**Manuscript type:** review

**Title:** Extraglycemic effects of sodium glucose cotransporter 2 inhibitors with a systemic approach, from possibilities to certainty

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Extraglycemic effects of SGLT2 inhibitors with a systemic approach, from certainty to possibilities

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Dear, Dr. Richa Sharma I wish to submit a new manuscript entitled “Extraglycemic effects of SGLT2 inhibitors with a systemic approach, from certainty to possibilities” for consideration by the [British Journal of Clinical Pharmacology]. I confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

In this paper, we have reviewed on the pleotropic effects of SGLT2 inhibitors systemically. This is significant because any review in this regard to include all human systems is not done yet. This paper should be of interest to readers in the area of diabetes and anti-diabetic drugs.

In this review, we conducted a literature review on the effects of sodium glucose cotransporter 2 inhibitors on all human systems. The importance of this review is that, based on its extracts, we can use this drug relatively confidently in diabetic comorbid patients, and for more confidence in the usage of this drug, we will attract large clinical trials for shifting the possibilities to certainties. We wish to be interested in journal readers owing to its systemic approach.

Please address all correspondence concerning this manuscript to me at (mohammadbelalomari@gmail.com)

Thank you for your consideration of this manuscript.

Sincerely,

Dr. Mohammad Belal Omari

**Abstract**: Sodium-glucose cotransporter inhibitors (SGLT2 inhibitors) are novel drugs in the treatment of type 2 diabetes mellitus that prevent the absorption of glucose in the proximal tubules of the kidney and lower the blood glucose level. In addition to treating diabetes type 2, it influences all human systems. The aim of this study is to evaluate the effects of this drug (either beneficial or adverse) on all human systems and, based on that, a general opinion regarding the preference and safety of using this drug in diabetic patients with comorbidities. So far, no study has been conducted to evaluate the effects of this drug on all human systems.

Its beneficial effects on improving cardiovascular disease risk factors and reducing adverse events caused by cardiovascular and renal diseases have proven in most large clinical studies that these effects are almost certain. It also has beneficial effects on other human systems such as the respiratory system, the gastrointestinal system, the circulatory system, and the nervous system; more of them are at the level of clinical and pre-clinical trials but have not been proven in large clinical trials or meta-analyses, so the term possible is used. In this review, the beneficial effects of this drug and its mechanism on every system of humans have been studied, and finally, its adverse effects have also been discussed. The key impact of this study is to attract the attention of large clinical studies based on an overview of all possible effects for the determination of certainty.

**Method:** The search for relevant information is carried out in the PubMed and Google Scholar databases with no applied filters by using the following terms: diabetes mellitus type 2, SGLT, SGLT2 inhibitors, (SGLT2 inhibitors) AND (Pleotropic effects).

**Key words**: type 2 diabetes mellitus, sodium-glucose cotransporter 2 inhibitors, and extraglycemic effects.

**1. Introduction:** Diabetes type 2 has a close link to other comorbidities such as hypertension, high body weight, and lipid disorders [1]. These are components of metabolic syndrome, which in turn has relation to cardiovascular disease [2], which is mediated through atherosclerosis, oxidative stress, and inflammation [3] [4] [5]. Based on randomized clinical trial, strict lowering of systolic hypertension was associated with a lower risk of diabetes events than poor control of systolic hypertension [6], which may indicate a possible relationship between diabetes type 2 and hypertension. Improvement of type 2 diabetes mellitus with bariatric surgery indicates a close link between diabetes type 2 and obesity [7]. Improvement of glycemia with exercise [8] [9] [10] is more relevant to the attenuation of body weight and improvement of lipid profile [9] [11], which determine the correlation between dyslipidemia and diabetes mellitus type 2. Type 2 diabetes mellitus exerts acute and chronic complications [12] [13], which are associated with life-threatening morbidity and mortality [14]. These comorbidities related to diabetes mellitus are posed as extraglycemic effects of antidiabetic drugs, and we can express these effects approximately certainly. The Effects of this drug on other systems (such as neural, pulmonary, gastrointestinal, and blood circulation) that have not contributed to these comorbidities are in the realm of possibilities.

Because of the more complex pathophysiology of type 2 diabetes mellitus than type 1, we have multiple options in the treatment of type 2 diabetes mellitus [15]. In the new strategy of diabetes mellitus type 2 treatment, the focus has been on SGLTs [16], which have two types: SGLT1 and SGLT2; SGLT2 is predominantly located in the renal tubule, whereas SGLT1 is predominantly located in intestine [17]. But partially, SGLT1 is located in the terminal part of the proximal tubule [18]. SGLT2 inhibitors, by direct action in the early segment of the proximal tubule, reabsorb 80-90 percent of glucose, of which the remaining 10-20 percent is reabsorbed in the late segment of the proximal tubule in healthy persons[19]. Therefore, a normal healthy person doesn’t present glycosuria [19]. When glycemia exceeds 180 mg/dl, glycosuria takes place [19]. Therefore, for the consistency of glycosuria in diabetes mellitus type 2, the first drug was Phlorizin, which had non-selective action on both SGLT1 and SGLT2, with significant intestinal side effects [20]. In 2013, the FDA approved SGLT2 inhibitors as the treatment of type 2 diabetes mellitus [18], which have been established to have better cardiac and renal outcomes in multiple trials with a consequently lower rate of morbidity, mortality, and hospital stay in diabetic or non-diabetic patients.

As SGLT2 inhibitors act on the proximal tubule of the kidney [21], we must know the role of the kidney in glucose hemostasis. The kidney has different roles in glucose hemostasis [21], which consist of the renal glucogenic effect as liver after the absorptive process, the release of glucose after meals, and renal glucose absorption [22]. The glucose lowering effects of SGLT2 inhibitors are exerted via the last hemostatic effect [23]. SGLT2 inhibitors, by blocking SGLT2 in proximal tubules, exert different effects in addition to attenuating glycemic levels [24]. By exerting various metabolic changes, it causes not only correction of glucose, also cause improvement in multi-organ protection [25]. Any significant difference regarding the heart, kidney, and metabolic consequences has not been revealed between different agents of SGLT2 inhibitors [26]. Its effects are not dependent on insulin [27], but indirectly increase its sensitivity[28]. Therefore, it does not induce hypoglycemia [29].

The CHIEF-HF trial shows moderate evidence of improvement in heart failure symptoms after 12 weeks of therapy with canagliflozin in patients with or without diabetes and in low or normal ejection fractions [30]. Based on the DAPA-HF trial, treatment with dapagliflozin for the long term was associated with a reduction in mortality, hospital stay, and exercise tolerance in heart failure patients [31], with similar outcomes for empagliflozin in the EMPEROR-REDUCED trial [32]. The reduction of left ventricle mass with empagliflozin for the long term (e.g. 6 months) in the EMPA-HEART CardioLINK-6 trial also demonstrated a close link between these agents and the improvement of cardiovascular events [33]. The DAPA-CKD trial shows the strong evidence of decreasing the worsening of the filtration rate of glomeruli, attenuation of end-stage renal disease events, and renal disease-related mortality rate with treatment of dapagliflozin in diabetic or nondiabetic patients for long terms [34], with confirmation of these issues in the EMPA-KIDNEY trial by treatment with empagliflozin [35]. In addition to CKD, attenuation of injury markers in the proximal tubules of the kidney may have a role in protection against acute kidney injury [36].

The aim of this review is to learn about the effects of this drug on all systems of the body, which have not been reviewed yet. In other reviews, the cardiovascular and renal effects of this drug are more prominent; however, we also focus more in this regard but we also review the possible effects and some adverse effects of this drug in other systems.

**2. Cardiovascular effects of SGLT2i**

**2.1. Effects of SGLT2 inhibitors on the baseline pathology of cardiovascular disease (oxidative stress, inflammation, endothelial function, and atherosclerosis)**

Oxidative stress and inflammation have a key role in the pathogenesis of diabetes and its complications [37]. This concept is approved by reducing the progression and complications of diabetes mellitus type 2 by administering of antioxidant agents like zinc, FGFs, and metallothionein [38]. A close relationship between oxidative stress and inflammation is present [39] [40], because a randomized clinical trial with the participation of two groups (those who take concentrated juice of beetroot and the control group) suggests that beetroot juice(BJ), which has antioxidant materials, reduces inflammatory markers (i.e. IL6, TNF-a, and NF-kB) more than the control group [41]. Based on a randomized clinical trial, administration of MitoQ( an antioxidant) 20 mg per day for 6 weeks was associated with moderate evidence of improvement in flow-mediated dilation of the brachial artery and reducing the stiffness of the aorta compared to placebo, which may determine the relationship between oxidative stress and endothelial function [42]. The close relationship between these parameters is uniquely the predisposing factor of atherosclerosis [43], which is the underlined cause of diabetes-related mortality [44].

Usage of SGLT2 inhibitors for the treatment of type 2 diabetes mellitus regarding their antioxidant, anti-inflammatory effects, and improvement of micro- and macro vascular endothelial function is the better choice [45] [46] [47]. According to the clinical trial [48], The rest flow-mediated dilatation (FMD), which is an indicator of vascular function [49], was 3.3 (8.2%) and -1.2( 7.5%) respectively, for dapagliflozin and glibenclamide after 12 weeks of treatment, which may indicate the glucose-independent effects of SGLT2 inhibitors on endothelial function. This trial was carried out on the carotid artery with 75 percent thickening of the intima and media layers. Treatment with SGLT2i+GLP1-RA for 12 months was associated with a threefold decrease in the perfused boundary region (PBR) of the sublingual arterial microvessels compared to these drugs individually and insulin [50], which may indicate the modulation of the glycocalyx layer of the endothelium. An interventional double-blind randomized study has revealed a significant increase in antioxidant levels but a decrease in pro-inflammatory and pro-oxidant levels of serum in combination therapy (empagliflozin+ metformin) compared to each other individually [51]. All of these trials may show the beneficial effects of SGLT2 inhibitors on the improvement of oxidative stress, inflammation, and endothelial function.

**2.2. Effects of SGLT2 inhibitors on cardiovascular disease**

**2.2.1. Heart failure**

A systemic review and meta-analysis have revealed an overt reduction in cardiovascular mortality and hospitalization for heart failure with long-term therapy of SGLT2 inhibitors in type 2 diabetes mellitus [52]. These events are not limited only to diabetics, based on the EMPATROPISM trial [53], which demonstrated the reduction of LV mass and volume with consequent improvement of exercise tolerance and life style in nondiabetic patients, with confirmation of this issue in the EMPEROR-reduced trial [32] and the multicentre trial in diabetics or prediabetics [54].

SGLT2 inhibitors, by exerting favorable remodelling effects [55], reduce the hospitalization and mortality rates regarding cardiac failure [54]. The components in the pathophysiology of HF in diabetic patients (which is also called diabetic cardiomyopathy) may be reversed by SGLT2 inhibitors [56], Since this implicates the efficiency of this drug in cardiovascular events. There have been established cardioprotective mechanisms of SGLT2 inhibitors [57] [58] [19], which include two principle mechanisms that contain metabolic and hemodynamic pathways. The metabolic regarding mechanism consist of catabolic exerting effects that predominate in response to hypoglycemia due to glycosuria, with the consequence of lipolysis and a decrease in body weight. The hemodynamic mechanism is mediated through attenuation of heart muscle stress via improvement of foreward and backward forces. These forces are due to hypertension and venous blood volume, which in turn attenuate by decreasing the blood pressure and natriuretic effects of these drugs. Also, cardiac structure and metabolism improve by decreasing fibrosis deposition (partially due to modulation of inflammatory mediators and inhibition of Na+/H+ exchange) and enhancing cardiac muscle contractility (partially due to ketones overproduction and increased oxygen carrying capacity via erythropoiesis) [56]. Attenuation of sympathetic activity is another aspect of the cardioprotection of these drugs [59], and its overactivity has a key role in the pathophysiology of heart failure [60]. According to Gary D. Lopaschuk et al, empagliflozin in diabetic or non-diabetic patients, by reducing the oxidative damage of mitochondria and modulating the intra-cytoplasmic Na, which influences Ca handling, improves the potential of the cardiac muscle and subsequently the HF [61]. According to the scientific workshop report, the cardioprotective mechanism of SGLT2 inhibitors may not be purely related to glycemic control, which is supported by evidence that concomitant use of other anti-glycemic agents in type 2 diabetes mellitus does not reduce the CV risk [62].

**2.2.2. Cardiac fibrosis**

Cardiac remodellingat the base of cardiac fibrosis is the leading cause of diabetic cardiomyopathy and, subsequently, HF [63]. Based on the rat model [64], dapagliflozin may play a role in the improvement of cardiac remodeling after removing aneurysmal scar tissue, which is likely mediated through modulation of hub genes. This issue was confirmed in another preclinical study [65], with a possible mechanism that is mediated through inhibition of the STAT3 pathway, toll-like receptor 4, and activation of M2 macrophages, which finally inhibit the proliferation of myofibroblast [65] [66]. Anti-fibrotic effects of SGLT2 inhibitors may be partially due to inhibition of sodium hydrogen exchanger 1 (NHE1) [67] (which consists in cardiac remodeling and fibrosis) [68], attenuation of high glucose-induced endoplasmic reticulum stress, reducing apoptosis and oxidative stress [69] [70], suppression of NLPR3, MyD88, and inflammatory cytokines [71] [72]. Similar studies have also demonstrated the anti-oxidative and anti-fibrotic effects of dapagliflozin and empagliflozin in diabetic and non-diabetic mice by down-regulating TGF-B and the smad signaling pathway [70] [73] [74], which is more likely mediated through modulation of angiotensin 2 [73]. Similar outcomes are also yielded in a comparative study of SGLT2 inhibitors and GLP1 agonists in diabetic mice, with the superiority of SGLT2 inhibitors over GLP1 agonists in attenuating cardiac fibrosis [75]. The pathogenesis of arrhythmogenic cardiomyopathy (ACM) may be partially reversed by dapagliflozin’s anti-fibrotic effects in the heart [76]. According to the human study, dapagliflozin treatment after 4 weeks in type 2 diabetes mellitus associated with acute heart failure has demonstrated a significant decrease in inflammatory mediators and an improvement in systolic and diastolic functions compared to the control group [77]. A similar result has been yielded from the porcine model regarding improvement in diastolic function in heart failure without diabetes over 2 months with empagliflozin [78]. Based on the rat model, the improvement of doxorubicin-induced cardiotoxicity with empagliflozin also poses the anti-oxidative and anti-fibrotic role of this drug in the heart [79] [71]. Finally, suppression of inflammatory mediators, anti-oxidation, and modulation of the extracellular matrix on the surface of cardiac cells have a key role in the anti-fibrotic effects of SGLT2 inhibitors [63].

**2.2.3. Ischemic heart disease**

Diabetes mellitus type 2 patients are prone to coronary artery disease [80]. The efficacy of SGLT2 inhibitors in improving major cardiovascular outcomes, among them ischemic events, has been revealed in multiple clinical trials and meta-analyses [33] [81] [82] [83] [84]. These effects may be partially due to the suppression of the sympathetic tone and attenuation of the left ventricle mass index (LVMi) [85] [33]. An animal model also has showed decreasing the infarct size of the heart after treatment with empagliflozin in diabetic or nondiabetic mice [86]. Based on meta-analysis, one of the possible anti-diabetic and anti-ischemic properties of these drugs may be mediated through different choline (especially glycine) metabolites [87]. As has been demonstrated, alleles contributing to increasing glycine may be responsible for the attenuation of coronary artery disease [88]. Based on meta-analysis, treatment with SGLT2 inhibitors is not associated with any significant difference in the incidence of atherosclerotic-induced ischemic changes (as stable angina, unstable angina, or myocardial infarction) in type 2 diabetes mellitus [89].

**2.2.4. Arrhythmias**

Hyperglycemia due to diabetes mellitus is a potential stimulator of the arrhythmia-producing pathway. As glycemia level disorders may cause structural remodeling and metabolic changes, both cause electrical disorders and consequently arrhythmias [90] [91]. SGLT2 inhibitors, by improving ion hemostasis, modulating cardiac remodeling, attenuating sympathetic nervous system activity, and improving mitochondrial function, exert antiarrhythmic properties [92] [93]. Several meta-analyses and clinical studies have shown a significant decrease in arrhythmia risk in type 2 diabetes mellitus with the treatment of SGLT2 inhibitors [94] [95] [96] [97].

**2.3. Effects of SGLT2 inhibitors on cardiovascular disease risk factors**

**2.3.1. Components of metabolic syndrome**

**2.3.1.1. Body weight**

According to the double-blind randomized placebo-controlled study, dapagliflozin has revealed a greater loss of body weight in patients with type 2 diabetes mellitus and obesity after 32 weeks than the control group [98]. Similarly, the ADDENDA-BHS2 trial has revealed good evidence of fat mass reduction after 12 weeks of therapy with dapagliflozin (10mg/day) compared to glibenclamide (5 mg/ day) in type 2 diabetes mellitus [99]. A systemic review and meta-analysis also revealed very strong evidence of weight reduction in non-diabetic but obese patients by SGLT2 inhibitor treatment [100]. Based on the rat model, empagliflozin was associated with weight reduction in the mice who were fed a high fat diet [101]. Regarding the comparative efficacy of anti-diabetic drugs in weight reduction, the systemic review and meta-analysis are responsible for this issue [102]. Attenuation of body weight with SGLT2i was less than semaglutide but greater than metformin. Based on a clinical trial [103], 52-weeks treatment with canagliflozin was associated with a greater reduction of serum leptin than glimepiride, which has contributed to the improvement of lipid metabolism and the reduction of body weight. Attenuation of other inflammatory markers and increasing adiponectines were also seen in this trial, but they did not show a contribution to improvement in lipid metabolism or body weight.

Glycosuria, induced by therapeutic ranges of SGLT2 inhibitors, causes a loss of 300 kcal of energy per day, which is responsible for a total of 10 Kg of body weight loss over one year[104]. SGLT2 inhibitors primarily attenuate the availability of glucose, and in the late after depletion of glucose, the body consumes other energy-containing storage as lipid, resulting in high fat utilization and decreasing body weight [105]. Luseogliflozin has been shown to decrease total body fat more than visceral fat at the beginning and after a long time interval [106]. Based on a randomized controlled trial, we can determine the contribution of the the fibrinolytic process to body weight and other hormones (leptin and adiponectines), which has shown a reduction of body weight and leptin associated with a 25 percent reduction of plasminogen activator inhibitor 1 (PAI-1) after 12 weeks of therapy, whereas the body weight reduction has not contributed to the adiponectine level [107]. Also, by reducing the ratio of insulin to glucagon, arise lipolysis and subsequent fat and weight loss [108]. Through direct and indirect effects (lipolysis and loss of calories by osmotic dieresis), SGLT2 inhibitors cause an imbalance of energy intake and expenditure that otherwise decreases the body weight [109].

**2.3.1.2. Blood pressure (BP)**

A systemic review and network meta-analysis have revealed that SGLT2i and semaglutide are more efficient than metformin in reducing blood pressure in patients with type 2 diabetes mellitus [102]. According to the randomized, placebo-controlled trial, treatment with empagliflozin for one month is associated with a systolic and diastolic pressure reduction in 24 hours of ambulation in patients without diabetes and hypertension [110].

SGLT2 inhibitors may play a role in decreasing hypertension via different mechanisms such as excretion of glucose and sodium, neuro-hormonal and kidney system modulation [111] [112] [113], lowering body weight, reducing arterial stiffness, modulation of endothelial function [112] [113] [114], and decreasing uric acid [115]. Among them, osmotic diuresis and natriuresis may be the major components of SGLT2 inhibitors in blood pressure reduction [116], which make them loop diuretics [114]. SGLT2 inhibitors, via antioxidant and anti-inflammatory effects, may induce the release of NO with a consequent reduction in blood pressure [112]. The inflammatory process in the pathogenesis of blood pressure will be more clearly defined in a meta-analysis that shows the immunity-firing character of garlic in the treatment of hypertension [117] and, based on Philip Wenzel [118], that they demonstrate the role of monocytes as inflammatory markers in the pathogenesis of hypertension. Anti-inflammatory effects of SGLT2 inhibitors via reducing the RAAS (especially angiotensin II) minimize blood pressure [111]. In an interventional study on patients with type 2 diabetes mellitus, dapagliflozin reduced cardiac output and vascular stiffness by 5% and 11% respectively, and was associated with a mean arterial pressure reduction [119]. Also, a remarkable increase in hematocrit via SGLT2 inhibitor [120] is also contained in the blood pressure-lowering effects of this drug [121].

**2.3.1.3. Lipid profile**

A retrospective study has revealed a mean reduction of total cholesterol, LDL, and triglycerides of 17.6 mg/dl, 13.4 mg/dl, and 25.9 mg/dl, respectively, after three months of treatment with dapagliflozin in type 2 diabetes mellitus [122]. But conversely, the systemic reviews and meta-analysis, revealed different effects regarding lipid components: as a result, there was a significant increase in LDL cholesterol, HDL cholesterol, and non-HDL cholesterol but a decrease in triglycerides [123] [124]. Also, a clinical study was conducted to evaluate the comparative effects of SGLT2 inhibitors (monotherapy) and insulin+SGLT2 inhibitors (combine therapy) on lipid profiles, which demonstrated the better impact of SGLT2 inhibitors (monotherapy) on lipid profiles (increasing HDL cholesterol and decreasing triglyceride), whereas the addition of insulin to SGLT2 has not shown any additional benefit to lipid profiles [125].

Relative glucose deficiency stimulates the catabolic state with lipolysis and improves the lipid profile [126]. Also, increasing the glucagon/insulin ratio exerts a lipolyitc character [127], which furthermore effects the lipid profile. Effects on lipid profile may be mediated directly or indirectly, as mentioned above: directly improve lipid profile via catabolic lipolysis and disturbance of insulin-glucagon ratio [126] [127], and indirectly by reduction of body weight, attenuation of oxidative stress, inflammation, and improvement of beta-cell function, sensitize the insulin receptors, and improve metabolic profile according to lipid profile improvement (increasing HDL and decreasing triglyceride) [127]. Based on a rat model, SGLT2 inhibitors increase LDL level in the blood by increasing its synthesis via enhancing the lipoprotein-lipase activity and delayed turnover of LDL via increasing the LDL hepatic receptors[128]. Conversely, by increasing the LpL activity, triglyceride and total cholesterol decline [129]. The small increase in LDL is counterbalanced by decreasing the atherogenic form of LDL (small dense LDL) [130] and the remarkable increase in HDL-c [131].

**2.3.2. Serum uric acid level**

Hyperuricemia has a close link to the pathogenesis of metabolic syndrome (obesity, hypertension, diabetes mellitus, and hypertriglyceridemia), non-alcoholic steatohepatitis, acute renal failure, chronic renal failure, ischemic heart disease, and cardiovascular dysfunction [132] [133] [134] [135]. Its relation to other comorbidities, including heart failure, is clarified the in EMPEROR-reduced [136] and DAPA-HF trials [137]. An interventional study has revealed that uremic acid-induced cardiovascular and renal events may be mediated by pro-inflammatory effects and overexpression of inflammatory mediators (IL-6, IL8, and IL-1β mRNA) [138]. The attenuation of episodes, adverse outcomes, and drug dosage for the treatment of gout with SGLT2 inhibitors may pose a lowering effect of SGLT2 inhibitors on serum uric acid levels [139] [140]. Based on human studies, the level of urinary excretion of uric acid and serum uric acid is conversely proportionate to each other during SGLT2 inhibitor therapy. This issue declares the uric acid lowering mechanism of SGLT2 inhibitors [141], which is more likely dependent on glycosuria [142], and may be mediated through modulation of GLUT9 and URAT1 transporters [143], and down-regulation of xanthine oxidase [144]. A cohort study has also shown a reduction in the risk of gout in people with type 2 diabetes mellitus who are treated with SGLT2i rather than GLP1 agonists [145]. Uric acid-lowering effects of SGLT2 inhibitors in type 2 diabetes mellitus are influenced by the severity of type 2 diabetes mellitus and CKD [146]. Excretion is reduced in high levels of HbA1C and advanced kidney disease (GFR less than 60 ml/min), whereas hyperuricemia is in turn an independent risk factor for cardiovascular disease (e.g., CKD) irrespective of diabetes or the normal population [147]. This uric acid-lowering effect of SGLT2 inhibitors may be unlikely to be related to the baseline concentration [137].

**2.3.3. Nonalcoholic fatty liver disease (NAFLD)**

Excess fat deposition in the liver unrelated to alcohol is called NAFLD [148], with an incidence of 2-3 percent worldwide[149]. NAFLD has a close link to the metabolic syndrome [150]. Among metabolic syndrome, association of both diabetes mellitus and Non-alcoholic fatty liver disease, complicate each other with adverse consequence of diabetes complications and advanced liver disease, cirrhosis and even liver carcinoma[151] [152]. Therefore, the lowering of high blood glucose is beneficial in the treatment of NAFLD [153]; for this reason, we must choose a safe anti-diabetic drug that at least attenuates these adverse events. Among the new anti-diabetic drugs, SGLT2 inhibitors and GLP1 agonists are preferred for the treatment of diabetes associated with NAFLD [154]. Several clinical trials have shown the efficiency of empagliflozin and dapagliflozin in attenuating of liver fat and improving metabolic parameters of the liver in type 2 diabetes mellitus [155] [156] [157] [158] [159] [160] [161], with confirmation by several meta-analyses and systemic reviews [162] [163] [164] [165] [166]. Their effects on NAFLD are demonstrated in clinical trials and reviews without diabetes mellitus [167] [168] [169]. The key components in the pathogenesis of NAFLD are derived from environmental and genetic causes, with resultant lipotoxicity and consequent mitochondrial dysfunction, ER stress and the release of ROS, autophagy, and apoptosis [170]. Effective drugs in the treatment of NAFLD must block these pathogenic series [153], which According to a review of human, animal, and in vitro data by Theodoros Androutsakos et al., all of these parameters in the pathogenesis are modulated by SGLT2 inhibitors, which demonstrate the efficiency of these drugs in the treatment of NAFLD irrespective of associated diabetes mellitus [171].

**3. Effects of SGLT2 inhibitors on the pulmonary system**

A population-based cohort study and a meta-analysis have revealed a lower incidence of exacerbations of COPD and asthma in diabetic patients with SGLT2 inhibitors [172] [173]**.** Adecrease in the new onset of obstructive sleep apnea with empagliflozin compared to placebo was also demonstrated in a randomized controlled trial [174]. Another retrospective cohort study has revealed a lower risk of pneumonia in SGLT2 inhibitors than DPP4 inhibitors in type 2 diabetes mellitus [175]. A preclinical study on a rat model has revealed the possible therapeutic role of dapagliflozin-induced hypoglycemia in respiratory pseudomonas infection in diabetic mice [176]. Diabetic patients, according to the COVID-19, are prone to some complications [177]. The role of SGLT2 inhibitors in SARS-CoV-2 infection therapy has been revealed in a meta-analysis, that may be due to the down-regulatory effects on inflammatory cascade, improvement of pulmonary ventillatory perfusion, and oxygenation [178], but we must be careful in diabetic patients, which increase the risk of euDKA [179]. Several clinical studies also pose the role of SGLT2 inhibitors in declining pulmonary hypertension and RV systolic pressure [180] [181] [182] [183] [184] [185] [186], which may be related to improvement of vascular wall stiffness and the release of NO [187] [188] [189]. Based on the rat model, empagliflozin has been evaluated as a treatment in rats, with strong evidence of pulmonary better evidence as: improvement of pulmonary function and ischemia/ reperfusion induced lung injury [190] [191], which is likely to be related to the ERK1-mediated signaling pathway [190]. Other pulmonary protective effects may be based on anti-inflammatory effects because a rat model has revealed LPS-mediated lung damage [192] [193], whereas LPS is an activator of inflammation and its markers [194]. The DEFINE- HF trial shows a remarkable decrease in lung fluid volume with dapagliflozin over placebo over 12 weeks of therapy [195]. The distinct diuretic effects of SGLT2 inhibitors may have a role in treating lung edema [196]. Possibly, the progression of early-stage lung adenocarcinoma is mediated via SGLT2 receptors, which clarifies the protective role of SGLT2 inhibitors in this regard [197].

**4. Effects of SGLT2 inhibitors on the urogenital system**

**4.1. Urinary system (beneficial effects)**

**4.1.1. Kidney**

The DAPA-CKD trial [198] has investigated the effects of dapagliflozin in CKD, irrespective of diabetes mellitus, with or without cardiovascular disease. The primary outcomes of this therapy (e.g., progression to end-stage kidney disease) have been attenuated with the treatment of dapagliflozin, with more attenuation in patients without cardiovascular disease (primary prevention). Although, based on the EMPA-REG OUTCOME trial, short-time (e.g., 4 weeks) treatment with empagliflozin may be associated with a lower eGFR than placebo, which may not be attributed to cardiac and kidney adverse effects over a long period of time [199].SGLT2i, increases the adenosine (via delivery of sodium to the macula densa, which is known as tubule-glomerular feedback) and relatively attenuates the NO, with the resultant of vasoconstriction of afferent arterioles and vasodilation of efferent arterioles that ensue with the decline of glomerular pressure [200] [201]. Increasing glomerular pressure is the leading cause of proteinuria, which subsequently deteriorates the nephron and causes kidney disease [202]. Thus, SGLT2i, by decreasing GFR, prevents the progression of the kidney disease. Also theoretically, co-localization of SGLT2 with sodium hydrogen exchanger 3 (NHE3) in proximal tubule and effect of SGLT2i as loop diuretic on loop of hanle, which inhibits Na-K-2Cl co-transporters, exerts the natriuretic effects and subsequently decreases blood pressure, and protective effects in the tubular tissue of the kidney [203] [204]. Albuminuria, which is located as a cornerstone in the progression of advanced kidney disease [205], is reduced by SGLT2 inhibitors in type 2 diabetes mellitus [206] [207] [208], which may be a lack of this effect in non-diabetic patients [209].

The reno-protective effects of SGLT2 inhibitors may be more related to glycosuria and natriuresis, whose mechanisms are classified as direct and indirect effects [58] [210]. The direct renal protection mechanism (also called hemodynamic effects), as mentioned above, exerts its protective effect through tubule-glomerular feedback and increased production of adenosine, which lowers the GFR by vasoconstriction of afferent arterioles [58] [204] [201]. indirect protective effects (also called metabolic effects) of SGLT2i are mediated by treatment of risk factors( blood pressure reduction through neuro-hormonal modulation, decreasing body weight via alteration of adipose tissue metabolism, and lowering uric acid level) [58] [211]. In addition to the direct and indirect protection mechanisms, glucosuria-induced deprivation of nutrition is an important stimulator of hypoxia-inducible factors [212]. There are two types of hypoxia-inducible factors (HIF 1α and HIF 2α), among which HIF1α has a role in the remodeling of tubules and the interstitium of the kidney, which is inhibited by SGLT2 inhibitors [213]; but Hypoxia-inducible factor 2α (HIF-2α), which is responsible for erythrocytosis and the improvement of oxygen transport to the kidney, is also produced by SGLT2 inhibitors in the tubule-glomerular feedback process, which in turn plays a role in renal protection [212]. Based on the experimental model, treatment with SGLT2 inhibitors (canagliflozin) was associated with decreased expression of inflammatory mediators and attenuation of fibrosis in renal tubules[214],whereas inflammation and fibrosis have a close relation to kidney dysfunction [215]. Therefore, SGLT2 inhibitors modulates the inflammatory and fibrotic processes and play a partial role in kidney function improvement. Because of inhibition of glucose reabsorption, the load of work in tubules is also decreased with attenuation of oxygen demand; therefore, the improvement of hypoxia plays an important role in kidney protection [216].

**4.2. Genital system** (see adverse effects)

**5. Effects of SGLT2 inhibitors on the gastrointestinal tract**

The first study of the effect of SGLT2 inhibitors on the gastrointestinal tract was an in vivo study by Taskaldiran et al. in a rat model. They investigated the efficiency of empagliflozin on the gastric mucosa that was injured by indomethacin, with the best effects on the production of mucin and the treatment of gastritis [217]. In vitro and in vivo studies on rat models explain the possible role of SGLT2 inhibitors in the treatment of IBD, which is more likely mediated through suppression of the inflammatory cascade and multiple pathways [218] [219] [220] [221]. An animal model has also shown the possible beneficial effects of SGLT2 inhibitors in irritable bowel syndrome [222]. Dysregulation of intestinal microflora has a relation to diabetes [223], which may be regulated with SGLT2 inhibitors. These effects have been demonstrated in several preclinical studies [224] [225] [226]. confirmation of these preclinical studies comes from a recently conducted clinical study on Japanese patients with type 2 diabetes mellitus [227]. These evidences potentiate the beneficial role of SGLT2 inhibitors in gastritis, IBD, and IBS [228].

**6. Effects of SGLT2 inhibitors on the components of blood circulation**

**6.1. Hematocrite**

According to meta-analysis, SGLT2 inhibitors are associated with a significant increase in haemoglobin and hematocrite [229] [230] [120], which may be due to increasing erythropoietin [231] [232] via the recovery of renal erythropoietin-producing cells (REPs) or neural crest-derived fibroblasts from myofibroblast (dysfunctional fibroblast), with resultant decrease of renal glucotoxicity and hypoxia[233] [234] [235] [236]. This issue is confirmed by the DAPA-HF trial, which has shown the improvement of anemia with dapagliflozin [237] and the decline of the need for erythropoiesis-stimulating agents in CKD and type 2 diabetes mellitus with canagliflozin treatment [238]. Also, the two case reports declare the role of SGLT2 inhibitors in raising hemoglobin and hematocrite in type 2 diabetes mellitus [239]. Increasing the delivery of oxygen to the myocardium with SGLT2 inhibitor therapy is also known to be related to erythropoiesis, which, as mentioned, is associated with better cardiovascular outcomes [240].

**6.2. Leukocytes**

Two clinical trials have shown the therapeutic role of empagliflozin in neutropenia [241] [242], with confirmation by Veiga-da-Cunha et al [243]. But in another randomized clinical trial, canagliflozin showed a converse effect on the count of white blood cells, which has shown that canagliflozin reduces the count of leukocytes more than glimepiride in type 2 diabetes mellitus [244].

**6.3. Platelets**

Hyperactivation of thrombocytes has a close relationship to diabetes mellitus [245], which is a major component of atherosclerosis [246]. According to the two clinical studies, this component (hyperactivation of thrombocytes) has been suppressed by the administration of dapagliflozin and empagliflozin in type 2 diabetes mellitus and ischemic heart disease [247] [248], with confirmation of this issue by Valentina Spigoni et al [249].

**6.4. Electrolytes**

SGLT2 inhibitors exert different effects on serum electrolytes [250], which may be more prominent than sulfonylurea [251]. According to the CREDENCE trial, canagliflozin was associated with more improvement in hyperkalemia than placebo in type 2 diabetes mellitus and CKD [252], with confirmation by Pierre Gabai et al [253]. Maintaining an adequate level of serum magnesium diminishes the cardiovascular risk in diabetic patients [254] [255]. Based on a met-analysis and a case report, SGLT2 inhibitors are associated with an increase in magnesium levels in type 2 diabetes mellitus that otherwise exerts beneficial effects on cardiovascular events.

**7. Effects of SGLT2 inhibitors on the neurological system**

SGLTs have multiple isoforms, from SGLT1 to SGLT6; with the exception of SGLT5, the other forms express themselves in the brain [256]. Expression of SGLT1 is more prevalent than SGLT2 [257], but colocalization of them is attributable to SGLT2 expression [256]. SGLT2 inhibitors are lipid-soluble, and transfer via the transcytosis mechanism from the blood-brain barrier [258] [257], and modulate its receptors in the brain [259]. So, based on the characteristics of SGLT receptor expression and the passing of SGLT2 inhibitors through the blood-brain barrier and their modulatory effects on their receptors, they exert neural effects. Based on a clinical trial, DAPA-Lira was shown to increase the immature neurons in the dentate gyrus and synaptophysin in the stratum pyramidal layer by 44-69% and 50%, respectively (P value< 0.01) [260]. A retrospective cohort study has revealed a lower incidence of new-onset stroke in diabetic patients in the SGLT2 group than in the non-SGLT2 group [261]. Based on a rat model, stimulation of microglial cells with empagliflozin shows a decrease in NO, a reduction of pro-inflammatory cytokines, and an anti-inflammatory effect in microglial cells [262], which are the key cells in neurogenesis, synaptic connectivity, and prevent excitotoxicity [263]. So these characters play a neuroprotective role by improving synaptic activity, memory function, and cognitive function [264]. Neurocognitive function may be improved by SGLT2 inhibitors via the treatment of hyponatremia by free water clearance, whichever role is useful in the treatment of SIADH [265]. A retrospective study on type 2 diabetes mellitus, whose primary outcome was to investigate the new onset of dementia, Alzheimer disease, and Parkinson disease, has revealed significant improvements in these parameters (p < 0.0001, p = 0.0047, and p = 0.0006, respectively) [266]. Anti-oxidative effects, regulation of metabolic processes, and inhibiting choline esterase enzyme may be used as treatment option in the autism spectrum of the disease (ASD) [257]; and anti-apoptotic, anti-inflammatory, and anti-glycolytic effects exert therapeutic roles in Huntington disease [267]. By interacting with AChE and A 2A Adenosine (A2AAR) receptors, they play a treatment role in Alzheimer disease [268]. In the murine model, randomization of laboratory rats with pentylenetetrazol (PTZ)-induced seizure for dapagliflozin was significantly improved [269], and this effect may be mediated through GABAB2 activation and up-leveling of GABA [270]. AB amyloid plaque and synapsis dysfunction related to Alzheimer disease [271] have a contribution to the mTOR signaling pathway [259], which is restored by SGLT2 inhibitors [272].

**8. Skeletal system** (see adverse effects)

**9. Adverse effects of SGLT2 inhibitors**

**9.1. Diabetic ketoacidosis (DKA)**

DKA is a life-threatening complication of diabetes, which is more common in type 1 than type 2 diabetes mellitus and in children than in adults [273] [274]. Based on clinical data, the type of DKA in SGLT2i is more likely to be euglycemic and is more difficult to recover from than other causes of it [275] [276] [277] [278]. The infection was the most common risk factor for euDKA [278]. A systemic review shows that euglycemic DKA is 3.7 times more common in SGLT2 inhibitors than other drugs [279]. Similarly, a cohort study also has shown 3-fold increase in DKA events with SGLT2 inhibitor treatment [280]. Several meta-analyses have also demonstrated the increasing risk of DKA in SGLT2 inhibitors compared to placebo [281] [282] [283]. Euglycemic diabetic ketoacidosis (euDKA) is contributed to declining insulin, increasing glucagon, shifting substrate from carbohydrate to lipid (lipolysis and FFA production) which produce ketone bodies [284]. Furthermore, SGLT2 inhibitors are associated with attenuation of renal ketone body clearance and relative ketone enhancement due to volume contraction in the base of glycosuria [284]. Sodium-coupled monocarboxylate transporter (SMCT2), which is located in the apical membrane of the proximal renal tubules [285], is responsible for the absorption of ketones, lactates and has some contribution to the SGLT2-inhibitors induced DKA [286]. Its activity is related to the trans-apical membrane gradient of sodium and the availability of sodium to its receptors, which is provided by SGLT2 inhibitors directly (increasing sodium gradient and supply to SMCT2 receptors) and indirectly (via attenuation of Na/K ATPase and increasing sodium gradient between lumen and proximal tubule cells) [286].

**9.2. Urogenital infections**

As glucosuria plays a key role in predisposing diabetic patients to urinary tract and genital infections [287], and SGLT2 inhibitors, by their mechanistic effects, accelerate glucosuria [288], and therefore precipitate the urogenital tract infections. In this regard, a double-blind study with randomization of 198 diabetic females with type 2 diabetes mellitus has revealed the role of canagliflozin in the adverse events of candidal vulvovaginitis [289]. The increasing events of mycotic infection in type 2 diabetes mellitus with SGLT2 inhibitors over 30 days are also demonstrated by a retrospective cohort study [290]. The emergence of UTI or genital tract infection may be dose-dependent; higher doses may cause UTI, whereas lower doses may be associated with genital infections [291]. In an observational study of diabetic patients with SGLT2 inhibitors and non-SGLT2 inhibitors, the incidence of UTI was higher in the SGLT2 group than non-SGLT2 group [292] and was more common in women than men [292]. Another observational study exhibits the increased risk of UTI in type 2 diabetes mellitus when SGLT2 is added to the other anti-diabetic dugs [293]. In the murine model, which was randomized to dapagliflozin and canagliflozin, it also demonstrated the role of SGLT2 inhibitors in increasing UTI events [294].

**9.3. Lower limb amputations**

Amputation may be at the base of low blood perfusion to the lower limb due to the diuretic-like effects of these drugs [295], because an observational cohort study of diabetes mellitus type 2 who were treated with diuretic has demonstrated an increasing incidence of lower limb events [296]. Regarding these effects of SGLT2 inhibitors on amputations, a brief review of the risk of SGLT2 inhibitors in amputations is required. Several cohort studies have demonstrated adverse events regarding lower limb amputation, but these events are not significantly elevated [297] [298]. The increased risk of lower limb amputations with canagliflozin has been determined in several meta-analyses [299] [300] [301], but is not definitely determined in other agents of SGLT2 inhibitors (e.g., dapagliflozin and empagliflozin) [302] [300]. According to the WHO universal database of case reports, lower limb amputation may not be related only to canagliflozin but also may be caused by empagliflozin and probably by dapagliflozin [303].

**9.4. Skeletal disorders**

SGLT2 inhibitors By disturbing the axis of the 1,25-dihydroxyvitamin D-PTH [304] [305], weight loss-induced increases bone turnover [306] and possibly increase bone fragility[307] have relation to the bone health issues. Regarding these effects of SGLT2 inhibitors on bone health, a brief review of the risk of SGLT2 inhibitors in fracture is required. Based on a randomized controlled trial that was carried out in 90 centers in 17 countries, the main point was to investigate the effects of SGLT2 inhibitors (canagliflozin) on bone mineral density. It has been shown that canagliflozin reduces bone mineral density in the hip bone [308], which has a close link to osteoporosis [309] and fractures [310]. Another RCT also confirmed this effect of canagliflozin on the bone [311]. Based on a cohort study, dapagliflozin is not related to those with fractures who seek immediate treatment [312]. Based on a meta-analysis [313], empagliflozin is also less related to significant bone fracture events than placebo. Although the relation of SGLT2 inhibitors to bone fractures in type 2 diabetes mellitus has not been demonstrated in several meta-analyses [314] [315] [316].

**Conclusion**

This drug has beneficial effects on all human systems, while its adverse effects are minor. Learning more about its effects on other systems except the cardiovascular and renal systems requires more systemic reviews and meta-analyses. But currently, as a new drug in medicine, it seems favorable to treat diabetes patients associated with other comorbidities and even some comorbidities in prediabetics or without diabetes.

Therefore, its beneficial effects counterbalance its adverse effects, and we can suggest its favorable use in diabetic comorbid patients and even in prediabetics and non-diabetics.

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