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ООО Tadqiqot город Ташкент,
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Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Тел: (+998-94) 404-0000

Editorial staff of the journals of www.tadqiqot.uz
Tadqiqot LLC the city of Tashkent,
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Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
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Pulatova Sh.Kh.,
Tasheva F.A.
Bukhara State Medical Institute

A NEW APPROACH TO THE TREATMENT OF DIABETIC NEPHROPATHY WITH HEART FAILURE

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ABSTRACT

The development of chronic kidney disease (CKD) is a risk factor not only for the formation of cardiovascular diseases, but also for chronic heart failure (CHF). The article is a literature review on the problem of the use of sodium-glucose cotransporter type 2 inhibitors (NGLT2) in patients with CKD and CHF. The article presents in detail the mechanisms of action of NGL-2 inhibitors in the light of reno- and cardioprotection. In addition to the glucosuric effect of NGLT2 inhibitors, they have a natriuretic and diuretic effect. One of the effects of NGL-2 inhibitors is the ability to lower blood pressure. Another effect of NGLT2-2 inhibitors, explaining their renoprotective effect, is the effect on glomerular filtration.

Keywords: chronic kidney disease, type 2 sodium-glucose cotransporter inhibitors.

Пулатова Ш.Х.,
Тошева Ф.А.
Бухарский государственный медицинский институт

НОВЫЙ ПОДХОД ЛЕЧЕНИЕ ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

АННОТАЦИЯ

Развитие хронической болезни почек (ХБП) является фактором риска не только формирования сердечно-сосудистых заболеваний, но и хронической сердечной недостаточности (ХСН). Статья представляет собой литературный обзор по проблеме применения ингибиторов натрий-глюкозного котранспортера 2 типа (НГЛТ2) у больных с ХБП и ХСН. В статье детально представлены механизмы действия НГЛТ2-ингибиторов в свете рено- и кардиопротекции. Помимо глюкозурического эффекта НГЛТ2-ингибиторов они обладают натрийуретическим и диуретическим эффектом. Одним из эффектов НГЛТ2-ингибиторов является способность снижать артериальное давление. Другим эффектом НГЛТ2-2 ингибиторов, обьясняющим их рено-протективное действие, является влияние на гломерулярную фильтрацию.

Ключевые слова: хроническая болезнь почек, ингибиторы натрий-глюкозного котранспортера 2 типа.

Пулатова Ш.Х.,
Тошева Ф.О.
Бухоро давлат тиббиёт институти

ЮРАК ЕТИШМОВЧИЛИГИ БИЛАН ДИАБЕТИК НЕФРОПАТИЯНИ ДАВОЛАШДА ЯНГИ ЁНДАШУВ

АННОТАЦИЯ

Сурункали буйрак касаллигининг (СКД) ривожланиши нафақат юрак-қон томир касалликларининг шаклланиши, балки сурункали юрак етишмовчилиги (ЧФ) учун ҳам хавф омилидир. Мақола СКД ва ЧФ билан оғриган беморларда натрий-глюкоза котранспортер тури 2 ингибиторлари (НГЛТ2) дан фойдаланиш муаммоси бўйича адабиётларни кўриб чиқишдир. Мақолада НГЛ-2 ингибиторларининг рено - ва кардиопротекция нурида таъсир қилиш механизмлари батафсил келтирилган. НГЛТ2 ингибиторларининг глюкозурик таъсиридан ташқари улар натриуретик ва диуретик таъсирга ега. НГЛ-2 ингибиторларининг таъсиридан бири қон босимини пасайтириш қобилиятидир. НГЛТ2-2 ингибиторларининг ренопротектив таъсирини тушунтирувчи яна бир таъсири гломеруляр филтрацияга таъсир қилади.

Калит сўзлар: сурункали буйрак касаллиги, 2-тоифа натрий-глюкоза котранспортер ингибиторлари.

Introduction. In the case of the development of chronic kidney disease (CKD) in cardiovascular diseases (CVD), chronic heart failure (CHF) is formed more often and proceeds more severely [1]. Conversely, the development of CKD is a risk factor not only for the formation of CVD, but also for CHF [2]. It is urgent to search for new medicinal approaches to the management of patients with CHF, including in the case of CKD. It has been >30 years since the studies using the natural glycoside florizin in relation to models of diabetes mellitus (DM), which demonstrated its glucosuric effect, and later the ability to block the receptors of sodium glucose co-transporter types 1 and 2 (NGLT1, 2) [3]. Currently, a large number of compounds from the category of NGL-2 inhibitors have been approved for use in clinical practice, including those approved in the USA and Europe: kanagliflozin, dapagliflozin, empagliflozin and ertugliflozin, as well as those approved in Japan, ipragliflozin, luseogliflozin and tofogliflozin, in India — remogliflozin Mechanisms of action of NGL-2 inhibitors in the light of reno- and cardioprotection Normally, in a healthy person, ~ 180 g of glucose is filtered daily in the kidneys, while its almost complete reabsorption (~ 99.9%) is observed. Up to 97% of glucose is reabsorbed in the proximal tubule in its initial part, where most of the NGLT2 is concentrated, the remaining part is reabsorbed in the final part of the proximal tubule using NGLT1 transporters [4]. In the case of diabetes, glomerular filtration of glucose increases significantly, but this is accompanied by an increase in its reabsorption to 600 g/day. [5].

In addition to the glucosuric effect of NGL-2 inhibitors, they have a natriuretic and diuretic effect, which is manifested by an increase in urine volume by about 300 ml / day. during the first 2-3 days and returning to the initial level of diuresis for several weeks due to the restoration of the sodium-water balance. Diuresis with the use of NGL-2 inhibitors increases both with euglycemia and to a greater extent with hyperglycemia, and also remains elevated with CKD stages 3-4, CHF and acute heart failure (HF) [6].

A decrease in plasma volume during therapy with NGL-2 inhibitors occurs by about 7% (5-12%) by the third month of treatment [7]. Normally, NGLT2 is responsible for the reabsorption of ~5% sodium in tubular urine, whereas with DM, the volume of reabsorption increases to 15%, which is explained by an increase in the expression of NGLT2 and NGLT1 in the epithelium of the proximal tubules [8]. Thus, the blockade of NGLT2 is accompanied by natriuresis. Moreover, NGLT2 inhibitors can also affect the sodium-hydrogen exchanger isoform 3 (NHE3) in the proximal tubules, also reducing sodium reabsorption [9]. The effect of NGLT2 inhibitors on NHE3 can be explained by the close functional and organic relationships of NGLT2 and NHE3 [10]. In experimental models, it was shown that the use of the NGLT inhibitor florizin significantly increases the excretion of sodium and HCO3- in the urine. These data are consistent with the data of stationary microperfusion

of the proximal tubule in vivo, in which the addition of florizine to the luminal fluid sharply reduces the activity of NHE3 even. This indicates that the effect of inhibition of NGLT cannot simply be mediated by an osmotic diuretic mechanism induced by luminal glucose. Moreover, using immunofluorescence experiments, it was shown that NGLT2, but not NGLT1, are expressed together with NHE3 on the apical membrane of the epithelium of the proximal tubule [10]. In addition, the literature data indicate the existence of a multimeric protein complex in the proximal tubule of the kidney, including 2 transport-frame proteins PDZK1 and MAP17 [11-13]. It has been shown that the MAP17 protein directly interacts with NGLT2, which is necessary for the realization of the NGLT2 transport function. The MAP17 protein, in turn, interacts with PDZK1, which directly interacts with NHE3 [12].

This indicates that the effect of inhibition of NGLT cannot simply be mediated by an osmotic diuretic mechanism induced by luminal glucose. Moreover, using immunofluorescence experiments, it was shown that NGLT2, but not NGLT1, are expressed together with NHE3 on the apical membrane of the epithelium of the proximal tubule [10]. In addition, the literature data indicate the existence of a multimeric protein complex in the proximal tubule of the kidney, including 2 transport-frame proteins PDZK1 and MAP17 [11-13]. It has been shown that the MAP17 protein directly interacts with NGLT2, which is necessary for the realization of the NGLT2 transport function. The MAP17 protein, in turn, interacts with PDZK1, which directly interacts with NHE3 [12].

One of the effects of NGL-2 inhibitors is the ability to lower blood pressure (BP). Systolic blood pressure in patients with type 2 diabetes and hypertension decreases on average by 3-5 mmHg, diastolic — by 1-2 mmHg [14]. Moreover, this effect persists in full in patients, despite a decrease in renal function [15]. One of the key effects of NGL-2 inhibitors, explaining their renoprotective effect, is the effect on glomerular filtration. By means of NGLT2, not only glucose is reabsorbed, but also sodium, and in the case of NGLT2 blockade, the sodium concentration in the primary urine increases, which causes an effect on the juxtaglomerular apparatus (macula densa) at the level of the distal tubule. This, in turn, leads to the release of adenosine triphosphate from the cells of the juxtaglomerular apparatus, which is cleaved to adenosine. Adenosine acts on the adenosine A1 receptors in the wall of the adductor arteriole, which is accompanied by its contraction and a decrease in pressure, as well as the relief of hyperfiltration in the renal glomerulus. To a lesser extent, the effect of adenosine on A2 receptors in the diverting arteriole, the excitation of which is accompanied by dilation of the vessel, has been shown [13][14]. The use of NGL-2 inhibitors is accompanied by a decrease in the level of albuminuria. In a meta-analysis of 48 randomized clinical trials using NGL-2 inhibitors for >12 weeks, including 50 thousand patients, a decrease in the ratio of albumin to creatinine of urine was shown (weighted average difference -14.6 mg/g, p=0.006), with a more pronounced effect in individuals with a higher initial ratio of albumin to creatinine of urine [12]. In particular, it was shown to reduce the risk of developing microalbuminuria (relative risk (RR) 0.69, p=0.032), macroalbuminuria (RR 0.49, p<0.001), progression of nephropathy (RR 0.73, p=0.012) and the development of end-stage renal failure (RR 0.70, p=0.001).

In recent years, the focus has gradually shifted from hyperfiltration as an independent factor of damage to the renal parenchyma to the proximal tubules. Hyperfiltration is considered as a factor of increasing the functional load on the proximal tubular epithelium, which leads to its damage. And damage to the epithelium of the proximal tubules can be considered as a key universal mechanism of kidney damage not only in DM, but also in a number of other pathological processes occurring with hyperfiltration phenomena. When using NGL-2 inhibitors, due to the relief of hyperfiltration, the transport load on the proximal tubules decreases. However, a direct renoprotective effect of this class of drugs on the tubular epithelium has also been shown

The ability of NGLT2 inhibitors to suppress the processes of peroxidation in the mitochondria of the epithelium of the proximal tubules has been shown. Hyperglycemia in DM and activation of the renin-angiotensin-aldostenorone system can cause inflammatory reactions, as well as hyperproduction of reactive oxygen species in human proximal tubule cells, and these effects are suppressed with the use of NGL-2 inhibitors [1]. Against the background of therapy, there is a decrease in the expression of inflammation genes in the renal tissue and oxidative stress [2]. The anti-

inflammatory effects of NGLT2 inhibitors are manifested in a decrease in the level of interleukin-6, tumor necrosis factor in the blood, as well as nuclear factor-kB and interleukin-6 in the renal tissue of rats with DM [3]

Since the action of NGL-2 inhibitors increases the reabsorption load in the lower zones of the tubular apparatus, which traditionally consume and are provided with less oxygen, this leads to the activation of HIF (hypoxia inducible factor)-dependent mechanisms for combating hypoxia, followed by an increase in the production of erythropoietins and improved oxygen delivery to the renal tissue [4]. This mechanism is also considered among the possible tubuloprotective mechanisms of action of NGL-2 inhibitors. Therapy with NGL-2 inhibitors is accompanied by a decrease in leptin production, as well as a decrease in fat deposition in the perivisceral, pericardial and perivascular space, which may play a role in improving the course of metabolic processes [5]

The use of NGLT2 inhibitors is also accompanied by a decrease in the level of uric acid in the blood due to a decrease in the reabsorption of urates by the epithelium of the proximal tubules through GLUT9b [7]. In a large meta-analysis of 62 clinical trials using NGL-2 inhibitors, it was shown that the level of uric acid in the blood decreased by about 35-45 mmol/l, while the effect developed rapidly and persisted throughout the treatment period [8]. The cardioprotective effect of NGL-2 inhibitors is explained by a number of reasons. Despite the fact that cardiomyocytes do not express NGLT2, NGLT2 inhibitors are able to have a direct effect on cardiomyocytes by influencing NHE1. An increase in its activity is shown in CHF, this leads to an increase in the concentration of sodium and calcium in the cytoplasm of cardiomyocytes and may be associated with the activation of oxidative stress of arrhythmogenesis [9] Accordingly, the use of the NGLT2 inhibitor empagliflozin in an in vitro experiment demonstrated the ability to inhibit NHE1 in cardiomyocytes, reducing intracellular levels of sodium and calcium [30]. Most cardioprotective effects of NGLT2 inhibitors are mediated. Among them are the sodium-diuretic effect, a decrease in the number of glycation products with pro-inflammatory and endotheliotoxic properties, normalization of carbohydrate metabolism and a decrease in blood pressure, weight loss and a number of others [31]. The use of NGL-2 inhibitors is accompanied by a decrease in the activity of the intrarenal renin-angiotensin-aldostenorone system, as well as a decrease in plasma renin secretion [2]. Another proposed mechanism of organoprotective action of NGL-2 inhibitors is their ability to restrain the activation of the sympathetic nervous system. Sympathetic hyperactivity in the proximal tubule area is associated with impaired renal regulation of glucose, sodium and water [5]. The argument in favor of this mechanism is that carrying out renal sympathetic denervation in diabetic OLETF rats led to an improvement in glucose metabolism, which was explained by an increase in its excretion in urine due to the suppression of overexpression of NGL T2 [6]. When the sympathetic innervation of the kidneys was stimulated, an increase in the activity of NHE3 in the apical membrane of the proximal tubule was observed, which was accompanied by an antinatriuretic and antidiuretic effect [7]. In turn, in experimental models, NGL-2 inhibitors reduce sympathetic activity in the kidneys and heart [8]

Thus, the cardioprotective effect of NGL-2 inhibitors in CHF is realized both through direct action on cardiomyocytes and indirect action (diuretic, hypotensive effects, suppression of the activity of the sympathetic nervous system, effective treatment of type 2 diabetes). The presence of NGLT2-inhibitors of the renoprotective effect in conditions of CHF is the key to a beneficial effect on the cardio-renal continuum. Results of studies using empagliflozin in CHF and CKD.

In a randomized, double-blind, placebo-controlled EMPA-REG OUTCOME study, the effects of empagliflozin administered 1 time/day were evaluated. at a dose of 10 mg or 25 mg, compared with placebo for cardiovascular events in adults with type 2 diabetes, high cardiovascular risk and glomerular filtration rate >30 ml/min/1.73 m2 [9]. It was shown that in patients with type 2 diabetes and concomitant CVD, the use of empagliflozin led to a 35% reduction in the risk of hospitalization due to decompensation of CHF, as well as (in subgroup analyses) to an improvement in a number of CHF outcomes, such as the risk of the first administration of loop diuretics, the risk of re-hospitalization due to CHF [4]. There was also an early and sustained relative reduction in the risk of cardiovascular death by 38%, regardless of the initial kidney function. In patients with type 2 diabetes and CVD, empagliflozin treatment resulted in a rapid 59% reduction in the relative risk of developing

or progressing nephropathy, 44% relative risk of. It should be noted that the positive effect of empagliflozin on cardiovascular mortality and cases of hospitalization due to CHF persisted regardless of the presence of such CVD as HF [4], atrial fibrillation [2] (Böhm M, et al., 2020), kidney disease [1], as well as ongoing hypoglycemic therapy [40]. Empagliflozin continues to be studied in the EMPOWER clinical research program, which includes patients with HF, CKD, and myocardial infarction. Thus, the results of the double-blind placebo-controlled EMPEROR-Reduced study were among the first to be obtained, in which the effect of empagliflozin at a dose of 10 mg was studied in patients with a reduced ejection fraction (EF) compared with placebo. The study included 3730 patients of average age 67 years, 24% of them were female, 75% with CHF II, 24% — III and <1% - IV functional class according to the NYHA classification. Half of the patients had a history of type 2 diabetes, 73% had left ventricular LV of 30% or less, 79% had a level of N—terminal propeptide natriuretic hormone of at least 1000 pg/ml, 48% had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2, and almost 20% of patients received sacubitril/valsartan [43]. It is important to note that the researchers had planned in advance the inclusion of severe patients with a left ventricular fraction <30%, or hospitalized due to decompensation of HF during the previous 12 months. or having high levels of N-terminal propeptide natriuretic hormone, as well as eGFR >20 ml/ min / 1.73 m2.

The primary endpoint (cardiovascular mortality or hospitalizations due to CHF) was 25% less common in the empagliflozin group compared to placebo, and primary or repeated hospitalizations due to CHF were 30% less common [3]. It should be noted that the positive effect of empagliflozin on the primary endpoint was observed regardless of the presence or absence of DM, initial renal function, basic intake of mineralocorticoid receptor antagonists or angiotensin receptor inhibitor — neprilysin.

One of the secondary endpoints was the dynamics of eGFR reduction throughout the study. The difference in the magnitude of eGFR reduction in the empagliflozin group compared to placebo was 1.73 ml/min per year ($p<0.001$) in favor of the NGLT2 inhibitor. Empagliflozin therapy in patients with CHF reduced the risk of developing a combined renal endpoint by 50% (initiation of renal replacement therapy, kidney transplantation or detection of a stable decrease in eGFR >40% of the baseline) — RR 0.50 (95% confidence interval 0.32-0.77).

It is worth saying that according to the results of EMPERORReduced empagliflozin showed a favorable safety profile, since no cases of ketoacidosis were recorded, and the frequency of hypoglycemia was comparable to placebo. In addition, there were no clinically significant differences with the placebo group in adverse events, including hypovolemia, hypotension, impaired renal function, hyperkalemia. The results of this study open up additional prospects for the use of empagliflozin in patients with CHF without DM, including those with reduced renal function and regardless of the use of a number of drugs for basic therapy of CHF.

The results of the currently ongoing EMPAKIDNEY study involving adult patients with confirmed CKD should be expected within a year. This study examines the renoprotective and cardioprotective efficacy of empagliflozin in patients with GFR >20 ml/min [4]. Obtaining information about the effect of empagliflozin in this study will provide additional information about the effectiveness of the drug in patients with CKD and CHF.

Conclusion: NGLT2 inhibitors have a number of direct and indirect cardio- and renoprotective effects that ensure the effectiveness of their use in CHF, including in patients with CKD. The results of studies show that empagliflozin is effective in reducing the risk of cardiovascular death and hospitalization due to HF in patients with type 2 diabetes and CVD, and these effects persist in various subgroups of patients. In patients with HF with reduced LV, empagliflozin also showed efficacy in reducing the risk of hospitalization due to HF and cardiovascular death, as well as slowing the decline in kidney function compared with placebo. Thus, empagliflozin prevents the progression of CVD in patients with type 2 diabetes, with HF with reduced LV, regardless of the presence of diabetes, providing a holistic approach to the treatment of patients with CVD. Empagliflozin EMAGLIV research program will expand the range of its pharmacological effects in patients where modern therapy has serious limitations

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1 МАХСУС СОН

УЗБЕКСКИЙ МЕДИЦИНСКИЙ ЖУРНАЛ

СПЕЦИАЛЬНЫЙ НОМЕР 1

UZBEK MEDICAL JOURNAL

SPECIAL ISSUE 1

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