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EMPAGLIFLOZIN REDUCES THE PROGRESSION OF CHRONIC KIDNEY DISEASE

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ABSTRACT

Empagliflozin is a pharmaceutical utilized for the management and treatment of CKD and type 2 DM. Classified under the sodium-glucose co-transporter (SGLT-2) category of diabetes medications, this overview delineates the indications, mechanism of action, and contraindications associated with empagliflozin, underscoring its significance as a valuable therapeutic agent. In the context of diabetic kidney disease, particularly in cases with elevated albuminuria levels, large-scale placebo-controlled trials have demonstrated the efficacy of renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and the non-steroidal mineralocorticoid receptor antagonist finerenone in reducing the risk of progressing to kidney failure. However, given that the majority of CKD cases globally involve individuals with less lower levels of albuminuria (urinary albumin-to-creatinine ratio [ACR] less than 300 mg/g) and without diabetes, studying a diverse range of CKD patients is of paramount public health importance. The SGLT2 inhibitor dapagliflozin has shown kidney benefits in patients with CKD and a urinary ACR of at least 200 mg/g, even extending to those without diabetes. Studies involving individuals with non-alcoholic fatty liver disease were sought using the following databases; Medline, Pubmed, Embase, NCBI, and Cochrane. The findings suggest that empagliflozin could be a valuable adjunctive therapy in the management of CKD, particularly in populations with diabetes.

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Introduction

Diabetes leads to an increased possibility of renal and cardiovascular complications. Over 35% of patients with type 2 diabetes also developed kidney disease [1]. CKD is usually progressive, and staples include the presence of albuminuria and a declining glomerular filtration rate (GFR). Both of these increase the risk of developing kidney failure [2]. Slowing down CKD progression is crucial to avoid the necessity of dialysis or kidney transplantation. These interventions not only impact the patient's quality of life but also contribute to increased cardiovascular mortality and morbidity, along with the high expense of kidney replacement therapy [3].

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In the context of diabetic kidney disease, particularly in cases with elevated albuminuria levels, large-scale placebo-controlled trials have demonstrated the efficacy of renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and the non-steroidal mineralocorticoid receptor antagonist finerenone in reducing the risk of progressing to kidney failure [4]. However, given that the majority of CKD cases globally involve individuals with lower levels of albuminuria (urinary albumin-to-creatinine ratio [ACR] less than 300 mg/g) and without diabetes, studying a diverse range of CKD patients is of paramount public health importance. The SGLT2 inhibitor dapagliflozin has shown kidney benefits in patients with CKD and a urinary ACR of at least 200 mg/g, even extending to those without diabetes [5].

In type 2 diabetic patients, intensive glucose-lowering methods are effective in minimizing surrogate signs of renal problems, but for patients with an estimated GFR under 30 ml per minute per 1.73 m2, the amount of available information is limited. We are also uncertain whether these benefits vary, and how, across the larger population of CKD patients. To address these gaps, the EMPAgliflozin once-daily trial (EMPA-KIDNEY), a multicenter international randomized parallel-group double-blind placebo-controlled clinical trial, was designed in 2022. This trial aimed to assess the impact of SGLT2 inhibition with empagliflozin on the progression of kidney disease, cardiovascular outcomes, and safety in a diverse population of CKD patients. It specifically sought to include a significant number of patients free from diabetes, those with an eGFR of less than 30 ml per minute per 1.73 m2, and patients with low levels of proteinuria [6]. This trial showed significantly fewer first and subsequent hospitalizations in the empagliflozin group (beyond those hospitalizations/deaths due to other causes such as cardiovascular causes).

Empagliflozin was related to slower progression of kidney disease and lower rates of clinically meaningful renal events for patients with type 2 diabetes who were at risk of a cardiovascular event. Originally established in its role against hyperglycemia, empagliflozin is poised to have applications that will diverge significantly due to its many therapeutic effects. Indeed, Empagliflozin has shown improvements in hyperfiltration and in lowering intraglomerular pressure in type 1 diabetes patients [7, 8], thus suggesting better renal outcomes [9].

Epidemiology

A large body of research has studied the prevalence of CKD on a global scale, with numerous research findings contributing to a comprehensive understanding. While the individual discussions of these studies are beyond the scope of this review, their collective data allows for an aggregate analysis of global CKD prevalence across diverse categories of patients and many geographies. In a CKD study in 2010, findings from 33 population-based representative studies worldwide were pooled [10]. The age-standardized global prevalence of CKD stages 1–5 in individuals above 20 years old was reported at 10.4% for males and 11.8% for females. Notably, variations were observed based on geographic regions classified by income levels. In high-income countries, the CKD age-standardized prevalence was 8.6% for males and 9.6% for females, whereas in low and middle-income countries it was higher at 10.6% for males and 12.5% for females. Specifically focusing on CKD stages 3–5 in patients 20 years and older, the prevalence was found to be 4.7% in males and 5.8% in females [11]. In addition, a more recent and comprehensive analysis that included one hundred studies with 6,908,440 patients revealed that the global prevalence of CKD stages 1–5 was 13.4%, while that of stages 3–5 was 10.6%. The incidence rates of 3.5% for stage 1, 3.9% for stage 2, 7.6% for stage 3, 0.4% for stage 4, and 0.1% for stage 5 were found when the prevalence of CKD was broken down into its component stages. Based on the combined results of global research on the prevalence of CKD, an estimated 843.6 million people worldwide are thought to be impacted by stages 1–5 [12].

Empagliflozin Pharmacology Characteristics

With a selectivity for SGLT2 over SGLT1 of about 2500-fold, Empagliflozin is a very selective SGLT2 inhibitor with a bioavailability of approximately 75%. Administered orally, it is rapidly absorbed, reaching a Tmax of 1.5 hours. This medication exhibits 86% protein binding, with a half-life (T1/2) of 13 hours. Its elimination primarily occurs through the fecal route (40%) and the renal route (55%) [13]. Upon initiating an SGLT2 inhibitor (SGLT2i) like empagliflozin, a typical initial decline in estimated glomerular filtration rate (eGFR) is observed. This effect is generally reversible over time or upon discontinuation of the medication.

Diabetes-related hyperfiltration models suggest that adenosine-related mechanisms enhanced distal natriuresis to the macula densa and activated tubuloglomerular feedback. There is disagreement, though, since some results suggest that preglomerular vasoconstriction may be replaced by a post-glomerular vasorelaxation effect. This mechanism may contribute to the observed reduction in microalbuminuria associated with this class of medications, alongside potential long-term positive effects related to a decrease in intraglomerular pressure [14].

In healthy human beings, oral administration of empagliflozin results in rapid absorption. There are dose-proportional increases in urine albumin exposure seen throughout the whole range of empagliflozin dosages (0.5-800 mg). The same results have been reported in healthy Japanese patients within the 1–100 mg dose range, potentially attributed to the generally lower weight of the Japanese population. Administration with food causes a slight delay in absorption, but the clinical significance of this is considered negligible, and empagliflozin can be taken with or without food [15]. For up to 72 hours, plasma quantities of empagliflozin can be detected, particularly at large dosages like 100 mg. Furthermore, regulatory guidelines, including those of the ICH (International Conference on Harmonization) and the FDA, recommend considering ethnic factors in clinical trials. However, pharmacokinetic parameters have shown no significant differences, suggesting no need for dose adjustments [16].

Empagliflozin Mechanism of Action

The inhibition of the sodium-glucose co-transporter-2 (SGLT-2) in the kidneys' proximal tubules is how empagliflozin works. This inhibition leads to a decrease in the renal reabsorption of glucose and an augmentation in the urinary excretion of glucose. Notably, the glucose-lowering impact of empagliflozin occurs independently of insulin. In patients suffering from type 2 diabetes, the administration of 10 mg of empagliflozin results in an increase of approximately 64 grams per day in urinary glucose excretion, while the 25 mg dosage is associated with a higher increment of 78 grams per day.

Beyond its glucose-lowering effects, empagliflozin brings about a reduction in sodium and volume load, inducing intravascular contraction due to its diuretic and natriuretic properties. Furthermore, the use of empagliflozin is correlated with weight loss and is accompanied by decreases in blood pressure, all achieved without a concurrent elevation in heart rate. These multifaceted effects underscore the diverse therapeutic benefits of empagliflozin in the management of diabetes and related cardiovascular risk factors [17].

Prospective Exploration of Empagliflozin

While the historical and current use of empagliflozin has primarily centered around glycemic control and reducing HgbA1c levels, its future applications are poised to diverge significantly from its established role in hyperglycemia. Past off-label experimentation by clinicians has explored its potential for weight management and fluid volume reduction. However, the trajectory of future investigations will delve into mechanistic pathways unrelated to hyperglycemia [18].

As discussed earlier, pivotal trials have unveiled empagliflozin's notable benefits in heart failure, encompassing both reduced and preserved ejection fraction. The positive outcomes in terms of decreased heart failure hospitalizations, cardiovascular deaths, and improvements in heart failure biomarkers are particularly promising. The ongoing expansion of the empagliflozin FDA label to encompass heart failure patients without diabetes is a positive development, substantiated by compelling data. The evolution of real-world data and its incorporation into cardiovascular practice remains a point of anticipation, especially when juxtaposed with other SGLT2 inhibitors like dapagliflozin and canagliflozin, both of which hold cardiac indications for cardiovascular disease and heart failure. While having multiple tools in the medical arsenal to address previously underserved patient populations is advantageous, the extent of empagliflozin's market share dominance will become clearer in the years to come [18].

Shifting the focus to the kidneys, the logical progression in considering empagliflozin's benefits is evident. The SGLT2 inhibitor class, demonstrated by the remarkable outcomes of canagliflozin and dapagliflozin, has shown significant advancements in mitigating chronic kidney disease (CKD) progression, reducing the need for dialysis, and improving cardiovascular and overall mortality [19]. The recently published EMPA-KIDNEY study in 2022 provides detailed insights into the examination of CKD patients. Notably, EMPA-KIDNEY delved into patients with an estimated glomerular filtration rate (eGFR) as low as 20 mL/min/1.73m2, further substantiating the notion that SGLT2 inhibitors can safely benefit individuals with more advanced kidney disease. While additional head-to-head studies are warranted, they may not be imminent, given the recent completion of large clinical trials within the SGLT2 inhibitor class. Furthermore, consideration should be extended to well-controlled Type 1 diabetes mellitus patients, as they share similar cardiovascular and kidney risks, highlighting the potential broad-reaching impact of empagliflozin across diverse patient profiles [19].

Conclusion

Empagliflozin stands out as the latest SGLT2 inhibitor demonstrating proven benefits not only in addressing hyperglycemia but also in the realms of cardiovascular disease, heart failure, and most recently, the progression of CKD. The recent EMPA-KIDNEY data establishes its efficacy in patients both with and without diabetes, expanding the range of people for whom it may be applicable, down to 20 mL/min/1.73m².

This medication solidifies its role as a crucial tool in the fight against CKD progression, contributing to the prevention and subsequent delay of cardiovascular risk factors. Moreover, detrimental events associated with empagliflozin do not seem to have any significance, aligning with findings from previous trials and other medications within the SGLT2 inhibitor class. It is recommended that clinicians carefully review and assimilate this data, contemplating the addition of SGLT2 inhibitors to RAAS inhibitors in suitable patients. Anticipated changes in guidelines further underscore the significance of advanced therapies like empagliflozin in the comprehensive management of chronic kidney disease, providing optimism for improved patient outcomes.

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References

1. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA. 2011;305(24):2532-9.
2. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012;380(9854):1662-73.
3. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329(20):1456-62.
4. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-46.
5. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165-80.
6. EMPA-KIDNEY Collaborative Group. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. Nephrol Dial Transplant. 2022;37(7):1317-29.
7. Škrtić M, Yang GK, Perkins BA, Soleymanlou N, Lytvyn Y, von Eynatten M, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. Diabetologia. 2014;57:2599-602.
8. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587-97.
9. Škrtic M, Cherney DZ. Sodium–glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens. 2015;24(1):96-103.
10. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015;88(5):950-7.
11. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease–a systematic review and meta-analysis. PloS one. 2016;11(7):e0158765.
12. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019;96:1048-50
13. van Bommel EJ, Muskiet MH, van Baar MJ, Tonneijck L, Smits MM, Emanuel AL, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. Kidney Int. 2020;97(1):202-12.
14. Garcia-Ropero A, Badimon JJ, Santos-Gallego CG. The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments. Expert Opin Drug Metab Toxicol. 2018;14(12):1287-302.
15. Scheen AJ. Pharmacokinetic/pharmacodynamic properties and clinical use of SGLT2 inhibitors in non-Asian and Asian patients with type 2 diabetes and chronic kidney disease. Clin Pharmacokinet. 2020;59(8):981-94
16. Sarashina A, Koiwai K, Seman LJ, Yamamura N, Taniguchi A, Negishi T, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in healthy Japanese subjects. Drug Metab Pharmacokinet. 2013;28(3):213-9.
17. Heise T, Jordan J, Wanner C, Heer M, Macha S, Mattheus M, et al. Acute Pharmacodynamic Effects of Empagliflozin With and Without Diuretic Agents in Patients With Type 2 Diabetes Mellitus. Clin Ther. 2016;38(10):2248-64.
18. 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(15):1413-24.
19. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2022;388(2):117-27.