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Journal of Health Study and Medicine

2023, Article 13
pp. 247–273
DOI 10.2478/jhsm-2023-0013

What Do We Know about Flozins: New, Pleiotropic Drugs

Submitted: 28 August 2023; Accepted: 10 January 2024;
Published: 02 February 2024

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Abstract

Civilization diseases affect more and more people globally. As a World Health Organization reports in 2016 more than 1.9 billion of adults were overweight and excess body mass is the leading risk factor for developing diabetes affecting approximately 422 million people worldwide (90% is DM2). It has seemed that the link between obesity, diabetes, and cardiovascular complications is a low-grade chronic inflammation that is observed in all tissues involved in energy homeostasis and is characterized by the activation of pro-inflammatory macrophages so-called M1. The increasing number of patients suffering from diabetes has challenged scientists to develop more and more powerful and pleiotropic antidiabetic drugs, which apart from better glycemia control will be able to decrease the total cardiovascular risk (a leading cause of death in diabetic patients). SGLT-2 inhibitors seem to show pleiotropic effects – cardioprotective, nephroprotective, and anti-inflammatory one.

Key words: *flozins, SGLT2-i, diabetes, inflammation, cardiovascular risk*

Introduction

Globally, the prevalence of overweight and obesity has been steadily increasing in recent years [1]. This problem is not only limited to adults but more and more often affects children as well. Approximately one-third of children and adolescents in the United States are classified as either overweight or obese [2].

The past two years have posed significant challenges; due to the COVID-19 pandemic more and increasing numbers of people were compelled to work from home, limit their social meetings and physical activities; opportunities for physical activity were significantly curtailed. The lockdown has not helped in weight loss. Even prior to the SARS-CoV-2 pandemic a sedentary lifestyle has engulfed the highly developed countries which leads to the induction of civilization diseases [4]. Here, there are some body mass statistics; as reported by the World Health Organization in 2016 more than 1.9 billion of

adults, were overweight. Of these, over 650 million were obese [5]. Unfortunately, the forecasts are not very optimistic. As we already know obesity, especially visceral fat, leads to chronic, low-activity inflammation which translates to the development insulin resistance, diabetes type 2, dyslipidemia, and cardiovascular diseases. Based on the data of the National Health Fund, it is estimated that in Poland there are about 3.5 million people with diabetes, and about 85–90% of cases are DM2. About 48% of people suffering from this disease are classified as overweight – BMI 25–29.9 kg/m2, and another 40% of patients as obese of the first degree (BMI 30–34.9) [6–7]. As the above statistics show, type 2 diabetes and excess body weight are closely related. Therefore, each new antidiabetic drug introduced to the market is met with great expectations.

Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) represent a new and promising class of drugs, presently approved not only for diabetes 2 treatment and are also extensively used in the therapy of patients with heart failure (HF) or chronic kidney disease (CKD) [72].

Excess body mass and inflammation

What is the definition of obesity? Characterized as a chronic disease involving abnormal or excessive fat accumulation that poses a threat to health and life. Body Mass Index (BMI) is calculated using an individual's height and weight. A BMI over 25 is considered overweight, and over 30 is obese, while the healthy range is 18.5 to 24.9; As per the World Health Organization, prevalence of excess body mass has been increasing since 1975, moreover, worldwide obesity has nearly tripled since that year. In 2019, a high body mass index was estimated to have caused 5 million deaths globally [6].

Adipose tissue is recognized as a highly active organ that secretes a variety of hormone-like substances with autocrine, paracrine, and endocrine effects. Besides hormones, adipocytes also release numerous peptides and cytokines, influencing immune processes, with their activity varying on cell composition. There is a close relationship and functional dependence

between the metabolic and immune systems. Consequently, excessive food intake by individuals is interpreted as a deleterious and stressful biological event, identified by molecular pattern recognition receptors (PRRs). This initiates an inflammatory response in tissues involved in metabolism, ultimately leading to low-grade inflammation, known as metabolic inflammation or 'meta-inflammation' [9–10].

As early as 1993, studies demonstrated that the expression of the pro-inflammatory cytokine – tumor necrosis factor-α (TNF-α) is increased in adipose tissue of obese mice, and its neutralization led to a marked increase in peripheral glucose uptake in response to insulin, which translates into a significant escalation in the insulin sensitivity of peripheral tissues [11]. These findings contribute to understanding the development of various metabolic disorders, such as insulin resistance, hypertension, asthma, hypertriglyceridemia, hypercholesterolemia, cardiovascular diseases, and type 2 diabetes. Increasingly, low-level chronic inflammation is recognized as the link between obesity, type 2 diabetes, and cardiovascular disease. As early as 2000, Paul M. Ridker et al. in a comprehensive study involving over 20,000 participants, demonstrated that inflammatory markers such as CRP and Interleukin 6 are associated with an increased risk of cardiovascular events not related to cholesterol levels [12–13]. 17 years later, a significant study was initiated with over 10,000 subjects, showing a significant reduction in cardiovascular re-events in patients receiving canakinumab, an antibody against IL-1B, a cytokine that plays a major role in the inflammatory and inflammatory response. directing the IL-6 signaling pathway [14].

Furthermore, obesity and excessive body mass significantly increase the risk of developing severe COVID-19 symptoms and also of dying from COVID19 [7–8].

Multipotent group of drugs – flozins

Sodium-glucose cotransporter 2 inhibitors (SGLT-2), commonly known as flozins, belong to a novel class of antidiabetic drugs. A closer examination of their mechanism of action is warranted; SGLT-2, located in the plasma

membrane of cells lining the proximal tubule, facilitates the reabsorption of glucose in the kidney. In a healthy adult, around 180g of glucose is filtered daily through a glomerular filter and is completely reabsorbed in the proximal nephron tubules. However, if the glucose load exceeds 260–350 mg/min/1,73 m^2, excess glucose appears in the urine (glycosuria) due to transporter saturation. In a healthy adult, this equates to a blood glucose concentration of approximately 11 mmol/L (200 mg/dL) – the renal threshold for glucose [32]. SGLT-2 accounts for 90 percent of the total glucose absorption during urine formation. Because of their key role in glucose reabsorption, the SGLT-2 were promising drug targets to alter blood glucose levels. In proximal tubular cells from patients with type 2 diabetes, SGLT-2 mRNA concentrations were found to be higher than in healthy individuals, which additionally justifies the use of this group of drugs [33]. Inhibiting this transporter results in the daily excretion of approximately 60–80 grams of glucose in the urine, leading to calorie loss. Moreover, considering that SGLT-2 transports one glucose molecule with one sodium cation from the channel lumen into the tubular epithelial cells, its inhibition induces natriuresis, lowers blood pressure, and, by reducing glucotoxicity, enhances tissue insulin sensitivity [34].

The first SGLT-2 inhibitor which to be approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes was canagliflozin, in March 2013. The FDA's approval was based on nine global, randomized, double-blind Phase III clinical studies of canagliflozin. These studies enrolled 10,285 patients with type 2 diabetes, assessing both the efficacy and safety of oral canagliflozin administration [35].

The CANTATA-SU trial demonstrated that, at 52 weeks, both 100 and 300 mg doses of canagliflozin were not inferior to glimepiride for reduction of HbA1c on the background of metformin therapy. Furthermore, the 300 mg dose of canagliflozin was associated with a modest yet statistically significant greater reduction in HbA1c compared to sulphonylureas [36].

The next accepted by FDA drugs were consecutively dapagliflozin and empagliflozin, approved in 2014 as well as announced on January 23, the FDA's approval of bexagliflozin.

Diabetes and its complications

Diabetes increases the risk of both microangiopathy and macroangiopathy, with this risk being related to the disease's duration and severity. Macroangiopathy encompasses cerebrovascular disease, coronary artery disease, and peripheral artery disease, while microangiopathy includes retinopathy, nephropathy, and peripheral neuropathy [37].

Individuals with type 2 diabetes mellitus (T2DM) experience higher cardiovascular morbidity and mortality, being disproportionately more affected by cardiovascular diseases (CVD) than non-diabetic individuals [38].

Type 2 diabetes (DM2) is linked to a two to threefold increased risk of cardiovascular disease and cardiovascular disease is a major cause of death and disability among diabetic patients [39, 40].

Consequently, new antidiabetic drugs apart from better glycemic control should be at least non-inferior for major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) when compared with conventional antidiabetic therapy. Based on concerns raised about rosiglitazone and its risk to increase cardiovascular events European and US regulators required extensive studies to demonstrate the safety of these drugs [41].

Flozins and the body mass

As of this date, none of SLT2i inhibitors have received FDA approval for treating overweight, data from clinical trials shows modest weight loss (~1–3 kg) [64]. This effect may be diminished in patients with chronic kidney disease, taking into account that glucosuria caused by SGLT-2 decreases while renal function declines [65].

Taking into account all studies which have been carried out, it can be said that dapagliflozin stands as one of the most extensively studied drugs.

The DAPA-DIET study, evaluating dapagliflozin's impact on body weight in obese and diabetic patients, which has demonstrated a mean body fat mass loss of 9.9 kg over 12 months, but it has to be said that participants were

on a diet with a limited amount of carbohydrates. Moreover, after 12 months of treatment, there was a significant reduction of mean serum leptin [66].

The DELIVER trial demonstrated that dapagliflozin treatment resulted in a modest yet significant greater weight reduction in more obese patients than others (2.5 vs. 0.88 kg). Participants with heart failure who took part in this research had preserved or mildly reduced ejection fraction and 78% of them were overweight or obese [67].

In the light of research not only dapagliflozin seems to have a positive effect on body mass reduction. Luseogliflozin starting at 2.5 mg and potentially increasing to 5 mg, significantly reduced total fat mass (mean decrease of –1.97 kg) as well as a downward trend in the average amount of visceral fat [68].

The most obvious mechanism leading to weight loss is the increase in urinary glucose excretion, which results in the loss of calories. The next likely factor responsible for kilogram loss is SGLT-2 inhibitors' modest diuretic effect causing mildly expressed dehydration or maybe, a combination of both listed factors. Perhaps, there are other mechanisms, unknown so far, responsible for the improvement in body fat mass.

Molecular influence of flozins on the inflammation

So far, few studies have assessed the impact of SGLT-2 inhibitors on inflammation developing in patients suffering from diabetes, chronic kidney disease, or just from obesity. Inflammation is a key contributor to atherosclerosis which is the leading cause of death worldwide.

As Paul. M. Ridker's team showed anti-inflammatory therapy could reduce recurrent cardiovascular events regardless of lipid level. This study involved over 10,000 participants with previous myocardial infarction and a high-sensitivity C-reactive protein level who received canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β. Canakinumab significantly reduced high-sensitivity C-reactive protein levels from baseline, as compared with placebo, without reducing the LDL cholesterol level, and the 150 mg dose resulted in a significantly lower incidence of recurrent cardiovascular

events than placebo, however, there was no significant difference between the canakinumab groups and the placebo group in all-cause mortality [56].

So far, numerous clinical trials have evaluated cardiovascular outcomes with flozin therapy, but still, there is limited knowledge about possible mechanisms in which SGLT-2i show their pleiotropic effects. Most of the findings come from studies in animal models.

A pioneering 2013 study investigated the effect of SGLT-2 inhibitors on inflammation in the article called "Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice". The authors conducted their research on diabetic mice which at the beginning presented increased plasma levels of inflammation markers (IL-6, TNF-α, MCP-1, and CRP). Ipragliflozin treatment significantly reduced all of these parameters, and dose dependency was observed [57].

A 2018 study demonstrated that canagliflozin at clinically-relevant concentrations inhibits IL-1β-stimulated IL-6 and MCP-1 secretion in cultured human endothelial cells. It's crucial to note that elevated levels of IL-1B, TNF-alpha, and IL-6 are linked to vascular endothelial dysfunction. Furthermore, the study also found canagliflozin's effect to be partly AMPK-dependent, reducing pro-monocytic cell adhesion [58].

Further research published in 2020 in the Biochemical Journal on canagliflozin's anti-inflammatory effects in mice; canagliflozin lowered IL-1β levels in the plasma and livers of ApoE-/- mice with the same trend present in the livers. To expand research and find a potential mechanism by which canagliflozin might suppress IL-1B Emily A. Day's team found that canagliflozin activates AMPK and reduces IL-1β mRNA and secretion in BMDMs, suggesting AMPK's role in inhibiting the NLRP3 inflammasome [59].

It is cautiously suggested that this anti-inflammatory effect might be a class characteristic of these drugs, because similar results were received in studies with empagliflozin. Studies in obese mice indicated that empagliflozin reduces inflammatory cytokines like IL-6, IL-1β, Mcp1, and Ccr2, especially in those on a high-fat diet. These findings were associated with attenuated nuclear factor-κB p65, p38 mitogen-activated protein kinase, and

extracellular signal-related kinase phosphorylation in the white adipose tissue of DIO mice [60].

Further mouse studies confirmed these results and empagliflozin's superiority to glimepiride, where empagliflozin treatment reduced the circulating levels of hsCRP, TNF-α, IL-6 and MCP-1. Not only plasma levels of cytokines were measured, as the scientist proved the mRNA expression of Tnf, Il6 and Mcp-1 was significantly lower in the fat tissues of empagliflozin-treated mice when compared with control or glimepiride-treated mice. Notably, empagliflozin-treated mice showed less M1 macrophage infiltration in fat tissue [61]; as a reminder- M1 macrophages are proinflammatory cells and this phenotype is dominant in obese people. The stimulated M1 macrophages produce pro-inflammatory cytokines such as a necrosis factor tumor-alpha (TNF-α), IL-6, IL-12 and IL-23 at the same time decreased synthesis of the anti-inflammatory cytokine IL-10 [62].

A study on primary microglial cells explored empagliflozin's potential in treating neurodegenerative disorders including Parkinson's disease and Alzheimer's disease. It is believed that the brain's microglia are crucial mediators of inflammation which plays a key role in the development of neurodegenerative disorders. This study showed empagliflozin reduces pro-inflammatory mediators like Nos2, IL6, TNF-alpha, and Il1b [69].

Another study confirmed SGLT2i's superiority over sulfonylureas assessing an antiinflammatory influence of empagliflozin and glimepiride. The SGLT2 inhibitor reduced IL-1β secretion more than sulfonylurea. Moreover, SGLT2 inhibitor treatment significantly reduced TNF-α secretion, known for its pro-atherosclerotic effect [70] which was not affected by glimepiride [71].

A notable study in Hindawi, one of the few assessing flozins' direct influence on cytokine secretion in which took part 60 patients with DM2 and were diagnosed as acute left heart failure or acute exacerbation of chronic left heart failure. Participants were divided into 2 groups-dapagliflozin treated or with conventional therapy including metformin or insulin. The samples were collected at the begging and after one and 4 weeks of the project. This study showed cytokine levels decreased with both therapies, but TNF-α,

IL-1β, IL-6, and hs-CRP were lower in dapagliflozin-treated patients than in those treated conventionally at 4th week of study [63].

Objectively, the 4-week duration of this research is not enough to fully evaluate whether dapagliflozin will develop more pronounced effects, but these results are very promising and give us knowledge of potential cardioprotective mechanisms.

Cardiovascular benefits of SGLT2 inhibitors

Reflecting on the rosglitazone case, where it took a decade from its authorization to withdrawal by EMA, because the benefits of this drug no longer outweighed the risks, it underscores the need for a robust evidence base to demonstrate the cardiovascular safety of antidiabetic drugs and the safety of drugs in general. Due to this, the FDA in 2008 and the EMA in 2012 mandated clinical trials for evaluating cardiovascular safety in new antidiabetic therapies [42, 43, 44]. Several trials have reinforced flozins' role in preventing cardiovascular events.

The 2010–2013 EMPA-REG OUTCOME trial, published in the New England Journal of Medicine has given the first positive reports about empagliflozin cardiovascular superiority to a placebo. This research involved 7,020 type 2 diabetes patients with established cardiovascular disease. Participants who met the inclusion criteria were randomly assigned to receive either 10 mg or 25 mg of empagliflozin or a placebo once a day. The primary outcome (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) occurred less frequently in the empagliflozin group compared to placebo, as well as, patients treated with SGLT-2 inhibitor had a meaningly lower risk of death from any cause and hospitalization for heart failure. This trial provided data to support the long-term use of empagliflozin, as well as a shred of strong evidence of its superiority over a placebo in improving cardiovascular parameters [45]. It has been a groundbreaking study that gave rise to new discoveries and indications for use of SGLT-2 inhibitors.

The 2017 CANVAS study concluded that patients with type 2 diabetes treated with canagliflozin had a lower risk of cardiovascular events than those

who received a placebo. CANVAS combined two trials with 10,142 high cardiovascular risk type 2 diabetes participants defined as a history of symptomatic atherosclerotic cardiovascular disease or 50 years of age or older with two or more of its risk factors [46].

In 2019, two significant trials highlighting cardiovascular benefits were reported; DECLARE-TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) and DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) both published in the pages of the New England Journal of Medicine.

In DECLARE-TIMI 58 trial evaluated 17,160 patients. Participants with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, dapagliflozin treatment led to fewer cardiovascular deaths or heart failure hospitalizations than placebo [47].

Earlier trials found SGLT-2 inhibitors superior to placebo in DM2 patients with heart failure, although more data was needed to evaluate whether flozins decrease the risk of worsening heart failure or death from cardiovascular causes regardless of the presence or absence of type 2 diabetes. Flozins' heart failure benefits were also noted in non-DM2 individuals.

DAPA-HF included patients with an ejection fraction of 40% or less, and New York Heart Association (NYHA) class II, III, or IV symptoms. Participants received standard heart-failure device (an implantable cardioverter–defibrillator, cardiac resynchronization therapy, or both) and standard drug therapy, including an angiotensin-converting – enzyme inhibitor, an angiotensin-receptor blocker, or sacubitril–valsartan plus a beta-blocker. They were also still receiving their antidiabetic therapy but in adjusted doses to avoid hypoglycemia episodes. Following screening, patients were randomly assigned to dapagliflozin (at a dose of ten mg once daily) or placebo. So, the primary composite result of worsening heart failure or death from vessel causes occurred in 386 patients (16.3%) within the dapagliflozin cluster and in 502 patients (21.2%) within the placebo cluster. To conclude, the danger of worsening heart failure or death from vessel causes was lower within the dapagliflozin group than within the placebo cluster [48]. EMPEROR-Reduced research observed similar results and patient characteristics (Empagliflozin

Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction), The full results of the phase III EMPEROR-Reduced study involving adults with heart failure with reduced ejection fraction, with and without co-existing diabetes mellitus, showed that the use of empagliflozin allows a significant 25% reduction in the risk of the primary endpoint – cardiovascular death or hospitalization for heart failure. The study looked at the effect of adding empagliflozin (10 mg) to the standard of care, compared with a placebo [49, 50].

Based on these studies, in the ESC 2021 guidelines for diagnosis and treatment of acute and chronic heart failure, dapagliflozin as well as empagliflozin were placed to improve life quality, decreasing the risk of hospitalization and moreover to extend the lifetime of patients with heart failure and reduced ejection fraction [51].

Originally for glycemic control, flozins have shown effectiveness in extending lives of heart failure patients and joined the pillars of heart failure treatment.

Possible mechanisms of beneficial effects of flozins in the setting of cardiovascular diseases

SGLT-2 inhibitors effectively lower glucose levels, help to better control of diabetes which is a powerful and independent risk factor for stroke, coronary artery disease as well as peripheral artery disease by nonenzymatic glycosylation of proteins and lipids, oxidative stress and protein kinase C (PKC) activation [79]. As mentioned earlier in this article, an cardioprotective mechanism of flozins is reducing low-grade chronic inflammation. Modest weight loss (about 2~3 kilograms) is also indifferent [73]. Flozins positively impact blood pressure, a key cardiovascular risk factor [74]. As a recent published meta-analysis concerning 64 studies has shown, SGLT-2 inhibiton is able to reduce a systolic and diastolic blood pressure of 2.89 and 1.44 mmHg in diabetic patients [75]. Natriuresis is integral to SGLT-2 inhibition. As the research shows there is a linear relathionship between dietary sodium intake and cardiovascular risk (up to 6% for every 1 g increase in sodium intake per

24 hours) [76]. Moreover, dapagliflozin similarly reduces plasma volume like thiazide diuretics [77], what is important taking into account that a rise of even a few milliosmoles per liter in plasma osmolality after an oral Na+ load leads to retention of free water through stimulation of thirst and arginine vasopressin release resulting in an edema and increased cardiac filling pressures [78]. Another mechanism is preventing adverse cardiac remodeling. As The EMPA-HEART CardioLink-6 study has showed, treatment with empagliflozin resulted in significant reduction in LV mass indexed to body surface area after 6 months of study when compared to placebo group [80]. Futher studies are crucial to fully explain how SGLT2 inhibitors exert these impressive cardiovascular effects.

Renal benefits of sglt-2 inhibitors

If beyond their cardiovascular benefits, flozins also positively on renal functions, sglt-2 inhibitors may be called super drugs.

SGLT-2 inhibitors' benefits extend beyond cardiovascular health, with complex effects. Hyperglycemia has a negative impact on the body in many ways.

Diabetes is a leading cause of chronic kidney disease (CKD). It has been estimated that it will affect more than 40% of people with diabetes [52]. For two decades, renoprotective effects were primarily attributed to RAS blockers like ACEIs and ARBsin these patients. The most common tool used to assess renal function is the estimated glomerular filtration rate. In addition to eGFR, albuminuria is an important, early indicator of renal dysfunction. This parameter is particularly useful in the first stages of chronic kidney disease, when filtration activity is still correct or when hyperfiltration occurs to maintain proper excretion. Evaluating albumin excretion in urine is best done using the ACR index in the first, morning urine sample. ACR is defined as the urine albumin to creatine ratio [53]. To make a full diagnosis of chronic kidney disease it is needed to assess eGFR, albuminuria and its cause.

Although, SGLT2 inhibitor trials have shown their potential to reduce composite renal outcomes such as (doubling of serum creatinine, development of macroalbuminuria, need for dialysis and/or transplantation or kidney death.

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial was among the first to show positive renal results with flozins. Eligible patients had type 2 diabetes and also chronic kidney disease, defined as an estimated glomerular filtration rate of 30 to <90 ml per minute per 1.73 m2 of body-surface area and albuminuria. Administering 100mg of canagliflozin daily lowered the risk of the primary composite outcome in these patients of end-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes than those who received placebo [54].

The DAPA-CKD study strongly demonstrated positive renal outcomes which showed that patients with chronic kidney disease who received dapagliflozin had a significantly lower risk of decreased in the estimated GFR of at least 50%, as well as end-stage kidney disease, or death from renal causes. Unlike CREDENCE, DAPA-CKD also evaluated SGLT-2 inhibitors' effects in non-diabetics (32,5% of all participants) [55].

The renoprotective effects of SGLT2 inhibitors, a new class of antidiabetic agents, are now established.

Possible mechanisms of beneficial effects of flozins in the setting of chronic kidney diseases

Diabetic kidney disease, a microvascular complication, affects around 30% of type 1 and 40% of type 2 diabetes patients. The natural history of structural abnormalities in diabetic kidney disease includes hypertrophy of the kidney, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis [81]. Clinical trials demonstrate SGLT-2 inhibitors slow GFR decline and reduce albuminuria. SGLT2 inhibitors lower the risk of dialysis, transplantation, or kidney-related death in DM2 patients [82]. Besides improving glycaemia control, SGLT2 inhibitors' renal benefits also stem from glucose-independent mechanisms. SGLT-2 inhibitors' renal benefits may relate to afferent glomerular arteriole vasoconstriction which reduces blood flow into the glomerulus, decreasing intraglomerular pressure and preserve glomerular viability [83]. Flozins also

enhance renal gene expression for gluconeogenesis, bicarbonate regeneration, and ammonium formation [84]. Hyperglyeacemia causes increased utilization of oxygen and impairs its delivery to further parts of the tubule, therefore flozins with their ability to reduce glucose reabsorption, may improve oxygen availability as well as reduce reactive oxygen species [85]. More studies should be conducted to fully explain SGLT-2 inhibitors' positive renal effects.

Conclusions

According to 2014 WHO data, over 422 million people have diabetes, with 95% having type 2. Given its rapid spread, type 2 diabetes can be called a non-infectious pandemic, and compared to COVID-19 pandemic, where there are over 700 million confirmed cases. Unlike COVID-19, type 2 diabetes can be influenced by lifestyle changes including achieving and maintaining a healthy body weight, being physically active; eating a healthy diet, and avoiding tobacco use -implementation of which may delay or protect us from developing diabetes type 2.

Given the problem's scale, SGLT-2 inhibitors' role in improving life quality and reducing cardiovascular issues is crucial.

Originally for glycaemic control, SGLT-2 inhibitors are now seen as pleiotropic drugs showing multidirectional nephro, cardioprotective and anti-inflammatory effects.

Author Contributions: *Conceptualization, E.W.; methodology, E.W.; resources, E.W.; writing – original draft preparation, E.W; writing – review and editing, B.O.; supervision, B.O.; final approval of the version to be published, B.O.; project administration, E.W*

Conflicts of Interest: *The authors declare no conflict of interest.*

Funding: *This research received no external funding.*

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