

# Drug Safety Evaluation of Sodium-Glucose Cotransporter 2 Inhibitors in Diabetic Comorbid Patients by Review of Systemic Extraglycemic Effects

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**Purpose:** The aim of this study is to evaluate the safety of this drug in diabetic patients with comorbidities of all systems.

**Method:** In this review, the beneficial effects of this drug and its mechanism on the disorders of every system of humans in relation to diabetes have been studied, and finally, its adverse effects have also been discussed. The search for relevant information is carried out in the PubMed and Google Scholar databases by using the following terms: diabetes mellitus type 2, SGLT, SGLT2 inhibitors, (SGLT2 inhibitors) AND (Pleiotropic effects). All English-published articles from 2016 to 2023 have been used in this study. It should be noted that a small number of articles published before 2016 have been used in the introduction and general informations.

**Results:** 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.

**Conclusion:** With the exception of a few adverse effects, this drug is considered a good choice and safe for all diabetic patients with comorbidities of all systems.

**Keywords:** safety, sodium-glucose cotransporter 2 inhibitors, type 2 diabetes mellitus, comorbidities and extraglycemic effects

## Introduction

Diabetic patients are mostly prone to multiple comorbidities, which may be diabetes-related or non-diabetes-related,<sup>1</sup> which have been posing an economic burden to the community.<sup>2</sup> Therefore, in choosing the appropriate anti-diabetic drug, not only the treatment of glycemia level should be considered, but the safety of the drug should also be considered in relation to these systemic comorbidities associated with diabetes. Therefore, there is a need to review the safety of antidiabetic drugs. Because there are many categories of anti-diabetic drugs,<sup>3</sup> among them we selected new anti-diabetic drugs, which are sodium glucose cotransporter 2 inhibitors, to evaluate their safety.

We want to study the safety of sodium-glucose co-transporter 2 inhibitors in diabetic patients associated with the comorbidities of all systems. Comorbidities associated with diabetes may arise in the pathophysiologic pathway of its complications (such as cardiac disease, risk factors for cardiovascular disease, renal disease, and some neurological diseases such as stroke), which are called diabetes-related comorbidities, but others arise independently of the pathophysiologic pathway of its complications (such as respiratory disease, gastrointestinal disease, neurological disease except stroke, and blood component-related disorders), which are called diabetes-associated but not related comorbidities.<sup>1,4</sup>

The safety and efficiency of SGLT2 inhibitors in treating diabetes-related comorbidities have been proven in many large clinical trials<sup>5–17</sup> and meta-analyses.<sup>18–25</sup>

However, no studies on the effectiveness and safety of SGLT2 inhibitors in all non-related but associated comorbidities of diabetes appear to have been discussed during the aforementioned (the method) time period; thus, the need was felt to, in addition to studying the safety of drugs for diabetes-related comorbidities, conduct a review of the safety of this drug for patients with diabetes-associated but non-related comorbidities. It should be noted that the majority of studies regarding the safety of this drug are limited to the cardiovascular and renal systems and do not include other systems.<sup>26,27</sup> In this review, in addition to including these systems, we also included other systems such as the respiratory system, the digestive system, the circulatory system, and the nervous system. In addition, we have reviewed its adverse effects briefly.

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 with low or normal ejection fractions.<sup>28</sup> 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,<sup>29</sup> with similar outcomes for empagliflozin in the EMPEROR-REDUCED trial.<sup>6</sup> The reduction of left ventricle mass with empagliflozin for the long term (eg, 6 months) in the EMPA-HEART CardioLINK-6 trial also demonstrated a close link between these agents and the improvement of cardiovascular events.<sup>7</sup> The DAPA-CKD trial shows 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,<sup>30</sup> with confirmation of these issues in the EMPA-KIDNEY trial by treatment with empagliflozin.<sup>31</sup> 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.<sup>32</sup>

Sodium glucose cotransporter 2 inhibitors inhibit the SGLT2 protein in the proximal tubules of the kidney and inhibit the reabsorption of glucose from the tubal lumen, therefore causing glucosuria and improving the glycemic level<sup>33</sup>

The aim of this review is to evaluate the safety of these drugs in diabetic comorbid patients through a review of their systemic extraglycemic effects (Figure 1).

## Cardiovascular System

### Atherosclerosis

Atherosclerosis is the baseline pathology of diabetes complications.<sup>34</sup> Three major factors contribute to the development of atherosclerosis: oxidative stress, inflammation, and damage to the endothelial layer.<sup>35</sup> These three factors improve with SGLT2 inhibitor treatment in diabetic patients and prevent atherosclerosis.<sup>36–38</sup>

## Risk Factors for Cardiovascular Diseases

### Components of Metabolic Syndrome

The components of metabolic syndrome have a direct relationship with cardiovascular diseases.<sup>39</sup> In this section, the drug safety and relative therapeutic role of SGLT2 inhibitors regarding the components of the metabolic syndrome associated with diabetes are studied. In relation to body weight, a clinical study has shown that treatment with dapagliflozin in obese and diabetic patients for 32 weeks causes a significant reduction in body weight compared to the control group.<sup>11</sup> Similarly, the ADDENDA-BHS2 trial showed that treatment with dapagliflozin (10 mg daily) in obese and diabetic patients compared to treatment with glibenclamide (five mg daily) for twelve weeks causes a significant reduction in body weight.<sup>12</sup> In addition to diabetic patients, a systemic review and meta-analysis have also shown the role of SGLT2 inhibitors in weight loss in non-diabetic patients.<sup>24</sup> The simultaneous reduction of leptin and body weight in a clinical trial with canagliflozin treatment compared to glimepiride may indicate the relationship between leptin and body weight.<sup>40</sup> The weight reduction may take place through two mechanisms: direct effect (loss of calories through urine in the form of glucose) and an indirect effect (arising of a catabolic process after consuming carbohydrate storage, such as lipolysis).<sup>41,42</sup>

High blood pressure is also an important component of metabolic syndrome and a major risk factor for cardiovascular diseases.<sup>39</sup> In relation to this risk factor, a systemic review and meta-analysis show that SGLT2 inhibitors are more effective in reducing high blood pressure than metformin.<sup>43</sup> According to another clinical trial, empagliflozin treatment in non-diabetic individuals for one month is associated with a 24-hour reduction in systolic and diastolic pressure.<sup>13</sup> Different mechanisms may be involved in reducing high blood pressure, but its main components are osmotic diuresis and natriuresis.

In a systemic review and meta-analysis, treatment with SGLT2 inhibitors in patients with type 2 diabetes was associated with a significant increase in LDL cholesterol, HDL cholesterol, and non-HDL cholesterol but a decrease in triglycerides.<sup>25,44</sup> According to the rat model, the increase in LDL cholesterol may be due to an increase in the activity of lipoprotein lipase and an increase in liver receptors for LDL, which increases the production of LDL and delays its turnover.<sup>45</sup> Despite the increase in LDL, its atherogenic form (small-dense LDL) decreases with SGLT2 inhibitor treatment.<sup>46</sup> Accordingly, reducing this form of cholesterol and significantly increasing HDL cholesterol<sup>47</sup> neutralize the risk of increasing LDL.

### Uric Acid Level

A high level of uric acid in the blood is one of the risk factors for cardiovascular diseases,<sup>48</sup> which is related to other disabilities such as heart failure, as clarified in the EMPEROR-reduced and DAPA-HF trials.<sup>49,50</sup> Reduction of gout attacks, reduction of its complications, and reduction of anti-gout drug dosage by SGLT2 inhibitor treatment suggest the role of reducing the uric acid level of this drug.<sup>51,52</sup> The mechanism of lowering the uric acid level of this drug may be glucosuria and inhibition of xanthine oxidase.<sup>53,54</sup>

### Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD has a close relationship with metabolic syndrome.<sup>55</sup> Among the new antidiabetic drugs, SGLT2 inhibitors and GLP1 agonists are preferred in the treatment of diabetes associated with NAFLD.<sup>56</sup> In this regard, several clinical trials show the effectiveness of empagliflozin and dapagliflozin in reducing NAFLD and improving liver parameters in type 2 diabetes.<sup>57–63</sup> These NAFLD-reducing effects of SGLT2i have also been observed in several clinical trials in non-diabetic patients.<sup>64–66</sup>

### Cardiovascular Diseases

Cardiac remodeling in the base of fibrous deposition in the heart muscle is the leading cause of diabetic cardiomyopathy and consequently heart failure,<sup>67</sup> and this process is basically modulated by treatment with SGLT2 inhibitors, which improve heart failure.<sup>68</sup> According to a systemic review and meta-analysis, long-term treatment with SGLT2 inhibitors in diabetic patients reduces the mortality and hospitalization rate of heart failure.<sup>18</sup> These beneficial effects of SGLT2 inhibitors are not only limited to diabetic patients, as according to the EMPATROPISM trial, treatment with empagliflozin in non-diabetic patients with heart failure has reduced the volume and mass of the left ventricle, resulting in increased tolerance for physical activity and improved quality of life.<sup>5</sup> These beneficial effects in diabetic and non-diabetic patients have also been confirmed by the EMPEROR-reduced trial and the multicenter trial.<sup>6,69</sup> These cardio-protective effects of the drug are probably caused by two basic mechanisms, which are the metabolic pathway and the hemodynamic pathway.<sup>70–72</sup>

Also, due to the atherosclerosis process, diabetic patients are prone to ischemic heart diseases.<sup>73</sup> The effectiveness of SGLT2 inhibitors in improving cardiovascular diseases, including ischemic heart diseases, has been proven in several clinical studies and meta-analyses.<sup>7,8,19–21</sup> The mechanism of its anti-ischemic effects may be due to the partial inhibition of the activity of the sympathetic system, the reduction of the mass index of the left ventricle, and the increase of choline metabolites (especially glycine).<sup>7,74,75</sup> According to a meta-analysis, no specific difference in the occurrence of different forms of ischemic heart disease (including stable angina, unstable angina, and myocardial infarction) has been observed by SGLT2 inhibitor treatment in patients with type 2 diabetes.<sup>76</sup>

Disorders of glycemic level cause structural and metabolic changes in the heart muscle and ultimately electrolyte disturbances, which in turn create a favorable environment for arrhythmias.<sup>77,78</sup> Accordingly, several clinical studies and meta-analyses have shown the role of SGLT2 inhibitors in reducing the risk of various arrhythmias in type 2 diabetes patients.<sup>9,23,79,80</sup>

### Respiratory System

A population-based cohort study and meta-analysis show a reduction in COPD and asthma exacerbations with SGLT2i treatment in diabetic patients.<sup>81,82</sup> A further reduction in the new onset of obstructive sleep apnea with empagliflozin

treatment in diabetic patients compared to placebo has also been observed in another clinical trial.<sup>83</sup> Another retrospective cohort study has also shown a greater reduction in the incidence of pneumonia in patients with type 2 diabetes with SGLT2 inhibitor treatment than DPP4i.<sup>84</sup> Several clinical studies suggest the role of SGLT2 inhibitors in reducing pulmonary and right ventricular pressure,<sup>85–91</sup> which is probably induced by reducing vascular stiffness and releasing nitric oxide.<sup>92–94</sup> The distinct diuretic effect of the drug may have a therapeutic role in pulmonary edema.<sup>95</sup> Based on the mediation of SGLT2 receptors in the initial course of lung adenocarcinoma, the role of SGLT2 inhibitors in the treatment of this type of carcinoma is suggested.<sup>96</sup> Based on these evidences, the use of SGLT2 inhibitors in patients with diabetes associated with lung diseases is considered safe.

## Urogenital System

### Urinary System

According to the DAPA-CKD trial, the use of dapagliflozin in CKD patients with or without cardiovascular diseases, regardless of diabetes, caused positive effects and prevented the progression to the end stages of kidney diseases.<sup>16</sup> While these favorable effects are more prominent in the absence of cardiovascular disorders. The increase in glomerular pressure and proteinuria have a fundamental role in the progression of kidney disease,<sup>97</sup> and according to an EMPA-REG OUTCOME trial, this glomerular pressure is reduced by short-term empagliflozin treatment.<sup>17</sup> Based on this, the reduction of glomerular pressure and the reduction of proteinuria are considered to be the basic mechanisms of SGLT2 inhibitors' drug safety in diabetic patients, which prevent the progression to the end stages of renal diseases. Here, there is a scientific gap about whether the use of this drug in patients with diabetes associated with AKI is safe or not.

### Genital System

Refer to the Adverse Effects Section.

## Gastrointestinal System

The first study that has been conducted regarding the safety of SGLT2 inhibitors in the gastrointestinal system is an in vivo study on a rat model in which the protective effects of empagliflozin on the mucous layer of the stomach have been observed.<sup>98</sup> In addition, several in vivo and in vitro studies have suggested the possible role of this drug in the treatment of IBD and IBS.<sup>99–101</sup> The imbalance of microflora is associated with diabetes,<sup>102</sup> and according to several pre-clinical studies, the use of SGLT2 inhibitors in diabetic patients balances these microflora.<sup>103–105</sup> Confirming the possible effects of this drug on the gastrointestinal system requires more clinical studies.

## Blood Components and Electrolytes

Several meta-analyses show that SGLT2 inhibitors increase the level of hemoglobin and hematocrit.<sup>106–108</sup> This increase in hemoglobin in diabetic patients associated with heart failure or kidney failure is effective because it increases oxygen supply to the heart myocardium and reduces the amount of erythropoietin used in the treatment of CKD-induced anemia.<sup>109,110</sup> Therefore, for patients with diabetes, if it is associated with anemia, it is a better choice. Here again, a scientific gap has been created, and that is whether the increase in hematocrit caused by this drug in diabetic patients without anemia predisposes the patients to a thrombotic state or not.

Regarding the number of white blood cells, two clinical trials show the therapeutic role of empagliflozin in neutropenia.<sup>111,112</sup> This issue has also been confirmed by Veiga-da-Cunha et al.<sup>113</sup> In relation to canagliflozin, another clinical trial showed the opposite effect and that treatment with canagliflozin causes a decrease in white blood cells.<sup>114</sup> In order to determine the role of this drug in relation to the number of white blood cells, large clinical trials are needed.

Since platelet hyperactivity in diabetic patients is directly related to the onset of atherosclerosis,<sup>115,116</sup> two clinical studies conducted in type 2 diabetes patients showed that dapagliflozin and empagliflozin suppress platelets activity and prevent the development of ischemic heart diseases.<sup>117,118</sup>

According to the CREDENCE trial, treatment with canagliflozin in diabetic patients associated with hyperkalemia lowered the potassium level more than placebo and corrected the hyperkalemia,<sup>119</sup> which was also proven by Gabai et al.<sup>120</sup> Maintaining a normal level of magnesium in diabetic patients prevents the development of cardiovascular diseases, and in this regard, the use of SGLT2 inhibitors in the treatment of diabetes mellitus increases the level of magnesium and prevents the development of heart diseases in diabetic patients.<sup>121,122</sup>

## Nervous System

SGLTs have different types, from SGLT1 to SGLT6; with the exception of SGLT5, all its other types are expressed in the brain.<sup>123</sup> The expression of SGLT1 is greater than that of SGLT2.<sup>124</sup> SGLT2 inhibitors are dissolved in fat, pass through the blood-brain barrier via the transcytosis mechanism,<sup>124,125</sup> and modulate their receptors in the brain.<sup>126</sup> Based on the location of these receptors, the ability of SGLT2 inhibitors to pass, and their modulatory effects on their receptors, these drugs have neural effects. According to a retrospective-cohort study, the treatment of diabetes patients by SGLT2-inhibitors is associated with a lower incidence of new strokes than other antidiabetic drugs.<sup>127</sup> Improvement of synaptic activity, increase of memory, and cognitive strength by SGLT2-inhibitor<sup>128</sup> may be related to the anti-inflammatory properties and reduction of nitric oxide in the microglial cells.<sup>129</sup> In a retrospective study conducted on patients with type 2 diabetes, SGLT2-inhibitor treatment showed a significant reduction in the incidence of new dementia, Alzheimer's disease, and Parkinson's disease.<sup>130</sup> The properties of Antioxidation, regulation of metabolic processes, and inhibition of the cholinesterase enzyme of SGLT2-inhibitor drugs may be used in the treatment of the autism spectrum of the disease.<sup>124</sup> It is still used in the treatment of Huntington's disease based on its anti-apoptotic, anti-inflammatory, and anti-glycolytic properties.<sup>131</sup>

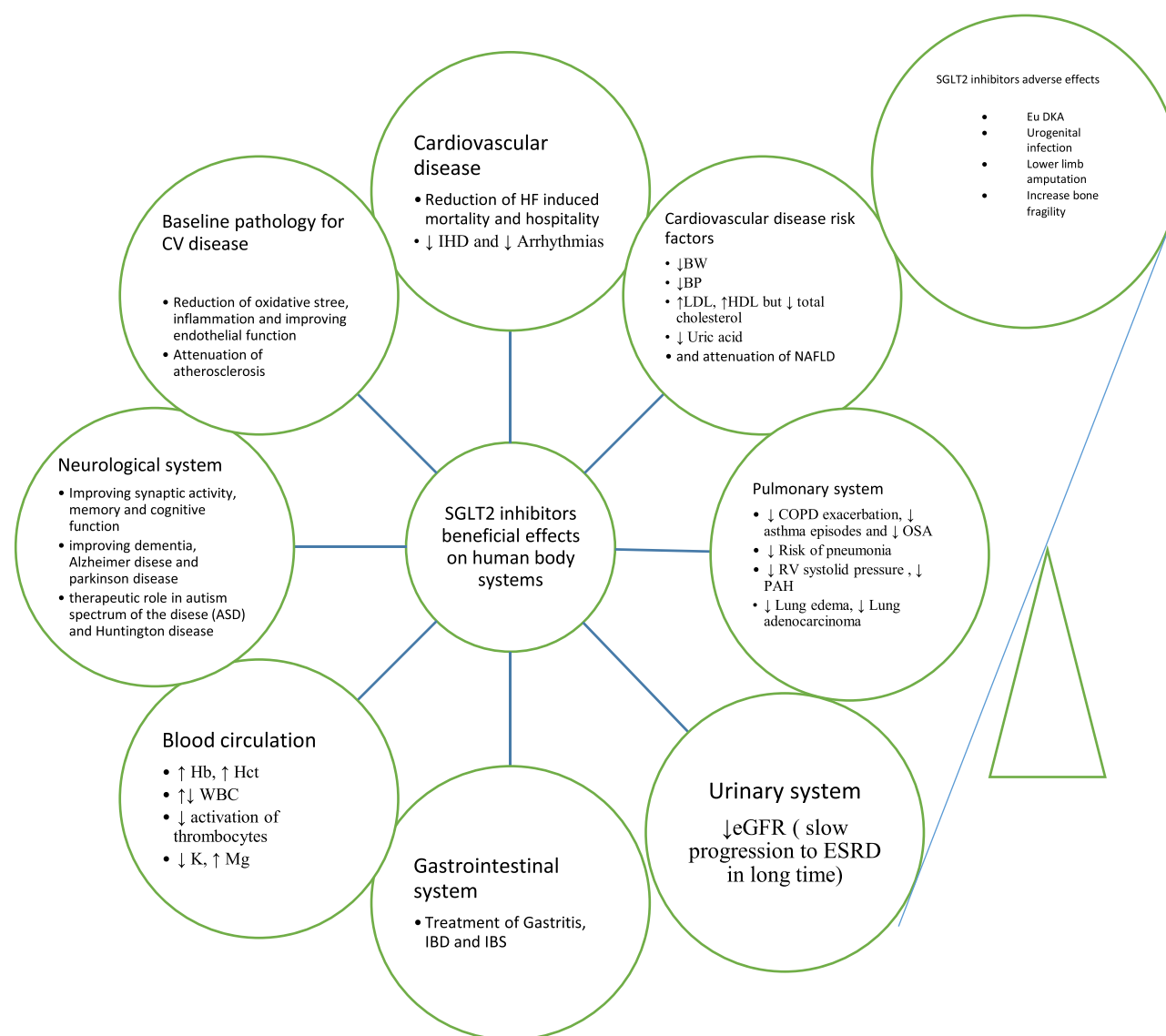
## Side Effects

Ketoacidosis is one of the adverse effects of SGLT2 inhibitors, which is of the euglycemic type.<sup>132</sup> A cohort study showed a threefold increase in the incidence of diabetic ketoacidosis with SGLT2 inhibitors.<sup>133</sup> The most common cause of this type of ketoacidosis is infection.<sup>134</sup> This type of ketoacidosis may be due to the decrease in the renal excretion of ketone bodies and the relative increase in the production of ketone bodies due to glucosuria-induced plasma volume contraction.<sup>135</sup>

Glucosuria caused by these drugs is the origin of urogenital infections.<sup>33,136</sup> A retrospective cohort study and a double-blind study show an increase in the incidence of genital fungal infections with SGLT2 inhibitor treatment.<sup>137,138</sup> The location of the infection may be related to the drug dose, such that a high dose causes urinary infections and a low dose causes genital infections.<sup>139</sup> Also, two observational studies show an increase in the incidence of UTI in the SGLT2 inhibitor group compared to other antidiabetic drugs.<sup>140,141</sup>

Lower limb amputation is another side effect of this drug. Several meta-analyses suggest the causative role of canagliflozin in lower extremity amputations,<sup>142–144</sup> but the definitive role of other agents (such as dapagliflozin and empagliflozin) in this regard is not clear.<sup>143,145</sup> While the global database of case reports of the World Health Organization supports the potential participation of other representatives of this medicine (such as dapagliflozin and empagliflozin).<sup>146</sup> The cause of this incident may be the reduction of blood perfusion to the lower extremities.<sup>147</sup>

Due to the disruption of the 1,25-dihydroxyvitamin D-PTH axis,<sup>148,149</sup> increased bone turnover due to weight loss,<sup>150</sup> and possibly bone loss<sup>151</sup> by SGLT2 inhibitors, these drugs are also associated with bone health problems. In this regard, a clinical trial was conducted in 90 centers in 17 countries, the purpose of which was to evaluate the effects of canagliflozin on bone mineral density. This clinical trial shows the role of canagliflozin in reducing hip bone mineral density.<sup>152</sup>



**Figure 1** All the findings of this study are shown briefly in this figure.

## Conclusion

With the exception of a few adverse effects, this drug is considered a good choice and safe for all diabetic patients with systemic comorbidities. 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.

## Disclosure

The authors report no conflicts of interest in this work.

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