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MUNDARIJA | СОДЕРЖАНИЕ | CONTENT

ОБЗОРНЫЕ СТАТЬИ | REVIEW ARTICLES | ADABIYOTLAR SHARHI

ОРИИНАЛЬНЫЕ СТАТЬИ | ORIGINAL ARTICLES | ORIGINAL MAQOLALAR

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ОБЗОР КЛИНИЧЕСКИХ ИСПЫТАНИЙ С ИНГИБИТОРАМИ НАТРИЙ-ГЛЮКОЗНОГО КОТРАНСПОРТЕРА ТИПА 2

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АННОТАЦИЯ

В этой обзорной статье обобщены и проанализированы клинические испытания, оценивающие эффективность и безопасность ингибиторов SGLT2, класса препаратов, используемых в основном для лечения сахарного диабета 2 типа. Обзор охватывает несколько ключевых исследований, включая исследования EMMY, EMPAREG OUTCOME, DAPA-HF, EMPULSE, SOLOIST-WHF и EMPACT-MI, в которых подчеркивается положительное влияние ингибиторов SGLT2 на снижение сердечно-сосудистых осложнений и улучшение показателей функции почек. Далее в статье обсуждается применение ингибиторов SGLT2 не только для лечения диабета, но и для лечения сердечной недостаточности и хронических заболеваний почек. Авторы приходят к выводу, что ингибиторы SGLT2 обладают значительными преимуществами в лечении диабета 2 типа и связанных с ним осложнений, а также демонстрируют перспективность в более широких терапевтических областях. Этот обзор важен для понимания меняющейся роли ингибиторов SGLT2 в современной клинической практике и дает ценную информацию о проводимых исследованиях.

Ключевые слова: Ингибиторы SGLT2, антиремоделирующий эффект, сердечная недостаточность, инфаркт миокарда, хроническая болезнь почек, скорость клубочковой фильтрации, антигипергликемический эффект

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REVIEW OF CLINICAL TRIALS WITH SODIUM GLUCOSE COTRANSPORTER TYPE 2 INHIBITORS

ANNOTATION

This review article summarizes and analyzes clinical trials assessing the efficacy and safety of SGLT2 inhibitors, a class of drugs used primarily for the treatment of Type 2 diabetes mellitus. The review covers several key studies, including the EMMY, EMPAREG OUTCOME, DAPA-HF, EMPULSE, SOLOIST-WHF and EMPACT-MI trials, highlighting the positive impact of SGLT2 inhibitors on reducing cardiovascular events and improving kidney outcomes. The article further discusses the expansion of SGLT2 inhibitors' use beyond diabetes treatment to address heart failure and chronic kidney disease. The authors conclude that SGLT2 inhibitors offer significant benefits in managing type 2 diabetes mellitus and related complications, while also demonstrating promise in broader therapeutic areas. This review is essential for understanding the evolving role of SGLT2 inhibitors in modern clinical practice and provides valuable insights into ongoing research. It is particularly relevant to my study on the cardiovascular benefits of medications and their long-term effects.

Key words: SGLT2 inhibitors, antiremodeling effect, heart failure, myocardial infarction, chronic kidney disease, glomerular filtration rate, antihyperglycemic effect

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NATRIY GLYUKOZA KOTRANSPORTERINING 2-TUR INGIBITORLARI BILAN O‘TKAZILGAN KLINIK SINOVLARNI KO‘RIB CHIQISH

ANNOTATSIYA

Ushbu maqolada asosan 2-tur qandli diabetni davolash uchun ishlatiladigan dorilar sinfi bo'lgan SGLT2 ingibitorlarining samaradorligi va xavfsizligini baholovchi klinik sinovlar umumlashtiriladi va tahlil qilinadi. Maqola EMMY, EMPAREG OUTCOME, DAPA-HF, EMPULSE, SOLOIST-WHF va EMPACT-MI kabi bir nechta asosiy tadqiqotlarni o'z ichiga oladi, ular SGLT2 ingibitorlarining yurak-qon tomir kasalliklarini kamaytirish va buyrak funktsiyasini yaxshilashdagi foydali ta'sirini ta'kidlaydi. Maqolada SGLT2 ingibitorlarini nafaqat qandli diabetni 2-turini davolashda, balki yurak yetishmovchiligi va surunkali buyrak kasalliklarini davolashda ham qo‘llash haqida so‘z boradi. Mualliflar SGLT2 ingibitorlari 2-tur qandli diabet va unga bog'liq bo'lgan asoratlarni davolashda sezilarli foyda keltiradi, shuningdek, kengroq terapevtik sohalarda ham qo`llash mumkin degan xulosaga kelishadi. Ushbu maqola zamonaviy klinik amaliyotda SGLT2 ingibitorlarining o'zgaruvchan rolini tushunish uchun muhim va davom etayotgan tadqiqotlar haqida qimmatli tushunchalarni beradi.

Kalit so'zlar: SGLT2 ingibitorlari, antiremodelirlanuvchi ta'siri, yurak etishmovchiligi, miokard infarkti, surunkali buyrak kasalligi, glomerulyar filtratsiya tezligi, antigiperglikemik ta'sir.

The beginning of the history of sodium-glucose cotransporter type 2 (SGLT2) inhibitors can be considered to be 1835. Then the French chemist C. Petersen isolated phlorizin from the bark of the apple tree root, which was first used to treat malaria [1].

In 1886, German professor of medicine von Mering discovered the glucosuric and, as a consequence, hypoglycemic effect of phlorizin [1].

In the first half of the 20th century, it became known that glucose, which is normally filtered at the glomerulus, is almost entirely reabsorbed by the proximal renal tubule. In the 1960s, it was shown that this reabsorption requires active transport and that glucose and sodium are cotransported. It became clear that when the molecule responsible for reabsorption, the cotransporter, is inhibited, both glucose and sodium are excreted in the urine.

In 1996, researchers from Kyoto University and Tanuba Seiygyu Co. (Japan) developed phlorizin analogues, the first chemically engineered SGLT2 inhibitors [1].

Canagliflozin, the first drug targeting SGLT2 to treat type 2 diabetes, was launched [2].

In March 2013, the FDA approved canagliflozin for the treatment of adults with type 2 diabetes, making it the first member of a new class of oral SGLT2 inhibitors approved for use in the United States [3].

The mechanism of action of gliflozins is due to inhibition of the SGLT2 transporter in the proximal tubules of the kidneys, which reduces the reabsorption of glucose and sodium from the lumen of the tubule, reduces the level of glucose in the plasma, and leads to moderate osmotic diuresis. About 60-90 g of glucose is excreted in the urine, which is about 330 kcal. Water loss is approximately 375 ml, which corresponds to approximately 1.5 urinations per day.

When using SGLT2 inhibitors, about 30% of glucose reabsorption is blocked. The action of these drugs has an insulin-independent mechanism, unlike other antidiabetic agents [3,4,5]. SGLT2 inhibitors reduce fasting plasma glucose concentration and postprandial glucose concentration. HbA1c concentration decreases slightly, by an average of 0.7%. It is noted that the risk of hypoglycemia when using gliflozins is insignificant. This may be due to the fact that when using SGLT2 inhibitors, the production of endogenous glucose and the secretion of glucagon increase.

It should be noted that the effect of SGLT-2 inhibitors is insulin-independent. However, it depends on the glucose level

and becomes minimal at values less than 5 mmol /l. Therefore, when using SGLT-2 inhibitors, compared with the use of other hypoglycemic drugs whose effect depends on the degree of insulin resistance or insulin secretion, the risk of hypoglycemia decreases [6].

SGLT2 inhibitors are also able to improve β-cell function and muscle tissue sensitivity to insulin [7], and protect target organs.

EMMY is the first multicenter, randomized , double-blind, placebo-controlled study evaluating the effects of empagliflozin on heart failure biomarkers and cardiac function and structure in patients with acute myocardial infarction. It is the first clinical trial to show beneficial effects of SGLT2 inhibitors in patients with acute myocardial infarction compared with placebo [8] and was published in the European Heart Journal [9].

The study showed a significantly greater improvement in left ventricular function in the empagliflozin group compared with the placebo group and a significantly better improvement in diastolic function in the empagliflozin group, with E/e' at week 26 being 6.8% lower than in the placebo group. Structural parameters also improved significantly, with left ventricular end-systolic and end-diastolic volumes being significantly lower in the empagliflozin group [10].

Moreover, with empagliflozin, we observed that body weight was significantly lower than in the placebo group and ketone bodies increased significantly after 26 weeks of treatment. It should be noted that no difference in HbA1c levels was observed, since only a minority (13%) of patients had type 2 diabetes [9].

Based on these results, the EMMY study is the first clinical trial to show a beneficial effect of SGLT2 inhibitors on biomarkers as well as cardiac function and structure in patients with acute myocardial infarction [10].

The pathophysiology of myocardial infarction is a complex mechanism. It involves acute myocardioischemia caused by energy depletion, followed by early reperfusion injury developing within the first minutes/hours of reperfusion , and a subsequent remodeling phase during the first days/weeks after myocardial infarction (MI), leading to irreversible necrotic damage to the affected area. In addition, the neurohumoral system is involved in the initiation of the renin -angiotensin -aldosterone system and the regulation of the sympathetic nervous system. These mechanisms lead to structural deterioration of the myocardium, called remodeling, affecting the functional processes in ischemic and non-ischemic areas. However, effective clinical therapy against reperfusion injury is still lacking, despite numerous treatments being effective in preclinical models [11–13].

The SGLT2 receptor is mainly expressed in the proximal tube of human nephrons and intestinal cells and thus plays an important role in renal glucose excretion and lowering blood glucose levels [14], but has not been detected in human myocardium so far [15]. Thus, there is no receptor -mediated effect of SGLT2 inhibitors on human myocardium, but various indirect pathways seem to play an important role in the anti-remodeling effects [16]. The key role of the SGLT2 pathway is to increase myocardial ketone body uptake, which leads to improved myocardial energy supply and thus affects the energetic state of myocardial cells, resulting in reduced cardiac necrosis and cardiac dysfunction [16]. Moreover, various experimental studies have shown potential beneficial effects of SGLT2 inhibition on myocardium through upregulation of cardioprotective proteins. Asencio et al. [17] reported an increase in the uptake of the enzyme GTP cyclohydrolase 1 by empagliflozin independent of diabetic status, affecting the GCH1-BH4/NO pathway and resulting in reduced cardiac dysfunction via its antiremodeling effect. SGLT2 inhibitors then demonstrate beneficial cardiac effects in reducing cytoplasmic sodium via inhibition of the sodium-hydrogen antiporter Na +/H+ 1 (NHE1) with changes in cellular calcium hemostasis due to intracellular calcium overload in rats and rabbits [18] as well as in mice [19], although the effects on NHE1 were independent of the SGLT receptor [18,19]. SGLT2 inhibitors improve left ventricular remodeling in heart failure via the adenosine monophosphate- activated protein kinase (AMPK) pathway, with a reduction in myocardial necrosis and cardiac inflammation [20] by increasing myocardial energetics [21] and attenuating ischemia and reperfusion injury [22]. Another mechanism of SGLT2 inhibition is to reduce oxidative stress levels, which mediates anti-inflammatory effects via BCL2 and signal transducer and activator of the 3/ janus pathway kinase 2 (STAT3/JAK2) and thus reducing myocardial necrosis and cardiac dysfunction [23–25]. All these preclinical molecular effects improve the inflammatory response and cardiomyocyte necrosis, resulting in smaller infarct size, less reperfusion injury and antiremodeling effect.

Based on this study, it can be suggested that the potential anti-inflammatory effects of SGLT2 inhibitors after AMI mediate favorable cardiovascular outcomes such as reduced infarct size and antiremodeling effects. In addition, a diuretic effect with effects on hemodynamics through lowering blood pressure as well as increasing hematocrit were described in the EMPA-REG OUTCOME trial [26-28]. The antiarrhythmic properties of SGLT2 inhibitors in patients with structural and functional heart disease are still unclear. The first study to show convincing evidence of beneficial effects was the DAPA-HF trial, which demonstrated in a post hoc analysis a significant reduction in serious ventricular arrhythmias, resuscitated cardiac arrest, and sudden death in patients with HFrEF with a relative risk reduction of 21% with dapagliflozin compared with placebo [29].

Another study, EMPULSE, was a multicenter, randomized , double-blind, 90-day study of the superiority of empagliflozin 10 mg once daily versus placebo in 530 patients hospitalized for acute heart failure (new onset or decompensated chronic heart failure). The condition was stable. The primary endpoint was based on clinical benefit, a hierarchical composite endpoint of all-cause mortality, incidence of heart failure events, time to first heart failure event, and symptoms measured by the KCCQ-TSS after 90 days of treatment, and was assessed by the benefit ratio [30].

The victory rate estimates the likelihood that a participant in the empagliflozin group will have a better clinical benefit than a participant in the placebo group; higher victory rates suggest greater clinical benefit with empagliflozin. For EMPULSE, patients were stratified by de novo versus decompensated chronic heart failure. In each stratum, each person in the empagliflozin group was compared with each person in the placebo group. The win rate was determined by dividing the total number of wins for empagliflozin by the total number of losses. The components of the primary endpoint were assessed in order of clinical importance, such that deaths took precedence over heart failure events and symptoms [31].

The EMPULSE and SOLOIST-WHF trials examined the benefits of SGLT2 inhibitors in AHF; however, both trials excluded patients who had a history of ACS prior to HF within 3 months of enrollment [32, 33].

James et al [34] demonstrated in the DAPA-MI trial that early initiation of dapagliflozin after STEMI and NSTEMI with impaired left ventricular systolic function on echocardiography or Q-wave myocardial infarction on electrocardiogram resulted in similar cardiovascular mortality and HF hospitalization compared with placebo. However, more than 66% of patients included in the DAPA-MI trial had an EF of 30%–49%, more than 21% had an EF ≥50%, and AHF was not taken into account, which may have affected the study results [35]. On the other hand, similar to our study population, EMPACT-MI is an ongoing clinical trial assessing the cardiovascular outcomes of adding empagliflozin to patients with acute myocardial infarction who developed symptoms or signs of fluid overload or a drop in EF below 45% [36].

Early initiation of SGLT2 inhibitors after ACS complicated by AHF is associated with cardioprotective effects due to a reduction in HF hospitalization. The observations of the study may provide early evidence to expand the indications for SGLT2 inhibitors and, therefore, to initiate SGLT2 inhibitors in patients with ACS complicated by new-onset HF [37].

In the second half of 2022, EMPA - KIDNEY (Empagliflozin in Patients with Chronic Kidney Disease) and DELIVER (Evaluation of Dapagliflozin to Improve Lives in Patients with Preserved Ejection Fraction in Heart Failure) — two large, placebo-controlled studies conducted in these populations — published their top-line results and expanded the evidence base in patients with and without diabetes. Approximately half of each of the respective study groups did not have diabetes at recruitment. [38, 39] Of note, EMPA - KIDNEY represents patients with low kidney function: mean estimated glomerular filtration rate (EGR) 37 ± 14 mL/min/1.73 m2.

Pooled results from five heart failure trials [40] and the Nuffield Department of Population Health Kidney Disease Study Group with SGLT 2 inhibitor Meta-analysis of Cardio - Renal The Trialists ' Consortium pooled standardized data from 13 large, placebo-controlled SGLT2 inhibitor trials in three different patient populations. It included results from studies examining 42,568 patients with type 2 diabetes at high risk of atherosclerotic cardiovascular disease, 21,974 patients in heart failure studies, and 25,898 patients in CKD studies [41].

In 13 trials, the risk of hospitalization for heart failure or cardiovascular death was reduced by almost a quarter, with consistent effects in patients with and without diabetes and in three different trial populations [41]. In a meta-analysis limited to heart failure trials, there were generally consistent proportional benefits across the range of left ventricular ejection fractions studied and across a wide range of other subgroups [40]. SGLT2 inhibitors are the first clearly effective disease-modifying therapy for HFpEF after large trials of renin-angiotensin system (RAS) inhibitors, angiotensin receptor/neprilysin inhibitors, and mineralocorticoid receptor antagonists (MRAs) failed to meet their primary efficacy endpoints.

The primary focus of the EMPA - KIDNEY study, which enrolled 6,609 people, was to determine the effect of SGLT 2 inhibition on kidney disease progression [39]. Empagliflozin reduced the risk of this composite primary outcome by 28%, including an apparent 27% reduction in the risk of the composite of cardiovascular death or need for maintenance dialysis or a kidney transplant.2 The rate of cardiovascular events was lower than expected, and consequently 888 of 990 participants with the primary outcome experienced kidney disease progression [38]. The EMPA - KIDNEY study enrolled 2,282 people with an SCF less than 30 mL/min/1.73 m2 and demonstrated remarkably consistent relative risk reductions for its primary outcome across the entire range of SCF up to (and below) an SCF of 20 mL/min/1.73 m2 [38].

Benefits of SGLT 2 inhibitors extend beyond CKD progression. Acute kidney injury (AKI) is common in patients with heart failure and in patients with CKD and was initially considered a potential safety concern due to the natriuretic and osmotic diuretic effects of SGLT 2 inhibition. However, AKI has emerged as a benefit of treatment. Across 13 studies, the risk of AKI was reduced by nearly a quarter [40]. Other meta-analyses have shown that the risk of severe hyperkalemia is reduced by approximately 16% [42]. Thus, SGLT 2 inhibitors may improve adherence to RAS and MRA inhibitors, which can cause AKI and hyperkalemia.

In the EMPA - KIDNEY study Empagliflozin also reduced the risk of all-cause hospitalizations by 14%, an effect that was not specific to any particular cause of hospitalization and did not appear to be affected by prior history of cardiovascular disease or kidney disease characteristics. SGLT 2 inhibitors were also well tolerated. Ketoacidosis was rare in the trials, despite its risk doubling with SGLT 2 inhibitors [40].

Results from two new trials and two new meta-analyses convincingly demonstrate the cardioprotective and renal protective effects of SGLT2 inhibitors in a broad range of heart failure and CKD patient populations studied, with absolute benefits clearly outweighing potential harms [40]. The two new trials cement SGLT2 inhibitors as backbone therapy for both conditions and provide clinicians with evidence that SGLT2 inhibitors can be prescribed at low eGFR levels and without the need for routine additional blood monitoring after treatment initiation.

SGLT2 inhibitors are strongly recommended in guidelines for the treatment of patients with heart failure with reduced ejection fraction, but their clinical benefits at higher ejection fractions are less well understood. Two large trials, DELIVER and EMPEROR - Preserved, have been conducted in heart failure with mildly reduced or preserved ejection fraction, providing the opportunity to examine treatment effects on cardiovascular mortality and in patient subgroups in combination with earlier studies in reduced ejection fraction.

Among 12,251 participants in DELIVER and EMPEROR - Preserved, SGLT 2 inhibitors reduced the combined endpoint of cardiovascular death or first heart failure hospitalization, with consistent reductions in both components: cardiovascular death and first heart failure hospitalization. In the broader context of five trials with 21,947 participants, SGLT 2 inhibitors reduced the risk of combined cardiovascular death or heart failure hospitalization, cardiovascular death, first heart failure hospitalization, and all-cause mortality.

SGLT2 inhibitors reduce the risk of cardiovascular death and hospitalization for heart failure in a wide range of patients with heart failure, supporting their role as foundational therapy for heart failure, regardless of ejection fraction or care setting [43].

CREDENCE study assessed the effect of the SGLT-2 inhibitor canagliflozin on renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and concomitant renal insufficiency. It enrolled patients from 34 countries. Participants were over 30 years old. HbA1c levels ranged from 6.5 to 12.0%. Estimated glomerular filtration rate (eGFR) was ≥ 30 and < 90 mL/min/1.73 m2. Due to renal insufficiency, all subjects

received monotherapy with a renin -angiotensin - aldosterone system (RAAS) blocker.

Patients were randomized to receive canagliflozin 100 mg or placebo, while continuing to take RAAS blockers (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers).

The primary composite endpoint included the occurrence of end-stage renal disease, doubling of serum creatinine, death from renal failure, and death from cardiovascular causes.

End-stage renal disease was defined as dialysis for at least 30 days, kidney transplantation, or eGFR <15 ml/min/1.73 m2 for 30 days or more, doubling of serum creatinine (compared to baseline) within 30 days.

Secondary endpoints are cardiovascular events (CVEs) (myocardial infarction, stroke, and hospitalization for HF).

After 2.5 years (mean follow-up 2.62 years), the study was stopped early because a preliminary interim analysis of data revealed a significant reduction in the primary endpoint in those receiving canagliflozin.

Patients treated with SGLT-2 inhibitors had 31–32% fewer hospitalizations for HF than patients treated with placebo, regardless of whether the meta-analysis included three (EMPA-REG, CANVAS, DECLARE studies) or four parameters (CREDENCE study) in the primary composite endpoint.

The pooled results of four studies—EMPA-REG, CANVAS, DECLARE, and CREDENCE—showed a 33% reduction in the risk of a composite endpoint of dialysis, transplantation, and death due to kidney disease, a 35% reduction in the risk of end-stage CKD, and a 25% reduction in acute kidney injury. These effects were similar across studies and in groups with different SCFs, including a group with a baseline SCF of 30–45 ml/min/1.73 m2 [43].

Currently, SGLT-2 inhibitors, at least canagliflozin, empagliflozin and dapagliflozin, are the antihyperglycemic agents that have the most impressive nephroprotective properties, exerting a positive combined effect on albuminuria, increasing eGFR and reducing the risk of progression to end-stage renal disease when used in combination with RAAS blockers [43].

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