Review Article

Three Levels of Disease Modification with SGLT-2 Inhibitors: Holy Grail in Vasculopathy

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ABSTRACT

SGLT2 inhibitors have an insulin-independent mechanism of action leading to increasing glycosuria and lowering plasma glucose concentration, which results in cardiovascular and renal benefits shown in various studies. Other benefits include improvements in hyperglycemia, decreased fluid retention, reduced weight gain, lower blood pressure, and decreased risk of hypoglycemia. SGLT2 inhibitors produce cardioprotective and renoprotective benefits by inducing a state of Fasting Mimicry. It is therefore noteworthy that SGLT2 inhibitors induce a transcriptional paradigm that closely mimics the cellular response to starvation. These drugs activate SIRT1/AMPK and suppress Akt/mTOR signaling and, consequently, they can promote autophagy, independent of their effects on glucose or insulin. SGLT2 inhibitors regulate the expression of MicroRNA and prevent the occurrence and development of atherosclerosis, and can improve blood vessel stiffness and aging.

Keywords: Hyperglycemia, SGLT-2, Inhibitors.

INTRODUCTION

SGLT-2 inhibitors are novel medications that reduce plasma glucose concentration. In a healthy person, the glomerulus filters 180 gm of glucose daily, followed by 100% reabsorption via the proximal convoluted tubule (PCT), hence leaving almost no urinary glucose.

SGLT-2 inhibitors have an insulin-independent mechanism of action leading to increasing glycosuria and lowering of plasma glucose concentration, which results in cardiovascular and renal benefits as shown in various studies.[1-3] Other benefits include improvements in hyperglycemia, decreased fluid retention, reduced weight gain, lower blood pressure, and decreased risk of hypoglycemia.[3]

The first SGLT-2 inhibitor was named Phlorizin, a naturally occurring phenolic glycoside derived from the root bark of the apple tree.[4] Various trials with Empagliflozin[5-8], Canagliflozin[9,10], and Dapagliflozin[11-13] have shown significant benefits from SGLT-2 inhibition in high cardiovascular (CV) risk patients. These drugs have demonstrated an impressive reduction in CV and all-cause mortality, heart failure hospitalizations, and progression of albuminuria.

Also, the use of SGLT-2 inhibitors has shown significant results for kidney disease and heart failure even in the absence of diabetes as a central pathology. Understanding the underlying physiological mechanisms and effects of SGLT-2 inhibition is essential to understand the diversity of clinical benefits (Figure 1).

CELLULAR EFFECTS:

Activation of SIRT1 and AMPK signaling as an adaptive response to starvation and cellular stress: When cells are stressed by starvation, they activate a transcriptional program that facilitates adaptation to low-nutrient conditions. The enzymes that play a critical role as low-energy sensors include sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK). SIRT1 responds to levels of nicotinamide adenine dinucleotide and serves as a redox rheostat, whereas AMPK discerns the balance between ATP and AMP in the cytosol.

SGLT-2 inhibitors produce cardioprotective and renoprotective benefits by inducing a state of 'Fasting Mimicry'. It is therefore noteworthy that SGLT-2 inhibitors induce a transcriptional paradigm that closely mimics the cellular response to starvation. These drugs activate

SIRT1/AMPK and suppress Akt/mTOR signaling and consequently, they can promote autophagy independent of their effects on glucose or insulin. Importantly, the effect of SGLT-2 to stimulate the activity of low-energy sensors is not mediated by interference with SGLT-2 protein on an individual cellular level, since it is seen in organs that do not express SGLT-2.

Inhibition of Na^+/H^+ exchanger (NHE): By inhibiting NHE-1 in cardiomyocyte, SGLT-2i reduce cytoplasmic sodium and calcium concentration, increase mitochondrial calcium concentration, and improve mitochondrial respiration. This results in improved excitation-contraction

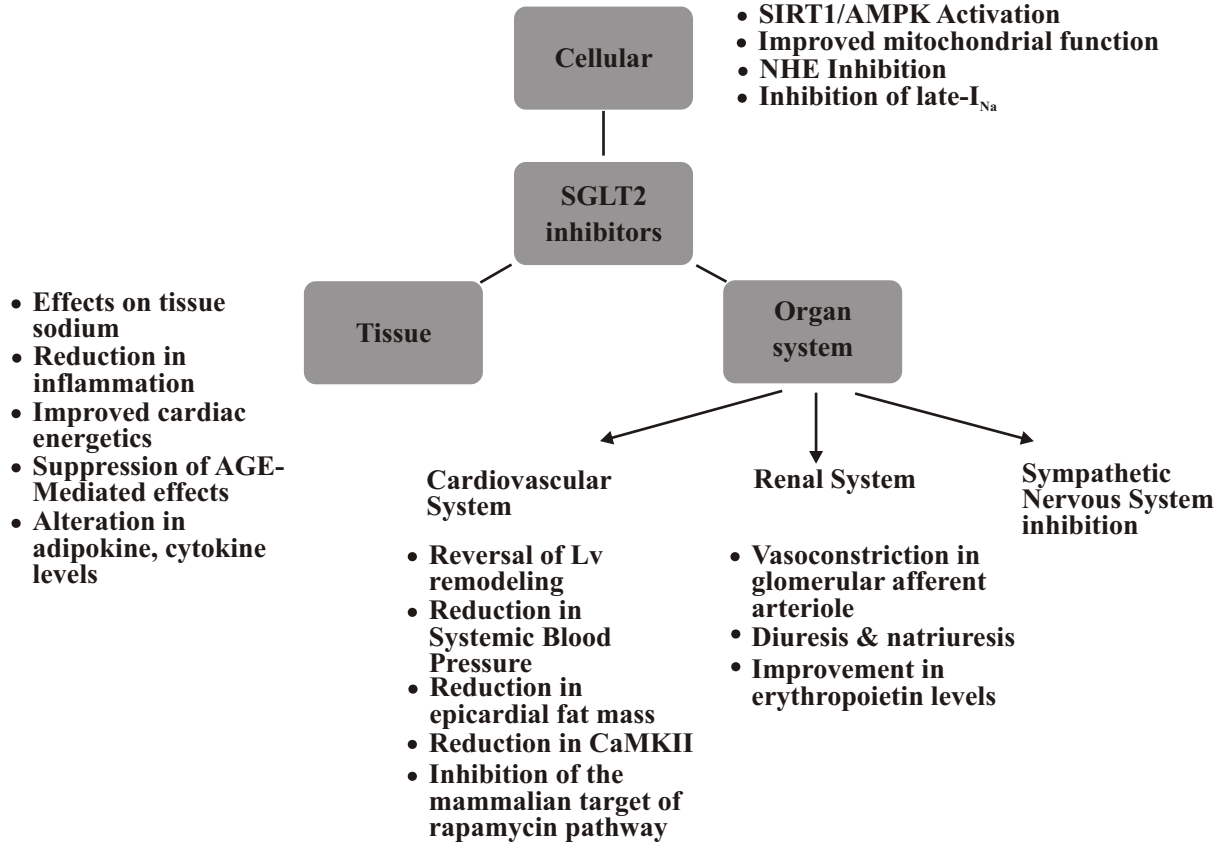

Figure 1: Mechanisms and effects of SGLT-2 inhibition.

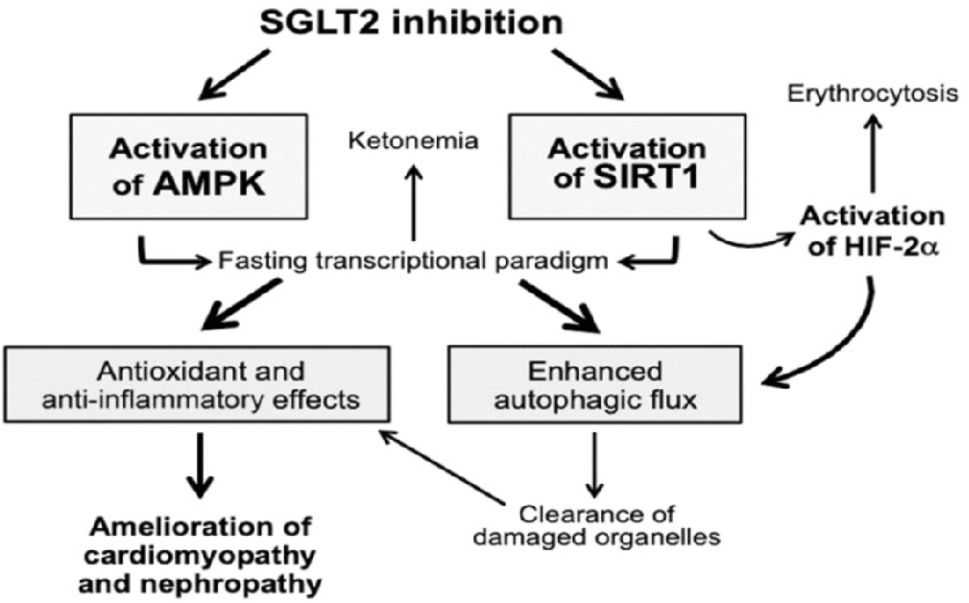

Figure 2: Mechanisms of action of SGLT-2 inhibition.

coupling and mitochondrial antioxidant capacity.[14]

NHE3 activity is markedly increased in heart failure (HF) and is believed to be responsible for resistance to diuretics as well as resistance to endogenous natriuretic peptides. SGLT-2i have been shown to interfere with the actions of NHE3 which could explain their natriuretic property, hence the effect on blood pressure and GFR.[15]

Inhibition of late cardiac sodium channel current (Late-INa): The cardiac sodium channel is an important molecular target in the heart. Empagliflozin demonstrated a significant and selective inhibitory effect on late-INa and also reversibly reduced the incidence of late-INa induced calcium disturbances in single cardiomyocytes.[16]

Klotho and SGLT-2 inhibition: Klotho has evolved as a novel cardioprotective factor, and its deficiency is a hallmark of cardiovascular disease progression. Modulation of signaling pathways like SIRT1/AMPK signaling, NO signaling, and RAS inhibition by Klotho eventually averts cardiovascular events, such as cardiac remodeling, cardiac hypertrophy, cardiomyopathy, and cardiac dysfunction. SGLT-2 inhibitors preserve Klotho levels thereby providing extra glycemic benefits in patients.[17]

TISSUE EFFECTS

Effects on tissue sodium content: Raised tissue sodium content is associated with an increase in hypertrophic stimuli and vasoconstrictive response, which leads to an increase in afterload in CHF patients. Empagliflozin significantly reduce skin sodium content without significant change in muscle and water sodium content. This decrease in skin sodium content may improve left ventricular remodeling and ejection fraction which leads to improved outcomes in this patient population.[18,19]

Improved cardiac energy metabolism: With the progression of heart failure, the heart increasingly becomes dependent on glycolysis as a source of energy. This is due to the continual decline in mitochondrial glucose oxidation in the failing heart, leading to reduced energy production and a fuel-starved heart. SGLT-2 inhibitors mobilize adipose tissue fatty acids and increase fat oxidation, resulting in an increase in the plasma concentration of ketone bodies.[20,21] Improved cardiac energy metabolism by SGLT-2 inhibitors may prevent adverse left ventricular remodeling and heart failure, independent of diabetes.[22] In addition, the increase in lipid oxidation might reduce the levels of toxic intracellular lipid metabolites leading to the reversal of lipo-toxicity and improvements in muscle insulin sensitivity and β cell function.[23]

Reduction in inflammation: Pro inflammatory biomarkers are elevated in patients with heart failure and correlate

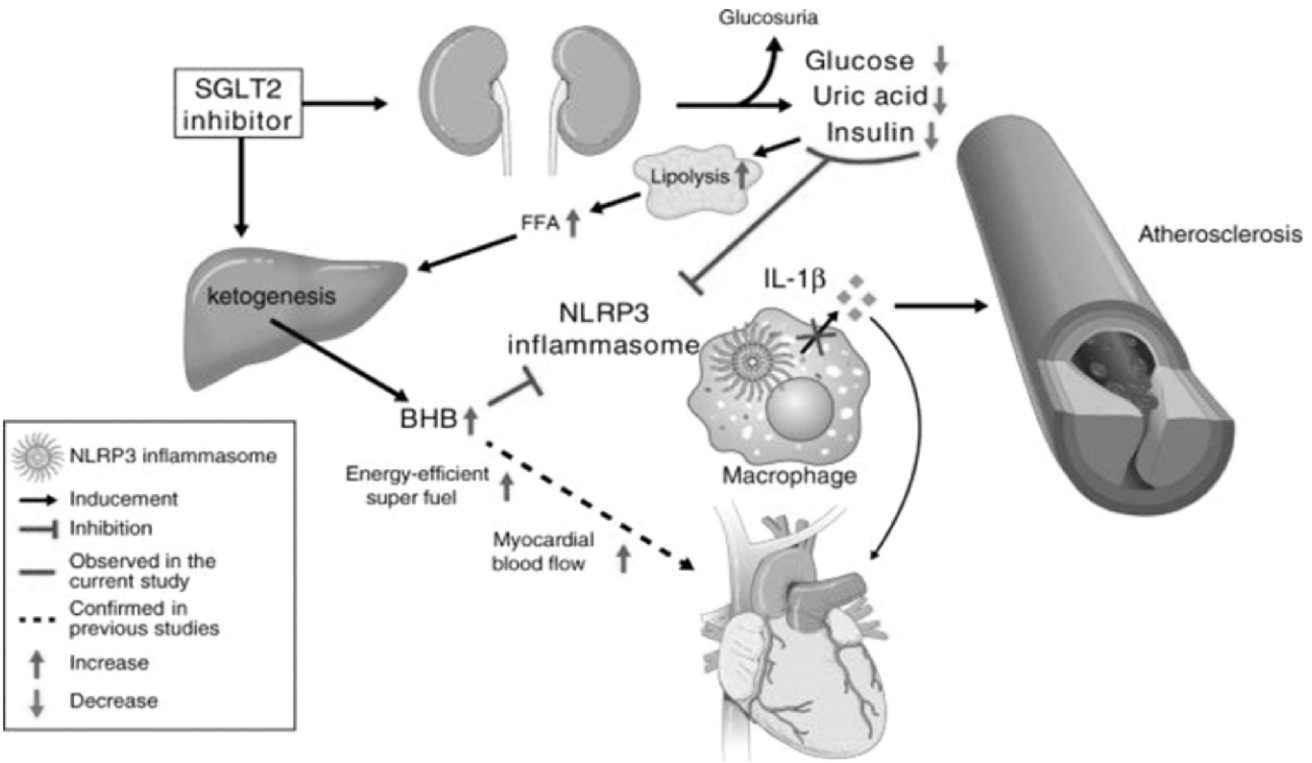

Figure 3: SGLT-2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease.

with the severity of the disease. Apart from the glucose-lowering actions, SGLT-2 inhibitors also directly target inflammatory pathways. NLRP3 inflammasome, a multimeric protein complex is responsible for various inflammatory responses including the production of IL-1β and IL-18, thereby playing an important role in heart failure pathophysiology. ß-hydroxybutyrate is an effective blocker of the NLRP3 inflammasome-mediated inflammatory process.[24]

SGLT-2 inhibitors increase circulating ß-hydroxybutyrate levels and it is likely that some of the beneficial effects of SGLT-2 inhibition could occur secondary to ketone inhibition of the NLRP3 inflammasome. Empagliflozin has shown an inhibitory effect on NLRP3 inflammasome independent of glucose-lowering action in the kidney, liver, macrophages, vasculature, and heart[25] (Figure 3).

Suppression of AGE-mediated effects: In diabetic patients, reducing sugars non-enzymatically modifies multiple proteins leading to early glycation products. These early glycated products are further processed into advanced glycated end-proteins (AGE's). AGE with help of their respective receptors (RAGE), present on endothelial cells, vascular smooth muscle cells, and monocytes promote oxidative stress responsible for inflammation and fibrotic reactions.[26] This activation of AGE-RAGE signaling is associated with an increase in the risk of coronary artery disease, acute myocardial infarction, HF, and nephropathy.[27] SGLT-2 inhibitors have shown a reduction in AGE generation and suppression of the AGE-RAGE axis in various animal and in-vitro models.[28] The importance of AGEs and AGE-RAGE signaling as mediators of the effects of SGLT-2 inhibitors in the human heart is uncertain and further studies are required to establish the role of the AGE-RAGE pathway in SGLT-2 inhibition.

Alteration in adipokine levels: Altered adipokine levels have been postulated as contributing factors in the pathophysiology of cardiovascular diseases. Raised adipokine leptin levels may lead to sodium retention, and volume expansion, as well as inflammation and fibrosis in the kidney and heart. SGLT-2 inhibitors may restore the balance between pro- and anti-inflammatory adipokines. Empagliflozin in a randomized control trial, significantly reduced PAI-1 by 25% and increased adiponectin levels in the treatment arm compared to the placebo.[29]

ORGAN SYSTEM EFFECTS

1. Cardiovascular system:

(a) Endothelial function improvement: Pre-clinical and clinical studies have demonstrated mixed results with respect to SGLT-2 inhibition and endothelial function. Uric acid metabolism is associated with increased inflammation and oxidative stress, leading to endothelial dysfunction. Reduction in uric acid levels may protect against endothelial damage and result in favourable cardiorenal outcomes. SGLT inhibitors in their respective trials have consistently shown a reduction in uric acid levels, which may possibly contribute to cardiovascular and kidney benefits.[30,31]

(b) Reduction in systemic blood pressure: Hypertension is one of the most common modifiable risk factors for the development of heart failure. A meta-analysis suggests that SGLT-2 inhibition is consistently associated with a reduction in systemic blood pressure: typically, of 4 mmHg systolic and 2 mmHg diastolic. Some of the beneficial effects of SGLT-2 inhibitors may be attributed to this blood pressure-improved cardiac energetics. Although the exact mechanism(s) for the antihypertensive effects of SGLT-2 inhibition is not fully understood, they are probably mediated by the osmotic and diuresis effects of SGLT-2 inhibitors because of inhibition of sodium reabsorption in the proximal tubules of the kidney. SGLT-2 inhibition can result in a 30% to 60% increase in urinary sodium excretion. Over a prolonged period of time, further reduction in body mass owing to loss of visceral and subcutaneous adipose tissue[32], modulation of the RAAS[33], and reduced plasma uric acid levels are also likely to contribute to the reduction in blood pressure.

Central systolic blood pressure, a surrogate parameter of after load and indicator of stiffness of large arteries, has been strongly linked to future cardiovascular outcomes. SGLT inhibitors their respective trials have demonstrated beneficial effects in CSBP and thus, arterial stiffness in T2DM patients.[34] However, the blood pressure lowering effects of SGLT-2 inhibition are modest and are unlikely to completely explain the beneficial cardiovascular and kidney effects of these drugs.

(c) Reduce CaMKII: Heart failure is associated with over-expression as well as activation of calcium calmodulin kinase-II. Pre-clinical animal models have shown inhibitory action of SGLT-2i on Ca2+/Calmodulin dependent kinase activity and Calcium calmodulin-dependent kinase-II dependent phosphorylation of cardiac ryanodine receptors in ventricular myocytes. This significantly reduces sarcoplasmic Ca2+ and improves cardiac contractility.[35]

(d) Autophagy and lysosomal degradation: SGLT-2 inhibitors induce a catabolic state in the patient by improving the lysosomal degradation and promoting autophagy of dysfunctional organelles. This occurs because of an increased glucagon-to-insulin ratio, a fuel switch from glucose to free fatty acids, and a decrease in circulating insulin and amino acids, resulting in the inhibition of the mammalian target of Rapamycin complex 1 (mTORC1). Some of the cardiorenal benefits of SGLT-2 inhibitors can be attributed to their stimulatory effects on autophagy.[36]

(e) Reversal of LV remodeling: Left ventricle remodeling is characterized by hypertrophy, raised extracellular matrix, inflammation, and myocyte death. Various preclinical heart failure models and in vitro studies have demonstrated the protective effects of SGLT-2i against LV remodeling pathways. Fibroblasts play a crucial role in the regulation of ECM, in-vitro studies in human cardiac fibroblasts have shown a reduction in extracellular matrix remodeling and suppression of profibrotic markers expression in presence of SGLT-2 inhibitors. SGLT-2 inhibitors reduce left ventricular hypertrophy by multiple effects i.e. decrease in blood pressure, lesser activation of the RAS system, natriuresis and diuresis, and weight loss. Empagliflozin has demonstrated a significant reduction in LV mass as compared to placebo in the EMPA-HEART study irrespective of HF status. Similarly, Empagliflozin ameliorated cardiac remodeling, reduced LV volumes, decreased LV mass, increased LV systolic function, and enhanced functional capacity compared to placebo in HFrEF patients in the EMPA-TROPISM trial.[37,38]

(f) Reduction in epicardial fat mass: Epicardial adipose tissue is highly metabolically active and is responsible for the production of pro-fibrotic and pro-inflammatory cytokines. These biomolecules can cause a negative impact on the cardiac tissue as well as the coronary arterial tree. SGLT-2 inhibition reduces epicardial adipose tissue mass, as well as the levels of bioactive molecules such as tumor necrosis factor-α and plasminogen activator inhibitor-1 (PAI-1).[39]

(g) Improvement in diastolic function: In a study conducted on isolated human HFpEF myocardial fibers, Empagliflozin reduced myocardial passive stiffness by improving the phosphorylation of myofilament regulatory proteins. SGLT-2 inhibition has also shown significant improvement in LV pump function in mice with Doxorubicin-induced cardiomyopathy. Taken together these findings point towards their favorable action in HFpEFpathophysiology.[40,41]

(h) Acute heart failure: In a recent study aiming to compare patients hospitalized for decompensated HF, the prescription of SGLT-2 inhibitors versus no prescription during admission showed that the administration of SGLT-

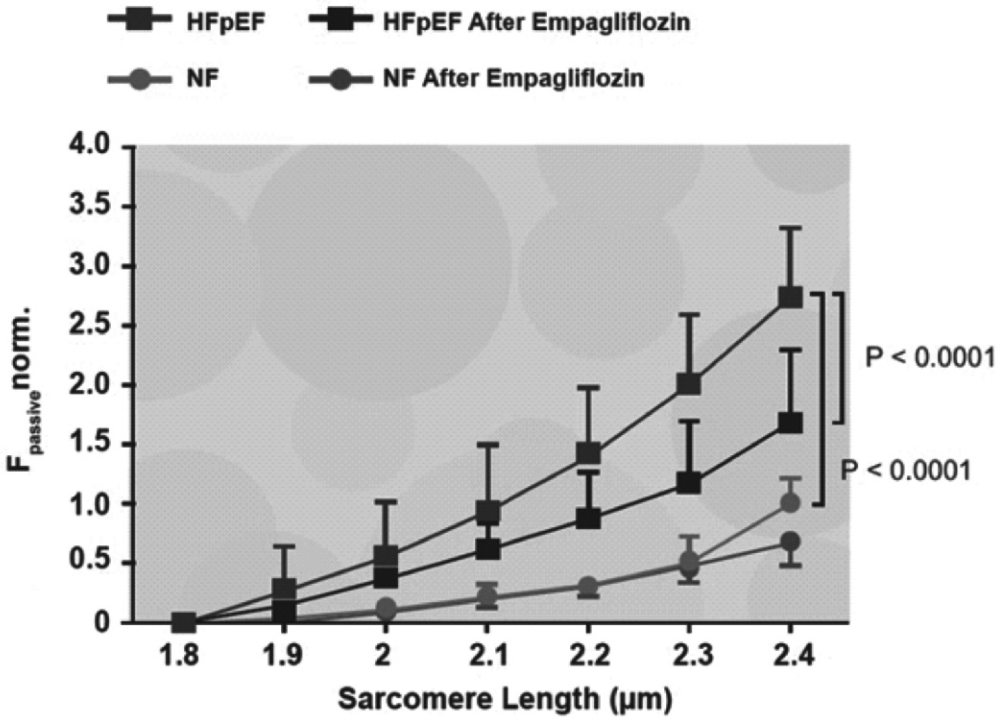

Figure 4: Empagliflozin improves diastolic function in human heart failure.

2 during acute HF admission reduces emergency department visits, re-hospitalization, and cardiovascular death at 6 months with an NNT of 3.58.[42]

2. Inhibiting the sympathetic nervous system:

Sympathetic nervous system hyperactivity plays a crucial role in the development of heart failure as well as arterial hypertension. Multiple trials with SGLT-2 inhibitors have shown significant reduction in blood pressure and plasma volume without any change in heart rate, this is suggestive of a SNS depressant action by SGLT-2 inhibitors.

The reduction by SGLT-2 is in sympathetic overactivity seen in patients with HF may contribute to the reduction in hospitalization for HF consistently reported with SGLT-2 is. Overactive SNS activity could also lead to diabetes-associated nephropathy. Renal sympathetic activation leads to an increase in renin and RAS activity, which further leads to sodium reabsorption and fluid retention thereby contributing to the pathophysiology of heart failure. Local renal sympathetic hyperactivity may induce proteinuria, glomerulosclerosis, and finally renal fibrosis, through the activation of proinflammatory/profibrotic markers. It's been postulated that SGLT-2 inhibitors may downregulate SNS hyperactivity, thereby providing cardiorenal benefits.[43]

3. Effect of SGLT-2 inhibitors on the kidneys:

(a) Glomerular afferent arteriolar vasoconstriction[44]: SGLT-2 receptors are responsible for <5% of sodium reabsorption in renal tubules, this increases to 15% in hyperglycemic patients due to the upregulation of SGLT-2 and SGLT1 in the kidney. Sustained glomerular hyper-filtration is a key pathophysiology behind development and progression of diabetic kidney disease.

SGLT-2 inhibitors have shown to cause acute lowering of GFR albeit preserving the same in the long run. This acute GFR reduction is due to attenuation of diabetes induced hyperabsorption of glucose and Na+ in PCT. SGLT-2 inhibitors achieve nephroprotection by increasing distal renal sodium delivery, improving the glomerular afferent arteriolar tone and by reducing renal hyper-filtration. Partial or more complete return of eGFR after the initial dip in response to sustained SGLT-2 inhibition, as seen in some clinical studies, may be because of compensatory up-regulation of NaCl reabsorption in the loop of Henle.

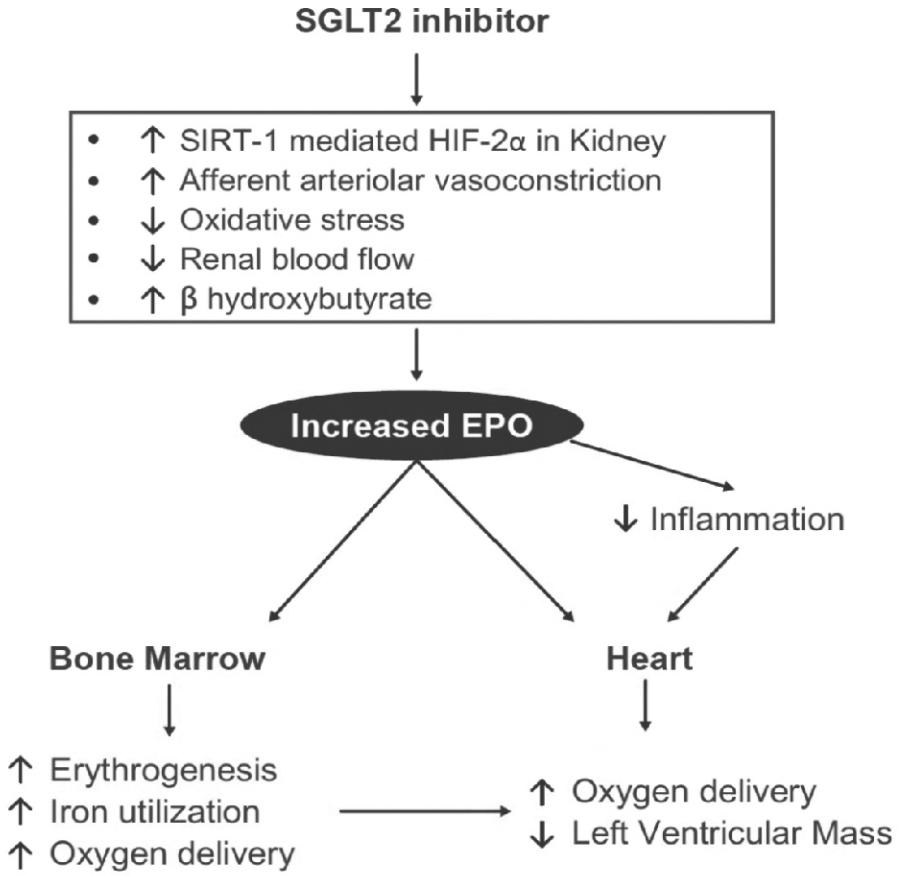

Figure 5: SGLT 2 inhibition and vascular euphoria.

(b) Diuresis and natriuresis: SGLT-2 inhibitors promote natriuresis and glucosuria, and the resultant osmotic diuresis has been hypothesized to improve heart failure outcomes. Unlike classical diuretics (Furosemide), SGLT-2 inhibitors reduce interstitial volume more as compared to intravascular volume. This may occur because of greater electrolyte-free water clearance by peripheral pooling of osmotically inactive sodium.[45] This differential effect in regulating interstitial fluid (v/s intravascular volume), may limit the reflex neuro humoral stimulation that occurs in response to intravascular volume contraction associated with traditional diuretics.

Natriuresis and a reduction in plasma volume are likely to be protective against the development of HF and might explain at least part of the rapid onset reduction in the risk of hospitalization for HF observed in the cardiovascular outcome studies, the EMPEROR-REDUCED trial, CREDENCE trial and the DAPA HF trial.

(c) Improvement in erythropoietin levels: Modest increases in haematocrit levels of 2-4% have been consistently observed in clinical trials of SGLT-2 inhibitors. SGLT-2 inhibitors may promote erythropoiesis via enhanced EPO secretion by the kidney. Such an increase in EPO may serve to favourably influence cardiomyocyte mitochondrial function, angiogenesis, cell proliferation, and inflammation, in addition to directly enhancing myocardial tissue oxygen delivery.[46]

CONCLUSION

SGLT-2 inhibitors are novel medications that reduce plasma glucose concentration which results in cardiovascular and renal benefits. SGLT-2 inhibitors also have promising prospects in improved cardiac energy metabolism, decreased fluid retention, reduced weight gain, lower blood pressure, and decreased risk of hypoglycemia. Additionally, SGLT-2 inhibitors can delay the aging of endothelial cells and smooth muscle cells, and reduce inflammation and oxidative stress, at the cellular level. They act by activation of sensors including sirtuin1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK). SIRT1 responds to levels of nicotin amide adenine dinucleotide and serves as a redoxrheostat, whereas AMPK discerns the balance between ATP and AMP in the cytosol, as an adaptive response to starvation and cellular stress. SGLT-2 inhibitors regulate the expression of Micro RNA and prevent the occurrence and development of atherosclerosis, and can improve blood vessel stiffness and aging.

REFERENCES

1. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT-2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31-39. doi: 10.1016/S0140-6736(18)32590-X.
2. Monami M, Dicembrini I, Mannucci E. Effects of SGLT-2 inhibitors on mortality and cardiovascular events: A comprehensive meta-analysis of randomized controlled trials. *Acta Diabetol*. 2017;54:19-36. doi: 10.1007/s00592-016-0892-7.
3. Dardi I, Kouvatsos T, Jabbour SA. SGLT-2 inhibitors. *Biochem Pharmacol*. 2016);101:27-39. doi: 10.1016/ j.bcp. 2015.09.005.
4. Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. *J Intern Med*. 2007;261:32-43.10. 1111/j.1365-2796.2006.01746.x.
5. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373: 2117-28. 10.1056/NEJMoa1504720.
6. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, Von Eynatten M, Mattheus M, et al.. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323-34.10.1056/NEJMoa1515920.
7. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with Empagliflozin in heart failure. *N Engl J Med*. 2020; 383: 1413-24. 10.1056/NEJMoa2022190.
8. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021:2021:111. 10.1056/NEJMoa2107038.
9. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-57. 10.1056/NEJMoa1611925.
10. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; 380:2295306. 10.1056/NEJMoa1811744.
11. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347-57. 10.1056/NEJ Moa1812389.
12. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; 381:1995-2008. 10.1056/NEJMoa1911303.

13. Heerspink HJL, Stefánsson B V, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436-46. 10.1056/NEJMoa2024816.
14. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, et al. Empagliflozin decreases myocardial cytoplasmic Na^+ through inhibition of the cardiac Na^+/H^+ exchanger in rats and rabbits. *Diabetologia*. 2017;60(3):568-73.
15. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *Journal of the American College of Cardiology*. 2020;75(4):422-34.
16. Philippaert K, Kalyaanamoorthy S, Fatehi M, Long W, Soni S, Byrne NJ, et al. Cardiac late sodium channel current is a molecular target for the sodium/glucose cotransporter 2 inhibitor Empagliflozin. *Circulation*. 2021 ;143(22):2188-204.
17. Kale A, Sankrityayan H, Anders HJ, Gaikwad AB. Klotho: A possible mechanism of action of SGLT-2 inhibitors preventing episodes of acute kidney injury and cardiorenal complications of diabetes. *Drug Discovery Today*. S1359-6446.
18. Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, Vallon V, et al. Acute and chronic effects of SGLT-2 blockade on glomerular and tubular function in the early diabetic rat. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2012; 302 (1): R75-83.
19. Kolwelter J, Kannenkeril D, Linz P, Jung S, Nagel AM, Bosch A, et al. The SGLT-2 inhibitor Empagliflozin reduces tissue sodium content in patients with chronic heart failure. *Journal of the American College of Cardiology*. 2021;77(18_Sp):585.
20. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, et al. Shift to fatty substrate utilization in response to sodium glucose co-transporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. *Diabetes*. 2016;65(5):1190-95.
21. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. *Diabetes Care*. 2016;39(7):1115-22.
22. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, et al. Empagliflozin increases cardiac energy production in diabetes: Novel translational insights into the heart failure benefits of SGLT-2 inhibitors. *JACC*: *Basic to Translational Science*. 2018;3(5):575- 87.
23. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, et al. Empagliflozin ameliorates adverse left ventricular remodeling in non-diabetic heart failure by enhancing myocardial energetics. *Journal of the American College of Cardiology*. 2019;73 (15):1931-44.
24. Iannantuoni F, M de Marañon A, Diaz-Morales N, Falcon R, Bañuls C, et al. The SGLT-2 inhibitor Empagliflozin ameliorates the inflammatory profile in type 2 diabetic patients and promotes an antioxidant response in leukocytes. *Journal of Clinical Medicine*. 2019 ;8(11):1814.
25. Kim SR, Lee SG, Kim SH, Kim JH, Choi E, et al. SGLT-2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nature Communications*. 2020 ;11(1):1-1.
26. Yamagishi SI, Nakamura K, Matsui T, Noda Y, Imaizumi T. Receptor for advanced glycation end products (RAGE): A novel therapeutic target for diabetic vascular complication. *Current Pharmaceutical design*. 2008;14(5):487-95.
27. Paradela-Dobarro B, Agra RM, Álvarez L, Varela-Román A, García-Acuña JM, González- Juanatey JR, et al. The different roles for the advanced glycation end products axis in heart failure and acute coronary syndrome settings. *Nutrition, Metabolism and Cardiovascular Diseases*. 2019;29(10):1050-60.
28. Ojima A, Matsui T, Nishino Y, Nakamura N, Yamagishi S. Empagliflozin, an inhibitor of sodium-glucose cotransporter 2 exerts anti-inflammatory and antifibrotic effects on experimental diabetic nephropathy partly by suppressing AGEs-receptor axis. *Hormone and Metabolic Research*. 2015;47(09):686-92.
29. Sakurai S, Jojima T, Iijima T, Tomaru T, Usui I, Aso Y. Empagliflozin decreases the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) in patients with type 2 diabetes: Association with improvement of fibrinolysis. *Journal of Diabetes and its Complications*. 2020;34(11):107703.
30. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, et al. Effects of sodium-glucose co- transporter 2 (SGLT-2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. *Diabetes, Obesity, and Metabolism*. 2018 ; 20 (2):458-62.
31. Tiwaskar M, Kalra S, Bantwal G, Bhattacharya A, Sahay M, et al. 2021. SGLT-2-inhibition and vascular euphoria a reconciliaiton of vascular health and disease homeostasis. *Journal of The Association of Physicians of India*. 69(4); 66-70.
32. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodiumglucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. *Annals of Internal Medicine*. 2013;159(4):262-74.
33. Wojcik C, Warden BA. Mechanisms and evidence for heart failure benefits from SGLT-2 inhibitors. *Current*

Cardiology Reports.2019; Oct 1;21(10):130.

34. Striepe K, Jumar A, Ott C, Karg MV, Schneider MP, Kannenkeril D, et al. Effects of the selective sodium-glucose cotransporter 2 inhibitor Empagliflozin on vascular function and central hemodynamics in patients with type 2 diabetesmellitus. *Circulation*. 2017;136(12):1167-69.
35. Mustroph J, Wagemann O, Lücht CM, Trum M, Hammer KP, Sag CM, et al. Empagliflozin reduces Ca/calmodulin-dependent kinase II activity in isolated ventricular cardiomyocytes. *ESC Heart Failure*. 2018;5(4):642-48.
36. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, et al. Randomized trial of Empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *Journal of the American College of Cardiology*. 2021;77(3):243-55.
37. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, et al. Effect of Empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: The EMPA-HEART CardioLink-6 randomized clinical trial. *Circulation*. 2019;140(21):1693-702.
38. Sato T, Aizawa Y, Yuasa S, Kishi S, Fuse K, Fujita S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovascular Diabetology*. 2018;17(1):6.
39. Pabel S, Wagner S, Bollenberg H, Bengel P, Kovacs A, et al. Empagliflozin directly improves diastolic function in human heart failure. *European Journal of Heart Failure*. 2018;20(12):1690-700.
40. Oh CM, Cho S, Jang JY, Kim H, Chun S, et al. Cardioprotective potential of an SGLT-2 inhibitor against doxorubicin-induced heart failure. *Korean Circulation Journal*. 2019 ;49(12):1183-95.
41. Bayes-Genis A, Iborra-Egea O, Spitaleri G, Domingo M, Revuelta-López E, et al. Decoding Empagliflozin's molecular mechanism of action in heart failure with preserved ejection fraction using artificial intelligence. *Scientific Reports*. 2021 ;11(1):01-09.
42. López-Vilella R, Trenado VD, Cervera BG, Sánchez-Lázaro I, Bonet LA. Sodium-glucose cotransporter 2 inhibitors reduce cardiovascular events in acute heart failure. A real- world analysis. *Eur J Intern Med.* 2022; 104: 128-130. doi: 10.1016/j.ejim.2022.06.008.
43. Scheen AJ. Effect of SGLT-2 inhibitors on the sympathetic nervous system and blood pressure. *Current Cardiology Reports*. 2019;21(8):01-70.
44. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJ, Boulton DW. Why do SGLT-2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes, Obesity, and Metabolism.* 2018;20(3): 479-87.
45. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, et al. How does Empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018 ;41(2):356-63.
46. Mazer CD, Hare GM, Connelly PW, Gilbert RE, Shehata N, Quan A, et al. Effect of Empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. *Circulation.* 2020 ;141(8):704-07.

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