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The impact of Empagliflozin on chronic kidney disease patient regardless of diabetes: A review

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ABSTRACT

Empagliflozin usually considered as an antidiabetic medication but it shows other beneficial effects like reducing the mortality rate of heart failure patients with reduced ejection fraction and nephroprotective effect. Recent studies revealed that the drug decline the incidence of renal events, including death from renal causes, as well as the risk of end stage renal failure regardless of Type II Diabetes Mellitus. Clinical trial related Empagliflozin on CKD patient confirmed that it has a consistent effect on the disease progression. This review aim to analysing the impact of Empagliflozin on Chronic Kidney Disease patient regardless of Diabetes.

INTRODUCTION

Chronic Kidney Failure (CKD) is progressive disease characterized by reduced Glomerular Filtration Rate (GFR) and albuminuria which leads to kidney failure (1). Due to the progressive nature of CKD and the requirement for dialysis and kidney replacement therapy made an extreme financial burden on health care system worldwide (2). In diabetic kidney disease with elevated albuminuria, the renin-angiotensin system (RAS) inhibitors (3, 4), sodium glucose cotransporter 2 (SGLT2) inhibitors (5, 6) and, the non- steroidal mineralocorticoid receptor antagonist Finerenone (7, 8) have shown reductions in the risk of progression to kidney failure.

In EMPA- KIDNEY trial, a recent study revealed that patients with CKD (eGFR of 20 -90 ml/min/ 1.73m^2), Empagliflozin can lower the risk of progression of CKD or death due to cardiovascular reason than placebo regardless of diabetic status (9).

PATHOPHYSIOLOGY OF CKD

Given the high renal blood flow (approximately 400 ml/100 g of tissue per minute), which surpasses that of organs like the heart, liver, and brain, the kidneys are more susceptible to exposure to harmful circulating agents or substances (10). Chronic kidney disease progression is significantly influenced by hypertension

and hyper filtration. The glomerular filtration barrier, characterized by negatively charged molecules, restricts the passage of anionic macromolecules. However, glomerular damage compromises this barrier, allowing plasma proteins to enter the filtrate. The unique arrangement of the nephron, with the tubule positioned downstream from the glomerulus, not only facilitates glomerulo-tubular balance but also exacerbates the effects of glomerular injury. This arrangement allows abnormal filtrate, resulting from glomerular damage, to reach the tubulointerstitial compartment, directly exposing tubular epithelial cells and contributing to disease progression (11). The close anatomical relationship between the glomerular and peritubular circulations allows mediators of glomerular inflammation to 'spill over' into the peritubular capillaries, contributing to the interstitial inflammation often seen in glomerular diseases. Moreover, reduced blood flow to the glomerulus, either pre-glomerularly or within the glomerulus itself, can lead to tubulointerstitial injury and subsequent tissue remodelling (12). Renal impairment can arise from various factors, including immunologic reactions, tissue hypoxia and ischemia, exposure to exogenous agents such as drugs, accumulation of endogenous substances like glucose or paraproteins, and underlying hereditary conditions (13).

MECHANISM OF ACTION

It inhibit SGLT2 channel predominantly localized to the S1 segment of the proximal convoluted tubule where more than 90% absorption of filtered glucose takes place, resulting glucosuria (14). It have sustained modest effect in blood pressure (BP) by reducing the systolic blood pressure and diastolic blood pressure approximately by 3 to 6mm Hg and 1 to 2 mm Hg respectively (15, 16). It is achieved by natriuresis and associated plasma volume contraction (17), reduction in arterial stiffness (18), and improvement in endothelial function (19).

In diabetic patients, the increased proximal tubular sodium absorption by decreased sodium delivery to the macula densa and afferent arteriolar vasodilation by tubuloglomerular feedback causes glomerular hypertension and hyperfilteration (20). It elevate distal sodium delivery and inhibit tubuloglomerular feedback which leads to afferent vasoconstriction and decline in intraglomerular pressure (21, 22).

Other mechanism include decrease in inflammatory mediators like interleukin- 6, nuclear factor- kB, and profibrotic factors (23, 24). Also, it may attenuate renal hypoxia by conserving energy needed to absorb the filtered load of glucose and sodium (23, 25, 26).

CURRENT INDICATIONS

Primarily, it is used for Type II Diabetes Mellitus (27). It can be given as an adjunct to other hypoglycemic agents or when metformin is not tolerated (28). It supress mean fasting glucose (29), postprandial glucose (30) and lower HbA1c (28).

The EMPEROR- Reduced trial outlined that in heart failure patients with reduced ejection fraction (HFrEF), it will declined the deterioration of renal, with or without Type II Diabetes Mellitus. It also shows benefit in heart failure patients regardless of diabetes (31).

PHARMACOKINETICS

Empagliflozin was rapidly absorbed after oral administration in a single rising oral dose (0.5-800mg) study in healthy subjects and showed a biphasic decline (32). The time it took to reach the peak concentration (Cmax) ranged from 1.5 to 2.1 hours, and the time it took for the concentration to halve in the body (terminal elimination half-life, t½) was up to 13.1 hours (32). The mean plasma concentration profile of empagliflozin was similar whether people took it with or without food. This means empagliflozin can be taken with or without food, which was confirmed by a study specifically looking at the effect of food on the drug (32, 33). Over 72 hours, the kidneys cleared empagliflozin at a rate of 32.1 to 51.3 milliliters of blood per minute. During this time, 11.0 to 18.7% of the empagliflozin in the body was excreted in the urine (32).

PHARMACODYNAMICS

On average, empagliflozin caused the excretion of 3.1 grams of glucose in urine over the first 24 hours at a dose of 0.5 milligrams, and 61.6 grams at a dose of 800 milligrams

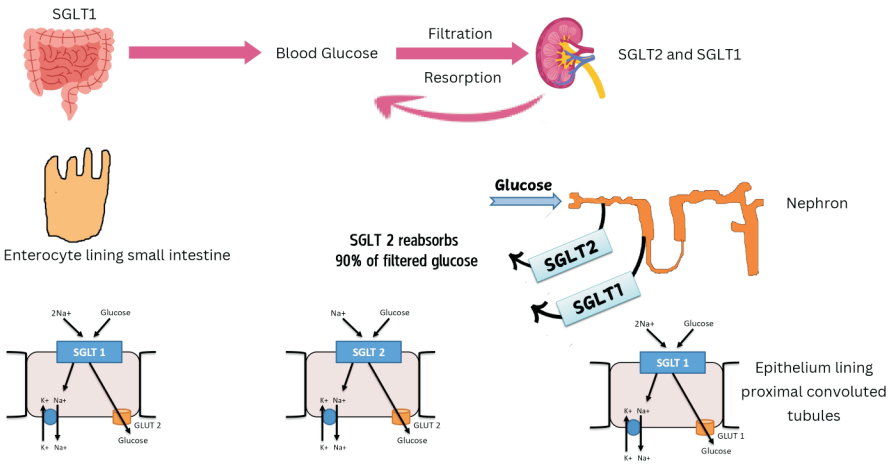

Fig.1: Protective mechanism of Empagliflozin on kidney.

(compared to 0.06 grams with placebo). The maximum amount of glucose excreted in urine (UGE) was 90.8 grams, observed at the 400-milligram dose. The total amount of glucose excreted in urine over 72 hours increased proportionally with the dose of empagliflozin, but this increase leveled off at around the 100-milligram dose. The time it took to reach the peak rate of glucose excretion in urine was similar across all dose groups, occurring around 7 hours. Blood glucose levels remained consistent among healthy individuals treated with any dose of empagliflozin or placebo, as anticipated (32).

SIDE EFFECTS

Risk of hypotension in elderly patients with low BP, impaired renal function or using diuretics while using Empagliflozin. It enhance hypoglycaemia in patients on potent hypoglycemic agents like insulin and insulin secreting agents (34, 28). Fungal infection such as genital candidiasis and urinary tract infection mostly mild in nature. But, rarely causes sepsis and death (34, 35, 36). Rare but, serious complication called ketoacidosis may develop due to the excess production of ketone by increasing glucagon secretion and increasing glucosuria causes decreasing insulin secretion leads to the upregulated production of free fatty acids (34, 35, 37). Patients with pancreatic disorder and have alcohol dependence are highly susceptible. Other side effects include arthralgia, acute kidney injury, dyslipidemia and Fournier's gangrene (34, 38).

CONTRAINDICATIONS

It is not recommended in patients with type I diabetes mellitus, severe hypersensitivity reactions like angioedema or anaphylaxis, ketoacidosis, people over 85 years of age, end stage renal disease or those on dialysis (34, 38). It is contraindicated in patients with GFR < 30ml/min/1.73m^2 and its use is not recommended < 45ml/min/173m^2. Its use in pregnancy during 2nd and 3rd trimesters is not recommended (34, 35). It may cause serious side effects in lactating women (28).

CLINICAL TRIALS CONDUCTED ON EMPAGLIFLOZIN IN PATIENTS WITH CKD WITH OR WITHOUT DIABETES

EMPA- KIDNEY collaborative group conducted a study in-order to identify the effects of Empagliflozin in CKD patients. It was a follow-up study in which 6609 patients were selected randomly and follow-up after a median of 2 years. In the Empagliflozin group, 432 of 3304 (13.1%) patients and in the placebo group, 558 of 3305 (16.9%) patients were underwent progression of kidney disease or death from cardiovascular causes. The study imply that Empagliflozin therapy led to lower risk of progression of kidney disease or death from cardiovascular causes than placebo in patients with CKD who were at risk for disease progression (39).

Masaomi Nangaku et al assessed the effects of Empagliflozin 10mg once daily vs placebo in 6609 CKD patients at risk of

Table 1 :

SL. NO	TITLE	AUTHORS	YEAR	SAMPLE SIZE	METHODOLOGY	RESULT
1	Empagliflozin in patients with chronic kidney disease	EMPA-KIDNEY collaborative group	2023	6609	Randomisation of subjects into study group and placebo	It was conducted to identify the effects of Empagliflozin in CKD patients It concluded that the drug reduce the risk of the composite outcome of kidney disease progression in ckd progression.
2	Effect of empagliflozin in patients with chronic kidney disease from Japan exploratory analysis from EMPA- KIDNEY	Masaomi Nangaku et al	2024	6609	Post-hoc comparisons	The study used to find out the effects of Empagliflozin 10mg once daily vs placebo in CKD patients at risk of progression. study concluded that Empagliflozin safely decreased the risk of kidney disease progression or cardiovascular death in CKD patients
3	Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the empa-kidney trial	Natalie Staplin et al	2024	241 centres	randomised, controlled, phase 3 trial	It aimed to recognise the effect of Empagliflozin on progression of CKD both overall and among specific type of participants in the EMPA- KIDNEY trial. It declined the rate of progression of CKD among all types of participants in the trial, containing those with little albuminuria.

progression. The primary outcome include the time to first occurrence of the composite outcome of kidney disease progression or cardiovascular death. A follow-up period of 2 years, 432 patients (13.1%) in the Empagliflozin group and 558 patients in the placebo group developed a primary outcome. The study concluded that Empagliflozin safely decreased the risk of kidney disease progression or cardiovascular death in CKD patients (40).

A phase 3, randomised controlled trial was conducted at 241 centres by Natalie Staplin et al mainly aimed to recognise the effect of Empagliflozin on progression of CKD both overall and among specific type of participants in the EMPA- KIDNEY trial. The study evaluated the effects of 10mg oral Empagliflozin once daily versus placebo on the annualised rate of change in estimated glomerular filtration rate (eGFR slope). It declined the rate of progression of CKD among all types of participants in the trial, containing those with little albuminuria (41).

CONCLUSION

Empagliflozin, a SGLT 2 channel inhibitor primarily given for the treatment of type II diabetes mellitus showed declined in the risk of progression of kidney disease or death from cardiovascular causes in the board range of CKD patients. The effects of Empagliflozin in CKD is beneficial with or without the presence of diabetes. The clinical trials had its own limitation. But, it provide a signal to the new beneficial role of empaglifozin. So, future studies were required to assess its clear cut importance in CKD and cardiac patient.

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