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352: 854-865.

21. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, et al. (2018) Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. Endocr Pract 24: 91-120.

22. Røder ME (2018) Major adverse cardiovascular event reduction with GLP-1 and SGLT2 agents: Evidence and clinical potential. Ther Adv Chronic Dis 9: 33-50.

23. Triplitt C, Solis-Herrera C, Cersosimo E, Abdul-Ghani M, Defronzo RA (2015) Empagliflozin and linagliptin combination therapy for treatment of patients with type 2 diabetes mellitus. Expert Opin Pharmacother 16: 2819-2833.

24. Wakisaka M, Nagao T (2017) Sodium glucose co-transporter 2 in mesangial cells and retinal pericytes and its implications for diabetic nephropathy and retinopathy. Glycobiology.

25. Furchgott RF, Zawadzki JV (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288: 373-376.

26. Roy D, Perreault M, Marette A (1998) Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues *in vivo* is NO dependent. Am J Physiol 274: 692-699.

27. Wang H, Wang AX, Barrett EJ (2011) Caveolin-1 is required for vascular endothelial insulin uptake. Am J Physiol Endocrinol Metab 300: 134-144.

28. Kolka CM, Bergman RN (2013) The endothelium in diabetes: Its role in insulin access and diabetic complications. Rev Endocr Metab Disord 14: 13-19.

29. Shenouda SM, Widlansky ME, Chen K, Xu G, Holbrook M, et al. (2011) Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus. Circulation 124: 444-453.

30. Sharma A, Bernatchez PN, de Haan JB (2012) Targeting endothelial dysfunction in vascular complications associated with diabetes. Int J Vasc Med.

31. Farb MG, Ganley-Leal L, Mott M, Liang Y, Ercan B, et al. (2011) Arteriolar function in visceral adipose tissue is impaired in human obesity. Arterioscler Thromb Vasc Biol 32: 467-473.

32. Liu J, Jahn LA, Fowler DE, Barrett EJ, Cao W, et al. (2011) Free fatty acids induce insulin resistance in both cardiac and skeletal muscle microvasculature in humans. J Clin Endocrinol Metab 96: 438-446.

33. Rask-Madsen C, Li Q, Freund B, Feather D, Abramov R, et al. (2010) Loss of insulin signaling in vascular endothelial cells accelerates atherosclerosis in apolipoprotein E null mice. Cell Metab 11: 379-389.

34. Tremolada G, Del Turco C, Lattanzio R, Maestroni S, Maestroni A, et al. (2012) The role of angiogenesis in the development of proliferative diabetic retinopathy: Impact of intravitreal anti-VEGF treatment. Exp Diabetes Res.

35. Satchell SC (2012) The glomerular endothelium emerges as a key player in diabetic nephropathy. Kidney Int 82: 949-951.

36. Stirban A (2014) Microvascular dysfunction in the context of diabetic neuropathy. Curr Diab Rep 14: 541.

37. Exalto LG, Whitmer RA, Kappele LJ, Biessels GJ (2012) An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol 47: 858-864.

38. Kanetsuna Y, Takahashi K, Nagata M, Gannon MA, Breyer MD, et al. (2007) Deficiency of endothelial nitric oxide synthase confers susceptibility to diabetic nephropathy in nephropathy-resistant inbred mice. Am J Pathol 170: 1473-1484.

39. Zhao HJ, Wang S, Cheng H, Zhang MZ, Takahashi T, et al. (2006) Endothelial nitric oxide synthase deficiency produces accelerated nephropathy in diabetic mice. J Am Soc Nephrol 17: 2664-2669.

40. Huber JD, Bentzien J, Boyer SJ, Burke J, De Lombaert S, et al. (2012) Identification of a potent sodium hydrogen exchanger isoform 1 (NHE1) inhibitor with a suitable profile for chronic dosing and demonstrated cardioprotective effects in a preclinical model of myocardial infarction in the rat. J Med Chem 55: 7114-7140.

41. Sarigianni M, Tsapas A, Mikhailidis DP, Kaloyianni M, Koliakos G, et al. (2010) Na+ H+ exchanger-1: A link with atherogenesis? Expert Opin Investig Drugs 19: 1545-1556.

42. Wang S, Peng Q, Zhang J, Liu L (2008) Na+/H+ exchanger is required for hyperglycemia-induced endothelial dysfunction via calcium-dependent calpain. Cardiovasc Res 80: 255-262.

43. Packer M (2017) activation and inhibition of sodium-hydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. Circulation 136: 1548-1559.

44. Katusic ZS, Austin SA (2016) Neurovascular protective function of endothelial nitric oxide - Recent advances. Circ J 80: 1499-1503.

45. Alves-Lopes R, Neves KB, Montezano AC, Harvey A, Carneiro FS, et al. (2016) Internal pudental artery dysfunction in diabetes mellitus is mediated by NOX1-derived ROS-, Nrf2- and Rho kinase-dependent mechanisms. Hypertension 68: 1056-1064.

46. Wu S, Gao X, Yang S, Liu L, Ge B, et al. (2013) Protective effects of cariporide on endothelial dysfunction induced by homocysteine. Pharmacology 92: 303-309.

47. Packer M. (2017) Role of the sodium-hydrogen exchanger in mediating the renal effects of drugs commonly used in the treatment of type 2 diabetes. Diabetes Obes Metab.

48. Chang HB, Gao X, Nepomuceno R, Hu S, Sun D (2015) Na(+)/H(+) exchanger in the regulation of platelet activation and paradoxical effects of cariporide. Exp Neurol 272: 11-16.

49. Osar Z, Samanci T, Demirel GY, Damci T, Ilkova H (2004) Nicotinamide effects oxidative burst activity of neutrophils in patients with poorly controlled type 2 diabetes mellitus. Exp Diabesity Res 5: 155-162.

50. Hansen SS, Aasum E, Hafstad AD (2017) The role of NADPH oxidases in diabetic cardiomyopathy. Biochim Biophys Acta.

51. Roy S, Kim D, Hernandez C, Simo R, Roy S (2015) Beneficial effects of fenofibric acid on overexpression of extracellular matrix components, cox-2 and impairment of endothelial permeability associated with diabetic retinopathy. Exp Eye Res 140: 124-129.

52. Othman A, Ahmad S, Megyerdi S (2013) 12/15-Lipoxygenase-derived lipid metabolites induce retinal endothelial cell barrier dysfunction: Contribution of NADPH oxidase. PLoS One 8: e57254.

53. Zheng Y, He M, Congdon N (2012) The worldwide epidemic of diabetic retinopathy. Indian J Ophthalmol 60: 428-431.

54. Wada J, Makino H (2013) Inflammation and the pathogenesis of diabetic nephropathy Clin Sci (Lond) 124: 139-152.

55. Yang B, Hodgkinson A, Oates PJ, Millward BA, Demaine AG (2008) High glucose induction of DNA-binding activity of the transcription factor NF-κB in patients with diabetic nephropathy. Biochim Biophys Acta 1782: 295-302.

56. Ha H, Yu MR, Choi YJ, Kitamura M, Lee HB (2002) Role of high glucose-induced nuclear factor-κB activation in monocyte chemoattractant protein-1 expression by mesangial cells. J Am Soc Nephrol 13: 894-902.

57. Park CW, Kim JH, Lee JH, KimYS, Ahn HJ, et al. (2000) High glucose-induced intercellular adhesion molecule-1 (ICAM-1) expression through an osmotic effect in rat mesangial cells is PKC-NF-κ B-dependent. Diabetologia 43: 1544-1553.

58. Kashihara N, Haruna Y, Kondeti VK, Kanwar YS (2010) Oxidative stress in diabetic nephropathy. Curr Med Chem 17: 4256-4269.

59. Jalal DI, Rivard CJ, Johnson RJ, Maahs DM, McFann K, et al. (2010) Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: Findings from the coronary artery calcification in type 1 diabetes study. Nephrol Dial Transplant 25: 1865-1869.

60. Ficociello LH, Rosolowsky ET, Niewczas MA, Maselli NJ, Weinberg JM, et al. (2010) High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: Results of a 6 year follow-up. Diabetes Care 33: 1337-1343.

61. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH (2009) Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: An inception cohort study. Diabetes 58: 1668-1671.

62. Yan D, Tu Y, Jiang F, Wang J, Zhang R, et al. (2015) Uric acid is independently associated with diabetic kidney disease: A cross-sectional study in a Chinese population. PLoS One 10: e0129797.

63. De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, et al. (2015) Serum uric acid and risk of CKD in type 2 diabetes. Clin J Am Soc Nephrol 10: 1921-1929.

64. Takae K, Nagata M, Hata J, Mukai N, Hirakawa Y, et al. (2016) Serum uric acid as a risk factor for chronic kidney disease in a Japanese community - The Hisayama study. Circ J 80: 1857-1862.

65. Bartáková V, Kuricová K, Pácal L, Nová Z, Dvořáková V, et al. (2015) Hyperuricemia contributes to the faster progression of diabetic kidney disease in type 2 diabetes mellitus. J Diabetes Complications.

66. Liu P, Chen Y, Wang B, Zhang F, Wang D, et al. (2015) Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3 year randomized parallel-controlled study. Clin Endocrinol (Oxf) 83: 475-482.

67. Kanji T, Gandhi M, Clase CM, Yang R (2015) Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: Systematic review and meta-analysis. BMC Nephrol 16: 58.

68. Erlandsson Harris H, Andersson U (2004) The nuclear protein HMGB1 as a proinflammatory mediator. Eur J Immunol 34: 1503-1512.

69. Cai W, Duan XM, Liu Y, Yu J, Tang YL, et al. (2017) Uric acid induces endothelial dysfunction by activating the HMGB1/RAGE signaling pathway. Biomed Res Int 2017: 4391920.

70. Vilsbøll T, Holst JJ (2004) Incretins, insulin secretion and type 2 diabetes mellitus. Diabetologia 47: 357-366.

71. Kalra S (2013) Glucagon-like peptide-1 receptors agonists (GLP1 RA). J Pak Med Assoc 63: 1312-1315.

72. Ross SA, Ekoé JM (2010) Incretin agents in type 2 diabetes. Can Fam Physician 56: 639-648.

73. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, et al. (2015) Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 38: 140-149.

74. Sivertsen J, Rosenmeier J, Holst JJ, Vilsbøll T (2012) The effect of glucagon-like peptide 1 on cardiovascular risk. Nat Rev Cardiol 9: 209-222.

75. Drucker DJ (2016) The cardiovascular biology of glucagon-like peptide-1. Cell Metab 24: 15-30.

76. Lepore JJ, Olson E, Demopoulos L, Haws T, Fang Z, Barbour AM, et al. (2016) Effects of the novel long-acting GLP-1 agonist, albiglutide, on cardiac function, cardiac metabolism and exercise capacity in patients with chronic heart failure and reduced ejection fraction. JACC Heart Fail 4: 559-566.

77. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, et al. (2016) Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: A randomized clinical trial. JAMA 316: 500-508.

78. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, et al. (2015) Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 373: 2247-2257.

79. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, et al. (2016) Liraglutide and cardiovascular

outcomes in type 2 diabetes. N Engl J Med 375: 311-322.

80. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, et al. (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375: 1834-1844.
81. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, et al. (2017) Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 377: 1228-1239.
82. Røder ME (2018) Major adverse cardiovascular event reduction with GLP-1 and SGLT2 agents: Evidence and clinical potential. Ther Adv Chronic Dis 9: 33-50.
83. Ferdinand KC, Botros FT, Atisso CM, Sager PT (2016) Cardiovascular safety for once-weekly dulaglutide in type 2 diabetes: A pre-specified meta-analysis of prospectively adjudicated cardiovascular events. Cardiovasc Diabetol 15: 38.
84. Thomas MC (2017) The potential and pitfalls of GLP-1 receptor agonists for renal protection in type 2 diabetes. Diabetes Metab 43: 220-227.
85. Aroor A, Zuberek M, Duta C, Meuth A, Sowers JR, et al. (2016) Angiotensin II stimulation of DPP4 activity regulates megalin in the proximal tubules. Int J Mol Sci 17: E780.
86. Girardi AC, Fukuda LE, Rossoni LV, Malnic G, Reboucas NA (2008) Dipeptidyl peptidase IV inhibition downregulates Na+-H+ exchanger NHE3 in rat renal proximal tubule. Am J Physiol Renal Physiol 294: 414-422.
87. Muskiet MH, Smits MM, Morsink LM, Diamant M (2014) The gut-renal axis: Do incretin-based agents confer renoprotection in diabetes? Nat Rev Nephrol 10: 88-103.
88. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, et al. (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 369: 1317-1326.
89. Udell JA, Bhatt DL, Braunwald E, Cavender MA, Mosenzon O, et al. (2015) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: Observations from the SAVOR-TIMI 53 Trial. Diabetes Care 38: 696-705.
90. Eun Lee J, Kim JE, Lee MH, Song HK, Ghee JY, et al. (2016) DA-1229, a dipeptidyl peptidase IV inhibitor, protects against renal injury by preventing podocyte damage in an animal model of progressive renal injury. Lab Invest 96: 547-560.
91. Glorie LL, Verhulst A, Matheeussen V, Baerts L, Magielse J, et al. (2012) DPP4 inhibition improves functional outcome after renal ischemia-reperfusion injury. Am J Physiol Renal Physiol 303: 681-688.
92. Holst JJ, Deacon CF (2005) Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. Diabetologia 48: 612-615.
93. Nistala R, Savin V (2017) Diabetes, hypertension and chronic kidney disease progression: Role of DPP4. Am J Physiol Renal Physiol 312: 661-670.
94. Deacon CF (2005) What do we know about the secretion and degradation of incretin hormones? Regul Pept 12: 117-124.
95. De M, I, Korom S, Van DJ, Scharpe S (1999) CD26, let it cut or cut it down. Immunol Today 20: 367-375.
96. Klemann C, Wagner L, Stephan M, von Horsten S (2016) Cut to the chase: A review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. Clin Exp Immunol 185: 1-21.
97. Lamer D, Famulla S, Wronkowitz N, Hartwig S, Lehr S, et al. (2011) Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. Diabetes 60: 1917-1925.
98. Chowdhury HH, Velebit J, Radić N, Frančič V, Kreft M, et al., (2016) hypoxia alters the expression of dipeptidyl peptidase 4 and induces developmental remodeling of human pre-adipocytes. J Diabetes Res 2016: 7481470.
99. Röhrborn D, Eckel J, Sell H (2014) Shedding of dipeptidyl peptidase 4 is mediated by metalloproteases and up-regulated by hypoxia in human adipocytes and smooth muscle cells. FEBS Lett 588: 3870-3877.
100. Girardi AC, Degray BC, Nagy T, Biemesderfer D, Aronson PS (2001) Association of Na(+)-H(+) exchanger isoform NHE3 and dipeptidyl peptidase IV in the renal proximal tubule. J Biol Chem 276: 46671-46677.
101. Girardi AC, Fukuda LE, Rossoni LV, Malnic G, Reboucas NA (2008) Dipeptidyl peptidase IV inhibition downregulates Na+-H+ exchanger NHE3 in rat renal proximal tubule Am J Physiol Renal Physiol 294: 414-422.
102. Aroor A, Zuberek M, Duta C, Meuth A, Sowers JR, et al. (2016) Angiotensin II stimulation of DPP4 activity regulates megalin in the proximal tubules. Int J Mol Sci 17: E780.
103. Gekle M (2005) Renal tubule albumin transport. Annu Rev Physiol 67: 573-594.

104. Dekan G, Miettinen A, Schnabel E, Farquhar MG (1990) Binding of monoclonal antibodies to glomerular endothelium, slit membranes and epithelium after in vivo injection. Localization of antigens and bound IgGs by immunoelectron microscopy. Am J Pathol 137: 913-927.

105. Alter ML, Ott IM, von WK, Tsuprykov O, Sharkovska Y, et al. (2012) DPP-4 inhibition on top of angiotensin receptor blockade offers a new therapeutic approach for diabetic nephropathy. Kidney Blood Press Res 36: 119-351.

106. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, et al. (2017) Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. Diabetes Care 40: 69-76.

107. Cornel JH, Bakris GL, Stevens SR, Alvarsson M, BaxW A, et al. (2016) Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: Outcomes from TECOS. Diabetes Care 39: 2304-2310.

108. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, et al. (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 369: 1327-1335.

109. Groop PH, Cooper ME, Perkovic V, Hocher B, Kanasaki K, et al. (2017) Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: The randomized MARLINA-T2D trial. Diabetes Obes Metab 19: 1610-1619.

110. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, et al. (2013) Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care 36: 3460-3468.

111. Kanasaki K, Shi S, Kanasaki M, He J, Nagai T, et al. (2014) Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. Diabetes 63: 2120-2131.

112. Shi S, Srivastava SP, Kanasaki M, He J, Kitada M, et al. (2015) Interactions of DPP-4 and integrin β1 influences endothelial-to-mesenchymal transition. Kidney Int 88: 479-489.

113. Lee CS, Kim YG, Cho HJ, Park J, Jeong H, et al. (2016) Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. Sci Rep 6: 29393.

114. Chung YR, Park SW, Kim JW, Kim JH (2016) Protective effects of dipeptidyl peptidase-4 inhibitors on progression of diabetic retinopathy in patients with type 2 diabetes. Retina 36: 2357-2363.

115. Packer M (2018) Have dipeptidyl peptidase-4 inhibitors ameliorated the vascular complications of type 2 diabetes in large-scale trials? The potential confounding effect of stem-cell chemokines. Cardiovasc Diabetol 17: 9.

116. Ferdousie VT, Mohammadi MM, Hassanshahi G, Khorramdelazad H, Falahati-Pour SK, et al. (2017) Serum CXCL10 and CXCL12 chemokine levels are associated with the severity of coronary artery disease and coronary artery occlusion. Int J Cardiol 233: 23-28.

117. Darisipudi MN, Kulkarni OP, Sayyed SG, Ryu M, Migliorini A, et al. (2011) Dual blockade of the homeostatic chemokine CXCL12 and the proinflammatory chemokine CCL2 has additive protective effects on diabetic kidney disease. Am J Pathol 179: 116-124.

118. Butler JM, Guthrie SM, Koc M, Afzal A, Caballero S, Brooks HL, et al. (2005) SDF-1 is both necessary and sufficient to promote proliferative retinopathy. J Clin Invest 115: 86-93.

119. DeFronzo RA, Hompesch M, Kasichayanula S, Liu X, Hong Y, et al. (2013) Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 36: 3169-3176.

120. van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, et al. (2017) SGLT2 Inhibition in the diabetic kidney - From mechanisms to clinical outcome. Clin J Am Soc Nephrol 12: 700-710.

121. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, et al. (2014) SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos 35: 391-404.

122. Wang J, Qin T, Chen J, Li Y, Wang L, et al. (2014) Hyperuricemia and risk of incident hypertension: A systematic review and meta-analysis of observational studies. PLoS One 9: e114259.

123. Bjornstad P, Lanaspa MA, Ishimoto T, Kosugi T, Kume S, et al. (2015) Fructose and uric acid in diabetic nephropathy. Diabetologia 58: 1993-2002.

124. Cristóbal-García M, García-Arroyo FE, Tapia E, Osorio H, Arellano-Buendía AS, et al. (2015) Renal oxidative stress induced by long-term hyperuricemia alters mitochondrial function and maintains systemic hypertension. Oxid Med Cell Longev 2015: 535686.

125. Ryu ES, Kim MJ, Shin HS, Jang YH, Choi HS, et al. (2013) Uric acid-induced phenotypic transition of renal

tubular cells as a novel mechanism of chronic kidney disease. Am J Physiol Renal Physiol 304: 471-480.

126. Yang Y, Zhang DM, Liu JH, Hu LS, Xue QC, et al. (2015) Wuling San protects kidney dysfunction by inhibiting renalTLR4/MyD88 signaling and NLRP3 inflammasome activation in high fructose-induced hyperuricemic mice. J Ethnopharmacol 169: 49-59.

127. Hayflick L (2003) Living forever and dying in the attempt. Exp Gerontol 38: 1231-1241.

128. Kitada K, Nakano D, Ohsaki H, Hitomi H, Minamino T, et al. (2014) Hyperglycemia causes cellular senescence via a SGLT2- and p21-dependent pathway in proximal tubules in the early stage of diabetic nephropathy. J Diabetes Complications 28: 604-611.

129. Panchapakesan U, Pegg K, Gross S, Komala MG, Mudaliar H, et al. (2013) Effects of SGLT2 inhibition in human kidney proximal tubular cells - Renoprotection in diabetic nephropathy? PLoS One 8: e54442.

130. Ojima A, Matsui T, Nishino Y, Nakamura N, Yamagishi S (2015) Empagliflozin, an Inhibitor of sodium-glucose co-transporter 2 exerts anti-inflammatory and antifibrotic effects on experimental diabetic nephropathy partly by suppressing AGEs-receptor axis. Horm Metab Res 47: 686-692.

131. Terami N, Ogawa D, Tachibana H, Hatanaka T, Wada J, et al. (2014) Long-term treatment with the sodium glucose co-transporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLoS One 9: e100777.

132. Cicerchi C, Li N, Kratzer J, Garcia G, Roncal-Jimenez CA, et al. (2014) Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: Evolutionary implications of the uricase loss in hominids. FASEB J 28: 3339-3350.

133. Wilding JPH (2014) The role of the kidneys in glucose homeostasis in type 2 diabetes. Clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. Metabolism 63: 1228-1237.

134. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, et al. (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375: 323-334.

135. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, et al. (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345: 861-869.

136. Yamout H, Bakris GL (2016) Diabetic nephropathy: SGLT2 inhibitors might halt progression of diabetic nephropathy. Nat Rev Nephrol 12: 583-584.

137. Grempler R, Thomas L, Eckhardt M, Himmelsbach F, Sauer A, et al. (2012) Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: Characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab 14: 83-90.

138. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, et al. (2014) Renal hemodynamic effect of sodium-glucose co-transporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 129: 587-597.

139. Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JWT, et al. (2018) Class effects of SGLT2 inhibitors in mouse cardio-myocytes and hearts: inhibition of Na+/H+ exchanger, lowering of cytosolic Na+ and vasodilation. Diabetologia 61: 722-726.

140. Vettor R, Inzucchi SE, Fioretto P (2017) the cardiovascular benefits of empagliflozin: SGLT2-dependent and -independent effects. Diabetologia 60: 395-398.

141. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, et al. (2017) Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia 60: 568-573.

142. Skrtić M, Yang GK, Perkins BA, Soleymanlou N, Lytvyn Y, et al. (2014) Characterisation of glomerular hemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyper filtration. Diabetologia 57:2599-2602.

143. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J (2013) Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab 15: 853-862.

144. Cherney DZ, Perkins BA, Soleymanlou N, Xiao F, Zimpelmann J, et al. (2014) Sodium glucose cotransport-2 inhibition and intrarenal RAS activity in people with type 1 diabetes. Kidney Int 86: 1057-1058.

145. Heerspink HJ, Desai M, Jardine M, Balis D, Meininger G, et al. (2018) Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol 28: 368-375.

146. Tang H, Li G, Zhao Y, Wang F, Gower EW, et al. (2018) Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in patients with type 2 diabetes mellitus: A network meta-analysis. Diabetes Obes Metab.

147. Di Marco E, Jha JC, Sharma A, Wilkinson-Berka JL, Jandeleit-Dahm KA, et al. (2015) Are reactive oxygen species still the basis for diabetic complications? Clin Sci (Lond) 129: 199-216.

148. Zoja C, Benigni A, Remuzzi G (2014) The Nrf2 pathway in the progression of renal disease. Nephrol Dial Transplant 29: 19-24.

149. Matzinger M, Fischhuber K, Heiss EH (2017) Activation of Nrf2 signaling by natural products - Can it alleviate diabetes? Biotechnol Adv pii: S0734-9750(17)30167-2.

150. David JA, Rifkin WJ, Rabbani PS, Ceradini DJ (2017) The Nrf2/Keap1/ARE pathway and oxidative stress as a therapeutic target in type II diabetes mellitus. J Diabetes Res 2017: 4826724.

151. Jiménez-Osorio AS, González-Reyes S, Pedraza-Chaverri J (2015) Natural Nrf2 activators in diabetes. Clin Chim Acta 448: 182-192.

152. Zhang X, He H, Liang D, Jiang Y, Liang W, et al. (2016) Protective effects of berberine on renal injury in streptozotocin (Stz)-induced diabetic mice. Int J Mol Sci 17.

153. Raish M, Ahmad A, Jan BL, Alkharfy KM, Ansari MA, et al. (2016) Momordica charantia polysaccharides mitigate the progression of STZ induced diabetic nephropathy in rats. Int J Biol Macromolecules 91: 394-399.

154. Yin Q, Xia Y, Wang G (2016) Sinomenine alleviates high glucose-induced renal glomerular endothelial hyperpermeability by inhibiting the activation of RhoA/ROCK signaling pathway. Biochem Biophys Res Commun 477: 881-886.

155. Bahadoran Z, Tohidi M, Nazeri P, Mehran M, Azizi F, et al. (2012) Effect of broccoli sprouts on insulin resistance in type 2 diabetic patients: A randomized double-blind clinical trial. Int J Food Sci Nutr 63: 767-771.

156. Brasnyó P, Molnár GA, Mohás M, Markó L, Laczy B, et al. (2011) Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr 106: 383-389.

157. Goh KP, Lee HY, Lau DP, Supaat W, Chan YH, et al. (2014) Effects of resveratrol in patients with type 2 diabetes mellitus on skeletal muscle SIRT1 expression and energy expenditure. Int J Sport Nutr Exerc Metab 24: 2-13.

158. Thazhath SS, Wu T, Bound MJ, Checklin HL, Standfield S, et al. (2016) Administration of resveratrol for 5 weeks has no effect on glucagon-like peptide 1 secretion, gastric emptying or glycemic control in type 2 diabetes: A randomized controlled trial. Am J Clin Nutr 103: 66-70.

159. Tomé-Carneiro J, Gonzálvez M, Larrosa M, Yáñez-Gascón MJ, García-Almagro FJ, et al. (2012) One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. Am J Cardiol 110: 356-363.

160. Tomé-Carneiro J, Larrosa M, Yáñez-Gascón MJ, Dávalos A, Gil-Zamorano J, et al. (2013) 1 year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. Pharmacol Res 72: 69-82.

161. Bo S, Ponzo V, Ciccone G, Evangelista A, Saba F, et al. (2016) Six months of resveratrol supplementation has no measurable effect in type 2 diabetic patients. A randomized, double blind, placebo-controlled trial. Pharmacol Res 111: 896-905.

162. Wong RH, Nealon RS, Scholey A, Howe PR (2016) Low dose resveratrol improves cerebrovascular function in type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis 26: 393-399.

163. Wong RH, Raederstorff D, Howe PR (2016) Acute resveratrol consumption improves neurovascular coupling capacity in adults with type 2 diabetes mellitus. Nutrients 8: E425.

164. Imamura H, Yamaguchi T, Nagayama D, Saiki A, Shirai K, et al. (2017) Resveratrol ameliorates arterial stiffness assessed by cardio-ankle vascular index in patients with type 2 diabetes mellitus. Int Heart J 58: 577-583.

165. Usharani P, Mateen AA, Naidu MU, Raju YS, Chandra N (2008) Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: A randomized, parallel-group, placebo-controlled, 8 week study. Drugs 9: 243-250.

166. Khajehdehi P, Pakfetrat M, Javidnia K, Azad F, Malekmakan L, et al. (2011) Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: A randomized, double-blind and placebo-controlled study. Scand J Urol Nephrol 45: 365-370.

167. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S (2012) Curcumin extract for prevention of type 2 diabetes. Diabetes Care 35: 2121-2127.

168. Na LX, Yan BL, Jiang S, Cui HL, Li Y1, et al. (2014) Curcuminoids target decreasing serum adipocyte-fatty acid binding protein levels in their glucose-lowering

effect in patients with type 2 diabetes. Biomed Environ Sci 27: 902-906.

169. Neerati P, Devde R, Gangi AK (2014) Evaluation of the effect of curcumin capsules on glyburide therapy in patients with type-2 diabetes mellitus. Phytother Res 28: 1796-1800.

170. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, et al. (2013) Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: A double-blind, placebo-controlled trial. Mol Nutr Food Res 57: 1569-1577.

171. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, et al. (2018) Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 61: 2461-2498.

172. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, et al. (2019) consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2019 executive summary. Endocr Pract 25: 69-100.

173. Turner MW (2003) the role of mannose-binding lectin in health and disease. Mol Immunol 40: 423-429.

174. Saraheimo M, Forsblom C, Hansen TK, Teppo AM, Fagerudd J, et al. (2005) Increased levels of mannan-binding lectin in type 1 diabetic patients with incipient and overt nephropathy. Diabetologia 48: 198-202.

175. Li XQ, Chang DY, Chen M, Zhao MH (2018) Complement activation in patients with diabetic nephropathy. Diabetes Metab pii: S1262-3636(18)30078-8.

176. Man X, Zhang H, Yu H, Ma L, Du J (2015) Increased serum mannose binding lectin levels are associated with diabetic retinopathy. J Diabetes Complications 29: 55-58.

177. Huang Q, Shang G, Deng H, Liu J, Mei Y et al. (2015) High mannose-binding lectin serum levels are associated with diabetic retinopathy in chinese patients with type 2 diabetes. PLoS One 10: e0130665.

178. Zhao SQ, Hu Z (2016) Mannose-binding lectin and diabetic nephropathy in type 1 diabetes. J Clin Lab Anal 30: 345-350.

179. Guan LZ, Tong Q, Xu J (2015) Elevated serum levels of mannose-binding lectin and diabetic nephropathy in type 2 diabetes. PLoS One 10: e0119699.

180. Hansen TK, Tarnow L, Thiel S, Steffensen R, Stehouwer CD, et al. (2004) Association between mannose-binding lectin and vascular complications in type 1 diabetes. Diabetes 53: 1570-1576.

181. Hovind P, Hansen TK, Tarnow L, Thiel S, Steffensen R, et al. (2005) Mannose-binding lectin as a predictor of micro albuminuria in type 1 diabetes: An inception cohort study. Diabetes 54: 1523-1527.

182. Pan L, Ye Y, Wo M, Bao D, Zhu F, et al. (2018) Clinical significance of hemostatic parameters in the prediction for type 2 diabetes mellitus and diabetic nephropathy. Dis Markers 2018: 5214376.

183. Pabalan N, Tiongco RE, Pandac JK, Paragas NA, Lasta SL, et al. (2018) Association and biomarker potential of elevated serum adiponectin with nephropathy among type 1 and type 2 diabetics: A meta-analysis. PLoS One 13: e0208905.

184. Ingelfinger JR, Rosen CJ (2019) clinical credence - sglt2 inhibitors, diabetes and chronic kidney disease. N Engl J Med.

185. American Diabetes Association (2016) Standards of medical care in diabetes. Diabetes Care 39: 1-109.

186. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, et al. (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med.