ROLE OF SODIUM GLUCOSE COTRANSPORTERS 2 INHIBITORS IN MYOCARDIAL ISCHEMIA-REPERFUSION

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Abstract:
The transport of glucose molecules in mammals is achieved by two structurally and functionally distinct mechanisms: facilitative glucose transporters (GLUTs) and sodium–glucose cotransporters (SGLTs). Each has its own substrate specificity, distribution, and regulatory mechanisms. Here, we reveal that sodium-glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin improves cardiovascular outcomes in patients with type-2 diabetes in a manner that is partially independent of its hypoglycemic effect. These observations suggest that it may exert a cardioprotective effect by another mechanism.

Keywords: Sodium Glucose Cotransporters 2 inhibitors, myocardial Ischemia-Reperfusion, Diabetes.

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Introduction:

Glucose molecule represents the most abundant and essential source of energy for most living cells. In mammals, glucose transport into and out of cells is mediated by two distinct mechanisms: facilitative glucose transporters (GLUTs) (1,2) and sodium–glucose cotransporters (SGLTs), which actively transport glucose against the concentration gradient by coupling with sodium(3,4). Each transporter has its own substrate specificity, distribution, and regulatory mechanisms. The SGLTs family comprises at least six different isoforms in humans (5). Sodium–glucose cotransporter 1 and sodium–glucose cotransporter 2 have been frequently investigated as therapeutic targets for various diseases due to their pharmaceutical potential in various diseases(3,6). SGLT receptors are symporters of sodium and glucose (moving both molecules in the same direction); they get the energy to move glucose against a concentration gradient by coupling it to the electromechanical gradient of the sodium ions flowing downwards. of reports revealed the most prevalent members of the six different SGLT receptor subtypes are SGLT1 and SGLT2 **(7).**

One molecule of glucose and one molecule of sodium are transported via high-capacity, low-affinity receptors called SGLT2 that are exclusively found in the S1 section of the proximal tubule of the nephron. SGLT1 are high-affinity, low-capacity receptors that mediate glucose absorption in small intestine enterocytes and the S3 segment of the proximal renal tubule. They transport two molecules of sodium and one molecule of glucose. Importantly, SGLT1 receptors are also present in the healthy myocardium albeit at lesser levels. However, in pathological states such ischaemia or heart failure, their expression is noticeably higher **(8).**

SGLT1 is responsible for glucose absorption in the small intestine, and for reabsorbing nearly 3% of the filtered glucose load in the renal proximal tubule segment 3 (S3). Recently, tissue localization studies of SGLT1 were hampered by the lack of well-functioning antibodies**(9)**. Examination of different species in the intestine revealed that SGLT1 is expressed in the luminal brush border of enterocytes, which are in responsible for nutrient absorption, while SGLT2 is in charge of glucose absorption in the proximal tubule segments 1 and 2 (S1/2), where it is reabsorbable for more than 90% of the filtered glucose load. But in cases of SGLT2 deletion (Sglt2), SGLT1 may make up for this and reabsorb up to 35% of the filtered glucose load.**(10).**

Table 1: Tissue expression and biochemical characteristics of sodium–glucose cotransporter 1 and sodium–glucose cotransporter 2**(11)**

Characteristics	SGLT1	SGLT2
Site	Mostly in small intestine some kidney, heart, brain etc.	Mainly in kidney
Renal location	S3 segment of proximal tubules	S1 and S2 segments of proximal tubules
Sugar selectivity	Glucose = galactose	Glucose > galactose
Sodium/glucose stoichiometry	1:2	1:1
Affinity for glucose	High (0.5 mmol/L)	Low (2 mmol/L)
Glucose transport capacity	Low	High

SGLT, sodium–glucose cotransporter.

- **Functional properties of SGLTs in the kidney**

Glucose is transported in the kidney by the facilitative transporters GLUT2 and GLUT1 through the basolateral membrane of the proximal tubule and out through the apical membrane of the proximal convoluted tubule by SGLT2 and SGLT1. In humans, SGLT1 is expressed in the S3 segment of the proximalconvoluted tubulebut while SGLT2 is expressed in the S1 and S2 segments. **(12)**.

While SGLT1 reabsorbs the remaining glucose, or about 5% of the filtered glucose, SGLT2 performs the primary role in the capacity of filtered glucose reabsorption in euglycemia, demonstrating the previously described ≥80% glucose reabsorption. Notably, there is a difference in the coupling ratio of sodium and glucose between the two cotransporters: The ratio of glucose to sodium transported by SGLT2 is 1:1, while the ratio of glucose to sodium transported by SGLT1 is 1:2**(13)**.

The concentrating ability to reabsorb the glucose given to the distal part S3 segment of the proximal tubule is improved by the transport characteristic of SGLT2. Additionally, it is said that SGLT1 primes the extremely repressed potential of glucose absorption**(14)**.

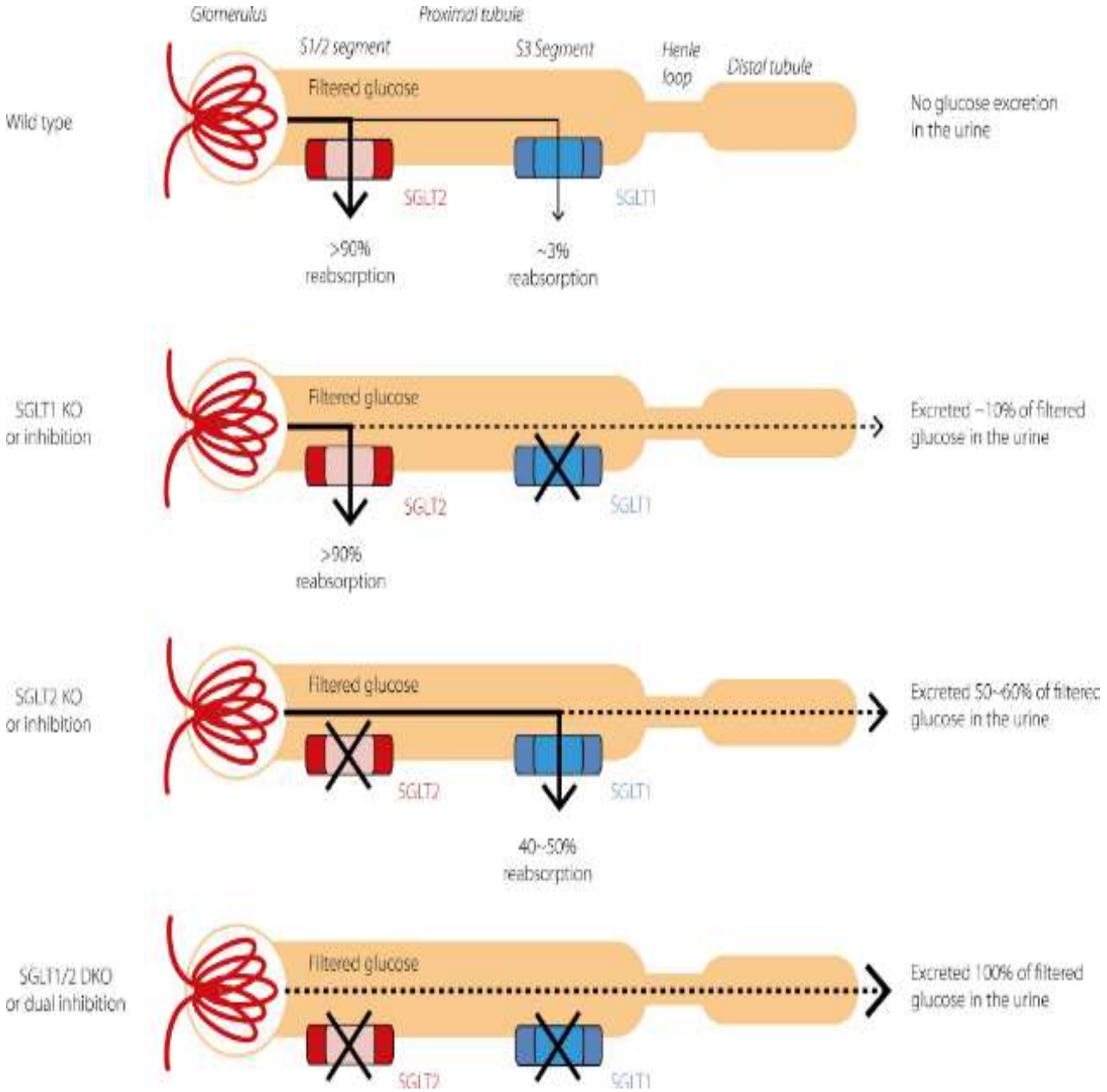

Figure 1: Ability of sodium-glucose cotransporters (SGLT)1 and SGLT2 to reabsorb filtered glucose when the blood sugar is at a normal level (11).

Extended high blood sugar levels lead to the proximal SGLT2's transport capacity being exceeded, which in turn increases the flow of glucose to the distal proximal tubule and improves SGLT1-mediated glucose absorption. Taking into account the physiological function, two noteworthy characteristics are the reserved capacity for glucose reabsorption and the compensatory action of SGLT1**(15)**.

While published results for renal SGLT1 levels are contentious, the renal SGLT2 protein level was reportedly raised in both type 1 and type 2 diabetes. In the renal cortex, streptozotocin-treated rats displayed elevated SGLT1 mRNA and protein expressions. In Zucker fatty rats, renal SGLT1 mRNA expression was also elevated**(9)**. It has been observed that both type 1 and type 2 diabetes are associated with elevated renal SGLT2 protein levels, however the published data for renal SGLT1 levels are controversial. Rats treated with streptozotocin showed increased expressions of SGLT1 mRNA and protein in the renal cortex. Renal SGLT1 mRNA expression was likewise increased in Zucker fatty rats**(16)**.

- **Functional properties of SGLTs in the heart**

While the expression of SGLT1 protein was not detected in the capillaries of the small intestine, it was localized in the human heart. Furthermore, it was revealed that human cardiomyocytes' cell membranes expressed SGLT1. Therefore, the transfer of glucose from capillaries into

cardiomyocytes may include cardiac SGLT1. On the other hand, the heart does not express SGLT2**(17)**.

GLUT1 and GLUT4, two facilitated glucose transporters, are primarily involved in glucose uptake in the heart: GLUT1 is responsible for basal glucose uptake while GLUT4 is responsible for insulin-dependent glucose uptake. **(18)**.

It has been observed that patients with type 2 diabetes and diabetic cardiomyopathy have higher levels of cardiac SGLT1 mRNA expression. GLUT4 mRNA and protein expressions were downregulated in streptozotocin-diabetic rats, while GLUT1 mRNA expression remained mostly unchanged. The development of diabetic cardiomyopathy and a decrease in glucose absorption were caused by a drop in cardiac GLUT4 activity; however, the physiological functions of GLUT1 in the heart are yet unknown**(19)**.

According to a recent study, SGLT1 overexpression in the heart over an extended period of time caused pathological cardiac hypertrophy and left ventricular failure in mice, although SGLT1 knockdown in the heart reduced the severity of the condition**(20)**.

- **Basal properties of SGLT1**

The SGLT1 protein, encoded by the SLC5A gene on chromosome 22q13.1, is composed of 664 comprised of 14 transmembrane α-helical domains, two phosphorylation sites, one between transmembrane helices 8 and 9, and a single glycosylation site between transmembrane helices 5 and 6. The external and intracellular membranes contain the NH2 and COOH terminals, respectively, and amino acid residues 457–460 are thought to be part of the glucose-binding domain **(21)**.

Galactose and glucose have a high affinity transporter in SGLT1 (Michaelis–Menten constant [Km] = 0.4 mmol/L), but fructose is not transported. Each glucose molecule travels through the SGLT1 with two sodium ions, and this cotransporter is permitted to carry glucose into the cells in opposition to its concentration gradient.**(22)**.

Reverse transcription polymerase chain reaction analysis has revealed the presence of SGLT1 mRNA expression in the following human tissues: testis, cervix of the uterus, stomach, mesenteric adipose tissue, pancreatic α-cells, brain, trachea, liver, lung, heart, small intestine, kidney, skeletal muscle, liver, lung, and heart.

It is reported that SGLT1 regulates many molecules, including protein kinases, to carry out the transport function. Protein kinase A (PKA) and protein kinase C (PKC) have established strain-specific regulatory sites in SGLT1; humans have one PKA site and five consensus PKC sites. PKA activation increased the amount of SGLT1 proteins in the rat small intestinal membrane, and PKA activator forskolin, 8-bromo-cyclic adenosine monophosphate, enhanced the plasma membrane's SGLT capacity and SGLT1 activity**(23)**.

Dietary carbohydrates control the expression and function of intestinal SGLT1. The presence of luminal nutrients in the human gut maintains SGLT1 expression and activity. Furthermore, there is a diurnal pattern associated with SGLT1 activity and expression, which associates waking hours with the highest levels of SGLT1 expression**(24)**.

The ability to absorb glucose is provided by the expression level of SGLT1, which is regulated both shortand long-term based on the nutrients available to the luminal cells. It has been shown that a diet high in glucose or sodium elevates the expression of SGLT1 in the small intestine. Also, GLUT2 translocation to the brush boundary membrane is induced by an increase in luminal glucose concentrations**(25)**.

Patients with type 2 diabetes had increased intestinal glucose absorption as well as higher brush border membrane expressions of SGLT1 mRNA and protein. The fast postprandial hyperglycemia in diabetes is thought to be caused by the small intestine's increase of SGLT1-mediated glucose absorption**(26)**

SGLT1's Intestinal Glucose Absorption:

Dietary carbohydrates, such as starch, fructose,sucrose, and lactose, are broken down by salivary amylase in the mouth, but pancreatic enzymes (amylases) and brush border hydrolases (maltase, isomaltase, sucrase, and lactase) are responsible for the majority of the breakdown, which results in monosaccharides (primarily glucose, galactose, and fructose). The facilitative transporter GLUT5 helps enterocytes in the duodenum and jejunum absorb glucose and galactose, while fructose is absorbed by SGLT1, which is situated in their brush boundary membrane ([Fig. 2]). SGLT1 cotransports sodium and glucose in a 1:2 ratio A sodium electrochemical potential gradient is maintained by the action of a Na+/K+-ATPase pump inserted into the basolateral membrane, enabling the active transport by SGLT1 as in figure 2 **(27).**

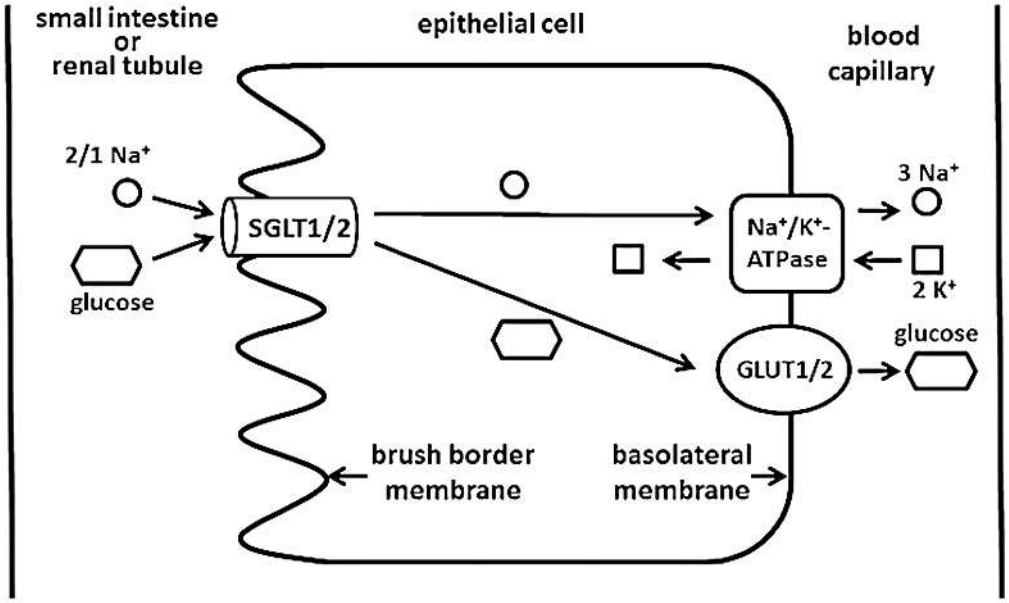

Fig 2: Absorption of glucose: The brush border membranes of the proximal tubule of the kidney's nephrons and the epithelial cells of the small intestine are integrated with SGLTs, which are in charge of absorbing glucose. GLUTs, which transport glucose into blood capillaries, and Na+/K+-ATPase, which maintains an electrochemical sodium gradient required for the active transport of glucose by SGLTs against its concentration gradient, are found in the basolateral membranes of epithelial cells. Small intestine: GLUT2 returns glucose to the bloodstream after SGLT1 and a sodium ion absorb one glucose molecule**.** S3 segment of proximal tubules: SGLT1 reabsorbs 1 glucose molecule together with 2 sodium ions and GLUT1 is responsible for glucose transport into blood capillaries**(27).**

- **Basal properties of SGLT2**

The 672 amino acid SGLT2 protein, which is encoded by SLC5A2, has extracellular NH2 and COOH termini. Human SGLT2 is a low-affinity, high-capacity glucose transporter that differs from SGLT1 in that its Km values for sodium and glucose are 2 and 25 mmol/L, respectively. The kidneys of both humans and rodents are where SGLT2 is mostly expressed. Low levels of mRNA expression were found in the testis, liver, lung, intestines, skeletal muscle, spleen, and cerebellum**(28)**.

It has also been found that SGLT2 is associated with glucagon secretion and expressed in pancreatic α-cells. In human and rodent renal proximal tubules, SGLT2 is located in the luminal membrane of segments S1 and S2, while SGLT1 is positioned in the luminal membrane of the S3 segment. Approximately 80% of the filtered glucose is reabsorbed in the S1 and S2 segments of the proximal tubules by SGLT2, which is primarily responsible for glucose reabsorption in the nephron**(29)**.

In human embryonic renal cells expressing SGLT2, protein kinase A and Protein kinase C (PKC) activation enhanced glucose absorption by 225 and 150%, respectively. The PKA-mediated effect may be associated with a higher rate of vesicle fusion with the membrane, but no similar mechanism was discovered for the PKC-mediated effect**(30)**.

Sodium glucose co-transporter inhibition

- **Sodium-glucose co-transporter 1 and 2 inhibition**

The first naturally occurring SGLT inhibitor with high affinity, specificity, and competitive inhibitory activity for both SGLT1 and SGLT2 is phlorizinwhich was extracted from apple trees. Although phlorizin was first used to treat fever, malaria, and other infectious disorders, it was soon found that phlorizin also caused glycosuria. Different phlorizin analogues with varying potencies and selectivities against SGLT have been produced**(31)**.

- **Sodium-glucose co-transporter 2 inhibition**

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are cutting-edge medications that effectively control people with T2D's glycemia. Because of these inhibitors' clinically proven cardiovascular protective properties, basic and clinical studies have recently focused on them.Although there has been a long-standing

interest in the study of different SGLT isoforms and how their blockage affects cardiovascular function, an explanation of the effects seen in clinical settings based on experimental data is still lacking. The striking decrease in cardiovascular (CV) mortality (38%), major CV events (14%), heart failure hospitalization (35%), and death from any cause (32%), which was seen in patients with T2D and high CV risk over a period of 2.6 years in the EMPA-REG OUTCOME trial involving the SGLT2 inhibitor empagliflozin (Empa), has raised the possibility that potential novel, more specific mechanisms of SGLT2 inhibition work in conjunction with the known modest systemic**(32).**
Numerous investigations looked into the pathophysiological function of SGLTs in the heart as well as the direct effects of SGLT2i on the circulatory system, but their results were mixed. Particularly given that the SGLT1 isoform is the only one expressed in the capillaries and myocardium of human and rodent hearts, the direct effect of SGLT2i on cardiac homeostasis is still debatable. This review summarizes the direct effects of SGLT2i on the cardiovascular system as well as suggested directions for further study. **(33)**
Based on a novel theory of antidiabetic action, SGLT2 inhibitors have been designed to increase urine glucose excretion while blocking renal glucose reabsorption. By reducing blood glucose, SGLT2 inhibitors prevent glucotoxicity. Studies have shown that they also have protective effects on the kidneys and a reduction in cardiovascular mortality **(34)**.

The following selective SGLT2 inhibitors have been approved for the treatment of type 2 diabetes: dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, luteogliflozin, and tofogliflozin. Compared to other antidiabetic medications, these SGLT2 inhibitors lower plasma glucose levels by a distinct mechanism that involves an increase in renal glucose excretion through SGLT2 in the proximal tubule, which reduces glucose toxicity.**(35)**.
The SGLT2 inhibitors improved glucose intolerance and reduced blood pressure, hemoglobin A1c, and fasting and non-fasting glucose levels in preclinical trials using diabetic animal models. Moreover, as previously mentioned, SGLT2 inhibitors work differently from the other antidiabetic medications and can be taken alone or in combination with them to treat type 2 diabetes**(36)**.
According to the research, SGLT2 inhibitors protected the kidneys in animal models of diabetic nephropathy **(37)**. In clinical trials, SGLT2 inhibitors have also demonstrated kidney protective benefits. **(7, 38)**.Here are some theories regarding the mechanism of action: By inhibiting sodium absorption in the proximal tubule, SGLT2 inhibitors increase the quantity of sodium delivered to the distal tubule. Consequently, the activation of the tubuloglomerular feedback via the macula densa permits afferent arteriolar contraction and restores normalcy to the glomerular filtration rate**(39)**.

- **Empagliflozin(Empa)**

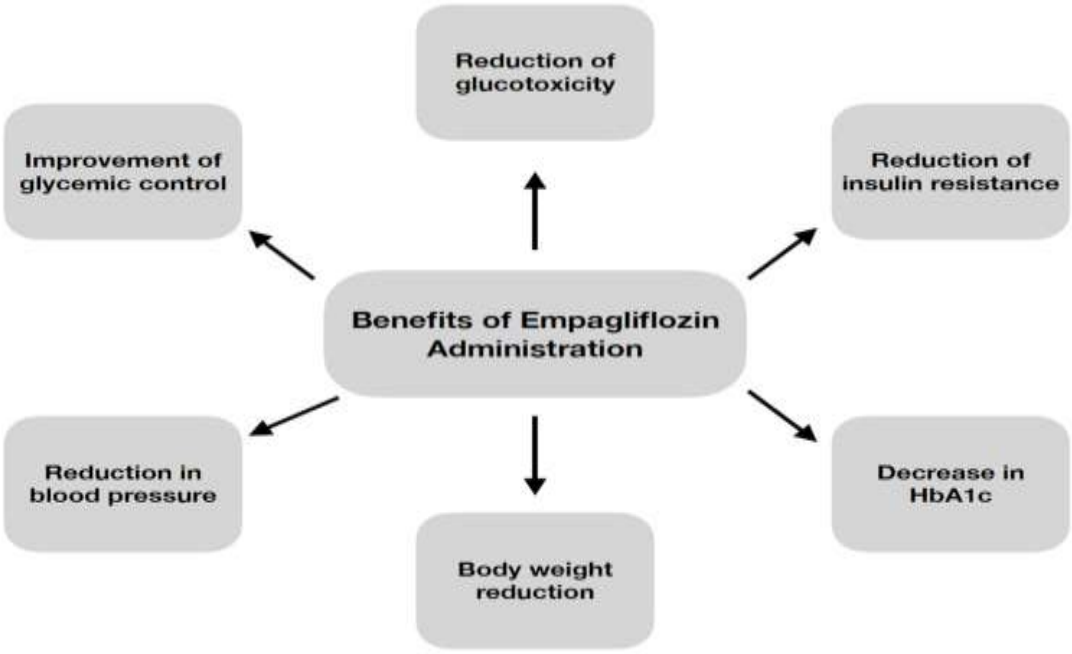

Figure 3: Beneficial effects of empagliflozin administration. HbA1c, glycated hemoglobin A1C**(34)**

1 – Functions of empagliflozin :

- **Empagliflozin and traditional cardiovascular risk factors**

❖ **Body weight**

One independent risk factor for CV events is obesity. Urine glucose excretion is elevated when SGLT2 is inhibited. With a daily diuresis of 400 mL, it is predicted that 75 gr of glucose (or around 300 kcal) are lost in the urine. According to data from clinical trials, these medications result in a combined weight loss of 2-3 kg. The initial few weeks of treatment result in noticeable weight loss, which plateaus after six months and is sustained for a considerable amount of time. But since the projected weight decrease would have been larger, the expected energy loss does not convert to the expected weight loss**(41)**.

Since Empagliflozin has no effect on postprandial or resting energy expenditure, a progressive increase in caloric intake is implied by the discrepancy between expected and observed weight loss.**(42)**

❖ **Blood pressure**

It is commonly recognized that in people with diabetes mellitus, lowering arterial blood pressure (BP) is linked to a decrease in CV morbidity and mortality. Empagliflozin decreased systolic and diastolic blood pressure in the EMPAREG-OUTCOME study without raising heart rate**(43)**.Numerous investigations have replicated these findings, and two meta-analyses have confirmed SGLT2i's positive impact on blood pressure. To be more precise, SGLT2i lower blood pressure by 2.46 mmHg and 1.46 mmHg in the systolic and diastolic phases, respectively. They also lower blood pressure by 3.76 mmHg and 1.83 mmHg in the 24-hour ambulatory phase**(44)**.

For this impact, a number of underlying pathophysiologic processes have been suggested. First off, higher excretion of glucose itself has an extra osmotic diuretic impact, while inhibition of the co-transporters in the proximal tubule induces a moderate rise in sodium urine output. Second, the lowering of blood pressure has been linked to weight loss and a decrease in sympathetic nerve activity. Furthermore, SGLT2i's positive effects on arterial stiffness may have an impact on blood pressure**(45)**.

Furthermore, as previously mentioned, the improvement of conventional CV parameters like weight and arterial blood pressure may eventually benefit renal function. Nevertheless, given that patients in these trials received treatment with RAASI, it is unclear that the latter can adequately account for the striking impact of SGLT2i on renal outcomes. As a result, additional mechanisms have been suggested**(46)**:

- ❖ First of all, SGLT2i are known to induce natriuresis and volume depletion, which raises the levels of renin, angiotensin, and aldosterone in the blood. When SGLT2i and RAASI are given together, they activate the Mas receptor, which increases the synthesis of prostaglandin and nitric oxide and causes systemic arteriolar vasodilation, natriuresis, decreased oxidative stress, and anti-proliferative action.
- ❖ Secondly, by substituting ketones for free fatty acids, SGLT2i raise kidney oxygen consumption.

❖ **Empagliflozin and cardiac fibrosis**

Additionally, the results showed that Empagliflozin reduces pro-fibrotic markers such type I collagen, a-smooth muscle actin, connective tissue growth factor, and matrix metalloproteinase 2 and attenuates TFG-β1-induced fibroblast activation.It is clear that SGLT2i benefits cardiac fibroblasts, which are among the key elements of heart failure**(47)**.

2-Mechanism of action :

Empagliflozin is a potent and selective inhibitor of the sodium glucose cotransporter 2 (SGLT2) used in the treatment of type 2 diabetes. By inhibiting SGLT2, empagliflozin reduces renal glucose reabsorption and increases urinary glucose excretion **(48).**

EMP (like other SGLT2 inhibitors) has a minimal intrinsic risk of hypoglycaemia since glucuretic activity is reliant on blood glucose concentration and GFR but independent of insulin (secretion and action)]. produces mild osmotic diuresis and natriuresis in addition to glucosuria, which reduces plasma volume**.(49)**

Furthermore, it has been shown that empagliflozin lessens oxidative stress. When this drug is administered, the generation of reactive oxygen species (ROS) is inhibited, prooxidant factor activity is decreased, and mitochondrial function is enhanced**(50)**.

3 - cardiovascular protection mechanisms :

empagliflozin, an SGLT2 inhibitor, protects the cardiovascular system (CV), particularly in heart failure .There are a number of theories that suggest empagliflozin reduces preload through diuresis and natriuresis by inhibiting sodium-hydrogen exchangers 1 (NHE1) in the heart muscles and 3 (NHE3) in the proximal tubule,

which is responsible for the majority of electrolyte and water reabsorption in the kidneys. **(51)**

With empagliflozin, a variety of processes that are unrelated to atherosclerosis promote cardiovascular health. First off, empagliflozin significantly lowers systolic blood pressure (SBP) and arterial stiffness which improves the myocardium's ability to use oxygen and, in turn, lowers cardiac afterload .Additionally, it assists by modestly lowering body weight (**52**)Second, empagliflozin also helps by reducing the plasma volume through increased salt and glucose excretion in the urine. Because excessive sodium is excreted in the urine as a result of SGLT2 inhibition, the amount of sodium in the body as a whole quickly decreases. Additionally, the Renin Angiotensin System (RAAS) is inhibited by the enhanced NACL supply to the macula densa cells found in the distal convoluted tubule of the kidneys (**52**).

Myocardium and kidneys treated with empagliflozin experience a switch in fuel metabolism from fat oxidation to ketone bodies, which improves oxygen consumption in mitochondria and aids in heart and kidney recovery**.** Additionally, the tissues' decreased ability to absorb carbohydrates, chronic glucosuria's high plasma glucagon and low plasma insulin **(51)**

- **Impact of Empagliflozin in patients with heart failure**

The main goal of SGLT2 inhibitors was to be an antidiabetic medication with encouraging outcomes. At first, these were extra medications used in DM treatment, but after more research, the findings were significantly more significant than anticipated. Evidence from the EMPA-REG outcome trial suggests that SGLT2 inhibitors may rank among the most significant medications used to treat heart failure. This study altered the guidelines for treating DM and HF and sparked a rapid expansion in the investigation of further potential benefits of this class of drugs**(53).**

Empagliflozin not only lowers hyperglycemia but also has positive effects on markers of arterial stiffness and vascular resistance, osmotic diuresis, weight loss, and blood pressure decreases without raising heart rate and thus has good effect on heart failure. **(54)**

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