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The influence of SGLT2 inhibitors on oxidative stress in heart failure and chronic kidney disease in patients with type 2 diabetes

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Abstract

There is increasing interest in sodium-glucose cotransporter 2 inhibitors (SGLT2i) as not only a new oral glucose-lowering drug class but also one with cardio- and nephroprotective potential. Understanding the underlying mechanisms is therefore of great interest, and postulated benefits have included increased natriuresis, lower blood pressure, increased haematocrit, enhanced cardiac fatty acid utilization, reduced low-grade inflammation, and decreased oxidative stress. In particular, redox homeostasis seems to be crucial in the pathogenesis of heart and kidney disease in diabetes, and there is accumulating evidence that SGLT2i have beneficial effects in this perspective.

In this review, we aimed to summarize the potential mechanisms of the influence of SGLT2i on oxidative stress parameters in animal and human studies, with a special focus on heart failure and chronic kidney disease in diabetes mellitus. **(Endokrynol Pol 2023; 74 (4): 349–362)**

Key words: *sodium-glucose cotransporter 2 inhibitors; oxidative stress; diabetes mellitus; chronic kidney disease; heart failure*

Introduction

Oxidative stress (OS), defined as a disturbance of pro- and antioxidant homeostasis, leads to cellular damage [1, 2]. The oxidative imbalance stems from both excessive generation of highly reactive oxygen (ROS) and reactive nitrogen species (RNS) and/or reduced antioxidative potential of the organism [1, 2]. Overproduction of highly reactive species is an important factor in the pathogenesis of cardiovascular (CV) complications in the course of diabetes mellitus (DM).

DM affects 537 million adults worldwide, and patients with diabetes mellitus type 2 (T2DM) account for about 90% of them [3]. Cardiovascular diseases (CVDs) are the leading cause of death in T2DM patients, with heart failure (HF) emerging as a new epidemic both among patients with and without diabetes [4, 5]. Moreover, chronic kidney disease (CKD), a microvascular complication of DM, adds another puzzle to the increased incidence of CVD and cardiovascular deaths as a part of cardio-renal continuum [6].

Since the early 2000s, new classes of glucose-lowering drugs emerged, namely sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), which changed the perspective on the treatment algorithms in T2DM patients. Nowadays the glucocentric approach prevailing for decades has been changed towards a more cardio- and nephroprotective approach, in which the choice of glucose-lowering drug in a particular patient is driven mainly by the presence of cardiovascular and renal diseases. This shift has been made following the publication of the landmark cardiovascular outcome trials, such as the Canagliflozin Cardiovascular Assess-

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ment Study (CANVAS) program, the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME), and the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial [7–9]. These studies prove that new classes of glucose-lowering drugs are not only safe in terms of the cardiovascular system but also clearly decrease the risk of cardiovascular and renal events.

Specifically, it has been suspected and then confirmed that the cardiac and renal benefits of SGLT2i may be independent of glycaemic control. Following further studies like the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR- Preserved), the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced), the Study of Heart and Kidney Protection With Empagliflozin (EMPA-Kidney), the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), and the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), SGLT2i are now considered the first-line treatment in patients with HF and CKD, both with and without DM [10–15]. These trials were overviewed more thoroughly in a recent editorial [16]. Hence, there has been much interest on the possible pathophysiology and mechanistic insights into the universally positive influence of these drugs on cardiovascular and renal systems. Possible pathways include increased osmotic diuresis and natriuresis [17], mild hypotensive effect [18], increased haematocrit – possibly secondary to hypoxia inducible factor signalling [19], reduced low-grade inflammation by reduced proinflammatory cytokine production [20], enhanced myocardial metabolism – including increased fatty acid or glucose oxidation or ketogenesis [21, 22], and decreased OS [23, 24].

In particular, their interference with oxidative stress has emerged as one of the biochemical pathways involved in this protective process [25, 26].

The aim of this narrative review is to analyse the influence of SGLT2i on OS as one of the possible mechanisms of its protective action in HF and CKD.

Search strategy

A search of the Medline, Embase, and Scopus databases as well as the search engine Google Scholar was conducted to find published research about mechanisms of SGLT2i related to OS. Additionally, we searched for relevant studies in the references of other included articles. The search was limited to English language articles published up to 31 December 2022.

The inclusion criteria were as follows:

1. Original research studies that tested the effects of SGLT2i on OS:
— in animal models of either HF or CKD, or diabetes when tested samples included myocardial, vascular, or kidney tissue;
— in humans with HF, CKD, or diabetes type 2 (either patients treated or tissues treated ex vivo).
2. Original research studies on the influence of diabetes type 2, HF, or CKD on OS in human subjects

The exclusion criteria were as follows:

— studies that researched mechanisms of action of SGLT2i but did not assess its impact on the extent of ROS generation, any markers of OS, or markers of antioxidant capacity;
— studies on animal models of a disease did not include any of the following groups: healthy controls, a model of the disease untreated, and a model of the disease treated with SGLT2i.

The search included terms such as: "SGLT2 inhibitors", "oxidative stress", "diabetes", "heart failure", and "chronic kidney disease".

Oxidative stress and heart failure in diabetes mellitus type 2

T2DM is a significant risk factor for the development of HF [27]. Similarly, HF predisposes to new-onset T2DM [28]. The fact that consequences of one disease underly the pathogenesis of another one is thought to explain this peculiar relationship.

For example, hyperglycaemia appearing in T2DM can lead to myocardial and endothelial damage, which may result in HF development. On the other hand, metabolic changes seen in HF, such as increased lipolysis and increased insulin resistance, increase the risk of new-onset T2DM [29, 30]. Both phenomena are also associated with increased OS. This interaction is sometimes referred to as a vicious circle because both T2DM and HF exacerbate each other [31].

Increased OS has long been associated with T2DM and HF. Sources of ROS in diabetic heart and endothelial cells include leakage of superoxide anions generated in mitochondrial electron transport chain (ETC), and excess activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, uncoupled nitric oxide synthase, and arachidonic acid metabolism [32]. In both T2DM and HF sources of ROS are upregulated, and the hyperglycaemic state elevates ROS by several mechanisms. Various studies related to OS in HF of patients with T2DM are summarized in Table 1.

Glucose autoxidation delivers additional substrates for ETC in mitochondria, thus increasing output of su-

Table 1. *Oxidative stress and heart failure in type 2 diabetes mellitus*

Study	Participants	Sample	Outcomes	Conclusion
Anderson et al. (2009) [78]	11 T2DM patients and 13 nondiabetic patients undergoing CABG	Atrial tissue obtained during CABG	↑ mitochondrial H_2O_2 generation, HNE, 3-NT ↓ GSH/GSSG ratio ↓ fatty acid and glutamate oxidative capacity ↑ intramyocellular triglyceride content	Increased OS and impaired antioxidant defence in patients with T2DM Deranged mitochondrial metabolism among T2DM patients is associated with lipid accumulation in cardiomyocytes
Montaigne et al. (2014) [79]	45 T2DM patients and 94 nondiabetic patients undergoing CABG	Atrial tissue obtained during CABG	↑ ROS, MnSOD, catalase activities ↑ mitochondrial dysfunction ↓ impaired intrinsic contraction Increased OS and disturbances of the mitochondrial function correlated with HbA_{1C}, but not with BMI or HOMA-IR	Increased OS, upregulated antioxidant enzymes, dysfunctional mitochondria and myocardial contraction are associated with worse glycaemic control, but not with insulin resistance or obesity
Connelly et al. (2014) [80]	7 T2DM patients and 7 nondiabetic patients undergoing CABG	Atrial myocardium obtained during CABG	↓ thioredoxin expression and activity ↑ expression of TxnIP	Diminished thioredoxin antioxidant system is associated with increased expression of TxnIP. Experimental studies on animal models showed that increased TxnIP expression appears in diabetes, and it both increases OS and reduces antioxidant capacity of thioredoxin.
Wang et al. (2011) [81]	18 T2DM patients and 18 nondiabetic patients undergoing CABG	Atrial tissue and coronary sinus blood collected during CABG	↑ 15-F_{2t}-isoprostane in coronary sinus plasma ↑ PTEN expression in atrial myocardium ↓ Bcl-2 expression, eNOS and Akt phosphorylation Highly significant correlation between 15-F_{2t}-isoprostane concentration, PTEN expression, and fasting plasma glucose	PTEN and Akt signalling is inversely correlated in diabetic hearts, with downstream effects of increased OS and downregulation of cardioprotective signalling pathways
Polidori et al. (2004) [82]	30 patients with class II or III NYHA heart failure and 30 controls	Blood	↑ levels of 8,12-isoprostane F2a-VI, levels correlate with HF severity ↓ vitamins A, C, and E ↓ uric acid, carotenoids ↓ SOD and GPx activities	Patients with HF had increased OS and depleted antioxidative systems
Gupte et al. (2007) [83]	8 heart failure patients with HF secondary to infarction undergoing surgical ventricular restoration and 5 donor hearts not suitable for transplantation as control	Non-infarcted left ventricular tissue obtained during surgery or from donor hearts	↑ superoxide and hydrogen peroxide ↑ expression of NOX2, NOX4 and G6PD ↑ activity of NOX, G6PD Inhibition of NOX, PKC, Src kinase or G6PD decreased superoxide generation	NOX is a major source of OS in failing hearts OS attenuation is achieved by inhibition of NOX, G6PD, which produces substrate for NOX, or signalling pathways that activate G6PD

3-NT — 3-nitrotyrosine; Bcl-2 — B-cell lymphoma 2; BMI — body mass index; CABG — coronary artery bypass grafting; CVD — cardiovascular disease; eNOS — endothelial nitric oxide synthase; G6PD — glucose-6-phosphate dehydrogenase; GPx — glutathione peroxidase; GSH — glutathione; GSSG — glutathione disulphide; HbA_{1c} — glycated hemoglobin; HF — heart failure; HNE — 4-hydroxynonenal; H2O2 — hydrogen peroxide; HOMA-IR — homeostatic model assessment for insulin resistance; MnSOD — manganese-dependent superoxide dismutase; NOX — NADPH oxidase; NOX2 — NADPH oxidase 2; NOX4 — NADPH oxidase 4; NYHA — New York Heart Association; OS — oxidative stress; PKC — protein kinase C; PTEN — phosphatase and tensin homolog; ROS — reactive oxygen species; SOD — superoxide dismutase; Src kinase — tyrosine protein kinase; T2DM — type 2 diabetes mellitus; TxnIP — thioredoxin-interacting protein

peroxide anions [32]. Another mechanism is activation of polyol pathway [33]. High glucose concentration can activate Ca2+/calmodulin-dependent protein kinase II [34], protein kinase C [35] and stimulate production of angiotensin II [36] and advanced glycation end-products (AGE) in cardiomyocytes or endothelial

cells, all of which activate NOX and thus induce ROS production [34–37].

Both T2DM and HF are characterized by metabolic alterations. Failing hearts rely increasingly on glucose metabolism; however, in experimental studies, diabetic hearts shift from glucose metabolism toward free fatty acid (FFA) oxidation [38]. An increase of circulating FFA in patients with either HF or T2DM is observed [39, 40]. Elevated uptake of FFA by cardiomyocytes activates peroxisome proliferator-activated receptor α (PPAR-α), which in turn increases fatty acid oxidation [41]. Despite increased FFA oxidation, superfluous FFA is combined to form triglycerides and other lipid intermediates. This may lead to intramyocardial lipid accumulation, which was observed in patients with either T2DM or HF [42, 43] and was experimentally shown to impair cardiac function [44, 45]. In addition, FFA oxidation has been shown to decline in advanced HF, though high FFA serum levels persist [46], which could exacerbate intracellular lipid accumulation. Both overload of cardiac mitochondria with FFA and increased FFA oxidation in PPAR-α overexpressing mice has been shown to increase ROS generation [47, 48]. Trimetazidine, which has been shown to be beneficial in HF in some studies [49], acts by decreasing FFA oxidation in patients with HF [50]. However, it attenuates OS as well, which could be responsible for its cardioprotective properties [51].

Despite compensatory metabolic changes, HF results in an "energy crisis", with a decreased phosphocreatine to adenosine triphosphate ratio [52], which is also a predictor of mortality in patients with dilated cardiomyopathy [53]. In this energetic state, a "low-energy sensor" such as Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) becomes activated in HF [54]. On the other hand, diabetes is perceived by cardiomyocytes as a state of energy abundance because AMPK phosphorylation was shown to be decreased in a model of diabetic cardiomyopathy [55]. Sirtuin 1 (SIRT1) is another enzyme responsible for energy metabolism, dependent on the nicotinamide adenine dinucleotide+/nicotinamide adenine dinucleotide hydrogen (NAD+/NADH) ratio. However, SIRT1 is downregulated in both diabetes and HF alone [56], [57]. Furthermore, AMPK and SIRT1 signalling are also related to OS. SIRT1 overexpression by transgenic mice is protective against oxidative stress, and it reduces cardiomyocyte apoptosis [58]. Moreover, decreased SIRT1 expression is associated with OS in HF [57].

Robust evidence exists on the importance of OS in the pathogenesis of T2DM and HF. OS in DM facilitates the development of HF and comorbidities predisposing to HF due to damage to the endothelium, contributing to both macrovascular and microvascular complications as well as to cardiac remodelling [33]. Even when DM is not complicated by hypertension or coronary artery disease, diabetic cardiomyopathy may still be present, a condition with a pathophysiology strictly associated with OS [34]. Cardiac hypertrophy, interstitial fibrosis, cardiomyocyte apoptosis, and disturbed calcium handling are thought to result from increased OS, mediated by various signalling pathways [35–37].

Oxidative stress and chronic kidney disease in diabetes mellitus type 2

OS plays an important role in the pathogenesis of CKD in DM, especially because the kidneys are particularly vulnerable to OS due to their high energy consumption and content of mitochondria (especially in proximal tubules) [1, 38]. The main kidney sources of ROS include mitochondrial respiratory chain and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activities [39]. Under normal conditions, only 1% of molecular oxygen (O_2) is converted to superoxide anion O_2^- in the final stage of the mitochondrial respiratory chain [40]. However, the state of chronic hyperglycaemia (in the course of DM) leads to electron deficiency in the mitochondrial respiratory process, which becomes the main O_2^- generator [40]. Hyperglycaemia, both acute and chronic, also affects endothelial nitric oxide synthase (eNOS), causing an excess synthesis of nitric oxide (NO), one of the RNS agents and a factor contributing to OS [41].

Studies related to OS in CKD in T2DM are summarized in Table 2. Another contributor to excess OS in patients with CKD is an overproduction of indoxyl sulphate (uraemic toxin that also accelerates CKD progression) inducing NOX and mitochondrial respiratory chain and entailing renal endothelial damage in the mechanism of OS [42]. Moreover, one of the relevant factors in the hyperoxidation is zinc deficiency (ZnD), observed among CKD patients [43]. Of note, zinc ions (Zn^{2+}) possess antioxidative properties, and a Zn^{2+} shortage induces NOX enzymes, a major renal source of ROS [43].

In the pathophysiology of OS, apart from intensification of prooxidative mechanisms, there is also an antioxidant inefficiency [44]. The picture of CKD also includes reduction of enzymatic antioxidant agents, proportionally to the advancement of the disease [45, 46]. Studies analysing one of the main intracellular (superoxide dismutase [SOD], peroxidase) and extracellular (reduced glutathione [GSH]) antioxidative enzymes indicate significant impairment of antioxidant capabilities among CKD patients [47, 48].

OS as a crucial factor in the pathogenesis of CKD has been investigated for decades [49–51]. In rats

Table 2. *Oxidative stress and chronic kidney disease in type 2 diabetes mellitus*

Study	Participants	Samples	Outcomes	Conclusions
Aksun et al. (2003) [57]	68 T2DM patients with or without albuminuria aged 57 ± 9.7 years and 32 healthy controls	Blood and urine	↑ both serum and urine NO and MDA levels in diabetic patients with and without albuminuria	NO and MDA upregulation may lead to renal hyperfiltration and hyperperfusion, and causes progression of CKD
Bondor et al. (2015) [56]	44 patients T2DM lasting for at least 6 months with GFR > 30 mL/min and 20 healthy controls	Blood	↑ levels of serum MDA in diabetic patients ↑ correlation between MDA and adiponectin in patients with DKD	Adiponectin is a significant predictor of DKD

CKD — chronic kidney disease; DKD — diabetic kidney disease; GFR — glomerular filtration rate; MDA — malondialdehyde; NO — nitric oxide; T2DM — type 2 diabetes mellitus

with streptozotocin-induced diabetes, increased production of ROS, the source of which is to be found in NAD(P)H and NO synthase, is suspected to be a common pathway connecting different pathogenic mechanisms of microvascular complications of diabetes, including CKD [52, 53]. In diabetic db/db mice, agents with antioxidative properties such as rosiglitazone and pigment epithelium-derived factor were found to relieve diabetic renal injuries [54, 55]. Nonetheless, only limited research on animal models has been performed in relation to levels of OS markers in the kidney in the course of diabetes.

Studies performed among CKD patients with T2DM treated with SGLT2i analysed various OS markers and antioxidative enzymes to identify factors correlated with diabetic kidney disease (DKD). Analogous to the animal models, hyperglycaemia leads to enhanced levels of oxidative stress markers such as serum and urine nitric oxide (NO), malondialdehyde (MDA), and SOD, observed among patients with DM [56, 57]. OS markers were higher not only among patients with DKD but also in normoalbuminuric DM patients presenting with hyperfiltration [57]. In addition, Roumeliotis et al. identified specific genetic factors (e.g. secreted phosphoprotein 1 [SPP1], thyroid peroxidase [TPO], shugoshin 2 [SGO2] and others) that were related to OS and had an impact on the risk of DKD occurrence [58].

In summary, hyperglycaemia leads to suppression of antioxidative potential and an increase in OS. Consequently, progressive oxidative damage of renal tissue and microvasculature constitutes a significant component of the subsequent complications of T2DM, such as CKD, atherosclerosis, and CVD.

SGLT2i — mechanisms of action

Physiologically, in healthy organisms, glucose becomes completely reabsorbed in the proximal tubules of the kidneys. The renal threshold for glucose is approximately 160–180 g/day, which means that this amount of glucose could be filtered without resulting in glycosuria [59]. Exceeding this threshold, as caused by profoundly impaired carbohydrate metabolism, leads to marked glycosuria – a distinctive feature of poorly controlled DM [60]. Resorption of 80–90% of glucose is provided by SGLT2, a glucose transporter located in the first segment (S1) of proximal renal tubules. The process consists of transporting one molecule of glucose coupled with 2 sodium ions through epithelial tubular cells via a sodium-potassium pump (Na+/K+-ATPase). Next, glucose exits the cell passively by facilitated diffusion through glucose transporter 2 (GLUT2) [61]. Afterwards, 10-20% of residual glucose is reabsorbed by other glucose transporters (SGLT1 and GLUT1) located in the following segments (S2/S3) of proximal tubules [60].

The newly developed SGLTi drugs may act selectively on SGLT2 and interact with the renal (tubular) handling of glucose. Inhibiting SGLT2 leads to increased excretion of glucose in urine. Consequently, SGLT2i decrease blood glucose levels and improve glycated haemoglobin A1c by about 0.5–1% [86]. Moreover, glycosuria causes body weight loss (2–3 kg in the first 6 months of treatment) because glucose urine excretion equates to about 200 kcal/day [84]. Through simultaneous inhibition of glucose and sodium reabsorption, SGLT2i improve tubule-glomerular feedback in kidneys, decrease renal hyperfiltration, and reduce sodium and glucose levels in proximal tubules [87]. In addition, SGLT2i exert protective action on beta-cell function [88].

Apart from their impact on renal sodium handling, SGLT2i may also decrease the cutaneous (interstitial) Na+ content (correlated with left ventricular (LV) hypertrophy) and thus may improve LV remodelling and ejection fraction (EF) [60, 62]. The other mecha-

nisms of action improving cardiovascular condition include reduction of cardiac preload and afterload, improvement of myocardial metabolism with reduction of cardiomyocyte apoptosis, reduction of epicardial adipose tissue, and attenuation of sympathetic nerve activity [60, 62].

Antioxidative potential of SGLT2i in heart failure

Several mechanisms have been proposed to explain the protective effects of SGLT2i in HF. These mechanisms include the following: increased osmotic diuresis and natriuresis [17], mild hypotensive effect [18], increased haematocrit [19], reduced low-grade inflammation and proinflammatory cytokine production [20], as well as increased fatty acid oxidation as a source of energy [21] and decreased OS [23, 24].

Treatment with empagliflozin in animal models of diabetes attenuates ROS generation in myocardium [90–92] and endothelium [90, 92, 93]. Moreover, reduced levels of myocardial and vascular OS biomarkers of lipid peroxidation and nitrosative stress are evident and consistent among most published studies using either empagliflozin or dapagliflozin [90, 94, 95]. However, one study found no influence of empagliflozin treatment on OS biomarkers [96]. Reduction of OS has been associated with improved functional and structural parameters such as increased left ventricular systolic and diastolic function, vascular dilatation, and decreased cardiac fibrosis and hypertrophy [55, 91, 92, 94–96]. Decreased OS results from reduced NOX expression and activity [55, 90, 93–95], and increased activation of eNOS [91, 93] and AMPK [55, 91].

Nonetheless, there is some inconsistency regarding the impact of SGLT2i on antioxidative systems. Li et al. [94] reported increased myocardial SOD and glutathione peroxidase (GPx) activities with the use of empagliflozin, while another study using dapagliflozin showed decreased SOD activity and no change of GPx or catalase activities [95]. Similarly, conflicting results exist regarding the role of heme oxygenase-1 (HO-1) and AGE/receptors of AGEs (RAGE) signalling, though some studies found an association between RAGE downregulation and SGLT2i treatment [90, 93]. These discrepancies among animal studies may be due to the large heterogeneity of methodologies, such as the use of various models of diabetes and analysis of different tissues (e.g. HO-1 expression was increased in myocardium [94] but decreased in aorta [90, 93]). Notably, no studies have assessed the influence of SGLT2i on OS in animal models of HF.

Studies on human subjects analysing the association between SGLT2i and OS in diabetes and HF are lacking. In the only randomized clinical trial, dapagliflozin reduced the urine 8-hydroxy-2′-deoxyguanosine (8-OHdG)/creatinine ratio in patients with T2DM [22]. Other studies were ex vivo analyses of tissues obtained from patients without prior treatment with SGLT2i. For example, Kondo et al. [97] showed that canagliflozin reduces OS by AMPK and eNOS activation in patients with T2DM, but this was not repeated when empagliflozin was used. On the other hand, a study utilizing myocardium of patients with heart failure with preserved ejection fraction (HFpEF) showed a reduction of OS with the use of empagliflozin, which was associated with decreased cardiomyocyte stiffness [23]. Details of animal and human studies related to the potential influence of SGLT2i on OS in diabetes and HF are presented in Tables 3 and 4.

Although SGLT2 protein is not expressed in the heart, it can still stimulate the activity of low-energy sensors [63], which has an impact on sustaining the cardiac muscle in the optimal state [64]. The protective role of SGLT2i in the HF may be driven by activation of SIRT1/AMPK and inhibition of protein kinase B/mammalian target of rapamycin (Akt/mTOR) signalling, which can lead to improved autophagy and reduced OS, lowering the inflammation state, resulting in improvement in heart contractility [63, 65]. Moreover, cardiac benefits may be driven by enhancement of hypoxia-inducible factor (HIF-1α/HIF-2α) signalling by SGLT2i, which in turn can increase autophagy by AMPK/SIRT1 signalling pathways [66].

Antioxidative potential of SGLT2i in chronic kidney disease

OS partakes in the pathogenesis of CKD; however, the exact mechanisms of the link between OS and CKD development are unknown. SGLT2i can directly reduce oxidative stress induced by high glucose levels in the proximal tubules, as was presented in experimental studies [67–69].

Several animal studies examined renal OS factors, [NOX, nuclear factor kappa B (NF-kB), ribonucleic acid (RNA)/deoxyribonucleic acid (DNA) damage], messenger RNA (mRNA) expression of OS cytokines, glycation end-product levels, and markers of renal inflammation, as an effect of increased OS in renal tissues [70–72]. Most of the studies confirmed the impact of SGLT2i treatment on decreased markers of OS or reduced levels of inflammation markers [70, 73, 74]. Two studies analysed the effects of SGLT2i in combination with ursolic acid or irbesartan in the treatment of DKD [75, 76]. In both studies, the groups treated with a combination of the drugs achieved improved renal parameters due to improving the antioxidative effect [75, 76].

Table 3. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in myocardial and vascular tissues of animal models of diabetes*

Study	SGLT2i	Animal model	Material	Outcomes after treatment with SGLT2i (compared to diabetic untreated)	Conclusion
Li et al. (2019) [84]	Empagliflozin	Diabetic KK-Ay mice and control C57BL/6J mice	Myocardium	↓ lipid hydroxyperoxide, MDA ↑ SOD, GPx activity ↓ NOX4 expression ↑ Nrf, HO-1 expression ↓ LVH, myocardial fibrosis ↑ systolic and diastolic function	Empagliflozin attenuates cardiac OS by downregulating NOX and by activating Nrf2/ARE signalling and alleviates myocardial remodelling, thereby improving cardiac function
Steven et al. (2017) [85]	Empagliflozin	Zucker diabetic fatty rats (ZDF-Lepr$^{fa/fa}$) and lean control (ZDF-Lepr$^{+/+}$)	Myocardium	↓ superoxide, 3NT, HNE ↑ ALDH-2 activity	Empagliflozin attenuates cardiac and aortic OS, increases activity of cardioprotective ALDH-2 and inhibits AGE/RAGE signalling, a major pathway inducing OS Effects of SGLT2 inhibition were not dose-dependent for most of the studied parameters
			Aorta	↓ superoxide, 3NT, HNE ↓ NOX2, HO-1 expression ↓ methylglyoxal, RAGE expression	
Habibi et al. (2017) [86]	Empagliflozin	Diabetic db/db mice and control wild-type C57BLKS/J mice	Left ventricular myocardium	↓ LVH, myocardial fibrosis ↑ diastolic function No change in diabetes-induced increase of 3-NT levels, AGE and RAGE expression	Empagliflozin improves cardiac structure and function but does not alleviate OS
Zhou et al. (2018) [65]	Empagliflozin	Streptozotocin-induced diabetic C57BL/6J and control C57BL/6J wild-type mice	Myocardium	↓ mitochondrial and intracellular ROS generation, mitochondrial fission ↑ eNOS phosphorylation ↑ AMP/ATP ratio, AMPK phosphorylation ↑ myocardial blood flow ↑ systolic and diastolic function ↓ myocardial and vascular fibrosis	Empagliflozin attenuates cardiac OS by suppressing diabetes-induced mitochondrial fission probably via AMPK activation Empagliflozin ameliorates microvascular dysfunction and improves myocardial perfusion, systolic and diastolic function
Oelze et al. (2014) [87]	Empagliflozin	Streptozotocin-induced diabetic Wistar rats and control healthy Wistar rats	Aorta	↓ aortic and endothelial superoxide generation ↓ NOX2 activity ↓ NOX1, NOX2, HO-1, eNOS expression ↓ AGE, RAGE expression ↓ aortic fibrosis ↑ endothelial function Significant changes compared to untreated rats usually achieved only with high dose of empagliflozin	Empagliflozin attenuates vascular OS by inhibiting NOX and HO-1 expression and AGE/RAGE axis Empagliflozin ameliorates structural and functional vascular disturbances Empagliflozin effects are dose-dependent
Lin et al. (2014) [88]	Empagliflozin	Diabetic db/db mice and lean, control db/m mice	Myocardium	↓ superoxide ↓ myocardial fibrosis, coronary arterial fibrosis and thickening	Empagliflozin attenuates cardiac and vascular OS Empagliflozin ameliorates cardiac fibrosis, coronary arterial remodelling, and vascular dysfunction
			Thoracic aorta	↓ superoxide ↑ vascular dilating function	

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Table 3. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in myocardial and vascular tissues of animal models of diabetes*

Study	SGLT2i	Animal model	Material	Outcomes after treatment with SGLT2i (compared to diabetic untreated)	Conclusion
Xing et al. (2021) [89]	Dapagliflozin	Streptozotocin-induced diabetic Sprague-Dawley rats and control healthy Sprague-Dawley rats	Left ventricular myocardium	↓NOX subunits expression, gp91phox, p22phox, membrane p67phox ↓MDA, Cu/Zn-SOD expression, total SOD activity No change of GPx, Mn-SOD, and catalase expression ↑ Systolic function	Dapagliflozin improves LV systolic function, possibly by alleviating OS via NOX inhibition Dapagliflozin normalizes diabetes-induced upregulation of antioxidative enzymes
Tian et al. (2021) [90]	Dapagliflozin	Sprague -Dawley rats fed with high-fat diet followed by streptozotocin injection, and control healthy Sprague-Dawley rats	Myocardium	↓NOX4 ↑AMPKa phosphorylation ↓myocardial fibrosis and endothelial-to-mesenchymal transition ↑ systolic and diastolic function ↓ superoxide in endothelial cell line (HUVECs) AMPKa siRNA suppressed antioxidant effects of dapagliflozin	Dapagliflozin ameliorated structural and functional cardiac disturbances by AMPK activation, which is engaged in antioxidative response

3-NT — 3-Nitrotyrosine; AGE — advanced glycation end product; ALDH-2 — mitochondrial aldehyde dehydrogenase; AMPK — AMP-activated protein kinase; eNOS — endothelial nitric oxide synthase; GPx — glutathione peroxidase; HNE — 4-Hydroxynonenal; HO-1 — heme oxygenase-1; HUVECs — human umbilical vein endothelial cells; LVH — left ventricular hypertrophy; NOX — NADPH oxidase; OS — oxidative stress; PKC — protein kinase C; RAGE — receptor for AGE; ROS — reactive oxygen species; SOD — superoxide dismutase

Table 4. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in diabetes type 2 or heart failure: human studies*

Study	SGLT2i	Participants	Sample	Outcomes after treatment with SGLT2i	Conclusion
Kondo et al. (2021) [91]	Canagliflozin (*ex vivo*)	364 patients with or without T2DM undergoing cardiac surgery not treated with SGLT2i	Right atrial appendage biopsy obtained during cardiac surgery	↓ superoxide (NOX- and uncoupled NOS-derived) ↓ NOX activity, Rac1 activation ↑ AMPKα2, eNOS phosphorylation No change in OS markers after empagliflozin use	Canagliflozin attenuated OS, reduced Nox activity via SGLT1/AMPK/Rac1 signalling and improved NOS coupling to a greater extent in diabetic patients Empagliflozin, the most selective SGLT2i, did not influence oxidative stress ex vivo
Shigiyama et al. (2017) [23]	Dapagliflozin	80 patients with T2DM treated with 750 mg/day metformin randomized to metformin or dapagliflozin (5 mg/day) added to metformin for 16 weeks	Urea	↓ urine 8-OHdG/creatinine ratio No change in FMD ↑ FMD in the subgroup of patients with HbA_{1c} at baseline over 7.0%	Dapagliflozin reduces OS in diabetic patients and improves endothelial function only in subgroup with inadequately controlled diabetes
Kolijn et al. (2021) [24]	Empagliflozin (*ex vivo*)	30 patients with HFpEF and 10 healthy donor hearts not treated with SGLT2i	Left ventricular biopsy	↓ cytosolic and mitochondrial H_2O_2 ↓ lipid peroxidation, 3-NT ↑ GSH ↓ uncoupled eNOS ↑ NO/sGC/cGMP/PKG and PKA activity ↓ cardiomyocyte stiffness	Empagliflozin reversed OS dependent impairment of NO/sGC/cGMP/PKG signalling and reduced cardiomyocyte stiffness likely by its antioxidative properties

3-NT — 3-Nitrotyrosine; 8-OHdG — 8-hydroxy-2-deoxyguanosine; AMPK — adenosine monophosphate-activated protein kinase; AMPKa2 — adenosine monophosphate-activated protein kinase alpha 2; cGMP — cyclic guanosine monophosphate; eNOS — endothelial nitric oxide synthase; FMD — flow mediated dilation; GSH — glutathione; HbA_{1c} — glycated hemoglobin; H2O2 — hydrogen peroxide; HFpEF — heart failure with preserved ejection fraction; NO — nitric oxide; NOS — nitric oxide synthase enzyme; NOX — NADPH oxidase; OS — oxidative stress; PKA — protein kinase A; PKG — protein kinase G; Rac1 — ras-related C3 botulinum toxin substrate 1; sGC — soluble guanylate cyclase T2DM — type 2 diabetes mellitus

Table 5. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — animal diabetic kidney disease studies*

Study	SGLT2i	Animal model	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Conclusion
Vallon et al. (2014) [71]	Empagliflozin	Akita/+ ($Ins2^{+/c96y}$) and littermate $Ins2^{+/+}$ control mice	Kidney tissue	↓ NFκB ↓ CCL2, CD14 ↓ IL-6, TIMP2 No change in expression of NADPH oxidases, NOX2, NOX4, CCL5 cytokine	Empagliflozin attenuated the increase in renal inflammatory markers, but not the OS ones. Diabetes-induced renal changes may be caused by renal hyperfunction, albuminuria and inflammation rather than increased OS.
Terami et al. (2014) [92]	Dapagliflozin	*db/db* and *db/m* mice	Kidney tissue	↓ gene expression of CD14, CD11c ↓ gene expression of TGF-β, MCP-1, OPN and ICAM ↓ NOX4 ↓ ROS	Dapagliflozin ameliorated diabetic nephropathy by reducing hyperglycaemia and macrophage infiltration in the kidney and suppressing OS and proinflammatory gene expression both in the renal tissue and mProx24 cells.
			Proximal tubular epithelial cells (mProx24)	↓ NOX4 ↓ ROS ↓ gene expression of MCP-1 and $_{OPN}$	
Ojima et al. (2015) [71]	Empagliflozin	Streptozotocin-induced diabetic and non-diabetic Sprague-Dawley rats	Kidney tissue	↓ expression of AGEs, RAGEs, 8-OHdG and F4/80 ↓ gene expression of MCP-1, ICAM-1, PAI-1, CTGF, TGF-β	Empagliflozin treatment could decrease oxidative, inflammatory, and fibrotic reactions in DKD models via suppression of AGE-RAGE axis.
			Urine	↓ 8-OHdG ↓ L-FABP	
Shin et al. (2016) [93]	Dapagliflozin	Otsuka Long-Evans Tokushima Fatty rats and Long-Evans Tokushima Otsuka rats	Kidney tissue	↓ H_2O_2 ↓ MDA ↓ interstitial fibrosis ↑ SOD, CAT	Dapagliflozin treatment could be beneficial in DKD via suppression of OS and interstitial fibrosis.
Tang et al. (2017) [73]	Dapagliflozin	uninephrectomized *db/db* and *db/m* mice	Kidney cortex	↓ TGF-β1, PAI-1, FN, a1(IV) collagen ↓ expression of NF-kB, p65, MCP-1, NOX4, NOX2, p47phox	Dapagliflozin could slow the progression of diabetes-induced glomerulosclerosis improving the hyperglycaemia-induced inflammation and OS.
			Urine	↓ TBARS ↓ MCP-1	
Abdel-Wahab et al. (2018) [75]	Dapagliflozin	nicotinamide-streptozotocin-induced diabetic and non-diabetic Wistar rats	Plasma	↓ TGF-β ↓ TOS ↑ sRAGE	Treatment with dapagliflozin, led to increased sRAGE level and reduced inflammatory and oxidative markers with amelioration of renal histopathological changes.
			Kidney tissue	↓ MDA ↑ GSH-Px, SOD	

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Table 5. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — animal diabetic kidney disease studies*

Study	SGLT2i	Animal model	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Conclusion
Tanaka et al. (2018) [74]	Ipragliflozin	BTBR *ob/ob* and BTBR wild type mice	Kidney cortex	↓ GSH ↓ GSSG signals ↓ MDA ↓ mesangial expansion	Ipragliflozin is efficient in reducing the OS in the renal tissue.
Kamezaki et al. (2018) [94]	Ipragliflozin	*db/db* and *db/m* mice	Kidney cortex	↓ 8-OHdG ↓ NOX4 ↓ Slc34a1, megalin, KIM-1, NGAL ↑ oxygen tension in the kidney cortex	Ipragliflozin treatment reduced renal cortical hypoxia on early DKD in vivo. Dapagliflozin dose-dependently reduced OS in tubular epithelia and glomerular podocytes.
Cooper Woods et al. (2019) [95]	Canagliflozin	New Zealand obese mice with and without diet-induced T2DM	Urine	↓ urinary 8-isoprostane levels	Canagliflozin prevented the upregulation of OS, renal tubular fibrosis, and renal inflammation in T2DM.
			Kidney tissue	↓ tubular fibrosis ↓ macrophage infiltration ↓ cell proliferation	
Ali et al. (2019) [96]	Canagliflozin	Wistar rats with and without adenine-induced CKD	Plasma	↓ IL-6, IL-1β and TNF-α ↑ SOD, CAT, GR, and TAC	Canagliflozin given with adenine ameliorated adenine-induced CKD in rats reducing inflammatory and OS parameters.
Hasan et al. (2020) [97]	Canagliflozin	Long Evans rats with and without ISO-induced oxidative stress	Plasma and kidney tissue	↓ MDA, NO, MPO, APOP ↑ CAT, SOD	Canagliflozin reduced ISO-induced OS in the kidney and improved endogenous antioxidant action.
Kim et al. (2021) [98]	Dapagliflozin	*Db/db* and *db/+* mice	Kidney tissue	↓gene expression of p21, p16, p53 ↓ β-gal and γH2AX ↓ROS ↑SOD	Dapagliflozin treatment inhibited senescence processes and reduced OS, both in vitro and in the kidney tissue. Its anti-senescent and anti-inflammatory properties could exist independently of glucose-lowering effects of SGLT2i.
			Human renal tubular epithelial cell line (HK-2)	↑ β-HB ↑ Nrf2	
Wu et al. (2021) [76]	Empagliflozin	Sprague Dawley rats with and without streptozotocin-induced DM	Kidney tissue	↓ TNF-α, IL-1β, IL-6 ↓ MDA, NO ↑ SOD, GSH, CAT	Empagliflozin is effective in treatment of DKD, and its protective effect is related to reduced inflammation, renal fibrosis, and OS in the kidney tissue.
Ahmed et al. (2021) [99]	Empagliflozin	Streptozotocin-induced diabetic and non-diabetic Albino Wistar rats	Kidney tissue	↓ NGAL, KIM-1 ↓ NOX-2,4, TLR-2,4, MyD88 ↓TNF- α, IL-1β	Empagliflozin can protect against subclinical AKI after myocardial infarction, reducing kidney injury, inflammation, and OS.

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Table 5. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — animal diabetic kidney disease studies*

Study	SGLT2i	Animal model	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Conclusion
Hudkins et al. (2022) [72]	Empagliflozin	BTBR *ob/ob* mice	Kidney tissue	↓8-OHdG, 8-OHG ↓carbonyl oxidation in situ No change in accumulation of glycation-end products.	Empagliflozin treatment may DKD through the mechanisms leading to podocyte restoration and delay of DKD progress.
Po-Jui et al. (2022) [100]	Dapagliflozin	Streptozotocin-induced diabetic and non-diabetic C57BL6 mice	Plasma	↓ TNF-α, IL-1β, IL-6	Dapagliflozin decreased inflammatory cytokines and ROS levels after LPS-induced endotoxic shock.
			NRK52E cells	↓ NFκB ↓ CCL2, TNF-α, IL-1β, IL-6 ↑AMPK, Nrf2, HO-1	
			Kidney tissue	↓KIM-1 ↓ renal tubular injury score ↑ E-cadherin	

8-OHdG — 8-hydroxy-2′-deoxyguanosine; 8-OHG — 8-hydroxyguanine; AGE — advanced glycation end product; AKI — acute kidney injury; AMPK — adenosine monophosphate-activated protein kinase; APOP — advanced photochemical oxidation process; b-gal —b-galactosidase activity; b-HB — β-hydroxybutyrate; CAT — catalase; CCL2 -chemokine (C-C motif) ligand 2; CCL5 — chemokine (C-C motif) ligand 5; CD11c — integrin alpha X; CD14 — a cell surface marker of macrophages; CTGF — connective tissue growth factor; DKD — diabetic kidney disease; F4/80 — EGF-like module-containing mucin-like hormone receptor-like 1; FN — fibronectin; gH2AX — phosphorylated form of H2A histone family member X; GR — glutathione reductase; GSH — glutathione; HO-1 — heme oxygenase 1; H2O2 — hydrogen peroxide; ICAM — intercellular adhesion molecule; ICAM-1 — intercellular adhesion molecule-1; IL — interleukin; KIM-1 — kidney injury molecule-1; L-FABP — L-fatty acid binding protein; LPS — lipopolysaccharides; MCP-1 — monocyte chemoattractant protein-1; MDA — malondialdehyde; MPO — myeloperoxidase; mProx24 — murine proximal tubular epithelial cells; MyD88 — myeloid differentiation primary response 88; NADPH — nicotinamide adenine dinucleotide phosphate; NF-kB — nuclear factor kappa B; NGAL — neutrophil gelatinase-associated lipocalin; NO — nitric oxide; NOX — NADPH oxidase; Nrf2 — nuclear erythroid 2-related factor 2; NRK52E cells — immortalized rat tubular epithelial cell line; OPN — osteopontin ; OS — oxidative stress; PAI-1 — plasminogen activator inhibitor-1; p47phox — neutrophil cytosol factor 1; RAGE — receptor of AGEs; ROS — reactive oxygen species; SA b-gal — senescence-associated b-galactosidase activity; Slc34a1 — solute carrier family 34 member 1; SOD — superoxide dismutase; sRAGE — soluble receptor for AGEs; TAC — total antioxidant capacity; TBARS — thiobarbituric acid-reactive substances; TGF-b — transforming growth factor beta; TIMP2 — tissue inhibitor of matrix metalloproteinases; TLR-2,4 — toll-like receptor 2,4; TNF-a — tumour necrosis factor alpha; TOS — total oxidant status. Mice types: db/db — diabetic mice; db/m — non-diabetic mice; db/+ — non diabetic mice; Akita/+ (Ins2+/c96y) — diabetic mice; littermate Ins2+/+ — non-diabetic mice; BTBR ob/ob — diabetic mice; BTBR wild type — non-diabetic mice

Table 6. *Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — chronic kidney disease human studies*

Study	SGLT2i	Participants	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Findings
Osonoi et al. (2018) [101]	Canagliflozin	20 patients with T2DM and microalbuminuria	Urine	↓8-OHdG No changes in other kidney injury and inflammation markers.	Canagliflozin treatment was associated with decrease of one urinary OS marker
Liu et al. (2021) [102]	Ertugliflozin	468 adults with T2DM and CKD stage 3	Plasma	↓ KIM-1 ↑ eotaxin-1 No changes in the other OS, inflammatory and tubular injury markers.	Ertugliflozin treatment was associated with reduced kidney injury marker regardless of baseline renal function

8-OHdG — 8-hydroxy-2′-deoxyguanosine; KIM-1 — kidney injury molecule-1; OS — oxidative stress; T2DM — type 2 diabetes mellitus

There are only a few reports analysing the antioxidative potential of SGLT2i per se in patients with DKD. Two recent studies reported on the antioxidative and anti-inflammatory activity of these agents on renal tissue in patients with DM and impaired renal function [93, 94]. Both studies analysed diverse parameters, e.g. kidney injure molecule-1 (KIM-1), eotaxin, and 8-OHdG in different study groups; consequently, more human studies are needed (see Tab. 5 and Tab. 6).

Conclusions

Since being registered as a new class of oral glucose-lowering drugs (canagliflozin being the first one approved by the FDA in March 2013), almost 10 years later SGLT2i has apparently become not only an glucose-lowering but maybe a new class of cardio- and nephroprotective agent [77]. The underlying mechanisms of this phenomenon are still being studied, but one of the possible mechanisms of these protective properties is the reduction of OS and inflammation.

The reduction of OS as a part of interplay between heart and kidney may link the 2 newly acknowledged protective actions of this class of drugs, namely cardiac and renal protection. Under disease circumstances, the heart and the kidney create a deadly axis of pathophysiological linkage known as the cardio-renal continuum. Increasing evidence suggests that SGLT2i may help to restore the heart-kidney partnership.

REVIEW

Conflict of interest

The authors declare that they have no conflict of interest.

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