

# Nephroprotective Effects of 2nd Type Sodium-Glucose Co-Transporter Inhibitors: A Literature Review

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## Abstract

**Introduction:** A wide range of oral hypoglycemic drugs with various mechanisms of effect are available for the treatment of patients with 2nd type diabetes mellitus today. Despite the high effectiveness of these agents in the normalization of glycemia, they cause different chronic complications in many patients with 2nd type diabetes mellitus. However, during the last years, a range of principal new data has been accumulated on the pleiotropic effects of the last classes of oral hypoglycemic agents — inhibitors of the 2nd type sodium-glucose cotransporter (SGLT2).

**Materials and Method:** Three electronic databases were checked to find out studies reporting the data on the mechanisms and clinical significance of the nephroprotective effect of inhibitors of the sodium-glucose cotransporter of 2nd type (glyphlozines) in patients with 2<sup>nd</sup> type diabetes mellitus. The primary outcome was to learn the worldwide tendency on this matter and to compare the results of different researchers.

**Results:** We found 25 studies as eligible for our review. The review presents data on the mechanisms and clinical significance of the nephroprotective effect of inhibitors of the sodium-glucose cotransporter of 2nd type (glyphlozines). The effects associated with the influence of representatives of this pharmacological group on the glomerular filtration rate, glycemia, diuresis, ketogenesis and other factors are discussed. The results of recent experimental and clinical studies aimed at studying certain aspects of the nephroprotective effect of SGLT2 inhibitors in 2nd type diabetes mellitus and other pathological conditions were analyzed.

**Conclusion.** SGLT2 inhibitors associate with a multicomponent nephroprotective effect, which confirmed by the results of both experimental and clinical studies. The nephroprotective potential of SGLT2 inhibitors is maximally realized in the presence of diabetes and remains not entirely clear in the case of another kidney pathology.

**Keywords:** *Diabetes mellitus, oral hypoglycemic drugs, 2nd type sodium-glucose cotransporter inhibitors, chronic kidney disease, diabetic nephropathy, nephroprotection.*

## Introduction

Currently, a large number of oral hypoglycemic agents (OHAs) with various mechanisms of action

are available for the treatment of patients with 2nd type diabetes mellitus (Thrasher, 2017)<sup>1</sup>. In spite of high effectiveness of OHA for normalizing glycemia,

in a significant proportion of patients with 2nd type diabetes chronic complications may develop<sup>2</sup>. Namely, the most unfavorable prognostic value associate with diabetic nephropathy and cardiovascular complications (Demidova, 2016)<sup>1</sup>. Thus, all modern drugs for the treatment of 2nd type diabetes are examined for their nephron- and cardioprotective properties (Muskiel et al, 2015; Bandanna et al, 2016)<sup>2,3</sup>. In recent years, a lot of principal novel data has been collected on the pleiotropic effects of representatives of the last classes of OHA — inhibitors of the 2nd type sodium-glucose cotransporter (SGLT2) (Vallianou et al, 2016; and Satoh, 2018)<sup>3</sup>.

The main contribution of the kidneys to the regulation of carbohydrate metabolism is due to the processes of renal reabsorption of glucose<sup>4</sup>. Normally, in a one day, about 180 g of glucose is filtered through the kidneys (Maltese et al, 2015)<sup>5</sup>. Reabsorption of glucose from the lumen of the renal tubule is provided by the carrier proteins (sodium glucose cotransporters) family of SGLT, which carry out active glucose transport<sup>6</sup>, coupled with sodium, into the tubule cell<sup>7</sup>. Further, carrier proteins of the GLUT family located on the basolateral membrane, passively transport glucose from the cell to the interstitial space according to its concentration gradient (Prie, 2014)<sup>8</sup>. Almost 90% of glucose is reabsorbed in the S1 segment of the proximal convoluted renal tubule with the participation of SGLT2 transporters<sup>9</sup>, which have low affinity but very high capacity<sup>10</sup>. About 10% of glucose is absorbed more distally - in the S3 tubule segment using SGLT1 transporters, which, on the contrary, are characterized by high affinity, but low capacity.<sup>11</sup>

The combination of sequential effects of these transporters ensures the achievement of aglucosuria in healthy people.<sup>12</sup> The kidneys are the main location for SGLT2 transporters.<sup>13</sup> The presence of a mutation in the SLC5A2 gene encoding these transporters leads to the development of a hereditary disease that occurs with a frequency of up to 0.3% in the family - renal glucosuria population (Vallon, 2015)<sup>6,14</sup>. In familial renal glucosuria<sup>15</sup>, in the absence of carbohydrate metabolism disorders and signs of tubular dysfunction<sup>16</sup>, constant glucosuria is observed, which may exceed 100 mg/day.<sup>17</sup> In most patients, the disease proceeds without severe clinical symptoms, and renal function does not change<sup>18</sup>.

Purpose of the study is to learn the current literature data on the functional mechanisms and clinical

significance of the nephroprotective effect of inhibitors of the sodium-glucose cotransporter of 2nd type<sup>19</sup>, to investigate the clinical results and outcomes of treatment with hypoglycemic drugs in patients with 2<sup>nd</sup> type diabetes mellitus<sup>20</sup>.

## Materials and Method

**Protocol and registration:** The review was conducted following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al, 2009)<sup>21</sup>.

**Eligibility and exclusion criteria:** Both primary and secondary studies were included for this review. We applied 10-year time filter (from 2010 to 2020)<sup>22</sup> for eligible studies. Only English papers were included. The review covered both prospective as well as retrospective data analyses. We did not use any restrictions regarding the place of publication<sup>23</sup>.

**Search Strategy:** Three medical electronic databases (PubMed, EMBASE and Cochrane) were searched to find the studies reporting the conservative (influence of medicaments) effects on the renal function in patients with diabetes mellitus<sup>24</sup>. We applied 10-year time filter for eligible studies<sup>25</sup>. In the search strategy techniques on the web sites mentioned above, we used the following key words:

*Diabetes mellitus, oral hypoglycemic drugs, 2nd type sodium-glucose cotransporter inhibitors, chronic kidney disease, diabetic nephropathy, nephroprotection.*

**Study Selection:** Titles and abstracts of the papers screened by the authors of the review using the search method mentioned above in order to identify the studies that match the inclusion criteria<sup>26</sup>. Found items were searched and compared again for duplicate papers, deleted one were found any similar studies.<sup>27</sup> Eligible studies were checked to find any more interesting sources for our review. As soon as we found any interesting paper that suitable for our criteria of eligibility, full texts the study were reached and read till the end. Any disagreements between reviewers, resolved by discussion.

## RESULTS

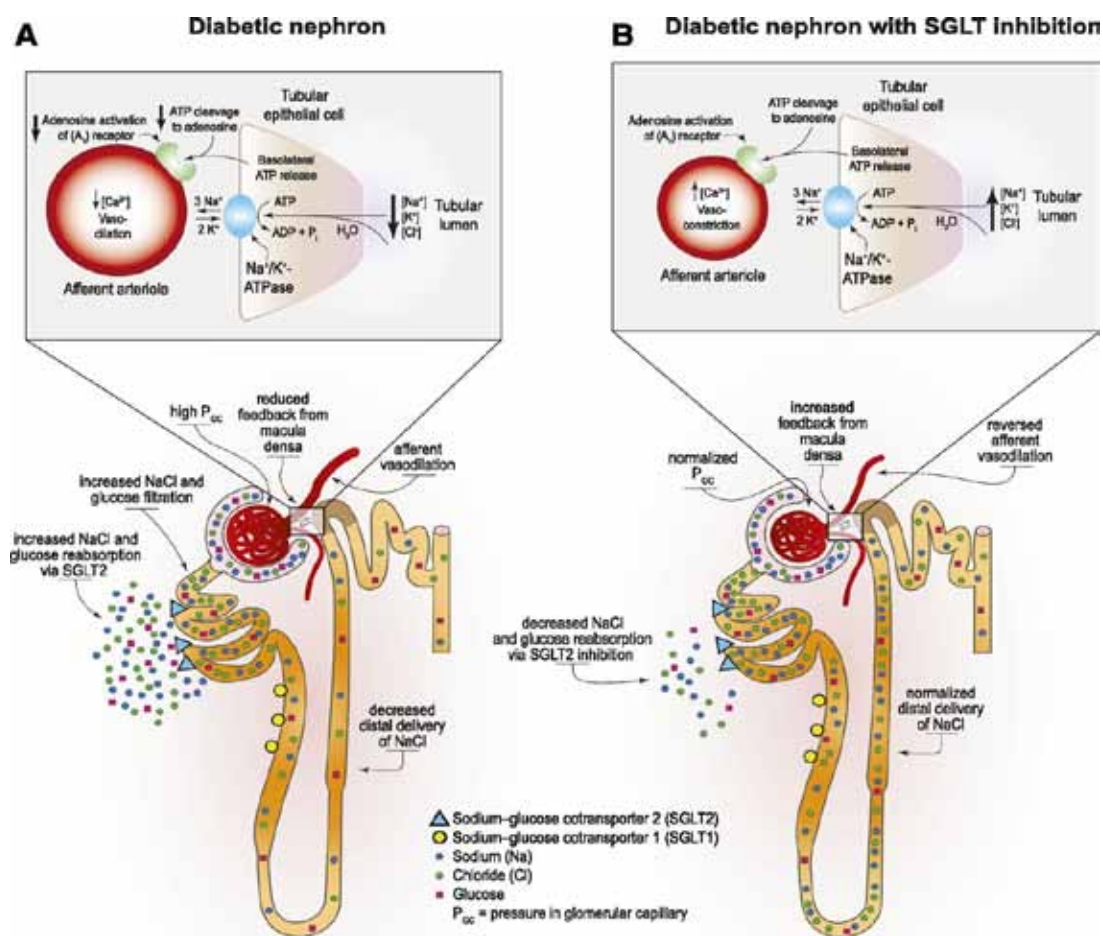
**Study Selection:** Overall, 1224 items found searching through electronic databases outlined above. Double checked the records obtained reviewing the titles and abstracts.<sup>28</sup> Next, we identified 450 identical studies that were deleted after wards.<sup>29</sup> Then, remaining 382

records were screened excluding 296 findings owing to different reasons. Further, the titles of 114 studies were read, 72 articles found as potentially eligible, which obtained in full text.<sup>30</sup> All full text articles were learnt by the authors of the review. Finally, we included 25 studies to our review. Owing to the colorful style, method and outcomes of the studies (heterogeneity), we did not perform meta-analysis.<sup>31</sup>

**Study Characteristics:** It was established that one of the mechanisms of regulation of SGLT2 expression is autocrine: pro-inflammatory cytokines (interleukin-6 and alpha tumor necrosis factor) produced by renal epithelial cells are capable of increasing SGLT2 expression by the same type of cells (Fig. 1.) (Maldonado-Cervantes et al, 2012).<sup>32</sup>

In another study, conducted using proximal tubules of human kidney cells, it was shown that up-regulation of SGLT2 does not occur directly under the influence of elevated glucose concentrations, but as a result of exposure to these cells transforming growth factor beta, overproduction of which is characteristic for diabetic kidney damage (Panchapakesan et al, 2013)<sup>33</sup>.

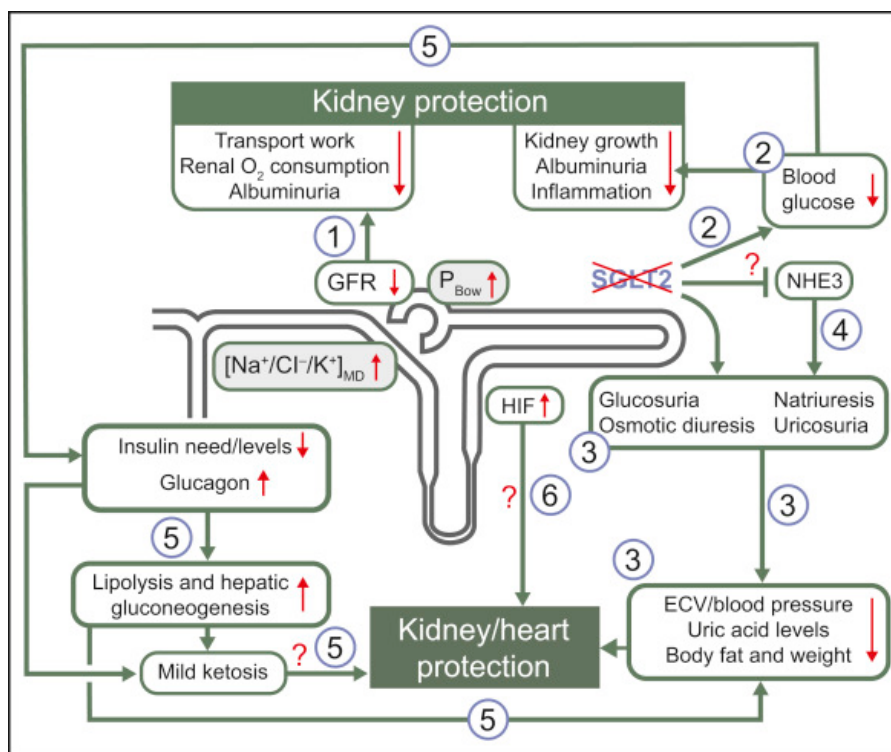
A large number of studies have proved that inhibition of SGLT2 leads to a wide range of physiological changes that are potentially favorable for 2nd type diabetes<sup>11</sup>. The main direct and indirect renal effects of SGLT2 inhibitors in 2nd type diabetes are summarized in Fig. 2. Below, based on an analysis of the results of key experimental and clinical studies of recent years, certain aspects of the nephroprotective effect of SGLT2 inhibitors are discussed<sup>34</sup>.



**Fig. 1. The effect of diabetes mellitus and inhibition of SGLT2 on the hemodynamics of nephron. A: Increased glucose reabsorption with SGLT2 in the proximal tortuous tubule reduces the delivery of solutes to the dense spot. As a result, the release of ATP from the basolateral membrane of the tubular epithelial cells is reduced, the production of adenosine is reduced and the vessels of the afferent arteriole dilate. B. SGLT2 inhibitors restore the delivery of solute to a tight spot, followed by activation of adenosine and prevention of vasodilation of the afferent arteriole (Maldonado-Cervantes et al, 2012).**

In the first experimental studies aimed at studying the nonprotective properties of the inhibition of the sodium-glucose cotransporter, florzin, a competitive

inhibitor of SGLT1 and SGLT2 of natural origin, was not suitable for use in clinical practice owing to the presence of pronounced side effects (Vallon & Thomson, 2017)<sup>35</sup>.



**Fig. 2. The main mechanisms of the nephroprotective action of SGLT2 inhibitors (Vallon & Thomson, 2017)** (1) A decrease in glucose and sodium reabsorption in the proximal tubules leads to an increase in pressure in the Bowman space (BPM), and a decrease in glomerular filtration rate (GFR), and also affects the function of dense spot cells of the juxtaglomerular apparatus.<sup>2</sup> By normalizing blood glucose levels, SGLT2 inhibitors indirectly block the increase in the level of glycation end products, the overproduction of pro-inflammatory cytokines and other negative effects of hyperglycemia.<sup>3</sup> SGLT2 inhibitors have a diuretic, natriuretic and uricosuric effect, which helps to reduce extracellular fluid volume, blood pressure, uric acid level in the blood and body weight.<sup>4</sup> It is suggested that there is a relationship between the activity of the 2nd type sodium glucose cotransporter and the sodium hydrogen ion exchange protein (NHE3), which may have an additional beneficial effect on blood pressure.<sup>5</sup> A decrease in insulin demand and an increase in glucagon levels lead to the activation of lipolysis and gluconeogenesis and, as a result, to a slight increase in the level of ketones, which can have cardio- and nephroprotective effects.<sup>6</sup> Inhibition of SGLT2 may increase the production of renal hypoxia-induced factor (HIF), which has nephroprotective properties.

In a study by Malatiali et al. (2015)<sup>14,36</sup>, florzin has been shown to reduce the severity of glomerular hyperfiltration in rats with streptozotocin-induced diabetes. The research conducted by Osorio et al. (2012)<sup>16</sup> proved a decrease in oxidative stress using the same model of diabetes<sup>37</sup>. In a study conducted on rat mesangial cells, the addition of Florizin blocked the resizing of these cells when they are incubated in a solution with a high glucose content (Wakisaka et al, 2016)<sup>38</sup>.

Most studies conducted on various genetic and non-genetic models of diabetic kidney damage using modern synthetic SGLT2 inhibitors (empagliflozin, dapagliflozin, luseogliflozin, tofogliflozin) also confirmed the presence of pronounced nephroprotective properties in this pharmacological group.<sup>39</sup> It was shown in BTBRob/ob mice that the use of empagliflozin was associated with a decrease in the level of albuminuria and expression of inflammatory markers, a decrease in glomerular hypertrophy, and expansion of the mesangial

matrix, however, when these laboratory animals were administered angiotensin II, only the antialbuminuric effect was preserved (Gembardt et al, 2014)<sup>40,17</sup>. In a study on db/db mice, the administration of empagliflozin reduced the expression of fibronectin and transforming growth factor beta genes<sup>18</sup>, but did not affect the level of albuminuria and urinary excretion of markers of tubular damage KIM-1 and neutrophilic gelatinase-associated lipocalin (NGAL) (Gallo et al, 2016)<sup>19,41</sup>. In a study where authors used of empagliflozin (unlike telmisartan) did not have a nephroprotective effect on mice with knockout of the endothelial nitric oxide synthase (eNOS) gene, in which diabetes was induced by the administration of low doses of streptozotocin (GangadharanKomala et al, 2014)<sup>42</sup>.

According to Ojima et al. (2015)<sup>43</sup>, the use of empagliflozin in rats with streptozotocin-induced diabetes reduced the expression of the receptor for glycation end products, as well as decreased urinary excretion of the oxidative stress marker 8-OH-deoxyguanosine and the tubular lesion marker L-FABP (hepatic protein that binds fatty acid)<sup>22</sup>. Moreover, in this study of relatively short duration (4 weeks), the antialbuminuric effect of SGLT2 inhibition was not observed<sup>44</sup>.

Another SGLT2 inhibitor, dapagliflozin, also showed pronounced nephroprotective properties in a study on db/db mice. In particular, there was a decrease in kidney infiltration by macrophages, suppression of mesangial expansion and interstitial fibrosis, and a decrease in albuminuria. At the same time, creatinine clearance and blood pressure did not undergo significant changes (Terami et al, 2014)<sup>45</sup>.

In a study on Akita mice (type 1 diabetes model), the effects of dapagliflozin and insulin therapy were compared<sup>25</sup>. After 12 weeks of treatment, no significant intergroup differences were observed in glycemia, HbA1c, body weight and blood pressure, but diuresis and fluid intake were higher in the group treated with the SGLT2 inhibitor. In mice treated with dapagliflozin, morphological changes in the kidneys (macrophage infiltration, interstitial fibrosis) were less pronounced than in animals that were on insulin therapy. When studying the proximal tubule cell culture, a decrease in the severity of oxidative stress under the influence of dapagliflozin was also demonstrated (Hatanaka et al, 2016)<sup>26</sup>.

Another comparative study that compared the nephroprotective effects of tofogliflozin and losartan

was conducted on db/dbline mice. It was shown that both tofogliflozin and losartan can reduce the level of albuminuria by 50-70%, however, only the SGLT2 inhibitor reduced the severity of glomerular hypertrophy (Nagata et al, 2013)<sup>27</sup>. Most researchers agree that a decrease in the level of albuminuria in experimental studies is observed when using high doses of SGLT2 inhibitors, while other effects (antifibrotic, anti-inflammatory, inhibition of oxidative stress) are manifested in a wider range of doses (Kawanami et al, 2017)<sup>28</sup>.

In a comparative study conducted using a non-genetic model of rats with insulin resistance against a high-fat diet, it was shown that the SGLT2 inhibitor dapagliflozin has a more pronounced nephroprotective potential than metformin (Jaikumkao et al, 2018)<sup>29</sup>.

A study of combination nephroprotective therapy on a model of streptozotocin-induced diabetes in salt-sensitive rats (Dahl S line) showed that the use of the SGLT2 inhibitor luseoglyphlozin in combination with the ACE inhibitor lisinopril is associated with more pronounced beneficial effects (hypotensive effect, decrease in renal hyperfiltration) than the appointment of any of these drugs separately (Kojima et al, 2015)<sup>30</sup>.

Gallo et al. (2016)<sup>31</sup> showed that the use of empagliflozin in conjunction with metformin has the advantage of influencing the synthesis of type IV collagen and connective tissue growth factor in the kidneys<sup>32</sup>. In recent years, the effectiveness and safety of SGLT2 inhibitors in chronic kidney disease with a significant reduction in glomerular filtration has been actively studied.<sup>33</sup>

In a study completed by L. Li et al. (2018)<sup>34</sup>, it was demonstrated that inhibition of SGLT2 in rats undergoing subtotal nephrectomy (without diabetes) does not lead to intrarenal and systemic activation of the renin-angiotensin-aldosterone system, which, according to several researchers, may be a side effect of this pharmacological effect in case of development of hyponatremia against the background of severe renal pathology<sup>35</sup>.

Use of dapagliflozin in rats undergoing subtotal nephrectomy is not associated with a decrease in the expression of profibrotic cytokines in the kidneys and a slower progression of nephrosclerosis (Zang et al, 2016)<sup>36</sup>. With a less significant decrease in the volume of functioning renal tissue against the background of

diabetes, the nephroprotective properties of SGLT2 inhibitors are preserved, which was demonstrated in mice with 2nd type diabetes KK/Ay line undergoing unilateral nephroectomy (Tahara & Takasu, 2018)<sup>37</sup>.

In a study of the effects of SGLT2 inhibition in animals with chronic kidney disease induced by a diet containing excessive amounts of oxalates, dapagliflozin did not show beneficial renal effects<sup>38</sup>.

Thus, the presence of nephroprotective properties in this class of drugs with non-diabetic kidney damage and their practical significance are currently in doubt (Ma et al, 2017)<sup>39</sup>.

Nevertheless, experimentally confirmed the presence of nephroprotective effects in SGLT2 inhibitors mediated by their effect on the expression of hypoxia inducible factor (HIF-1). Corresponding data were obtained on a model of ischemia-reperfusion of kidneys in mice (Chang et al, 2016).<sup>40</sup> Other authors have shown that under hypoxic conditions, the expression of SGLT1 and SGLT2 by tubule epithelial cells decreases (Zapata-Morales et al, 2014).<sup>41</sup>

Less studied is the question of possible organoprotective and, in particular, nephroprotective effects associated with the accumulation of ketogenesis products, which is activated against the background of SGLT2 inhibition. In an experimental study conducted by T<sup>42</sup>. Shimazu et al., It was shown that the administration of one of these metabolites, beta-hydroxybutyrate, to mice is associated with a decrease in the expression of oxidative stress and lipid peroxidation markers in the kidney after intravenous injection of paraquat (Shimazu et al, 2013)<sup>43</sup>. In addition, there are experimental strong evidence of the use of ketone bodies by the kidneys as an energy substrate. Under conditions of ketonemia, their utilization increases sharply, which inhibits the uptake of other substrates by the kidneys and reduces oxygen consumption (Guder et al, 1986).<sup>44</sup>

One of the largest clinical studies that examined the nephroprotective effects of SGLT2 inhibitors is the EMPA-REG OUTCOME study. In this study, the nephroprotective effect of empagliflozin was manifested not only when it was prescribed at a maximum dose of 25 mg per day, but also when using a dose of 10 mg per day. Adding empagliflozin to standard therapy (about 80% of patients received ACE inhibitors or angiotensin receptor blockers) was associated with a 38% reduction in the risk of nephropathy progression with macroalbuminuria, a 44% increase in serum creatinine, and a 55% increase

in renal replacement therapy. At the same time, SGLT2 inhibitor therapy did not reduce the likelihood of microalbuminuria in patients, which was a common event both in the main group and in the placebo group (51.5% and 51.2%, respectively).<sup>45</sup>

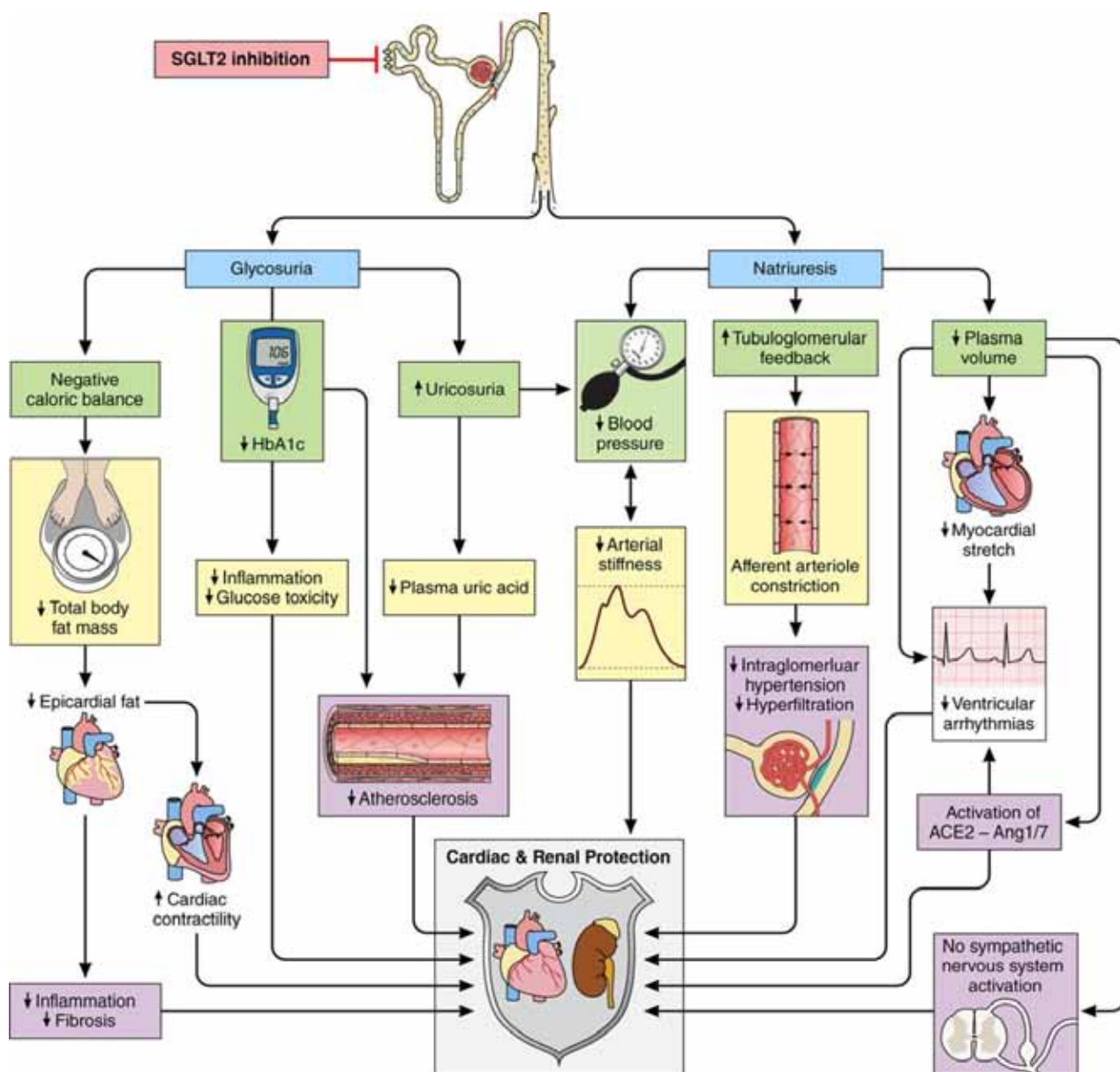
At the initial stage of empagliflozin therapy, predictable decrease was observed in GFR, however, in the future the GFR value in the main group remained relatively stable (decrease by  $0.19 \pm 0.11$  ml/min/1.73 m<sup>2</sup> per year), while in the placebo group, a more pronounced decrease in GFR (by  $1.67 \pm 0.13$  ml/min/1.73 m<sup>2</sup> per year).

In addition, after the cancellation of empagliflozin, an increase in GFR was observed, which further increased the intergroup differences in this indicator (Wanner et al, 2016)<sup>46</sup>. In addition to the obvious mechanisms of cardio- and nephroprotective effects of empagliflozin, clearly demonstrated in EMPA-REG OUTCOME, the possible clinical significance of enhancing ketogenesis and the role of the corresponding energy substrates are discussed in the scientific literature (Fig. 3) (Mudaliar et al, 2016).<sup>47</sup>

The CANVAS study examined the effect of the canagliflozin SGLT2 inhibitor on cardiovascular and renal outcomes in 2nd type diabetes. The results of the study showed that the addition of canagliflozin to standard therapy was associated with a 47% reduction in the risk of reaching a combined endpoint, which included a steady 2-fold increase in serum creatinine concentration, the development of the terminal stage of chronic kidney disease, and death from renal causes. In the placebo group, the average annual decrease in GFR was 1.2 ml/min/1.73 m<sup>2</sup> more. The mean urine albumin / creatinine ratio in the group of patients receiving canagliflozin was 18% lower (Perkovic et al, 2018).<sup>48</sup>

In the DECLARE-TIMI study, the administration of dapagliflozin to 58 patients with 2nd type diabetes in addition to standard therapy was associated with a 24% reduction in the risk of reaching a combined endpoint that included a sustained decrease in GFR of at least 40% to below 60 ml/min/1.73 m<sup>2</sup>, the development of the terminal stage of chronic kidney disease and death from renal or cardiovascular causes (Wiviott et al, 2018).<sup>49</sup>

The nephroprotective effect of SGLT2 inhibitors in 2nd type diabetes is considered a class effect, which is indirectly confirmed by the results of the above studies and some secondary analyzes (Clegg et al, 2019).<sup>50</sup>



**Fig. 3. Physiological mechanisms involved in cardio and nephroprotection during inhibition of SGLT2. (Mudaliar et al, 2016)**

There is little data on the ratio of the nephroprotective effects of various representatives of this pharmacological group, and they were obtained mainly using indirect comparisons. In a large meta-analysis, summarizing the treatment results of more than 39 000 patients from 58 studies, the superiority of empagliflozin was indirectly confirmed. In patients on dapagliflozin therapy, according to the results of this work, the relative risk of adverse renal outcomes was higher than in patients taking placebo. In addition, empagliflozin was the only inhibitor SGLT2, which can reduce the risk of acute

kidney damage compared with placebo (Tang et al, 2017). According to the results of the research conducted by Cherney et al. (2014), prescribed empagliflozin to patients with type 1 diabetes with renal hyperfiltration, lead to a decrease in serum nitric oxide concentration, an increase in renal vascular resistance, and a decrease in effective renal plasma flow and GFR. These changes were recorded both in hyper- and in normoglycemia. At the same time, these parameters did not significantly change with the use of empagliflozin in patients with type 1 diabetes and normal GFR values.

A secondary analysis of the results of this study with the calculation of the indicators of intrarenal hemodynamics according to the Gomez (1951) method showed that in patients with hyperfiltration even with normal systemic blood pressure and normoalbuminuria there was observed intrapulmonary hypertension, which decreased during treatment with empagliflozin due to a change in the resistance of afferent renal (Skrtec et al, 2014)<sup>42</sup>.

When analyzing the effect of the dopagliflozin SGLT2 inhibitor on the excretion of markers of inflammation and damage to the tubules of the kidneys, the ability of this drug to reduce the excretion of the kidney damage molecule KIM-1 and interleukin-6 with urine was established. At the same time, the excretion of other markers (monocytic chemoattractant protein 1, neutrophilic gelatinase-associated lipocalin, and the hepatic form of the protein binding fatty acids) did not change (Dekkers et al, 2018)<sup>43</sup>.

Researchers pay much attention to the study of the efficacy and safety of SGLT2 inhibitors in patients with CKD with a decrease in GFR. The EMPA-REG OUTCOME study demonstrated the beneficial renal effects of empagliflozin in 2nd type diabetes, both in patients with GFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> and in patients with GFR 30-59 ml/min/1.73 m<sup>2</sup> (Wanner et al, 2016)<sup>34</sup>. The DERIVE study evaluated the efficacy and safety of dapagliflozin in patients with 2nd type diabetes and stage 3 CKD. The use of dapagliflozin in this group of patients was associated with a statistically significant decrease in glycated hemoglobin, body mass index and systolic blood pressure without an increased risk of adverse events (Fioretto et al, 2014)<sup>44</sup>.

In a meta-analysis that included 11 clinical trials, it was shown that the effect of dapagliflozin on hematocrit, body weight, and systolic blood pressure does not depend on the initial values of GFR. In addition, a more pronounced decrease in albuminuria occurs in patients with the lowest GFR (Petrykiv et al, 2017).<sup>49</sup>

## Discussion

The review of the current literature on diabetic nephropathy showed that SGLT2 inhibitors were characterized with a multicomponent nephroprotective effect and it was confirmed by the results of both experimental and clinical researches. The renal influence of this pharmacological group is associated with many pathogenetic changes in diabetic nephropathy. Thus, the

nephroprotective effect of SGLT2 inhibitors is maximally realized in the presence of diabetes and remains not full clear in the case of other kidney pathologies.

Of considerable interest is the study of the nephroprotective effects of combination therapy, including SGLT2 inhibitors. A RACELINES study is currently underway to study the renal effects of a combination of empagliflozin and a dipeptidyl peptidase-4 linagliptin inhibitor. The design of the study involves the addition of metformin in the first group - empagliflozin for 8 weeks, followed by the transition to the combination of empagliflozin + linagliptin, in the second group - linagliptin for 8 weeks, followed by the transition to the combination of empagliflozin + linagliptin, in the control group - followed by an increase in its glycosid doses after 8 weeks. Based on the results, it is planned to evaluate the effect of empagliflozin and linagliptin on GFR, the excretion of albumin and electrolytes, urine pH, body mass index, pancreatic beta cell function, and biochemical parameters (US National Library of Medicine Clinical Trials Database). The safety of the combination of empagliflozin and linagliptin was demonstrated in a previous study (Lewin et al, 2015).<sup>47</sup>

Experience in studying the renal effects of SGLT2 inhibitors in non-diabetic patients is currently extremely limited. A study is currently being conducted in which, using the method of functional magnetic resonance imaging, the effect of empagliflozin on the oxygenation of the kidney tissue of healthy volunteers with different body mass index is evaluated (Muller et al, 2018).<sup>48</sup> studied the effects of dapagliflozin administration in patients with focal segmental glomerulosclerosis for 8 weeks and found no significant effect on renal hemodynamics and proteinuria.

The publication of the results of a placebo-controlled study RECEDE-CHF, dedicated to the study of the effects of adding empagliflozin to therapy with loop diuretics in a group of patients with heart failure. In addition to the effect on diuresis, the study plans to evaluate changes in the level of cystatin C, GFR, sodium and albumin excretion in the urine during combination therapy (Mordi et al, 2017).<sup>50</sup>

## Conclusion

Thus, SGLT2 inhibitors are characterized by the presence of a multicomponent nephroprotective effect, which is confirmed by the results of both experimental and clinical studies. The renal effects of representatives

of this pharmacological group have points of contact with a large number of links in the pathogenesis of diabetic nephropathy, and therefore the nephroprotective potential of SGLT2 inhibitors is maximally realized in the presence of diabetes and remains not entirely clear in the case of another kidney pathology. Currently, the greatest scientific and practical studies are devoted to the comparative effectiveness of various SGLT2 inhibitors in nephroprotection, as well as the possibilities of personalizing treatment and combination pharmacotherapy.

**Study Limitations:** The review did not include the quality assessment and risk of bias within included studies. This might affect the general outcomes as well as conclusion of this review. Thus, further literature review and meta-analyses on this topic can be conducted with the quality assessment.

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**Conflict of Interest:** The authors declare that they have no competing interests.

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