

Should We Change the Therapeutic Algorithm of Type 2 Diabetes Based on Accumulating Evidence?

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Abstract

In the last two decades, a dramatic shift in the paradigm of management of type 2 diabetes has been settled. Reduction of diabetic complications became the primary target instead of focusing on the mere glycemic control. The tight blood sugar control among type 1 (T1DM) and type 2 (T2DM) diabetes mellitus patients aimed at avoidance of long-term complications of diabetes. In spite of the significant impact of this approach on the incidence of these complications, the outcome is still not satisfactory. The frequent failure to achieve tight blood sugar control and the lack of hypoglycemic agents that are capable to combat the underlying pathogenic mechanisms of diabetic complications underlie this unsatisfactory outcome. These drawbacks are overcome in the newly introduced hypoglycemic agents. In this review, we are going to discuss these mechanisms and highlight the therapeutic value of the early use of these agents instead of the long-standing traditional approach.

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Index terms— type 1 diabetes; type 2 diabetes; micro-vascular complications; macrovascular complications; DPP4Is, SGLT2Is; nrf2 agonists.

1 Introduction

Diabetes mellitus is a pandemic disease that has exponentially increasing prevalence. In 1980, 108-million persons had diabetes worldwide while in 2014, 430-million persons were affected [1]. In spite of the increased awareness about this disease and the worldwide efforts to give optimum care, 3.7 million diabetic patients lost their lives in 2012 because of diabetes and its complication [2]. This figure exceeded 5 million deaths annually in the last few years [3]. The hazard of cardiovascular mortality among diabetic patients is 2.3 folds that in non-diabetic personnel [4]. The average life span of the diabetic patients is 10-15-years shorter than non-diabetic subjects [5]. Besides, diabetes is the cause of many disabling Besides, diabetes is the cause of many disabling morbidities. In spite of the optimal management of the established cases of diabetic retinopathy that reduces the risk of visual loss by 60%, diabetes remains the leading cause of blindness among working-age adults worldwide [6]. Diabetes is the leading cause of non-traumatic lower-extremity amputation [7]. Diabetic peripheral neuropathy (PN) is the most frequent cause of sensory neuropathy [8]. 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 [9,10]. The prevalence of congestive heart failure (CHF) among diabetic patients aged 55 to 64 years is 5.5 folds the prevalence among nondiabetic personnel of the same age [11]. Diabetes is an independent risk factor for the development of ischemic heart disease (IHD). CHF and IHD are the commonest causes of death in T1DM and T2DM patients [12]. Diabetes mellitus confers a high risk of cerebrovascular stroke [13]. Endothelial dysfunction is a common pathology underlying the etiopathogenic mechanism of all these complications [14]. This endothelial dysfunction is a sequel to many metabolic changes encountered in hyperglycemic personnel. These metabolic changes include increased oxidative stress [15], hyperuricemia [16], stimulation of sodium hydrogen exchangers (NHE) [14], and stimulation of renal sodium glucose transporters (SGLT) [17].

3 B) SODIUM HYDROGEN EXCHANGERS

44 Twenty-five years ago, the Diabetes Control and Complications Trial (DCCT) research group announced 50%
45 reduction of microvascular complications among T1DM patients in the tight blood sugar control group compared
46 to poorly controlled cases [18]. Five years later, the United Kingdom Prospective Diabetes Study (UKPDS) group
47 announced similar findings among T2DM patients [19]. However, tight blood sugar control only had a marginal
48 impact on cardiovascular disease and all-cause mortality among diabetic patients [20]. Additionally, blood sugar
49 control using sulphonylurea compounds and insulin carries increased risk of severe hypoglycemia and weight gain
50 [18,19]. IN UKPDS study, T2DM patients allocated to metformin had 32% reduction for any diabetes-related
51 endpoint, 42% for diabetes-related death, and 36% for all-cause mortality when compared with those prescribed
52 sulphonylurea or insulin [21]. These favorable effects of metformin were attributed to body weight reduction
53 and the almost absence of hypoglycemic attacks. According to these results and others, the American College
54 of Endocrinology (ACE), and the American Association of Clinical Endocrinology (AACE) recommend that
55 the choice of anti-diabetic therapies must depend on many attributes that include antihyperglycemic efficacy;
56 risk of inducing hypoglycemia; and risk of weight gain [22]. The last 15 years have witnessed the introduction
57 of three new hypoglycemic agents, namely, glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl
58 peptidase 4 inhibitors (DPP4Is), and sodium glucose cotransporter-2 inhibitors (SGLT2Is). These three agents
59 carry unique features, namely, the minimal incidence of hypoglycemic events and the favorable impact on body
60 weight. GLP-1RA and SGLT2Is are associated with body weight reduction, while DPP4Is are weight neutral
61 [23,24]. Compared to older hypoglycemic agents, these newer groups carry potential favorable protective effects
62 on endothelium, and can significantly reduce adverse cardiovascular events of diabetes in case of SGLT2Is and
63 GLP-1RA, and are reno-protective. SGLT2Is may also prevent or withhold diabetic retinal complications [25].
64 This review will highlight the possible new strategy to prevent the development and progression of diabetic
65 complications, the main target of this disease management.

66 2 a) The Endothelium in Diabetes

67 The first report on the role of the endothelium as an important regulator of local vascular tone was in 1980
68 [26]. The vascular endothelium is an important component of diabetic complications. Endothelial dysfunction
69 is eminent not only in diabetic patients but also in patients suffering obesity or metabolic syndrome. Decreased
70 synthesis of nitric oxide (NO), a potent vasodilator, is the salient feature of endothelial dysfunction. Decreased
71 NO underlies insulin resistance by reducing insulin access to target cells [27]. Insulin has also to cross endothelial
72 cells to reach target tissues [28,29]. Hyperglycemia can lead to endothelial mitochondrial fragmentation and
73 increased production of reactive oxygen species (ROS) [30]. Increased endothelial ROS is associated with increased
74 breakdown of NO [31]

75 3 b) Sodium Hydrogen Exchangers

76 The sodium hydrogen exchangers (NHE) are trans-membrane ion channels that are responsible for intracellular
77 pH regulation through the extrusion of hydrogen in exchange with sodium influx [Fig. 1]. NHE exist in nine
78 isoforms ??41, ??2]. NHE1 is present on the surface of endothelium, vascular smooth muscle cells (VSMCs),
79 cardiomyocytes and platelets, while in case of renal tubular and intestinal epithelium NHE3 is encountered.
80 Activation of the NHE1 within endothelium, VSMCs, and cardiomyocytes may underlie microvascular and macro-
81 vascular complications of diabetes. It can also have a role in insulin resistance and systemic hypertension.
82 These exchangers cause increased sodium influx that stimulates sodium-calcium exchanger with consequent
83 increase of intracellular calcium. Within endothelium, increased cytoplasmic calcium inhibits eNOS and thus
84 decreases NO synthesis (Fig. 2). Increased intracellular calcium is also associated with increased intracellular and
85 mitochondrial activity of calpain, the cysteine protease, that can damage the inner mitochondrial membrane, a
86 process that ends with cell apoptosis ??43]. Activation of NHE1 in diabetic patients is a consequence of high
87 blood glucose, insulin, angiotensin, or adipokines ??44]. Endothelial NHE1 activation increases the influx of
88 calcium into the cytoplasm and mitochondria associated with increased calpain enzyme activity. These changes
89 lead to endothelial dysfunction and senescence. The development of systemic hypertension, increased insulin
90 resistance, diabetic retinopathy, nephropathy, and neuropathy are consequences of decreased eNOS activity
91 and accelerated endothelial senescence. It can also explain the increased frequency of vascular calcification,
92 peripheral vascular disease, and diabetic cerebrovascular dysfunction ??45]. Mitochondrial injury is associated
93 with impaired antioxidant defense ??46]. Inhibition of NHE1 using cariporide was associated with increased NO
94 release; eNOS activity simultaneously decreased ROS production, decreased nuclear factor-?B (NF-?B) activation
95 and decreased the production of tumor necrosis factor-? and intercellular adhesion molecule-1 ??47]. Increased
96 intracellular calcium induced by NHE1 isoform on the surface of cardiomyocytes leads to cardiac hypertrophy.
97 Peripheral coronary ischemia secondary to endothelial dysfunction can further activate cardiac NHE1. Active
98 NHE1 increases intracellular and intra-mitochondrial calpain that contributes to degeneration, apoptosis, and
99 fibrosis of myocardium [44] [Fig. 3]. Activation of renal NHE3 within PCT and ascending loop of Henle causes
100 sodium retention and can thus contribute to the development of systemic hypertension in diabetic patients ??44,
101 ??8] [Fig. 4]. Activation of NHE1 on the surface of platelets plays a significant role in platelet activation. This
102 effect is mediated through increased intracellular calcium and can contribute to the pro-coagulant state in diabetes
103 [49]. Accordingly, activation of NHE1 on the surface of endothelial cells, VSMCs, platelets, and cardiomyocytes

104 Increased oxidative stress is one of the metabolic disorders encountered in diabetes. Diabetic patients have
105 overproduction of free oxygen radicals and decreased wash out of these radicals. Increased production of free
106 oxygen radicals is the sequel to increased activity of nicotinamide adenine dinucleotide phosphate (NADPH)
107 oxidase [50,51], cyclo-oxygenase [52], and lipoxygenase [53] enzymes. Hyperglycemia stimulates all these enzymes.
108 Sodium-glucose cotransporter 2 (SGLT2) within the brush border of the proximal convoluted tubular epithelium
109 (PCT) is another pathway of free oxygen radicals' overproduction. Increased intracellular uric acid (UA) induces
110 NADPH oxidase [54]. Mitochondrial damage results in impaired antioxidant defense [55,56]. Increased free oxygen
111 radicals activate NF-?B [55]. When NF-?B is free from its inhibitor, it translocates from the cytoplasm to the
112 nucleus where it triggers the genes encoding transforming growth factor-?1 (TGF-?1), and monocyte chemo
113 attractant protein-1 (MCP-1) and Intercellular Adhesion Molecule 1 (ICAM1) [56][57][58]. Reactive oxygen
114 species (ROS) stimulate overproduction of protein kinase C (PKC) and mitogen-activated protein (MAP) kinase
115 within mesangial cells (MCs) and pericytes. All these factors stimulate overproduction of extracellular matrix
116 proteins [59].

117 **4 d) Uric acid**

118 Serum uric acid (UA) is a strong predictor for the development of proteinuria in T1DM patients. The risk for
119 proteinuria increases by 80% with every 1mg/dL rise in serum UA [60]. The risk of decline of glomerular filtration
120 rate (GFR) is significantly higher (2.4 folds) in T1DM patients with serum UA>6.6 mg/dL when compared with
121 candidates with lower level [61]. In T1DM patients followed-up for more than 18 years, serum UA was an
122 independent predictor of overt proteinuria [62]. In T2DM patients, 68% of the hyperuricemic versus 41.5% with
123 normal serum UA had diabetic nephropathy (DN) [63]. Further prospective studies confirmed the increased risk
124 of development of proteinuria and accelerated decline of GFR among hyperuricemic T2DM [64,65]. Serum UA>
125 7mg/dL in males and > 6mg/dL in females were associated with a higher rate of DN progression, and overall
126 mortality among T2DM patients that have the disease for fifteen years or more [66]. Treatment of T2DM
127 patients suffering DN and high serum UA with allopurinol was associated with a significant decrease of urine
128 albumin excretion (UAE) and serum creatinine and a significant increase of GFR over three years of follow-up
129 [67]. A recent metaanalysis of 19 randomized controlled trials has confirmed the significant favorable effect of
130 uratelowering therapy on the rate of GFR decline. These 19 trials enrolled 992 patients [68].

131 Increased level of Serum UA is associated with endothelial dysfunction. High mobility group box chromosomal
132 protein 1 (HMGB1) is a pro-inflammatory mediator synthesized and secreted by activated phagocytes or
133 monocytes. When secreted extracellular, HMGB1 can interact with the receptor for advanced glycation end
134 products (RAGE), inducing the production of multiple cytokines, and the induction of vascular adhesion molecules
135 [69]. In a recent in vitro study, high UA concentration inhibited eNOS expression and NO production in
136 human umbilical vein endothelial cells (HUEVCs), increased extracellular HMGB1 secretion, up-regulated RAGE
137 expression, activated NF-?B, and increased the level of inflammatory cytokines. Blocking RAGE significantly
138 suppressed the DNA binding activity of NF-?B and the levels of inflammatory cytokines [70]. HighserumUA is
139 also a significant predictor of systemic hypertension [71].

140 **5 e) Role of glucagon like peptide-1 receptor agonists (GLP- 141 1RA)**

142 Glucagon-like peptide-1 (GLP-1), is a peptide hormone secreted by the neuro-endocrine cells within the mucosa
143 of the small intestine [72]. In healthy individuals, GLP-1 activates insulin secretion, inhibits glucagon secretion
144 and slows gastric emptying and controls appetite [72]. The susceptibility of this peptide hormone to enzyme
145 breakdown by the dipeptidyl peptidase-4 enzyme (DPP-4) is responsible for the very short plasma half-life
146 of GLP-1. It cannot be used therapeutically except as continuous intravenous infusion [73]. GLP-1RA are
147 exogenous GLP-1 analogues with variable sequence similarity to the human GLP-1 [74]. The variability involved
148 mainly two sites in the GLP-1 molecule susceptible to cleavage by DPP4; namely, alanine and lysine at positions
149 8 and 34 respectively. These changes, beside other modifications, have helped to find out many peptides that
150 simulate GLP-1 action but with longer half-life [73]. GLP-1RAs were found to decrease body weight, and
151 some cardiovascular morbidity, without increasing the risk of hypoglycemia [75]. Robust indications for GLP-
152 1RAs in T2DM patients not responding to metformin monotherapy, dual therapy, or insulin include overweight,
153 inability to control appetite, high risk of cardiovascular disease, and the need of high doses of insulin [73].
154 The use of GLP-1 RAs can also lower systolic, and to a minor degree, diastolic blood pressure [76]. However,
155 long term use of GLP-1 RAs was frequently reported to be associated with increased heart rate [76, 77].
156 The current evidence does not support any beneficial effect of GLP-1RAs in patients with heart failure and/or
157 impaired ventricular function [78, 79]. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)
158 trial was the first cardiovascular outcome trial (CVOT) of GLP-1RAs in T2DM. Based on this trial, treatment
159 with lixisenatide in addition to conventional therapy had no impact on the cardiovascular risk in patients with
160 T2DM and recent acute coronary syndrome [80]. In the Liraglutide Effect and Action in Diabetes: Evaluation of
161 Cardiovascular Outcome Results (LEADER) trial, that appeared in 2016, liraglutide use significantly decreased
162 mortality from any cause and cardiovascular events in patients with T2DM at high risk for cardiovascular events.
163 The benefit of liraglutide treatment is more prounced patients with eGFR <60 mL/min/1.73 m² and patients

7 G) SODIUM GLUCOSE CO-TRANSPORTERS INHIBITORS

164 aged 50 years or more. In spite of these benefits, hospitalization rate for heart failure was not different between
165 liraglutide and placebo groups ??81]. Although the incidence of

166 6 f) Dipeptidyl peptidase 4 inhibitors

167 The discovery of non-enzymatic functions for DPP4 within the kidney has attracted the attention for the renoprotective
168 action of this hypoglycemic agent especially after disclosure of the antiproteinuric effect of saxagliptin
169 in T2DM patients during "Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes
170 Mellitus -Thrombolysis in Myocardial Infarction 53" (SAVOR-TIMI 53) trial ??87] ??88] ??89] ??90][91].
171 Experimental pharmacologic and genetic inhibition of DPP4 had also proven efficacy in preventing progressive
172 renal damage in animal models of acute and chronic kidney disease [92,93].

173 The glucose-lowering action of DPP4Is is through inhibition of breakdown of endogenous GLP and glucose-
174 dependent insulinotropic peptide (GIP). These incretins improve the sensitivity of pancreatic ? cells to glucose
175 [94]. DPP4 exists in 2 forms; membrane-bound and soluble forms [95]. Membranebound DPP4 is present on
176 the cell membrane of epithelial cells in the kidneys, lungs, and small intestine. It also exists on endothelial, and
177 immune cells [96][97][98]. DPP4 on the surface of immune cells is also known as cluster of differentiation 26
178 (CD26) [97,98]. The soluble form (sDPP4) is the consequence of shedding of the membrane-bound form. sDPP4
179 level increases in obese subjects and T2DM patients and may participate in increased insulin resistance in these
180 cases [99]. Membrane-bound DPP4 expression is triggered in case of hypoxia as well as its' shedding [100,101].

181 Within the kidney, DPP4 in S1-S3 segments of the proximal convoluted tubules (PCT) are linked to NHE3
182 and plays a role in salt and water retention through stimulation of this exchanger, NHE3 activity decreases on
183 inhibition of angiotensin II synthesis by captopril [102], or inhibition of DPP4 [103]. Angiotensin II inhibits
184 megalin receptor endocytosis protein expression. This process is reversed by DPP4Is [104]. Treatment with
185 DPP4 inhibitors may reverse reduced uptake of albumin and other low molecular weight proteins by PCT [105].
186 DPP4 was also discovered on the glomerular endothelium and the base of the foot processes of podocytes [106].
187 DPP4 is expressed on Tcells, B-cells, macrophages, and dendritic cells in the kidney [98]. Stimulation of DPP4 on
188 the surface of different immune and inflammatory cells may mediate inflammation within the kidney in diabetic
189 patients. DPP4Is decrease inflammation in diabetes. This finding suggests inflammation as an eminent player in
190 DPP4mediated kidney injury [107].

191 However, in spite of the reduction in urine albumin excretion observed in 3 randomized controlled studies
192 (RCT) in T2DM patients treated with DPP4Is [108][109][110], the only study that specifically looked for the
193 anti-proteinuric effect of linagliptin failed to find a significant impact [111]. Moreover, DPP4Is failed to have a
194 significant impact on doubling of serum creatinine, change in GFR, or ESRD [108][109][110]. On the other hand,
195 administration of linagliptin to T2DM patients that had renal dysfunction and were prescribed ACE inhibitors
196 or ARBs has led to additive significant reduction in albuminuria [112].

197 In normoglycemic milieu, microRNA-29 (miR29) suppresses DPP4 gene. In hyperglycemic state, this
198 suppression is lost. As a consequence, cell surface DPP4 activity increases [113]. In diabetic mice, activated
199 endothelial DPP4 induces phosphorylation of adjacent integrin ?1 on the surface of the endothelium. The
200 activated DPP4, together with the phosphorylated integrin ?1 form a complex that up-regulates TGF ? receptor
201 and activates the surface vascular endothelial growth factor receptor type 1(VEGFR1). Up-regulated TGF
202 ? receptor and VEGFR1 stimulate endothelialmesenchymal transition (EndMT) that increases transition to
203 fibroblasts with subsequent increased fibrogenesis [114] [Fig. 6]. However, the lack of significant impact of
204 DPP4Is on GFR in human studies would cast doubts on their favorable effect on renal fibrosis in humans.

205 The effect of DPP4Is treatment on the retina is debatable. While some investigators reported an increase
206 in retinal endothelial leakage and vascularity [115], others have reported a significant reduction in the risk of
207 diabetic retinopathy progression [116].

208 The lack of the expected favorable effect of DDP4Is on diabetic microvascular and macrovascular complications
209 of diabetes in spite of the proven molecular and experimental mechanisms can be attributed to potentiation of
210 the stem cell chemokine, stromal cell-derived factor-1 (SDF-1), which promotes inflammation, proliferation and
211 neovascularization ??117]. SDF-1 enhances atheromatous plaque growth and instability, cardiac inflammation,
212 and fibrosis [118]. The renal effects of DPP4Is are mainly through potentiation of SDF-1leading to podocyte
213 injury and glomerulosclerosis. SDF-1 also induces natriuresis in the distal tubules, contrary to SGLT2Is and
214 NHE3 inhibitors that act on PCT. Hence, SDF-1 cannot utilize tubuloglomerular feedback to modulate the
215 glomerular hyperfiltration ??117,119] [Fig. 7]. SDF-1 may also aggravate both retinopathy and neuropathy
216 ??117,120].

217 7 g) Sodium glucose co-transporters inhibitors

218 SGLT2Is constitute a recently introduced group that has insulin independent hypoglycemic effect. Three members
219 of this group, namely empagliflozin, canagliflozin, and dapagliflozin are FDA approved and are now used
220 worldwide. By inhibiting the upregulated SGLT2 co-transporters in the brush border of the S1 segment of
221 the PCT, SGLT2Is can reduce the renal threshold for plasma glucose from 196 to 22 mg/dL, thereby enhancing
222 urinary excretion of glucose [121]. They also increase distal sodium delivery and hence distal tubular sodium
223 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, reverses hyperfiltration, and accordingly reduces renal injury [Fig. ??]. In addition, SGLT2Is exert other beneficial effects, including reductions in body weight, serum UA, and blood pressure ??[22]. Excess glucose within the tubular lumen triggers the uric acid transporter GLUT9 within the S3 segment of the PCT and in the collecting duct to excrete UA in exchange with glucose [123]. The antihypertensive effect of SGLT2Is is related to volume depletion, loss of body weight, inhibition of endothelial NHE1 and renal NHE3, and reduction in serum UA ??[21]. DPP-4=dipeptidyl peptidase; TGF= transforming growth factor; EndMT= endothelial mesenchymal transition.

SGLT2Is not only decrease serum UA but they can decrease intracellular fructose metabolism and UA synthesis in the PCT epithelium [124]. Intracellular UA is pro-oxidant. It stimulates NADPH oxidase enzyme activity with consequent increase in production of ROS. This leads to premature senescence of these cells, activation of the renin-angiotensin system, epithelialmesenchymal transition, and activation of the inflammatory cascade through activation of NF-?B [125][126][127] [Fig. 5]. 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 [128,129] [Fig. ??]. SGLT2Is also dampen 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 [130]. Moreover, fibrotic and inflammatory genes are suppressed within the diabetic kidney by SGLT2Is [131,132]. 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 [133]. 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 three fold [134].

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/1.73m². The median observation time in EMPA-REG trial was 3.1 years [135]. In comparison, losartan treatment of similar population having DN has led to a 28% delay in the onset of ESRD during a mean follow-up of 3.4 years [136]. Empagliflozin treatment resulted in 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 [137]. The favorable outcome of SGLT2Is is attributable to their effect on glomerular hyperfiltration, blood pressure, body weight, and serum UA in diabetic patients [137][138][139]. 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 [140][141][142]. Decreased renal blood flow induced by SGLT2Is is related to tubuloglomerular feedback and not related to the renin-angiotensin system (RAS) blockade. Empagliflozin and dapagliflozin increase plasma aldosterone and angiotensin II [143,144], together with increased activity of urinary angiotensin converting enzyme and angiotensin converting enzyme2 [145].

2-years treatment of T2DM patients (total of 1450 cases) already kept on metformin with either once-daily canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride titrated to 6-8 mg resulted in eGFR decline by 0.5, 0.9, and 3.3mL/min/1.73m² /year respectively (P<0.01 for each canagliflozin group versus glimepiride) in spite of comparable reductions in HbA1c. 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 [146]. Contrary to DPP4Is and sulfonylurea as 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 [147]. In the Canagliflozin Cardiovascular Assessment Study (CANVAS), 10 142 T2DM patients were assigned to canagliflozin or placebo. 34% of the patients had ?? risk factors for cardiovascular events but had no history of previous cardiovascular event (primary prevention cohort), while the remaining 66% had a positive history of cardiovascular event (secondary prevention cohort). The patients were randomly assigned in a ratio of 1:1:1 to either canagliflozin 100 mg, canagliflozin 300 mg or matching placebo. 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 [148,149]. 17,160 T2DM patients, including 6,974 with atherosclerotic cardiovascular disease, were assigned for 10 mg Dapagliflozin or placebo 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. The renal composite endpoint (?40% decrease in estimated glomerular filtration rate to <60 mL per minute per 1.73 m² of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) decreased by 24% in the Dapagliflozin group [150]. When patients with previous myocardial infarction (n = 3,584) were specifically looked for, adverse cardiovascular events were 16% less in the dapagliflozin arm [151]. According to these studies, SGLT2Is should be prescribed aiming at cardiovascular protection in patients with T2DM and ASCVD [152].

8 H) FREE OXYGEN RADICALS SCAVENGERS

287 T2DM patients suffering CKD and albuminuria (4400 patients) were randomly assigned to receive
288 canagliflozin100 mg daily or placebo in 1:1 ratio. All the patients had an eGFR of 30 to <90 mL/minute/1.73 m
289 2 and albuminuria (urine albumin/creatinine ratio>300 to 5000 mg/gm) that were receiving RAS blockers. The
290 primary outcome was a composite of ESRD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/
291 1.73 m²), a doubling of the serum creatinine, or death from renal or cardio-vascular causes. The projected
292 duration of the study was 5.5 years. Investigators of this study prematurely terminated the trial after a planned
293 interim analysis on the recommendation of the data and safety monitoring committee. This analysis has shown
294 a highly significant reduction of the primary composite endpoint by 34% in patients treated with canagliflozin
295 after 2.6 years of treatment. Patients in the canagliflozin group also had a lower risk of ESRD, hospitalization for
296 HF, and the composite of CV death, myocardial infarction, or stroke. These results indicate that canagliflozin
297 may be an effective treatment for renal and cardiovascular protection in T2DM patients suffering CKD [153].
298 The observed benefits were obtained mainly in patients whose basal eGFR was between 30 mL/min/1.73 m²
299 . In addition, these findings were observed despite very modest differences in blood sugar, weight, and blood
300 pressure between the placebo and the active treatment groups. This suggests that the mechanism of benefit is
301 independent of glycemic control and is likely related to the reduction in single nephron hyperfiltration related to
302 NHE3 inhibition.

303 The more recent results of the DECLARE -TIMI 58 have supported the favorable effects of SGLT2Is. In this
304 last mentioned trial, 17160 type 2 DM patients were studied using dapagliflozin 10 mg versus placebo in 1:1 ratio
305 for 4.2 years. 47.6% of these patients had GFR >90, 45.1% had GFR between 60 and 90, while only 7.4% of the
306 patients had GFR < 60 mL/min/1.73m² . In addition, more than two thirds of the patients had normal urine
307 albumin excretion. Contrary to CREDENCE trial patients where all patients were prescribed RAS blockers, only
308 81.3% of DECLARE study patients were on RAS blockers. The pre specified composite cardio-Renal end points
309 (sustained decline of at least 40% in eGFR to less than 60 mL/min/1.73m², end-stage renal disease (defined as
310 dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15mL/min per 1.73 m²),
311 or death from renal or cardiovascular causes were significantly reduced by 24% in the dapagliflozin group while
312 the prespecified composite renal end points (excluding the cardiovascular causes of death from the cardio-renal
313 composite endpoints) decreased by 47%, and the chance to develop ESRD decreased by 56% in the dapagliflozin
314 group. The significant impact of dapagliflozin was encountered in patients having baseline GFR >90, between
315 60 and 90, in normoalbuminuric patients, in patients with microalbuminuria and in those with overt proteinuria.
316 We would like to emphasize that these favorable effects were only encountered in patients already maintained on
317 either ACE inhibitors or ARBs [154].

318 8 h) Free oxygen radicals scavengers

319 Many preclinical studies have overwhelmed the role of reactive oxygen species (ROS) in the pathogenesis of
320 diabetic complications. However, the less favorable outcomes of different antioxidants to prohibit the development
321 or progression of diabetic complications in large clinical trials have dampened the enthusiasm for the use of
322 antioxidant agents in diabetes [155]. Clinical studies using vitamin A, C, and E as antioxidant agents in
323 pre-diabetic and T2DM patients were disappointing. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a
324 transcription factor that protects and restores cell homeostasis upon activation. Although Nrf2 is activated in
325 response to hyperglycemia, this activation does not reach the sufficient level capable to combat the oxidative
326 stress fueled by hyperglycemia [156]. Insufficient Nrf2 activity is often associated with the pathogenesis of
327 diabetes and its complications [157]. Natural products can activate Nrf2, as a potential therapeutic target to
328 control diabetic complications [157,158]. Cruciferous vegetables, grapes, buckwheat, black tea, citrus fruits, apple
329 peels, cinnamon, turmeric, Berberis Mahonia plant, kiwi fruits, the climbing plant Sinomenium acutum, garlic,
330 and Bitter Melon are rich sources of different natural Nrf2 activators [159][160][161][162].

331 Consumption of 10 gms of broccoli sprouts powder, a rich source of sulforaphane, daily for four weeks was
332 associated with significant improvement in insulin resistance in sixty-three T2DM patients [163]. In a double-
333 blind trial in T2DM patients, the study candidates consumed oral 2×5 mg resveratrol (resveratrol group) or a
334 placebo (control group) for four weeks. Resveratrol significantly decreased insulin resistance, and urine ortho-
335 tyrosine/creatinine ratio as an index of ROS production [164]. A more recent study of ten T2DM subjects,
336 daily consumption of 3 grams of resveratrol for 12 week has increased skeletal muscle Sirtuin1 and adenosine
337 monophosphate kinase enzymes expression. These findings can further support the insulin sensitizing effect of
338 resveratrol [165]. On the other hand, resveratrol supplementation over five weeks in fourteen T2DM patients
339 already kept on diet control did not have a significant effect on glycemic control [166].

340 In seventy-five patients undergoing primary cardiovascular disease prevention, resveratrol-rich grape supplement
341 significantly decreased high-sensitivity C-reactive protein, tumor necrosis factor-?, plasminogen activator
342 inhibitor type 1, and increased anti-inflammatory interleukin-10. The authors concluded that 1-year consumption
343 of a resveratrol-rich grape supplement improved the inflammatory and fibrinolytic activities in high cardiovascular
344 risk and diabetic patients [167]. The beneficial anti-inflammatory effect of resveratrol-rich grape supplement was
345 further supported in a later study of 35 T2DM male patients. One-year consumption of resveratrol-rich grape
346 supplement down-regulated the expression of pro-inflammatory cytokines in circulating mononuclear cells [168].
347 However, a more recent and larger study failed to prove a significant impact of low (40 mg/day) and high
348 doses (500 mg/day) used for 6 months on fasting blood sugar, glycated hemoglobin or c-reactive protein [169].

349 When 36 dementia-free, T2DM 49-78 years old patients consumed single doses of synthetic trans-resveratrol (75,
350 150 and 300 mg) at weekly intervals, trans-cranial Doppler ultrasound both before and 45 min after treatment
351 had shown that only the 75 mg dose was efficacious to improve the cerebral vasodilator responsiveness in both
352 middle and posterior cerebral arteries [170]. In addition, a single 75 mg dose of resveratrol was found to improve
353 neurovascular coupling and cognitive performance in Thirty-six T2DM adults aged 40-80 years [171]. A more
354 recent study has shown that a daily 100mg resveratrol supplementation for twelve weeks in 50 T2DM patients
355 was associated with a significant decrease of arterial stiffness estimated by cardio-ankle vascular index [172].

356 When the endothelial function was assessed using digital volume plethysmography to measure the changes
357 in the reflective index, oral intake of curcumin 150 mg twice daily for eight weeks has lead to a significant
358 improvement in endothelial function [173]. Supplementation of twenty T2DM patients suffering overt proteinuria
359 with 22mg of curcumin three times daily for two months significantly decreased urinary protein excretion and
360 urine IL-8 beside serum levels of TGF- β and IL-8 [174]. Curcumin 500 mg three times daily was administered for
361 nine months to 120 pre-diabetic patients and significantly improved insulin resistance and beta cell function with
362 consequent prevention of diabetes [175]. Further studies supported the favorable anti-diabetic effect of curcumin
363 [176][177][178].

364 **9 i) Recommendations of diabetes associations**

365 In October 2018, the European Association for the Study of Diabetes (EASD) and the American Diabetes
366 Association (ADA) issued an updated consensus statement on management of hyperglycemia in T2DM patients.
367 This consensus showed-up during the annual meeting of EASD in Berlin, Germany. In this consensus, patients
368 with clinical CV disease should receive one of SGLT2Is or GLP-1RAs, while in patients with CKD or clinical
369 HF and ASCVD, SGLT2Is should be considered [179]. The choice of diabetes therapies as recommended by the
370 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) must
371 be individualized based on many attributes including the risk reduction in heart and kidney disease [180].

372 **10 j) Novel markers of Diabetic complications**

373 Mannose-binding lectin (MBL) is a recognized protein of the innate immune system. It is composed of a lectin
374 (carbohydrate-binding) moiety attached to a collagenous moiety. MBL binds to a wide range of sugars that
375 permits MBL to interact with a wide range of viruses, bacteria, yeasts, fungi, and protozoa containing such
376 sugars within their cell walls or membranes. When bound to its target sugar moiety, MBL can activate the
377 complement system in the classic pathway or in C1-independent manner [181]. MBL is independently associated
378 with HbA1c among diabetic patients [182]. MBL is involved in complement activation within the diabetic kidney
379 [183] and was discovered as a possible independent predictor of DR, DN and other vascular complications in type
380 1 and type 2 diabetes [184][185][186][187][188][189].

381 In 297 newly diagnosed T2DM patients, serum fibrinogen was a strong predictor for DN [190]. Serum
382 Adiponectin was proved as a strong predictor of DN in both type 1 and type 2 diabetic patients according
383 to a recent meta-analysis of 13 studies of more than five thousand cases [190].

384 **11 II.**

385 **12 Discussion**

386 Diabetic complications pose a massive public health and economic burden. The introduction of GLP1RAs,
387 DPP4Is, and SGLT2Is has revived the hope to effectively prevent or slow down the rate of progression of
388 these complications. These hypoglycemic agents have, in addition, a favorable effect on body weight with less
389 likelihood to experience hypoglycemia. In parallel with their evolving evidence of CV and renal protective
390 effects, ADA recommended SGLT2Is as second-or thirdline antihyperglycemic treatment [191]. The updated
391 consensus statement on management of hyperglycemia in type 2 diabetes issued by EASD and ADA has also
392 recommended the early introduction of SGLT2Is and GLP1RAs to diabetic patients with clinical CV disease
393 and SGLT2Is to patients with CKD or clinical HF and ASCVD. These recommendations were founded on the
394 accumulating evidence of the significant impact of these agents in secondary prevention. The lack of similar
395 significant impact in primary prevention is likely related to the relatively short duration of CVOTs. The most
396 famous primary prevention trial in T2DM patients is UKPDS. It took ten years after the end of this study to get
397 significant differences in acute myocardial infarction and overall mortality between intensive therapy group and
398 the standard of care group [192]. In spite of the significant renoprotective effect of canagliflozin in CREDENCE
399 trial in the whole studied group, patients with eGFR ≥ 60 mL/min/1.73 m² and patients with UAE ≥ 1000 mg/gm
400 creatinine failed to get the expected benefit [153]. The planned duration of this study was 5.5 years. However,
401 the study was prematurely terminated according to the observed significant difference in the composite endpoints
402 between the 2 arms in the whole group. Given the known long duration of stage 4 DN, the short duration of
403 this study was not enough for patients recruited with eGFR ≥ 60 mL/min/1.73 m² and patients with UAE
404 ≥ 1000 mg/gm creatinine to develop enough number of primary endpoints. The rate of decline of GFR in DN
405 patients is around 6mL/min/1.73m² [146]. The more recent results of the DECLARE -TIMI 58 did support
406 this view. This last mentioned trial continued for 4.2 years. In this study, the significant impact of dapagliflozin

12 DISCUSSION

407 was encountered in patients having baseline GFR >90, between 60 and 90, in normoalbuminuric patients, and in
408 patients with microalbuminuria. These favorable effects in patients of DECLARE study are likely related to the
409 relatively longer duration of follow-up [154]. Taking these results into account and according to the accumulating
410 evidence, more energetic primary preventive studies should be designed. These new studies should select newly
411 diagnosed diabetic patients that have laboratory markers of likelihood to develop diabetic nephropathy later
412 during the future course of their disease. The main obstacle for such studies is the duration needed to have
413 enough number of endpoints for adequate statistical analysis. Such long duration may lend such studies very
414 costly and very exhaustive. Given the safety and noninferiority of SGLT2Is, GLP1RAs, and DPP4Is, and the
415 highlighted beneficial effects of these agents, we suggest a more reproducible approach to manage T2DM patients.
416 In addition to T2DM patients with clinical CV disease, and those with ASCVD, patients with high cardiovascular
417 risk should be prescribed SGLT2Is as second-line hypoglycemic agent after metformin. RAS blockers should be
418 additionally added to guarantee optimum benefit. In the case of morbid obesity, inability to control food avidity
419 or hyperglycemia, GLP1RAs can be used instead of SGLT2Is. In case of failure of SGLT2Is to achieve the
420 glycemic target, either DPP4I or GLP1RA should be added as the third-line agent. SGLT2I can be added on
421 top of GLP1RA if the later failed to achieve the glycemic target. Routine screening of diabetic patients for
422 likelihood to develop diabetic nephropathy using the early predictors like serum MBL, fibrinogen, or adiponectin
423 can help to select patients prone to develop diabetic nephropathy. These patients should be prescribed SGLT2Is
424 to prevent the development of the disease instead of waiting until they develop albuminuria. This primary
425 prevention approach can completely abort the development of DN instead of the current secondary prevention
that just postpones the event for few months or years.

¹

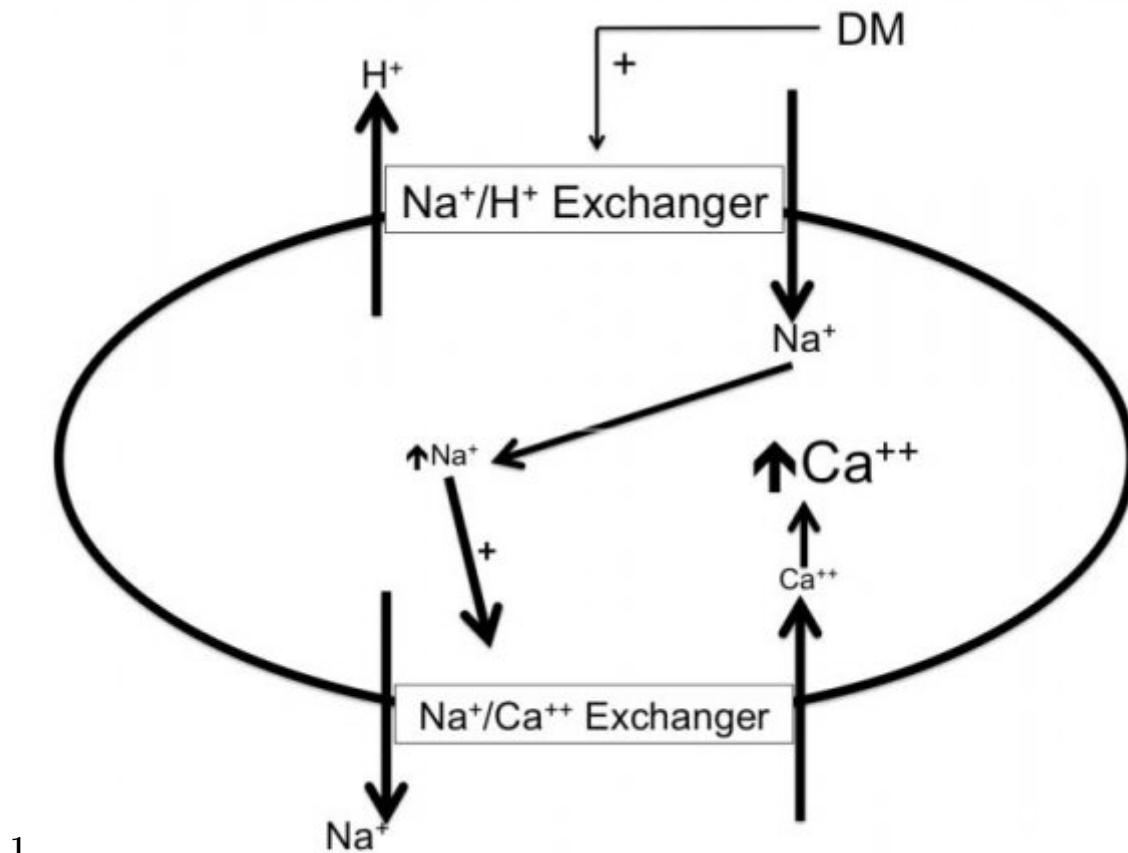


Figure 1: Fig. 1 :

426

¹Should We Change the Therapeutic Algorithm of Type 2 Diabetes Based on Accumulating Evidence?

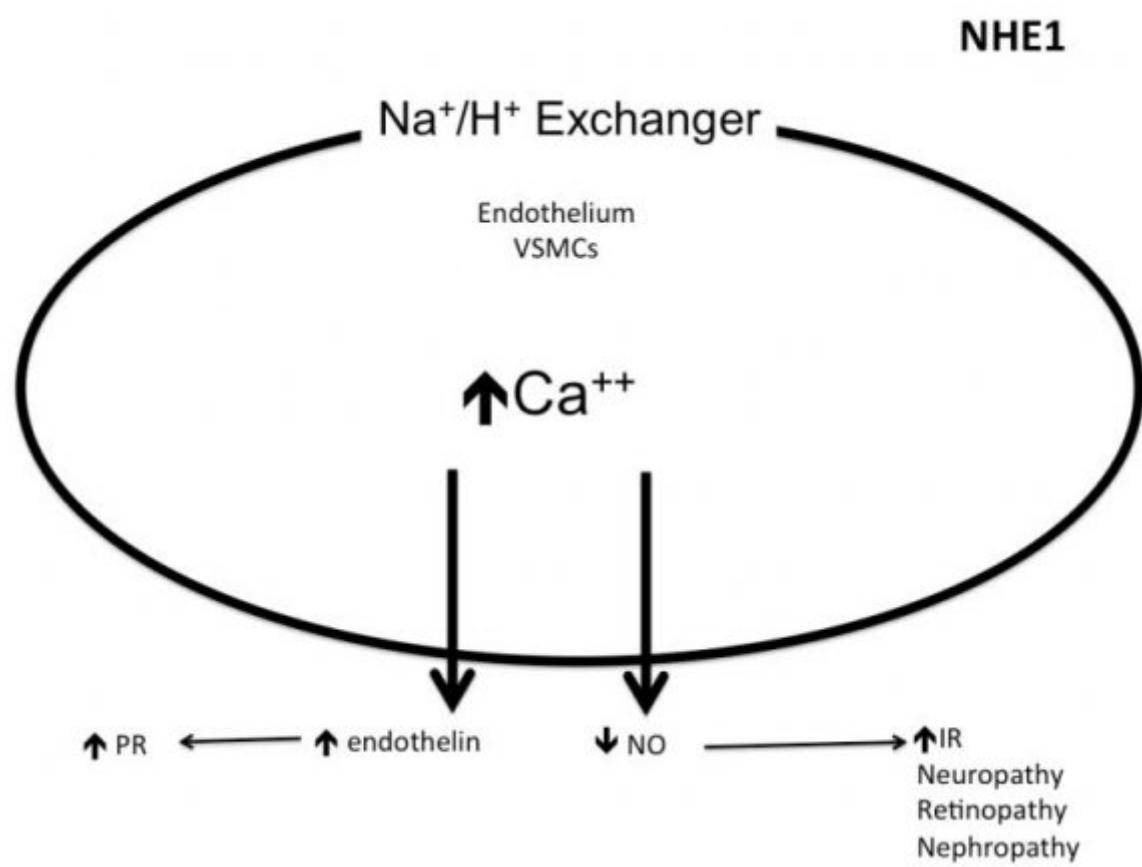


Figure 2: Fig. 2 :

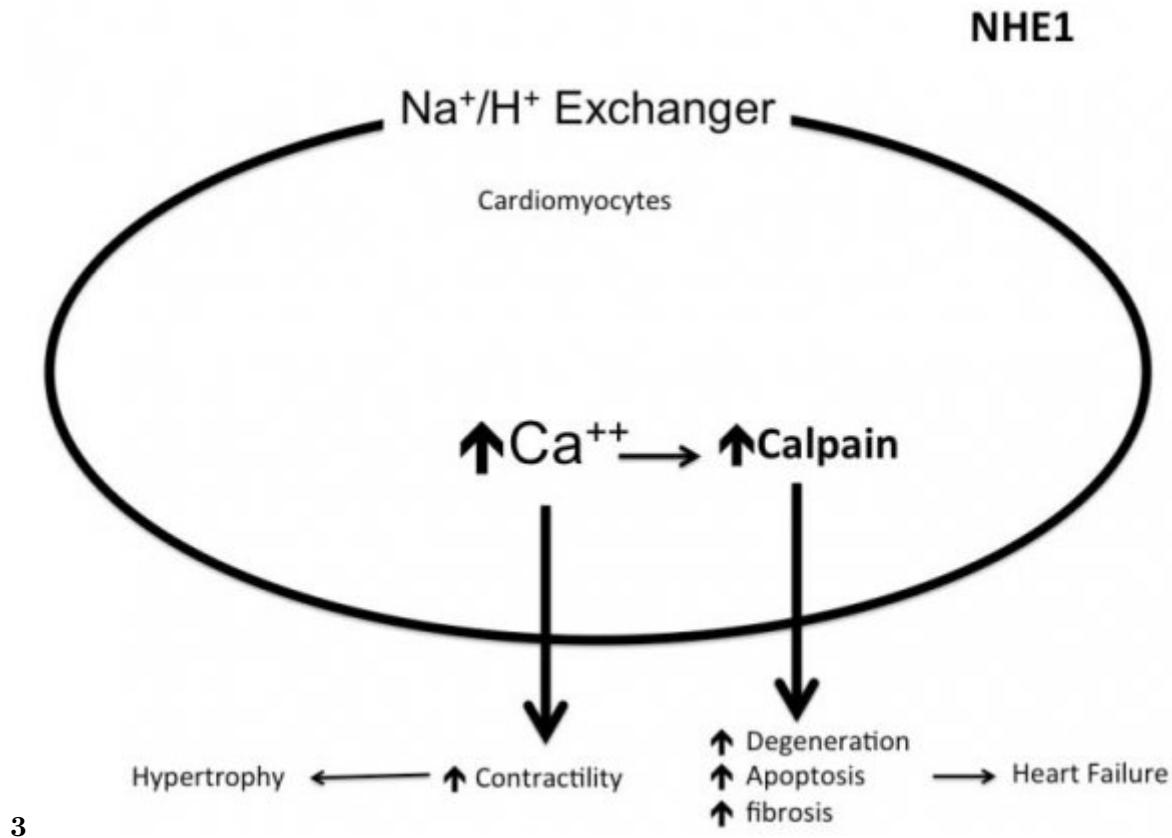


Figure 3: Fig. 3 :

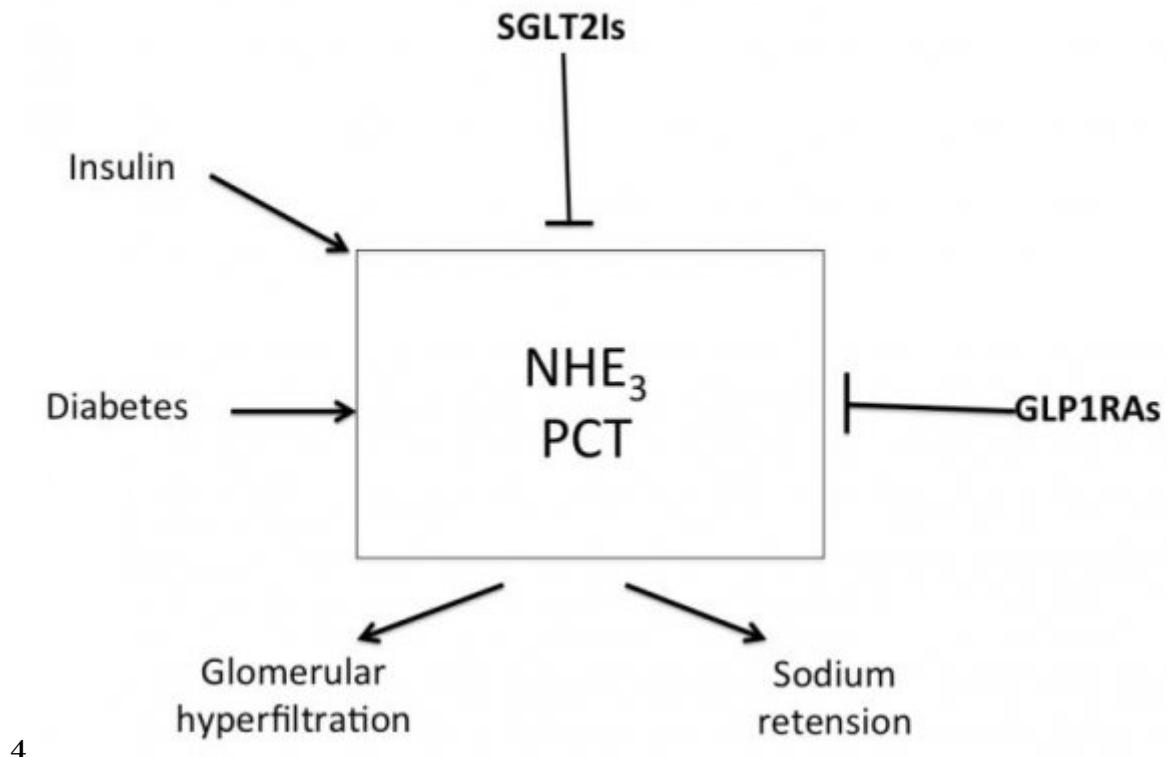
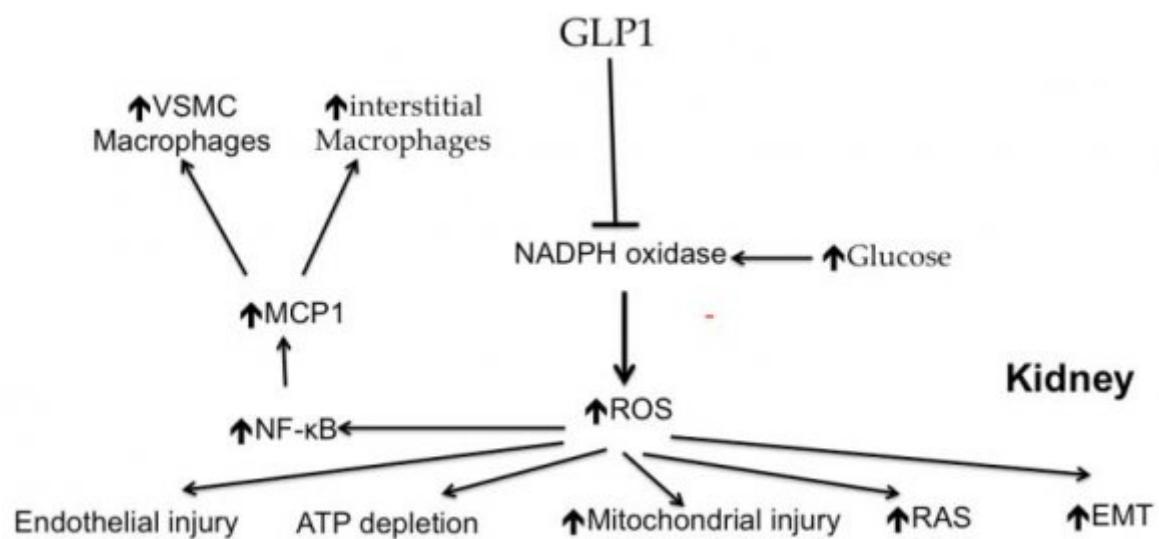
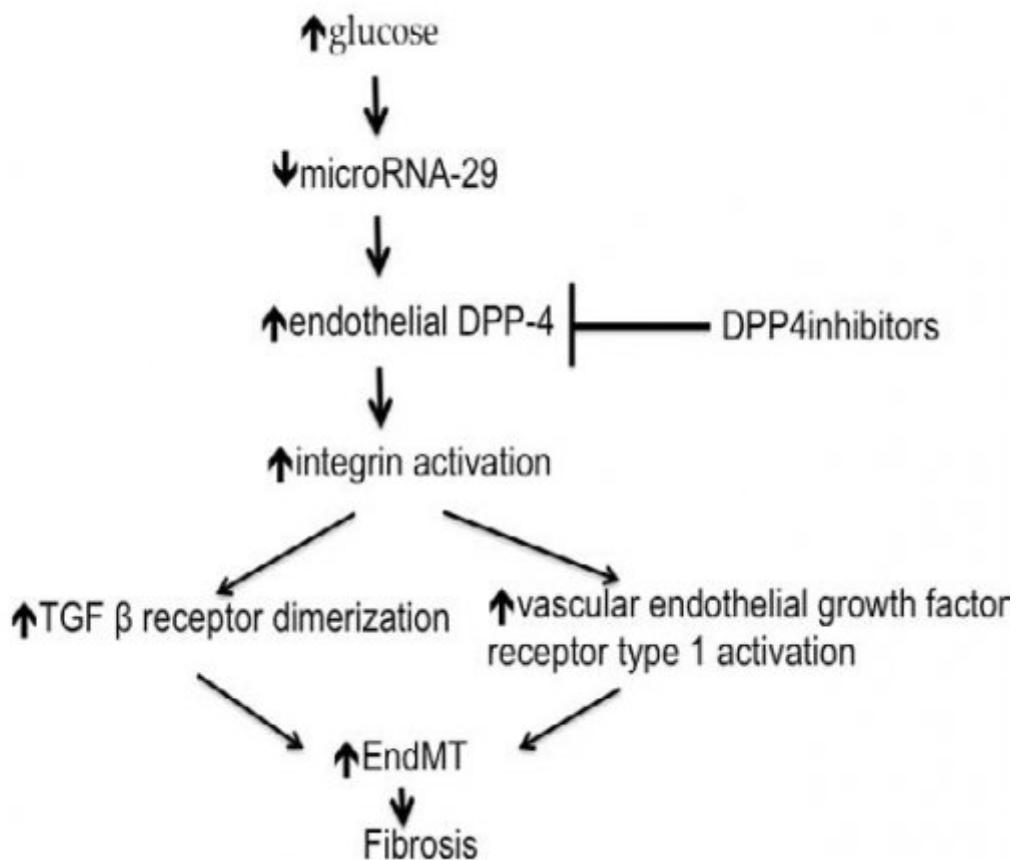


Figure 4: Fig. 4 :



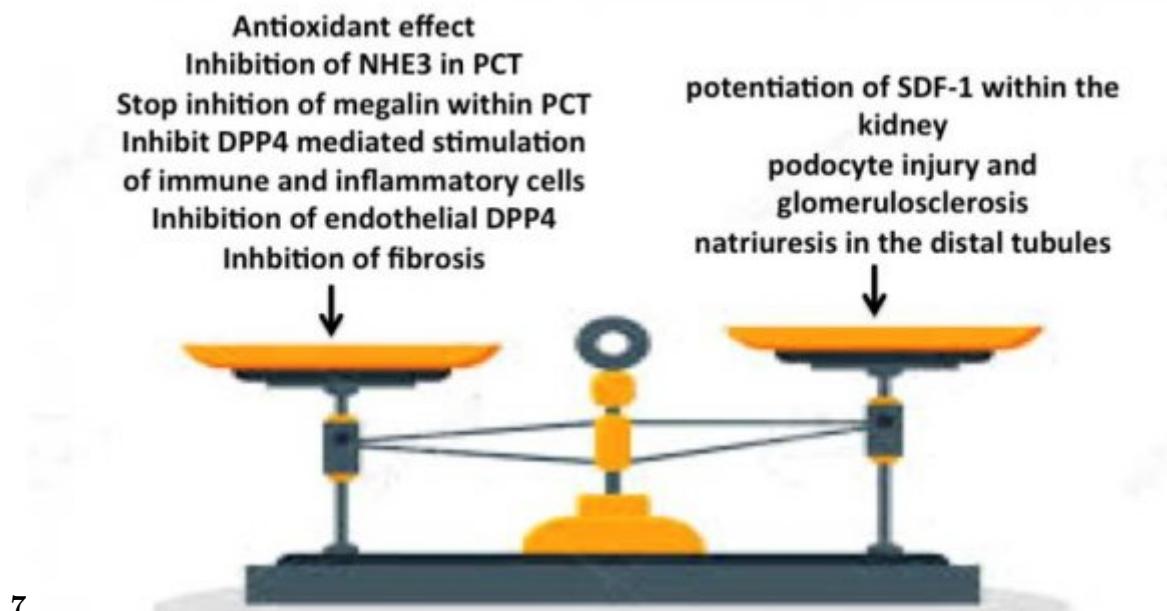
5

Figure 5: Fig. 5 :



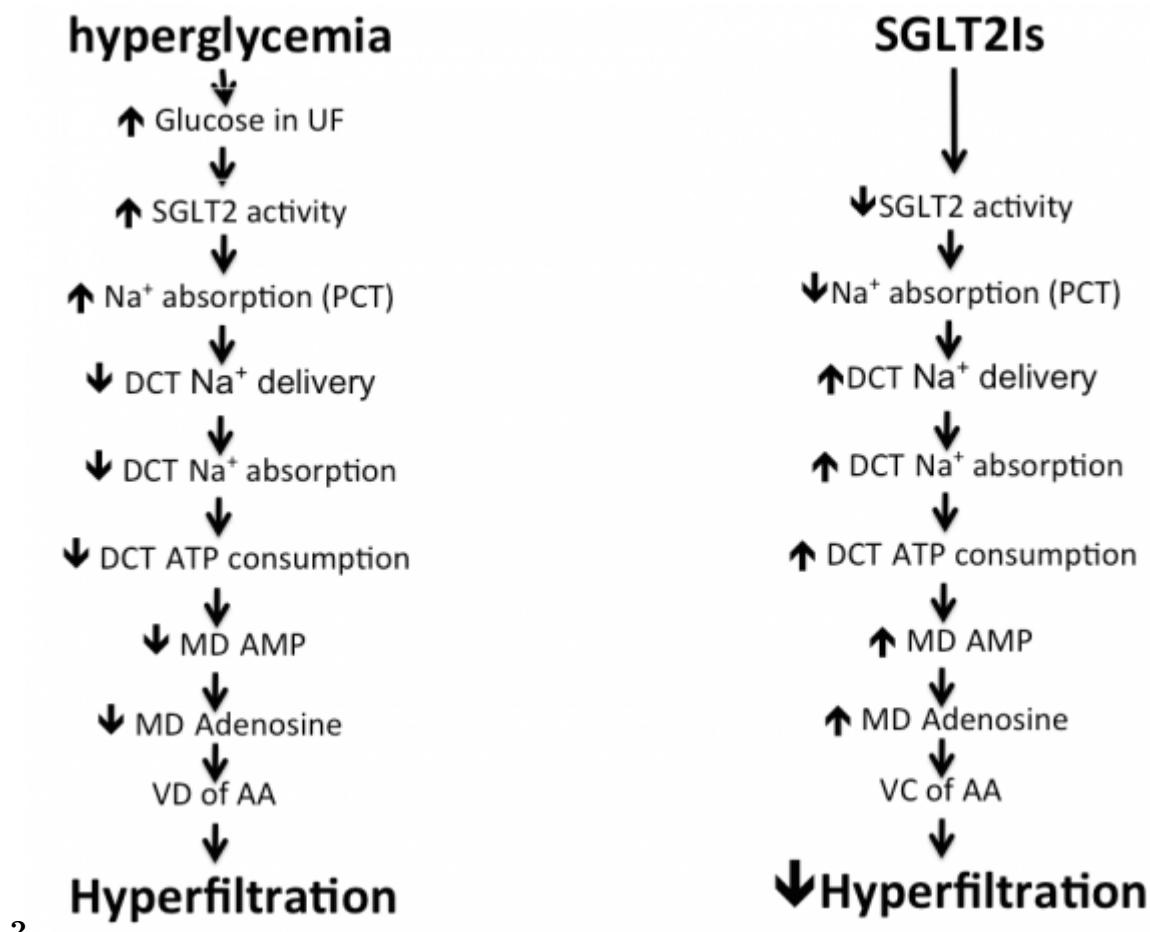
6

Figure 6: Fig. 6 :



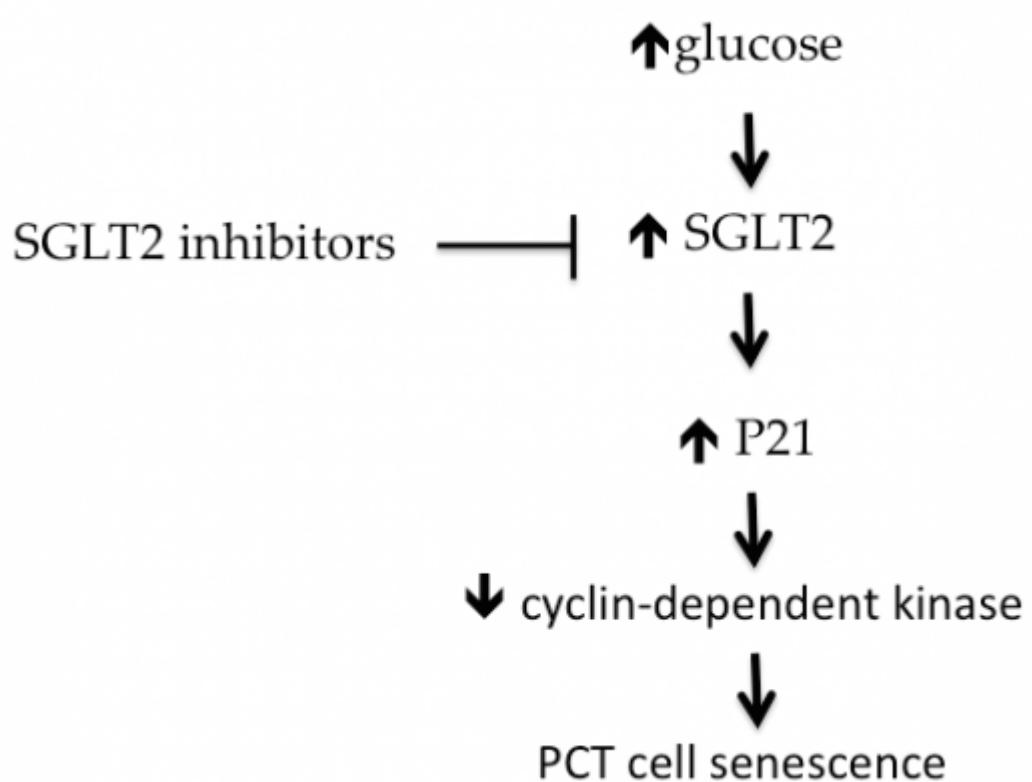
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Figure 7: Fig. 7 :



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Figure 8: kinase 2 .



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Figure 9: Fig. 9 :Fig. 8 :

endothelial dysfunction via calcium-dependent 66. Bartáková V, Kuricová K, Pácal L, Nová Z, calpain. *Cardiovasc Res.* 2008 Nov 1; 80(2): 255-62. 44. Packer M. 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.* 2017 Oct 17; 136(16): 1548-1559. Dvořáková V, Vrbaová M, et al., hyperuricemia: 3-year randomized parallel-45. Katusic Z S, Austin S A. Neurovascular Protective Function of Endothelial Nitric Oxide controlled study. *Clin Endocrinol (Oxf).* 2015 Oct; -Recent 83(4): 475-82. Advances. *Circ J.* 2016 Jun 24; 80(7): 1499-503. 46. Alves-Lopes R, Neves K B, A C, Harvey A, Carneiro F S, Touyz R M et al. Internal pudendal artery dysfunction in diabetes mellitus is mediated by NOX1-derived ROS-, Nrf2-, and Rho kinase-dependent mechanisms. *Hypertension.* 2016; 68: 1056-64. 47. Wu S1, Gao X, Yang S, Liu L, Ge B, Yang Q. Protective effects of cariporide on endothelial dysfunction induced by homocysteine. *Pharmacology.* 2013; 92 (5-6): 303-9. 48. Packer M. 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.* 2017 Dec 11. 68. Kanji T, Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. *PLoS One.* 2014 Dec 1; 9(12): e114259. 72. Vilsbøll T, Holst J J. Incretins, insulin secretion and type 2 diabetes mellitus. *Diabetologia.* 2004 Mar; 47(3): 357-366. 73. Kalra S Glucagon-like peptide-1 receptors agonists (GLP1 RA). *J Pak Med Assoc.* 2013 Oct; 63(10): 1312-5. 74. Ross S A, Ekoé J M. Incretin agents in type 2 diabetes. *Can Fam Physician.* 2010 Jul; 56(7): 639-48. 75.

Arterioscler Thromb Vasc Biol. 2011; 32(2): 467-473. 33. Liu J, Jahn L A, Fowler D E, Barrett E J, Cao W, Liu Z. Free fatty acids induce insulin resistance in both cardiac and skeletal muscle microvasculature in humans. *J Clin Endocrinol Metab.* 2011; 96(2): 438-446. 34. Rask-Madsen C, Li Q, Freund B, Feather D, Abramov R, Wu I H, et al., Loss of insulin signaling in vascular endothelial cells accelerates atherosclerosis in apolipoprotein E null mice. *Cell Metab.* 2010; 11(5): 379-389. 35. Tremolada G, Del Turco C, Lattanzio R, Maestroni S, Maestroni A, Bandello F, et al., The role of angiogenesis in the development of proliferative diabetic retinopathy: impact of intravitreal anti-VEGF treatment. *Exp Diabetes Res.* 2012; 10.1155/2012/728325 36. Satchell S C. The glomerular endothelium emerges as a key player in diabetic nephropathy. *Kidney Int.* 2012; 82(9): 949-951. 37. Stirban A Microvascular dysfunction in the context of diabetic neuropathy. *Curr Diab Rep.* 2014; 14(11): 541. 38. Exalto L G, Whitmer R A, Kappele L J, Biessels G J. An update on type 2 diabetes, vascular dementia and Alzheimer's disease. *Exp Gerontol.* 2012; 47(11): 858-864. 39. Kanetsuna Y, Takahashi K, Nagata M, Gannon M A, Breyer M D, Harris RC, et al., Deficiency of endothelial nitric-oxide synthase confers susceptibility to diabetic nephropathy in nephropathy-resistant inbred mice. *Am J Pathol.* 2007, 170: 1473-1484. 40. Zhao H J, Wang S, Cheng H, Zhang M Z, Takahashi deficiency produces accelerated nephropathy in diabetic mice. *J Am Soc Nephrol.* 2006, 17: 2664-2669. 41. Huber J D, Bentzien J, Boyer S J, Burke J, De Lombaert S, Eickmeier C, et al., Identification of a potent sodium hydrogen exchanger isoform 1 (NHE1) inhibitor with a suitable profile for chronic T, Fogo A B, et al., Endothelial nitric oxide synthase

427 .1 Conflict of Interest

428 The authors have nothing to declare.

429 [Apr-Jun] , Apr-Jun . 5 p. .

430 [Neal et al.] , B Neal , V Perkovic , K W Mahaffey , De .

431 [Am J Physiol Endocrinol Metab ()] , *Am J Physiol Endocrinol Metab* 2011. 300 (1) p. .

432 [Pharmacol Res (2013)] , *Pharmacol Res* 2013 Jun. 72 p. .

433 [Diabetes Mellitus -epidemiology. World health organization Global report on diabetes ()] , *Diabetes Mellitus -*
434 *epidemiology. World health organization Global report on diabetes* 2016.

435 [Diabetes. N Engl J Med (2017)] , *Diabetes. N Engl J Med* 2017 Aug 17. 377 (7) p. .

436 [Biomed Res Int ()] , *Biomed Res Int* 2017. 2017. p. 4391920.

437 [Chang et al. (2015)] ‘+)/H(+) exchanger in the regulation of platelet activation and paradoxical effects of
438 cariporide’. H B Chang , X Gao , R Nepomuceno , S Hu , Sun Dna . *Exp Neurol* 2015 Oct. 272 p. .

439 [Holman et al. ()] ‘10-year follow-up of intensive glucose control in type 2 diabetes’. R R Holman , S K Paul , M
440 A Bethel , D R Matthews , Haw Neil . *N Engl J Med* 2008. 359 p. .

441 [Othman et al. ()] ‘12/15-Lipoxygenase-derived lipid metabolites induce retinal endothelial cell barrier dysfunction:
442 Contribution of NADPH oxidase’. A Othman , S Ahmad , S Megyerdi . *PLoS One* 2013. 8 p. e57254.

443 [Davies et al. (2018)] ‘A consensus report by the American Diabetes Association (ADA) and the European
444 Association for the Study of Diabetes (EASD)’. M J Davies , D ’alessio , D A Fradkin , J Kernan , W
445 N Mathieu , C . *Diabetologia* 2018. 2018 Dec. 61 (12) p. . (Management of hyperglycaemia in type 2 diabetes)

446 [Das et al. ()] ‘ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction
447 in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American
448 College of Cardiology Task Force on Expert Consensus Decision Pathways’. S R Das , B M Everett , K K
449 Birtcher , J M Brown , W T Cefalu . *J Am Coll Cardiol* 2018. 2018. 72 p. .

450 [Packer (2017)] *Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the
451 Pathophysiology and Treatment of Diabetes Mellitus with That of Heart Failure*, M Packer . 2017 Oct 17.

452 [Matzinger et al. (2017)] ‘Activation of Nrf2 signaling by natural products-can it all evade diabetes?’. M
453 Matzinger , K Fischhuber , E H Heiss . S0734-9750. *Biotechnol Adv* 2017 Dec 28. 17 p. .

454 [Wong et al. (2016)] ‘Acute Resveratrol Consumption Improves Neurovascular Coupling Capacity in Adults with
455 Type 2 Diabetes Mellitus’. R H Wong , D Raederstorff , P R Howe . pii: E425. *Nutrients* 2016 Jul 12. 8 (7) .

456 [Thazhath et al. (2016)] ‘Administration of resveratrol for 5 wk has no effect on glucagonlike peptide 1 secretion,
457 gastric emptying, or glycemic control in type 2 diabetes: a randomized controlled trial’. S S Thazhath , T
458 Wu , M J Bound , H L Checklin , S Standfield , K Jones . *Am J Clin Nutr* 2016 Jan. 103 (1) p. .

459 [White et al. ()] ‘Alogliptin after acute coronary syndrome in patients with type 2 diabetes’. W B White , C P
460 Cannon , S R Heller , S E Nissen , R M Bergenstal , G L Bakris . *N Engl J Med* 2013. 369 p. .

461 [Shenouda et al. ()] ‘Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus’.
462 S M Shenouda , M E Widlansky , K Chen , G Xu , M Holbrook , C E Tabit . *Circulation* 2011. 124 (4) p. .

463 [De Cosmo et al. (2015)] ‘AMD-Annals Study Group. Serum Uric Acid and Risk of CKD in Type 2 Diabetes’. S
464 De Cosmo , F Viazzi , A Pacilli , C Giorda , A Ceriello , S Gentile , G Russo , M C Rossi , A Nicolucci , P
465 Guida , D Feig , R J Johnson , R Pontremoli . *Clin J Am Soc Nephrol* 2015 Nov 6. 10 (11) p. .

466 [American Diabetes Association: Standards of medical care in diabetes-2016 Diabetes Care ()] ‘American Diabetes
467 Association: Standards of medical care in diabetes-2016’. *Diabetes Care* 2016. p. . (Suppl 1)

468 [Aroor et al. (2016)] ‘Angiotensin II Stimulation of DPP4 Activity Regulates Megalin in the Proximal Tubules’.
469 A Aroor , M Zuberek , C Duta , A Meuth , J R Sowers , A Whaley-Connell . pii: E780. *Int J Mol Sci* 2016
470 May 20. 17 (5) .

471 [Marco et al. (2015)] ‘Are reactive oxygen species still the basis for diabetic complications?’. Di Marco , E Jha ,
472 J C Sharma , A Wilkinson-Berka , J L , Jandeleit-Dahm K A De Haan . *Clin Sci* 2015 Jul. 129 (2) p. .

473 [Pabalan et al.] ‘Association and biomarker potential of elevated serum adiponectin with nephropathy among
474 type 1 and type 2 diabetics: A metaanalysis’. N Pabalan , R E Tiongco , J K Pandac , N A Paragas , S L
475 Lasta . *PLoS ONE* 13 (12) p. e0208905.

476 [Hansen et al. (2004)] ‘Association between mannose-binding lectin and vascular complications in type 1 dia-
477 betes’. T K Hansen , L Tarnow , S Thiel , R Steffensen , C D Stehouwer . *Diabetes* 2004 Jun. 53 (6) p.
478 .

479 [Girardi et al. ()] ‘Association of Na(+)-H(+) exchanger isoform NHE3 and dipeptidyl peptidase IV in the renal
480 proximal tubule’. A C Girardi , B C Degray , T Nagy , D Biemesderfer , P Aronson . *J Biol Chem* 2001. 276
481 p. .

12 DISCUSSION

482 [Roy et al. ()] 'Beneficial effects of fenofibric acid on over expression of extracellular matrix components, cox-
483 2, and impairment of endothelial permeability associated with diabetic retinopathy'. S Roy , D Kim , C
484 Hernandez , R Simo , S Roy . *Exp Eye Res* 2015. 140 p. .

485 [Zhao and Zmannose (2016)] 'Binding Lectin and Diabetic Nephropathy in Type 1 Diabetes'. S Q Zhao , Hu
486 Zmannose . *J Clin Lab Anal* 2016 Jul. 30 (4) p. .

487 [Dekan et al. ()] 'Binding of monoclonal antibodies to glomerular endothelium, slit membranes, and epithelium
488 after in vivo injection. Localization of antigens and bound IgGs by immunoelectron microscopy'. G Dekan ,
489 A Miettinen , E Schnabel , M G Farquhar . *Am J Pathol* 1990. 137 p. .

490 [Cai et al.] W Cai , X M Duan , Y Liu , J Yu , Y L Tang , Z L Liu . *Uric Acid Induces Endothelial Dysfunction
491 by Activating the HMGB1/RAGE Signaling Pathway*,

492 [Zeeuw and Fulcher] *Canagliflozin and Cardiovascular and Renal Events in Type 2*, D Zeeuw , G Fulcher .

493 [Perkovic et al. (2019)] 'Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy'. V Perkovic ,
494 M J Jardine , B Neal , S Bompain , Hjl Heerspink . *N Engl J Med* 2019 Apr 14.

495 [Mahaffey et al. (2018)] *Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results
496 From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)*. *Circulation*, K W Mahaffey ,
497 B Neal , V Perkovic , D De Zeeuw , G Fulcher . 2018 Jan 23. 137 p. .

498 [Heerspink et al. (2017)] 'Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic
499 Effects'. H J Heerspink , M Desai , M Jardine , D Balis , G Meininger , V Perkovic . *J Am Soc Nephrol* 2017
500 Jan. 28 (1) p. .

501 [Wang et al.] *Caveolin-1 is required for vascular endothelial insulin uptake*, H Wang , A X Wang , E J Barrett .

502 [David et al. ()] 'Ceradini DJThe Nrf2/Keap1/ARE Pathway and Oxidative Stress as a Therapeutic Target in
503 Type II Diabetes Mellitus'. J A David , W J Rifkin , P Rabbani . *J Diabetes Res* 2017. 2017. p. 4826724.

504 [Skrti? et al. (2014)] 'Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients
505 with type 1 diabetes and renal hyperfiltration'. M Skrti? , G K Yang , B A Perkins , N Soleymanlou , Y
506 Lytvyn , M Von Eynatten . *Diabetologia* 2014 Dec. 57 (12) p. .

507 [Defronzo et al. ()] 'Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects
508 and subjects with type 2 diabetes'. R A Defronzo , M Hompesch , S Kasichayanula , X Liu , Y Hong , M
509 Pfister . *Diabetes Care* 2013. 36 p. .

510 [Humphry et al. ()] 'Chronic renal failure in non-insulin dependent diabetes mellitus. A population-based study
511 in'. L L Humphry , D J Ballard , P P Frohnert , C P Chu , O 'fallon , W M Palumbo , PJ . *Ann Intern Med*
512 1989. 111 p. .

513 [Uthman et al. (2018)] 'Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of
514 Na+/H+ exchanger, lowering of cytosolic Na+ and vasodilation'. L Uthman , A Baartscheer , B Bleijlevens
515 , C A Schumacher , Jvt Fiolet , A Koeman . *Diabetologia* 2018 Mar. 61 (3) p. .

516 [Ingelfinger and Rosen (2019)] 'Clinical Credence-SGLT2 Inhibitors, Diabetes, and Chronic Kidney Disease'. J
517 R Ingelfinger , C J Rosen . *N Engl J Med* 2019 Apr 14.

518 [Pan et al. (2018)] 'Clinical Significance of Hemostatic Parameters in the Prediction for Type 2 Diabetes Mellitus
519 and Diabetic Nephropathy'. L Pan , Y Ye , M Wo , D Bao , F Zhu . *Dis Markers* 2018 Feb 4. 2018. p. 5214376.

520 [Tang et al. (2018)] 'Comparisons of diabetic retinopathy events associated with glucose-lowering drugs in
521 patients with type 2 diabetes mellitus: A network metaanalysis'. H Tang , G Li , Y Zhao , F Wang , E
522 W Gower , L Shi . *Diabetes Obes Metab* 2018 Jan 25.

523 [Li et al. (2018)] 'Complement activation in patients with diabetic nephropathy'. X Q Li , D Y Chang , M Chen
524 , M H Zhao . *Diabetes Metab* 2018 Apr 16. (18) p. .

525 [Nichols et al. (2001)] 'Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors'. G A
526 Nichols , T A Hillier , J R Erbey , J Brown . *Diabetes Care* 2001 Sep. 24 (9) p. .

527 [Garber et al. (2018)] 'Consensus statement by the American Association Of Clinical Endocrinologists and
528 American College Of Endocrinology on the comprehensive type 2 diabetes management algorithm -2018
529 executive summary'. A J Garber , M J Abrahamson , J I Barzilay , L Blonde , Z T Bloomgarden , M A Bush
530 . *Endocr Pract* 2018 Jan. 24 (1) p. .

531 [Garber et al. (2019)] 'Consensus Statement by the American Association of Clinical Endocrinologists and
532 American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm -2019
533 Executive Summary'. Alan J Garber , Martin J Abrahamson , Joshua I Barzilay , Lawrence Blonde . *Endocrine
534 Practice* 2019. January 2019. 25 (1) p. .

535 [Hu et al. (2015)] 'Curbing the Diabetes Pandemic: The Need for Global Policy Solutions'. F B Hu , A Satija ,
536 J Manson . *JAMA* 2015 Jun 16. 313 (23) p. .

537 [Chuengsamarn et al. (2012)] *Curcumin extract for prevention of type 2 diabetes*. *Diabetes Care*, S Chuengsamarn
538 , S Rattanamongkolgul , R Luechapudiporn , C Phisalaphong , S Jirawatnotai . 2012 Nov. 35 p. .

539 [Na L X 1 et al. (2013)] ‘Curcuminoids exert glucoselowering effect in type 2 diabetes by decreasing serum free
540 fatty acids: a double-blind, placebocontrolled trial’. Na L X 1 , Y Li , H Z Pan , X L Zhou , D J Sun , M
541 Meng , X X Li , C H Sun . *Mol Nutr Food Res* 2013 Sep.

542 [Na L X 1 and Jiang S 1 (2014)] ‘Curcuminoids Target Decreasing Serum Adipocyte-fatty Acid Binding Protein
543 Levels in Their Glucose-lowering Effect in Patients with Type 2 Diabetes’. Yan Na L X 1 , Cui Jiang S 1 .
544 *Biomed Environ Sci* 2014 Nov.

545 [Klemann et al. (2016)] ‘Cut to the chase: a review of CD26/dipeptidyl peptidase-4’s (DPP4) entanglement in
546 the immune system’. C Klemann , L Wagner , M Stephan , Von Horsten , S . *Clin Exp Immunol* 2016. Jul.
547 185 (1) p. .

548 [Lee et al. (2016)] ‘DA-1229, a dipeptidyl peptidase IV inhibitor, protects against renal injury by preventing
549 podocyte damage in an animal model of progressive renal injury’. Eun Lee , J Kim , J E Lee , M H Song , H
550 K Ghee , J Y Kang , Y S . *Lab Invest* 2016 May.

551 [Heerspink et al. (2013)] ‘Dapagliflozin a glucoseregulating drug with diuretic properties in subjects with type 2
552 diabetes’. Lambers Heerspink , H J De Zeeuw , D Wie , L Leslie , B List , J . *Diabetes Obes Metab* 2013 Sep.
553 15 (9) p. .

554 [Furtado et al. (2019)] ‘Dapagliflozin and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Prior
555 Myocardial Infarction: A Subanalysis from DECLARE-TIMI-58 Trial’. Rhm Furtado , M P Bonaca , I Raz ,
556 T A Zelniker , O Mosenzon . *Circulation* 2019 Mar 18.

557 [Wiviott et al. (2019)] ‘Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes’. S D Wiviott , I Raz ,
558 M P Bonaca , O Mosenzon , E T Kato . *N Engl J Med* 2019 Jan 24. 380 (4) p. .

559 [Triplitt et al. ()] ‘Defronzo RAE mpagliflozin and linagliptin combination therapy for treatment of patients with
560 type 2 diabetes mellitus’. C Triplitt , C Solis-Herrera , E Cersosimo , M Abdul-Ghani . *Expert Opin Pharmac
561 other* 2015. 16 (18) p. .

562 [Chen et al. (2016)] ‘Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes’. R
563 Chen , B Ovbiagele , W Feng . *Am J Med Sci* 2016 Apr. 351 (4) p. .

564 [Rao Kondapally Seshasai et al. (2011)] ‘Diabetes mellitus, fasting glucose, and risk of cause-specific death’. S
565 Rao Kondapally Seshasai , S Kaptoge , A Thompson , Di Angelantonio , E Gao , P Sarwar , N . *N Engl J
566 Med* 2011 Mar 3.

567 [Nistala and Savin (2017)] ‘Diabetes, hypertension and chronic kidney disease progression: Role of DPP4’. R
568 Nistala , V Savin . *Am J Physiol Renal Physiol* 2017 Apr 1. 312 (4) p. .

569 [Defronzo ()] ‘Diabetic nephropathy: etiologic and therapeutic considerations’. R Defronzo . *Diabetes Rev* 1995.
570 3 p. .

571 [Yamout and Bakris (2016)] ‘Diabetic nephropathy: SGLT2 inhibitors might halt progression of diabetic
572 nephropathy’. H Yamout , G L Bakris . *Nat Rev Nephrol* 2016 Oct. 12 (10) p. .

573 [Lamers et al. ()] ‘Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic
574 syndrome’. D Lamers , S Famulla , N Wronkowitz , S Hartwig , S Lehr , D M Ouwens . *Diabetes* 2011.
575 60 p. .

576 [Girardi et al. ()] ‘Dipeptidyl peptidase IV inhibition downregulates Na⁺ -H⁺ exchanger NHE3 in rat renal
577 proximal tubule’. A C Girardi , L E Fukuda , L V Rossoni , G Malnic , Reboucas N A . *Am J Physiol Renal
578 Physiol* 2008. 294 p. .

579 [S (2016)] *Dipeptidyl Peptidase-4 Inhibitor Increases Vascular Leakage in Retina through VE-cadherin Phospho
580 rylation*. *Sci Rep*, S . 2016 Jul 6. Lee C S 1, 2, 3, Kim Y G 4, Cho H J 1, 2, 4, Park J 1, 2, 4, Jeong H 1, Lee
581 S E 1, 2, 4, Lee. 6 p. 29393.

582 [Alter et al. ()] ‘DPP-4 inhibition on top of angiotensin receptor blockade offers a new therapeutic approach for
583 diabetic nephropathy’. M L Alter , I Ott , W K Tsuprykov , O Sharkovska , Y Krause-Relle , K . *Kidney
584 Blood Press Res* 2012. 36 p. .

585 [Glorie et al. ()] ‘DPP4 inhibition improves functional outcome after renal ischemiareperfusion injury’. L L Glorie
586 , A Verhulst , V Matheeussen , L Baerts , J Magielse , N Hermans . *Am J Physiol Renal Physiol* 2012. 303
587 p. .

588 [Man et al.] ‘Du JIncreased serum mannose binding lectin levels are associated with diabetic retinopathy’. X
589 Man , H Zhang , H Yu , L Ma . *J Diabetes Complications*

590 [Darisipudi et al. ()] ‘Dual blockade of the homeostatic chemokine CXCL12 and the proinflammatory chemokine
591 CCL2 has additive protective effects on diabetic kidney disease’. M N Darisipudi , O P Kulkarni , S G Sayyed
592 , M Ryu , A Migliorini , C Sagrinati . *Am J Pathol* 2011. 179 p. .

12 DISCUSSION

593 [Bahadoran et al. (2012)] 'Effect of broccoli sprouts on insulin resistance in type 2 diabetic patients: a
594 randomized double-blind clinical trial'. Z Bahadoran , M Tohidi , P Nazeri , M Mehran , F Azizi , P Mirmiran
595 . *Int J Food Sci Nutr* 2012 Nov. 63 (7) p. .

596 [Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)]. *Lancet* 1998. 352 p. . UK Prospective Diabetes Study (UKPDS) Group

597 [Ray et al. ()] 'Effect of intensive control of glucose on cardiovascular outcomes and death in patients with
598 diabetes mellitus: a metaanalysis of randomised controlled trials'. K K Ray , S R Seshasai , S Wijesuriya , R
599 Sivakumaran , S Nethercott , D Preiss . *Lancet* 2009. 373 p. .

600 [Usharani et al. ()] 'Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and
601 inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-
602 controlled, 8-week study'. P Usharani , A A Mateen , M U Naidu , Y S Raju , N Chandra . *Drugs R D* 2008.
603 9 (4) p. .

604 [Mosenzon et al. ()] 'Effect of Saxagliptin on renal outcomes in the SAVOR-TIMI 53 Trial'. O Mosenzon , G
605 Leibowitz , D L Bhatt , A Cahn , B Hirshberg , C Wei . *Diabetes Care* 2017. 40 p. .

606 [Cornel et al. ()] 'Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2
607 diabetes: Outcomes from TECOS'. J H Cornel , G L Bakris , S Stevens , M R, Alvarsson , A Baxw , L
608 M Chuang . *Diabetes Care* 2016. 39 p. .

609 [Mosenzon et al. (2019)] 'Effects of dapagliflozin on development and progression of kidney diseasein patients
610 with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial'. O Mosenzon , S D Wiviott
611 , A Cahn , A Rozenberg , I Yanuv . *Lancet Diabetes Endocrinol* 2019 Published Online June 9. 2019.

612 [Brenner et al. (2001)] 'Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes
613 and nephropathy'. B M Brenner , M E Cooper , D De Zeeuw , W F Keane , W E Mitch , H H Parving , G
614 Remuzzi , S M Snapinn , Z Zhang , S; Renaal Study Shahinfar , Investigators . *N Engl J Med* 2001 Sep 20.
615 345 (12) p. .

616 [Goh et al. (2014)] 'Effects of resveratrol in patients with type 2 diabetes mellituson skeletal muscle SIRT1
617 expression and energy expenditure'. K P Goh , H Y Lee , D P Lau , W Supaat , Y H Chan , A F Koh . *Int
618 J Sport Nutr Exerc Metab* 2014 Feb. 24 (1) p. .

619 [Panchapakesan et al. ()] 'Effects of SGLT2 inhibition in human kidney proximal tubular cells–renoprotection in
620 diabetic nephropathy?'. U Panchapakesan , K Pegg , S Gross , M G Komala , H Mudaliar , J Forbes . *PLoS
621 One* 2013. 8 (2) p. e54442.

622 [Guan et al. (2015)] 'Elevated serum levels of mannose-binding lectin and diabetic nephropathy in type 2
623 diabetes'. L Z Guan , Q Tong , J Xu . *PLoS One* 2015 Mar 24. 10 (3) p. e0119699.

624 [Wanner et al. (2016)] 'Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes'. C Wanner , S E
625 Inzucchi , J M Lachin , D Fitchett , M Von Eynatten , M Mattheus . *N Engl J Med* 2016 Jul 28.

626 [Baartscheer et al. (2017)] 'Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the
627 cardiac Na+/H+ exchanger in rats and rabbits'. A Baartscheer , C A Schumacher , R C Wüst , J W
628 Fiolet , G J Stienen , R Coronel . *Diabetologia* 2017 Mar. 60 (3) p. .

629 [Grempler et al. (2012)] 'Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor:
630 characterisation and comparison with other SGLT-2 inhibitors'. R Grempler , L Thomas , M Eckhardt , F
631 Himmelsbach , A Sauer , D E Sharp . *Diabetes Obes Metab* 2012 Jan. 14 (1) p. .

632 [Ojima et al. (2015)] 'Empagliflozin, an Inhibitor of Sodium-Glucose Cotransporter 2 Exerts Anti-Inflammatory
633 and Antifibrotic Effects on Experimental Diabetic Nephropathy Partly by Suppressing AGEs-Receptor Axis'.
634 A Ojima , T Matsui , Y Nishino , N Nakamura , S Yamagishi . *Horm Metab Res* 2015 Aug. 47 (9) p. .

635 [Deshpande et al. (2008)] 'Epidemiology of diabetes and diabetes-related complications'. Ad1 Deshpande , M
636 Harris-Hayes , M Schootman . *Phys Ther* 2008 Nov. 88 (11) p. .

637 [Neerati P 1, Devde and Gangi (2014)] 'Evaluation of the effect of curcumin capsules on glyburide therapy in
638 patients with type-2 diabetes mellitus'. R Neerati P 1, Devde , A Gangi . *Phytother Res* 2014 Dec. 28 (12) p.
639 .

640 [Bjornstad et al. (2015)] 'Fructose and uric acid in diabetic nephropathy'. P Bjornstad , M A Lanaspa , T
641 Ishimoto , T Kosugi , S Kume , D Jalal . *Diabetologia* 2015 Sep.

642 [Holst and Deacon ()] 'Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors'. J J Holst
643 , C F Deacon . *Diabetologia* 2005. 48 p. .

644 [List and Whaley (2011)] 'Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and
645 humans'. J F List , J Whaley . *Kidney Int Suppl* 2011 Mar; (120). p. .

646 [Yang et al. ()] 'High glucose induction of DNAbinding activity of the transcription factor NF-?B in patients
647 with diabetic nephropathy'. B Yang , A Hodgkinson , P J Oates , B A Millward , A Demaine . *Biochim.
648 Biophys. Acta* 2008. 1782 p. .

649

650

651 [Park et al. ()] 'High glucose-induced intercellular adhesion molecule-1 (ICAM-1) expression through an osmotic
652 effect in rat mesangial cells is PKC-NF-? B-dependent'. C W Park , J H Kim , J H Lee , Y S Kim , H J Ahn
653 , Y S Shin . *Diabetologia* 2000. 43 p. .

654 [Huang et al. (2015)] 'High Mannose-Binding Lectin Serum Levels Are Associated with Diabetic Retinopathy in
655 Chinese Patients with Type 2 Diabetes'. Q Huang , G Shang , H Deng , J Liu , Y Mei . *PLoS One* 2015 Jul
656 2. 10 (7) p. e0130665.

657 [Ficociello et al. (2010)] *High-normal serum uric acid increases risk of early progressive renal function loss in
658 type 1 diabetes: results of a 6-year follow-up*. *Diabetes Care*, L H Ficociello , E T Rosolowsky , M A Niewczas
659 , N J Maselli , J M Weinberg , A Aschengrau , J H Eckfeldt , R C Stanton , A T Galecki , Doria A Waram
660 , J H Krolewski , A . 2010 Jun. 33 p. .

661 [Wong et al. (2016)] 'Howe P R Low dose resveratrol improves cerebrovascular function in type 2 diabetes
662 mellitus'. R H Wong , R S Nealon , A Scholey . *Nutr Metab Cardiovasc Dis* 2016 May. 26 (5) p. .

663 [Kitada et al.] 'Hyperglycemia causes cellular senescence via a SGLT2-and p21-dependent pathway in proximal
664 tubules in the early stage of diabetic nephropathy'. K Kitada , D Nakano , H Ohsaki , H Hitomi , T Minamino
665 , J Yatabe . *J Diabetes Complications*

666 [Loukine et al. ()] 'Impact of diabetes mellitus on life expectancy and healthadjusted life expectancy in Canada'.
667 L Loukine , C Waters , B C Choi , J Ellison . *Popul Health Metr* 2012. 10 p. 7.

668 [Saraheimo et al. (2005)] 'Increased levels of mannanbinding lectin in type 1 diabetic patients with incipient and
669 overt nephropathy'. M Saraheimo , C Forsblom , T K Hansen , A M Teppo , J Fagerudd . *Diabetologia* 2005
670 Jan. 48 (1) p. .

671 [Wada and Makino (2013)] 'Inflammation and the pathogenesis of diabetic nephropathy'. J Wada , H Makino .
672 *Clin Sci* 2013 Feb. 124 (3) p. .

673 [Bommel et al. (2017)] 'Inhibition in the Diabetic Kidney-From Mechanisms to Clinical Outcome'. E J Bommel
674 , M H Muskiet , L Tonneijck , M H Kramer , M Nieuwdorp , D H Van Raalte , Sglt2 . *Clin J Am Soc Nephrol*
675 2017 Apr 3. 12 (4) p. .

676 [Roy et al. ()] 'Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO
677 dependent'. D Roy , M Perreault , A Marette . *Am J Physiol* 1998. 274 (4) p. . (Pt 1)

678 [Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk complications in p
679 'Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and
680 risk complications in patients with type 2 diabetes (UKPDS 33)'. *Lancet* 1998. 352 p. . UK Prospective
681 Diabetes Study (UKPDS) Group

682 [Shi et al. (2015)] 'Interactions of DPP-4 and integrin ?1 influences endothelial-to-mesenchymal transition'. S Shi
683 , S P Srivastava , M Kanasaki , J He , M Kitada , T Nagai . *Kidney Int* 2015 Sep. 88 (3) p. ..

684 [De et al. ()] 'let it cut or cut it down'. M De , I Korom , S Van , D J , Scharpe S Cd26 . *Immunol Today* 1999.
685 20 p. .

686 [Groop et al. ()] 'Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes
687 and renal dysfunction: The randomized MARLINA-T2D trial'. P H Groop , M E Cooper , V Perkovic , B
688 Hocher , K Kanasaki , M Haneda . *Diabetes Obes Metab* 2017. 19 p. .

689 [Kanasaki et al. (2014)] *Linagliptin-mediated DPP-4*, K Kanasaki , S Shi , M Kanasaki , J He , T Nagai , Y
690 Nakamura . 2014 Jun. 63 p. .

691 [Hayflick ()] 'Living forever and dying in the attempt'. L Hayflick . *Experimental Gerontology* 2003. 38 p. ..

692 [Terami et al. (2014)] 'Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin,
693 ameliorates glucose homeostasis and diabetic nephropathy in db/db mice'. N Terami , D Ogawa , H Tachibana
694 , T Hatanaka , J Wada , A Nakatsuka . *PLoS One* 2014 Jun 24. 9 (6) p. e100777.

695 [Maiese K New Insights for Oxidative Stress and Diabetes Mellitus Oxid Med Cell Longev ()] 'Maiese K New
696 Insights for Oxidative Stress and Diabetes Mellitus'. *Oxid Med Cell Longev* 2015. 2015. p. 875961.

697 [Røder (2018)] *Major adverse cardiovascular event reduction with GLP-1 and SGLT2 agents: evidence and
698 clinical potential*. *Ther Adv Chronic Dis*, M Røder . 2018 Jan. 9 p. .

699 [Hovind et al. (2005)] 'Mannose-binding lectin as a predictor of microalbuminuria in type 1 diabetes: an
700 inception cohort study'. P Hovind , T K Hansen , L Tarnow , S Thiel , R Steffensen . *Diabetes* 2005 May. 54
701 (5) p. .

702 [Groop et al. (2013)] *MLinagliptin lowers albuminuria on top of recommended standard treatment in patients
703 with type 2 diabetes and renal dysfunction*. *Diabetes Care*, P H Groop , M E Cooper , V Perkovic , A Emser
704 , H J Woerle , Von Eynatten . 2013 Nov. 36 p. .

705 [Zeadin et al. ()] 'Molecular mechanisms linking diabetes to the accelerated development of atherosclerosis'. M
706 G Zeadin , C I Petlura , G Werstuck . *Can J Diabetes* 2013. 37 p. .

12 DISCUSSION

707 [Raish et al. (2016)] 'Momordica charantia polysaccharides mitigate the progression of STZ induced diabetic
708 nephropathy in rats'. M Raish , A Ahmad , B L Jan , K M Alkharfy , M A Ansari , K Mohsin . *Int J Biol
709 Macromol* 2016 Oct. 91 p. .

710 [González-Reyes and Pedraza-Chaverri (2015)] 'Natural Nrf2 activators in diabetes'. Jiménez-Osorio A S
711 González-Reyes , S Pedraza-Chaverri , J . *Clin Chim Acta* 2015 Aug 25. 448 p. .

712 [Osar et al. ()] 'Nicotinamide effects oxidative burst activity of neutrophils in patients with poorly controlled
713 type 2 diabetes mellitus'. Z Osar , T Samanci , G Y Demirel , T Damci , H Ilkova . *Exp Diabetes Res* 2004.

714 [Tomé-Carneiro et al. (2012)] 'One-year consumption of a grape nutraceutical containing resveratrol improves
715 the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease'. J Tomé-
716 Carneiro , M González , M Larrosa , M J Yáñez-Gascón , F J García-Almagro , J A Ruiz-Ros . *Am J Cardiol*
717 2012 Aug 1. 110 (3) p. .

718 [Tomé-Carneiro et al.] *One-year supplementation with a grape extract containing resveratrol modulates*, J Tomé-
719 Carneiro , M Larrosa , M J Yáñez-Gascón , A Dávalos , J Gil-Zamorano , M González .

720 [Khajehdehi et al. (2011)] 'Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-
721 ? and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind
722 and placebo-controlled study'. P1 Khajehdehi , M Pakfetrat , K Javidnia , F Azad , L Malekmakan , M H
723 Nasab . *Scand J Urol Nephrol* 2011 Nov. 45 (5) p. .

724 [Kashihara et al. ()] 'Oxidative stress in diabetic nephropathy'. N Kashihara , Y Haruna , V K Kondeti , Y
725 Kanwar . *Curr Med Chem* 2010. 17 p. .

726 [Candrilli et al. (2007)] 'Prevalence and the associated burden of illness of symptoms of diabetic peripheral
727 neuropathy and diabetic retinopathy'. S D Candrilli , K L Davis , H J Kan , M A Lucero , M Rousculp
728 . *J Diabetes Complications* 2007 Sep-Oct; 21. (5) p. .

729 [Zhang et al. (2016)] 'Protective Effects of Berberine on Renal Injury in Streptozotocin (STZ)-Induced Diabetic
730 Mice'. X Zhang , H He , D Liang , Y Jiang , W Liang , Z H Chi . *Int J Mol Sci* 2016 Aug 12. 17 (8) .

731 [Chung et al. (2016)] 'Protective Effects of Dipeptidyl Peptidase-4 Inhibitors on Progression of Diabetic
732 Retinopathy in Patients with Type 2 Diabetes'. Y R Chung , S W Park , J W Kim , J Kim . *Retina*
733 2016 Dec. 36 (12) .

734 [Cherney et al. (2014)] 'Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with
735 type 1 diabetes mellitus'. D Z Cherney , B A Perkins , N Soleymanlou , M Maione , V Lai , A Lee . *Circulation*
736 2014 Feb 4. 129 (5) p. .

737 [Cristóbal-García et al. ()] 'Renal oxidative stress induced by long-term hyperuricemia alters mitochondrial
738 function and maintains systemic hypertension'. M Cristóbal-García , F E García-Arroyo , E Tapia , H Osorio
739 , A S Arellano-Buendía , M Madero . *Oxid Med Cell Longev* 2015. 2015. p. 535686.

740 [Gekle ()] 'Renal tubule albumin transport'. M Gekle . *Annu Rev Physiol* 2005. 67 p. .

741 [Brasnyó et al. (2011)] 'Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt
742 pathway in type 2 diabetic patients'. P Brasnyó , G A Molnár , M Mohás , L Markó , B Laczy , J Cseh . *Br
743 J Nutr* 2011 Aug. 106 (3) p. .

744 [Ha et al. ()] 'Role of high glucose-induced nuclear factor-?B activation in monocyte chemo attractant protein-1
745 expression by mesangial cells'. H Ha , M R Yu , Y J Choi , M Kitamura , H Lee . *J. Am. Soc. Nephrol* 2002.
746 13 p. .

747 [Udell et al. ()] 'Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe
748 renal impairment: observations from the SAVOR-TIMI 53 Trial'. J A Udell , D L Bhatt , E Braunwald , M
749 A Cavender , O Mosenzon , P G Steg . *Diabetes Care* 2015. 38 p. .

750 [Butler et al. ()] 'SDF-1 is both necessary and sufficient to promote proliferative retinopathy'. J M Butler , S M
751 Guthrie , M Koc , A Afzal , S Caballero , H L Brooks . *J Clin Invest* 2005. 115 p. .

752 [Röhrborn and Eckel (2014)] 'Sell HShedding of dipeptidyl peptidase 4 is mediated by metalloproteases and up-
753 regulated by hypoxia in human adipocytes and smooth muscle cells'. D Röhrborn , J Eckel . *FEBS Lett* 2014
754 Nov 3.

755 [Ferdousie et al. ()] 'Serum CXCL10 and CXCL12 chemokine levels are associated with the severity of coronary
756 artery disease and coronary artery occlusion'. V T Ferdousie , M M Mohammadi , G Hassanshahi , H
757 Khorramdelazad , S K Falahati-Pour , M Mirzaei . *Int J Cardiol* 2017. 233 p. .

758 [Hovind et al. (2009)] 'Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes:
759 an inception cohort study'. P Hovind , P Rossing , L Tarnow , R J Johnson , H Parving . *Diabetes* 2009 Jul.
760 58 (7) p. .

761 [Takae et al. (2016)] 'Serum Uric Acid as a Risk Factor for Chronic Kidney Disease in a Japanese Community
762 -The Hisayama Study'. K Takae , M Nagata , J Hata , N Mukai , Y Hirakawa , D Yoshida , H Kishimoto ,
763 K Tsuruya , T Kitazono , Y Kiyoohara , T Ninomiya . *Circ J* 2016 Jul 25. 80 (8) p. .

764 [Jalal et al. (2010)] 'Serum uric acid levels predict the development of albuminuria over 6 years in patients with
765 type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study'. D I Jalal , C J
766 Rivard , R J Johnson , D M Maahs , K Mcfann , M Rewers , J Snell-Bergeon . *Nephrol Dial Transplant* 2010
767 Jun. 25 (6) p. .

768 [Chino et al. ()] 'SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal
769 tubule by increased glycosuria'. Y Chino , Y Samukawa , S Sakai , Y Nakai , J Yamaguchi , T Nakanishi .
770 *Biopharm Drug Dispos* 2014. 35 p. .

771 [Should We Change the Therapeutic Algorithm of Type 2 Diabetes Based on Accumulating Evidence?] *Should
772 We Change the Therapeutic Algorithm of Type 2 Diabetes Based on Accumulating Evidence?* ,

773 [Yin et al. (2016)] 'Sinomenine alleviates high glucose-induced renal glomerular endothelial hyperpermeability
774 by inhibiting the activation of RhoA/ROCK signaling pathway'. Q Yin , Y Xia , G Wang . *Biochem Biophys
775 Res Commun* 2016 Sep 2. 477 (4) p. .

776 [Bo et al. (2016)] 'Six months of resveratrol supplementation has no measurable effect in type 2 diabetic patients.
777 A randomized, double blind, placebo-controlled trial'. S Bo , V Ponzo , G Ciccone , A Evangelista , F Saba ,
778 I Goitre . *Pharmacol Res* 2016 Sep. 111 p. .

779 [Cherney et al. (2014)] 'Sodium glucose cotransport-2 inhibition and intrarenal RAS activity in people with type
780 1 diabetes'. D Z Cherney , B A Perkins , N Soleymanlou , F Xiao , J Zimpelmann , H J Woerle . *Kidney Int*
781 2014 Nov. 86 (5) p. .

782 [Wakisaka and Nagao (2017)] 'Sodium glucose cotransporter 2 in mesangial cells and retinal pericytes and its
783 implications for diabetic nephropathy and retinopathy'. M Wakisaka , T Nagao . *Glycobiology* 2017 May 23.

784 [Sharma et al. ()] 'Targeting endothelial dysfunction in vascular complications associated with diabetes'. A
785 Sharma , P N Bernatchez , J De Haan . *Int J Vasc Med* 201210. 1155/2012/750126.

786 [Imamura et al. (2017)] 'Tatsuno IResveratrol Ameliorates Arterial Stiffness Assessed by Cardio-Ankle Vascular
787 Index in Patients With Type 2 Diabetes Mellitus'. H Imamura , T Yamaguchi , D Nagayama , A Saiki , K
788 Shirai . *Int Heart J* 2017 Aug 3. 58 (4) p. .

789 [Vettor et al. (2017)] 'The cardiovascular benefits of empagliflozin: SGLT2-dependent and -independent effects'.
790 R Vettor , S E Inzucchi , P Fioretto . *Diabetologia* 2017 Mar. 60 (3) p. .

791 [Gall M A 1, Nielsen et al. (1993)] 'The course of kidney function in type 2 (non-insulindependent) diabetic
792 patients with diabetic nephropathy'. F S Gall M A 1, Nielsen , U M Smidt , H Parving . *Diabetologia*
793 1993 Oct. 36 (10) p. .

794 [The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development
795 'The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes
796 on the development and progression of long-term complications in insulin-dependent diabetes mellitus'. *N
797 Engl J Med* 1993. 329 p. .

798 [Kolka and Bergman (2013)] 'The endothelium in diabetes: its role in insulin access and diabetic complications'.
799 C M Kolka , R Bergman . *Rev Endocr Metab Disord* 2013 Mar.

800 [Zoja et al. (2014)] 'The Nrf2 pathway in the progression of renal disease'. C Zoja , A Benigni , G Remuzzi .
801 *Nephrol Dial Transplant* 2014 Feb. 29 (1) p. . (Suppl)

802 [Furchtgott and Zawadzki ()] 'The obligatory role of endothelial cells in the relaxation of arterial smooth muscle
803 by acetylcholine'. R F Furchtgott , J Zawadzki . *Nature* 1980. 288 p. .

804 [Turner (2003)] 'The role of mannose-binding lectin in health and disease'. M Turner . *Mol Immunol* 2003 Nov.
805 40 (7) p. .

806 [Hansen et al. (2017)] 'The role of NADPH oxidases in diabetic cardiomyopathy'. S S Hansen , E Aasum , A
807 Hafstad . *Biochim Biophys Acta* 2017 Jul 25.

808 [Wilding ()] 'The role of the kidneys in glucose homeostasis in type 2 diabetes: Clinical implications and
809 therapeutic significance through sodium glucose co-transporter 2 inhibitors'. Jph Wilding . *Metabolism* 2014.
810 63 p. .

811 [Zheng et al. (2012)] 'The worldwide epidemic of diabetic retinopathy'. Y Zheng , M He , N Congdon . *Indian J
812 Ophthalmol* 2012 Sep-Oct. 60 (5) p. .

813 [Zheng et al. (2012)] 'The worldwide epidemic of diabetic retinopathy'. Y Zheng , M He , N Congdon . *Indian J
814 Ophthalmol* 2012 Sep-Oct. 60 (5) p. .

815 [Yan et al. (2015)] 'Uric Acid is independently associated with diabetic kidney disease: a cross-sectional study
816 in a Chinese population'. D Yan , Y Tu , F Jiang , J Wang , R Zhang , X Sun , T Wang , S Wang , Y Bao ,
817 C Hu , W Jia . *PLoS One* 2015 Jun 1. 10 (6) p. e0129797.

818 [Cicerchi et al. (2014)] 'Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in
819 diabetes and starvation: evolutionary implications of the uricase loss in hominids'. C Cicerchi , N Li , J
820 Kratzer , G Garcia , C A Roncal-Jimenez , K Tanabe . *FASEB J* 2014 Aug. 28 (8) p. .

12 DISCUSSION

821 [Ryu et al. ()] 'Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic
822 kidney disease'. E-S Ryu , M J Kim , H-S Shin , Y H Jang , H S Choi , JoI . *Am J Physiol Renal Physiol*
823 2013. 304 p. .

824 [Deacon ()] 'What do we know about the secretion and degradation of incretin hormones?'. C Deacon . *Regul
825 Pept* 2005. 128 (2) p. .

826 [Yang Y 1 et al. (2015)] 'Wuling San protects kidney dysfunction by inhibiting renalTLR4/MyD88 signaling and
827 NLRP3 inflamma some activation in high fructose-induced hyperuricemic mice'. Yang Y 1 , Zhang D M 1 ,
828 J H 1 Liu , Hu L S 2, Xue Q C 1 , X Ding . *J Ethnopharmacol* 2015 Jul 1. 169 p. .

829 [Chowdhury et al. ()] 'Zorec RHypoxia Alters the Expression of Dipeptidyl Peptidase 4 and Induces Develop-
830 mental Remodeling of Human Preadipocytes'. H H Chowdhury , J Velebit , N Radi? , V Fran?i? , M Kreft .
831 *J Diabetes Res* 2016. 2016. p. 7481470.