Empagliflozin: a wonder drug in preventing diabetic nephropathy and cardiovascular effects

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ABSTRACT

Diabetes, a terrible disease, with highest incidence in world produces many complications which will end up in dreadful situations. Diabetes nephropathy is one of the complications which lead to dialysis, renal replacement. empagliflozin, sodium glucose cotransporter 2 inhibitors decreases plasma blood glucose level, HbA1C and weight by excreting glucose in urine. It by decreasing HbA1C results in decrease in complications of diabetes due to high blood sugar and fluctuating blood sugars. It decreases the blood pressure, arterial stiffness and vascular resistance. It decreases the risk factors of diabetic nephropathy like hyperglycemia and high blood pressure. It also decreases the diabetes-related glomerular hypertrophy, markers of renal inflammation, as well as mesangial matrix expansion and thus ameliorates the early signs of diabetic nephropathy. The efficacy in decreasing blood glucose levels was confirmed in four randomized placebo controlled studies. The safety concern was seen in studies were urinary and genital tract infections. It thus proves to be an efficient option for diabetes in preventing diabetes nephropathy and cardiovascular effects.

Keywords: Empagliflozin, Diabetic nephropathy, Diabetes, SGLT2

INTRODUCTION

Diabetes is one of the most dreadful diseases affecting mankind of all ages. According to a recent World Health Organization (WHO) report, India, with 32 million diabetic individuals in 2000, currently has the highest incidence of diabetes worldwide; these numbers are predicted to increase to 80 million by the year 2030. Diabetic nephropathy (DN), which carries a heavy clinical and economic burden, is present in up to 40% of patients with type 2 diabetes mellitus. Diabetic nephropathy, which is a progressive kidney disease caused by damage of capillaries in the glomeruli of kidney and characterized by nephrotic syndrome and diffuse scarring of glomeruli, is a prime reason for dialysis and renal replacement therapy in many developed countries. Hyperglycemia and increased blood pressure levels are the main risk factors for the development of diabetic nephropathy which increases the risk of death due to cardiovascular causes. Empagliflozin is one of the sodium glucose cotransporter 2 inhibitors and has shown a magnificent effect on lowering blood glucose level by excretion of glucose in urine and helps in decreasing blood pressure. We have reviewed the literature on empagliflozin bringing to focus the mechanism of action, efficacy, safety and pharmacokinetics of this molecule.

Mechanism of action

Kidney mainly contributes to maintenance of blood glucose levels by reabsorption of glucose from glomerular filtrate to blood. All filtered glucose is reabsorbed into the blood by sodium - glucose cotransporters (SGLTs) along with facilitative glucose transporters (GLUTs) in the proximal tubule of nephron. As the plasma concentration of glucose exceeds 180 - 200 mg/dl these transporters cannot reabsorb glucose, glucose starts appearing in urine. This reabsorbed glucose in diabetes contributes to increased plasma sugar levels.
In diabetes there is increased expression of SGLT2 in the proximal convoluted tubular cells which leads to increased absorption of glucose raising the blood glucose levels.\textsuperscript{9}

### Table 1: Summary of findings in placebo controlled studies on Empagliflozin.

| Study                        | Sample Size | Period of study | Study groups                                      | Adjusted mean changes for HbA1C | Adverse effects | % of Adverse effects reported | % of urinary tract infections reported | % of genital tract infections reported |
|------------------------------|-------------|-----------------|---------------------------------------------------|--------------------------------|----------------|--------------------------------|----------------------------------------|----------------------------------------|
| Hans-Ulrich Häring et al\textsuperscript{11} | 666         | 24 weeks        | Empagliflozin 10 mg (n = 225), Empagliflozin 25 mg (n = 216) and Placebo (n = 225) | -0.82% (p<0.001) -0.77% (p<0.001) -0.17% | Urinary tract infections and genital infections | 62.7% | 10.3% | 0.9% |
| Hans-Ulrich Häring et al\textsuperscript{12} | 637         | 24 weeks        | Empagliflozin 10 mg (n = 217), Empagliflozin 25 mg (n = 213) or Placebo (n = 207) | -0.70% (p<0.001) -0.77% (p<0.001) -0.13% | Urinary tract infections and genital infections | 49.5% | 5.1% | 4.7% |
| Michael Roden et al\textsuperscript{13}     | 899         | 24 weeks        | Placebo (n = 228), Empagliflozin 10 mg (n = 224), Empagliflozin 25 mg (n = 224) or Sitagliptin 100 mg (n = 223) | -0.74% (p<0.0001) -0.85% (p<0.0001) -0.73% (p<0.0001) | Urinary trials and genital infections | 61% | Not Accessed | AN |
| E. Ferrannini\textsuperscript{14}          | 408         | 12 weeks        | Empagliflozin 5 mg, Empagliflozin 10 mg, Empagliflozin 25 mg, Placebo/open-label metformin | -0.4% (p<0.0001) -0.5% (p<0.0001) -0.6% (p<0.0001) +0.09% | Urinary tract infections, genital tract infections, pollakiuria, thirst, nasopharyngitis | 29.1% | 1.6% | 2% |

Empagliflozin is an SGLT2 inhibitor and inhibits reabsorption of glucose from filtrate into blood through SGLT2. This leads to excretion of glucose, decreasing plasma glucose concentration. It decreases average glucose levels in the blood leading to decrease in HbA1C levels with improving glycaemic control. Besides inhibiting glucose reabsorption, it also blocks sodium reabsorption from the proximal tubule of nephron to blood. It increases plasma renin angiotensin aldosterone system (RAAS) mediators resulting in diuresis leading to decrease in blood pressure both systolic and diastolic blood pressure.\textsuperscript{10} It decreases arterial stiffness and vascular resistance by phleomorphogenic effects of SGLT2 inhibition.\textsuperscript{11} The energy deficit resulting from excretion of calories into urine induces weight loss or has a weight-neutral effect. Its action does not depend on presence of insulin or insulin resistance or impairment of pancreatic β-cell function. It doesn’t stimulate insulin release.

By decreasing blood glucose levels and blood pressure, the risks of developing diabetic nephropathy have been decreased resulting in prevention of diabetic nephropathy. It decreases the diabetes-related glomerular hypertrophy, markers of renal inflammation, as well as mesangial matrix expansion and thus ameliorates the early signs of diabetic nephropathy. It has been reported...
to decrease the onset of renal disease and prolong the progression of severity of renal disease.

**Efficacy**

The efficacy of Empagliflozin was tested in four randomized placebo controlled clinical trials in diabetic individuals. (Table 1) the first three studies were conducted for 24 weeks whereas the last study for 12 weeks. All the above studies affirmed the significant decrease HbA1C levels by using empagliflozin when compared to placebo. The adverse effects reported in placebo group were more or less similar to empagliflozin groups. In the study of Han Ulrich et al reported significant decrease in mean daily glucose, weight and systolic pressure. E. Ferrannini reported the decrease in body weight in empagliflozin group when compared to placebo groups. All the above studies had shown the higher incidence of urinary tract infections and genital tract infections in empagliflozin group than that in Placebo group. One of the above studies had declared the occurrence of frequent hypoglycemic episodes in some individuals in empagliflozin study group due to excretion of glucose in urine frequently. All the above studies had positive insight towards usage of empagliflozin as add on therapy or as monotherapy for treating type II diabetes. The mechanism of action of empagliflozin also suggests that it has the potential to be used in combination with other oral antidiabetic agents as well as insulin to exert additive or synergic effects on lowering glucose levels in type 2 diabetes.

**Safety**

The drug empagliflozin had no devastating side effects reported in the studies except minor side effects of urinary and genital tract infections. Headache was also reported as a frequent side effect. These neither decrease the efficacy of drug nor create miserable conditions. These can be treated symptomatically. Sometimes hypoglycemic episodes are also being reported. As the empagliflozin efficacy is based on Glomerular filtration rate and depends on the kidney function, it is ideal to monitor the renal function frequently.

**Pharmacokinetics**

Empagliflozin has an excellent oral bioavailability. It has no interaction with food. Median time to reach maximum plasma concentration ranged from 1.5 to 2.1 hours. It has a longer half-life (t½) of 13.1 hours allowing once daily administration. There are no active metabolites. Renal clearance (CLR) over 72 hours ranged from 32.1 to 51.3 mL/min, and the cumulative fraction of empagliflozin excreted in urine (fe) over 72 hours ranged from 11.0 to 18.7%. No drug-drug interactions were reported till date. Empagliflozin is co-administered with other medications commonly used in patients with type 2 diabetes mellitus. It is co-administered with other oral glucose-lowering agents (metformin, sitagliptin, linagliptin and glibperide) in combination therapy of diabetes management. It is also administered with cardiovascular/antihypertensive compounds (diuretics, verapamil, ramipril and digoxin) and cholesterol lowering agent (simvastatin) in cases of diabetes with hypertension and diabetes with hyperlipidemia. It can be administered with an anticoagulant (warfarin) and an oral contraceptive (ethinylestradiol/levonorgestrel). There is no effect of empagliflozin on the pharmacokinetics of the above drug and vice versa.

**Current status and future directions**

Currently empagliflozin is in use as a hypoglycemic agent for many patients suffering from diabetes mellitus. but there is a need to clear the efficacy of this drug in chronic renal failure as glomerular filtration rates decrease in it.

**CONCLUSION**

Empagliflozin, an SGLT2 inhibitor decreases blood glucose level thus reducing HbA1c. It also reduces arterial stiffness, vascular resistance and blood pressure. Excretion of glucose results in decrease in calories and weight loss. It has good safety profile with mild headache, urinary and genital tract infection. It has excellent oral bioavailability, longer t½ allowing once daily administration with little or no drug-drug interactions. Nevertheless it is a wonder drug in preventing the complications of diabetes mellitus mainly diabetic nephropathy and cardiovascular side effects.

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