Renal Effects of Empagliflozin in Patients with Type 2 Diabetes Mellitus

Running Title: Empagliflozin and kidneys in Type 2 DM

Habib Yaribeygi [1*], Mina Maleki [2], Thozhukat Sathyapalan [3], Tannaz Jamialahmadi [4,5], Amirhossein Sahebkar [6,7,8,9*]

[1] Research Center of Physiology, Semnan University of Medical Sciences, Semnan, Iran

[2] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Academic Diabetes Endocrinology and Metabolism, Hull York Medical School, University of Hull, UK of Great Britain and Northern Ireland, Hull, UK

[4] Department of Food Science and Technology, Quchan Branch, Islamic Azad University, Quchan, Iran

[5] Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[6] Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[7] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[8] School of Medicine, The University of Western Australia, Perth, Australia

[9] Department of Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

*** Corresponding Authors**: amir_saheb2000@yahoo.com; yaribeygih@yandex.com, Thozhukat.Sathyapalan@hyms.ac.uk

Abstract

Type 2 diabetes mellitus (T2DM) is one of the main causes of mortality and morbidity worldwide. It leads to various long-term such as diabetic nephropathy. Diabetes induced renal insufficiency is the leading cause of renal failure in patients with chronic kidney diseases undergoing hemodialysis. Hence preventing the development and progression of diabetic nephropathy is one of the main goals in the management of patients with type 2 diabetes. Sodium-glucose cotransporter 2 inhibitor such as is a potent anti-hyperglycemic agent. In addition, it has been shown to have some pharmacologic potential to provide renoprotective effects in patients with T2DM. In this current study, we review the available data on the potential renoprotective effects of this drug from a mechanistic and molecular viewpoint.

Keywords: Type 2 diabetes mellitus, empagliflozin, sodium-glucose cotransporter 2 inhibitor, chronic kidney disease, diabetic nephropathy.

Introduction

Diabetes mellitus (DM) is the most prevalent metabolic disorder with an increasing trend Worldwide (1). This chronic disorder has significant negative impacts on most physiologic organs and is considered the leading cause of many life-threatening complications including chronic kidney disease (CKD) (2). Various pathological pathways stimulated by chronic hyperglycemia in diabetes exert negative effects on various components of the kidneys such as podocyte, glomerulus, basement membrane and endothelial cells resulting in impaired renal function (3). Diabetes-induced CKD or diabetic nephropathy (DN) is the principal reason for renal failure in patients with end-stage renal disease (ESRD)[1] undergoing dialysis (4). Therefore, any improvement in renal efficiency in the diabetic milieu could simply translate to an increase in patients survival and improved quality of life (4).

There are several classes of anti-diabetic medications that are used primarily to normalize the level of serum glucose in patients with type 2 diabetes. But if they could provide further pharmacologic effects beyond their anti-hyperglycemic effects, they provide dual beneficial effects for patients with type 2 diabetes. Empagliflozin belongs to one of the relatively newer antidiabetes medications known as sodium-glucose co-transporter-2 inhibitors (SGLT2i) which are used alone or as adjunctive therapy to lower the serum glucose level in patients with type 2 diabetes (5). This antidiabetes medication has potent glucose-lowering effects through glucose excretion and thereby, can reduce the glycaemia near to the physiologic range. Moreover, recent studies were suggested that it has some cellular effects enabling it to maintain renal function and efficiency (6, 7). It has been proposed that empagliflozin has significant modulatory impacts on the renal system in the diabetic milieu (6, 7). In the current review, we present the updated knowledge about renal effects of empagliflozin in patients with type 2 DM.

Classification of Diabetes Mellitus

The common forms of diabetes mellitus (DM) are type 1 diabetes; type 2 diabetes and gestational diabetes (8). Type 1 DM (T1DM) or so-called Insulin-dependent diabetes mellitus (IDDM) is the lower circulatory insulin due to beta cells dysfunction (8). Type 2 DM (T2DM) is mainly linked to insulin resistance in peripheral tissues such as adipocytes and myocytes (8). Gestational diabetes is another type of DM which is developed in pregnant women possibly due to hormonal changes (9). There are also other forms of DM such as LADA (latent autoimmune diabetes in adults), maturity-onset diabetes of the young (MODY), secondary diabetes to different conditions such as pancreatitis and secondary diabetes to some drugs e.g. corticosteroids (10, 11). Among all types, T2DM is the most prevalent form (around 90%) of diabetes (8).

Renal Function in Physiologic and Diabetic Milieus

The kidney is an important organ with vital activities such as electrolytes and water balance as well as metabolic and homeostatic functions (12). It is involved in many physiologic functions such as hematopoiesis (through erythropoietin), blood pressure control (renin secretion), osmolality regulation and excess water and by-products excretion as urine (12). The

[1] End stage renal disorder

diabetic milieu makes many challenges for the kidneys (3). It can stimulate many pathophysiologic pathways which are inducible in chronic hyperglycemia such as polyol and hexosamine pathways, inflammatory responses, PKCs[2] activity, growth factors (e.g. TGF-β[3]) and matrix proteins (e.g. MMPs[4]) and adhesion molecules (e.g. ICAM[5] and VCAM[6]) up-regulation, apoptotic processes, RAS[7] hyperactivity, fibrotic events and oxidative pathways (e.g. lipid peroxidation) (13-18). Also, diabetes induces hemodynamic changes and intraglomerular hypertension which are directly linked to renal injury (19). Although chronic kidney disease (CKD) has multifactorial-complicated pathophysiology, its exact underlying cause is still unclear (3, 20, 21).

In kidneys, un-controlled DM is commonly followed by cellular damages through induction of aforementioned pathogen pathways (3). Various types of renal cells such as podocytes, glomerular cells, basement membrane and endothelial cells are very susceptible to higher levels of injurious biomolecules such as free radical species and inflammatory cytokines as well as hemodynamic variations which frequently exist in diabetic milieu (22). These injuries lead to renal insufficiency which is primarily detected by the presence of microalbuminuria and increased creatinine in the early stages (22). Damage to the basement membrane abolishes its intrinsic negative charge and allow proteins to pass the filtration barrier and are released into the urine (22). Also, podocyte insufficiency for different reasons such as apoptotic events and destroying cell-junction proteins e.g. nephrin, podocalyxin, and P-cadherin interfere with glomerular filtration balance and induce protein excretion (23). In advanced CKD, GFR[8] reduces (22) and failed kidneys will be unable to perform vital physiologic functions and thereby, patients will require renal replacement therapies such as dialysis and renal transplant (22).

Empagliflozin

Sodium-glucose co-transporters (SGLT) are two forms of active cotransporters (type 1 and 2) that are responsible for the co-transportation of sodium and glucose in the kidney and small intestine (24, 25). While SGLT1s are mainly located in the small intestine, SGLT2s is expressed principally in renal proximal tubules (S1 and S2 segments) and reabsorb the urinary filtrated glucose and thereby, leading to reduced glucose excretion (26). SGLT2 inhibitors (SGLT2i) are a class of antidiabetes medications that inhibit these active careers(27) . They reduce serum glucose levels by inducing urinary glucose excretion (fig 1) (28). Since these drugs work completely independent of insulin and are just likely related to the level of glucose in serum, have a lower risk of hypoglycemia (29). Also, they can provide more metabolic effects such as gluconeogenesis inhibition, improvement in peripheral insulin sensitivity, and increasing postprandial insulin and glucagon release (30-33). However, they may exert some side effects such as dehydration, dizziness, hypotension, urinary tract infections, and fainting

[2] protein kinase C
[3] Transforming growth factor beta
[4] Matrix metalloproteinases
[5] Intercellular Adhesion Molecule 1
[6] vascular cell adhesion molecule
[7] renin-angiotensin system
[8] Glomerular filtration rate

(34). Empagliflozin, canagliflozin, and dapagliflozin are some of the examples of SGLT2 inhibitors (34).

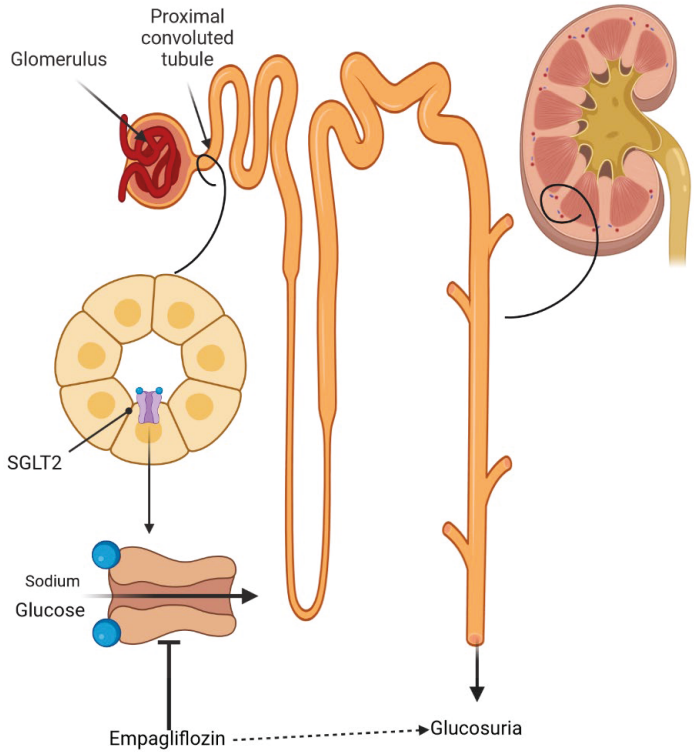

Fig 1: Schematic picture of empagliflozin-dependent glucose-lowering effects

Empagliflozin was approved by FDA in 2014 as an adjunct to diet and exercise to improve glycemic control in patients with T2DM (35). It has the highest selectivity for SGLT2 over SGLT1 at about 2500-fold (compared to dapagliflozin (about 1200 fold) and canagliflozin (about 250 fold)) (36). Empagliflozin is an orally active tablet with a chemical structure of $C_{23}H_{27}ClO_7$, a molecular weight of 450.91 g/mol and a long half-life of about 12.4 h which permits once-daily dosing (37). It inhibits glucose reabsorption of up to 40% at lower doses and 40-60% at higher doses (37). It has a population-based volume of distribution of approximately 73.8 L at the steady-state (37). Empagliflozin is mainly metabolized by a series of metabolizing enzymes known as UDP glucuronosyltransferase (UGT1A3, UGT2B7, UGT1A8, and UGT1A9) and then, excreted in urine (as about 54%) and feces (as about 46%) (36). It was the 146th most commonly prescribed medication in the US in 2019 (38).

Renal Effects of Empagliflozin in T2DM

Beyond the glycosuria and diuretic effects, empagliflozin has pharmacologic abilities which enable it to deal with renal functions in patients with type 2 diabetes (table 1) (39). It can improve renal function through both glycaemia control dependent and independent mechanisms as discussed in the following sections (26).

1. **Proteinuria**

Proteinuria which refers to the protein (chiefly albumin) excretion in urine is the main hallmark of renal insufficiency that occurs in most patients with diabetes with uncontrolled chronic hyperglycemia (40, 41). In this pathologic state, plasma proteins pass from the glomerular filtration barrier which consists of three layers as fenestrated endothelial cells, basement membrane and podocytes. The bulk filtration towards the luminal space and urine due to the destroyed or diminished negative charges in this barrier physiologically inhibits protein excretion (41, 42). The level of protein in urine is considered an insufficiency index. Hence, CKD or diabetic nephropathy (DN) are classified into different degrees based on the levels of proteinuria (43). While normal kidneys excrete ≤30 mg protein per day in a physiologic manner, insufficient kidneys with minor or overt proteinuria excrete more amount of protein (30-300 mg/day) and even ≥1000 mg/day in the end stages of CKD (43).

We now have strong evidence implying empagliflozin reduces proteinuria in the type 2 diabetes milieu (44, 45). Dinkov et al in 2020 demonstrated that empagliflozin reduces albuminuria in patients with T2DM (44). They found that 3 months of empagliflozin therapy ameliorates albuminuria as well as albumin to creatinine ratio (ACR), an index of renal sufficiency, in patients with T2DM (44). Wanner and colleagues in 2019 in EMPA-REG study on 7020 participants found that empagliflozin reduces proteinuria in patients with T2DM (46). A post hoc analysis of the EMPA-REG OUTCOME trial in 2020 showed that empagliflozin therapy is related to lower proteinuria and reduced ACR as well as decreased risk of renal injuries in patients with T2DM (47). Also, similar findings were reported by Cherney and coworkers in 2017 in which empagliflozin exerted short-term and long-term benefits on albuminuria irrespective of its baseline levels in patients with T2DM (48). They reported a 7%, 25% and 32% decrease in ACR after 12 weeks of empagliflozin therapy in normal, micro and macro albuminuric kidneys, respectively, which were maintained after about three years of follow-up (48). These clinical findings support the idea that empagliflozin improves proteinuria status in diabetic kidneys (7, 49). Although it was suggested that this effect may be independent of the metabolic or haemodynamic outcomes of empagliflozin (50), but other reports indicate that it reduces proteinuria via several pathways including a reduction in systemic blood pressure (51), decrease in glomerular hyperfiltration (52), modulating plasma volume (53), lowering the tubulointerstitial fibrosis (51) and reducing the serum level of uric acid (fig 2) (54).

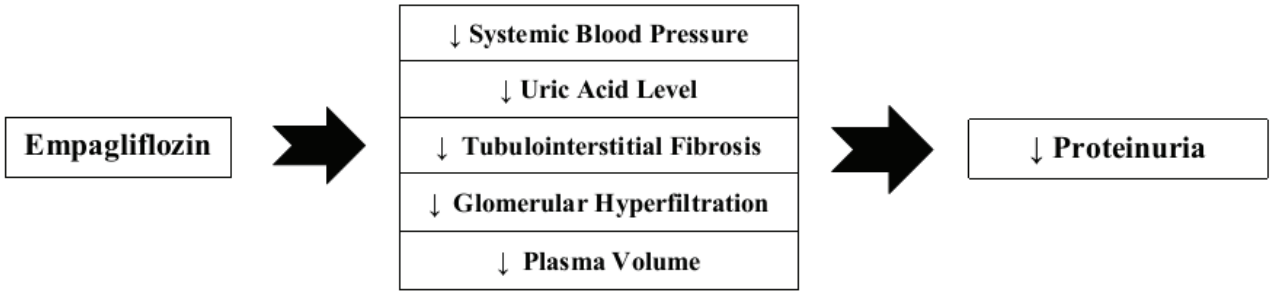

Fig 2; empagliflozin reduces proteinuria via at least five mechanisms

2. Glomerular Hyperfiltration

Glomerular hyperfiltration is a condition in which estimated eGFR increases supraphysiological to >60 mL/min due to different causes such as afferent arteriolar vasodilation, efferent arteriolar vasoconstriction, glomerular hypertrophy, or during pregnancy (55, 56). While it may occur physiologically in response to nephron loss or after a high-protein meal, it is also closely related to many forms of renal disorders as well as DN (55, 56). Glomerular hyperfiltration is seen in about 6%–73% of patients with T2DM and the long-term it can lead to intraglomerular hypertension, glomerulosclerosis and destroy and death of glomeruli, which in turn results in higher filtration rates in the remaining glomeruli and cause loss of more glomeruli and subsequent renal insufficiency and ESRD[9] (57, 58). Also, it is associated with more cardiovascular comorbidities and higher mortality (58). Thus, prevention and control of intraglomerular hypertension are one of the main goals in the management of diabetic kidney disease.

SGLT2i modulates eGFR and could potentially normalize it (59). The inhibition or knockout of SGT2, induces natriuresis and sodium delivery to macula densa, which in turn induces tubuloglomerular feedback, and afferent arteriolar vasoconstriction and thereby reduces hyperglycemia dependent hyperfiltration in diabetic kidneys (60, 61). SGLT2 inhibition reduces glomerular capillary pressure and readjusts hydrostatic balance between afferent and efferent arterioles of the glomeruli (62). We have clinical evidence confirming that empagliflozin has this ability. Cherney and colleagues in 2017 reported that both short-term and long term empagliflozin therapy ameliorates glomerular hyperfiltration in patients with T2DM (48). Findings from the EMPA-REG OUTCOME trial demonstrates that hemodynamic effects of empagliflozin reduce intraglomerular pressure as well as hyperfiltration in patients with T2DM compared to placebo (63). They suggested that eGFR modulating impacts of empagliflozin may be involved in long-term renoprotective effects of it in the diabetic milieu (63). Similar findings of Asian participants of the EMPA-REG OUTCOME trial were shown that empagliflozin therapy is associated with eGFR decline in patients with T2DM M patients (7). Also, Mayer and colleagues in 2019 reported that empagliflozin slowed kidney injuries via a reduction in intraglomerular pressure and eGFR in patients with T2DM who participated in the EMPA-REG OUTCOME trial (64). This evidence confirms that empagliflozin could modulate intraglomerular pressure by its hemodynamic effects to normalize eGFR and prevent further renal injuries in patients with T2DM.

3. Hematopoiesis and Renal Hypoxia

In addition to fluid and electrolyte handling, kidneys are also involved in other tasks as well as hematopoiesis by synthesizing and secreting the erythropoietin hormone from their interstitial fibroblasts (65). Erythropoietin is a glycoprotein hormone that is constantly produced and released by renal fibroblasts and then, stimulates the hematopoiesis process in the bone marrow through various pathways (65). But in CKD, the ability of kidneys to secrete erythropoietin is reduced. Hence, many patients with CKD have different degrees of anemia and anemia dependent renal hypoxia (66). Also, the T2DM milieu is commonly associated with hypoxia in kidneys which further decreases renal sufficiency (67).

Empagliflozin could improve renal hypoxia and hematopoiesis (68). It can increase hematocrit levels independent of its diuretic effects (69). Urine volume after empagliflozin therapy returns to the normal levels just within one week (69). But the hematocrit increase continues for at least two months and thereby, is not related to the volume depletion and diuretic effects of SGLT2 inhibition (69). Recent evidence is demonstrated that empagliflozin induces erythropoietin secretion in the diabetic milieu (70, 71). An analysis of the EMPA-HEART[10] trial study demonstrates that empagliflozin therapy is linked to increased erythropoietin and hematocrit levels as well as improved tissue oxygen delivery in patients with T2DM (71). Also, Thiele and coworkers recently in a randomized controlled trial found that three months of empagliflozin therapy increases erythropoiesis and hematocrit concentration in patients with T2DM (70). They reported that empagliflozin directly increases erythropoietin synthesis which in turn improve systemic oxygen delivery and renal hypoxia in these patients (70, 72). Empagliflozin could increase hematopoiesis in patients with severe anemia (68). The included pathways are not well understood, but they may induce erythropoiesis through reduction of metabolic stress around the proximal tubules or rectification of sympathetic hyperactivity (69).

In addition, empagliflozin may improve renal hypoxia by increasing ketone bodies (73, 74). Increased urinary glucose excretion develops glucose deficiency and the need for alternative substrates which in turn, induces lipolysis, fatty acid oxidation, and ketone body formation (73, 74). These active metabolic by-products are more energy-efficient fuels compared to glucose and produce more energy in renal tubular cells, and thereby, renal oxygen consumption is diminished in kidney tissues (73, 74). Patients receiving ketone bodies by infusions experience increased circulating erythropoietin levels and bone marrow activity (75). So, higher levels of circulating ketone bodies may be another link between empagliflozin therapy and improved renal hypoxia (75).

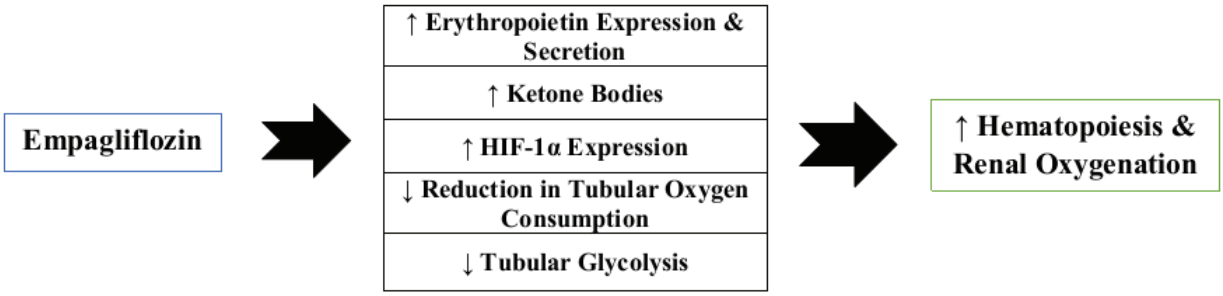

Fig 3; Mechanisms by which empagliflozin could improve hematopoiesis and renal oxygenation (HIFs=hypoxia-inducible factors). Details are explained in the text.

In animal experiments, empagliflozin could induce hematopoiesis and relieve renal hypoxia via hypoxia-inducible factors (HIFs); which are key proteins involved in response to hypoxia in various tissues (67, 76). Empagliflozin can reduce renal hypoxia via HIF-1α up-regulation (76), reduction in its expression (77), or modulating HIF-1α/ HIF-2α balance (67). Also, inhibition of SGLT2 cotransporters, which are active proteins dependent on Na-K ATPase activity, further reduces tubular oxygen consumption (78, 79). Moreover, the prevention of aberrant tubular glycolysis can be another link between empagliflozin and tubular

[10] Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes

oxygenation (80). However, further studies are still required to clearly understand potential mechanisms (fig 3).

4. Renal Tissues Injury

Irreversible injuries in different renal elements such as tubulointerstitial cells, glomerulus, podocyte, tubular cells and mesenchymal tissues are the main hallmarks of CKDs and DN progression (81). These cellular injuries; which mostly developed thru injurious pathways as apoptosis, ferroptosis, uncontrolled autophagy, and fibrotic processes; are the main underlying causes of cellular death, loss of efficient nephrons and reduced renal sufficiency in diabetic kidneys (81, 82). Therefore, reducing renal tissue injury is one of the main targets in the management of patients with CKD.

More recent evidence suggests that empagliflozin has pharmacologic abilities to modulate these injurious pathways and restore normal tubular histology which translates to improved renal efficiency (fig 4) (83). Empagliflozin can suppress the apoptotic events in kidneys via different pathways such as caspase-3 signaling (84), TXNIP[11] and SIRT-1[12] pathways (85), AMPK[13]/SP1[14]/PGAM5[15] pathway (86), or HMGB1[16]-TLR4[17] receptor axis (87). Also, it has shown anti-fibrotic properties independent of glucose-lowering effects in kidneys through several molecular mechanisms such as HIF-1α, PKM2[18] dimer formation, P-STAT3[19] (86), reduction in inflammatory events (88) or STAT1/TGF-β[20] signaling (89). It can also suppress ferroptosis (83), which is an iron-dependent form of programmed cell death characterized by the accumulation of lipid peroxides (90). It has been shown recently that ferroptosis is involved in tubular and kidney damages in the diabetic milieu (91). This inhibitory effect of empagliflozin may be another link between it and reduced renal injuries in CKD (83). However, it needs more experiments to substantiate yet. Empagliflozin could also modulate autophagic processes in kidneys (92, 93) via various molecular pathways such as caspase-3, LAMP-1 (a lysosomal protein) or Beclin-1 dependents pathways or normalizing the AMP-to-ATP ratio and reducing the mitochondrial fragmentation in renal tubular cells (92, 94). Moreover, a recent study found that ketone bodies, which increases during empagliflozin therapy, inhibit the mechanistic target of rapamycin complex 1, a mediator of kidney damage, and so reduce renal injuries in diabetic mice [46].

[11] Thioredoxin-interacting protein
[12] Sirtuin 1
[13] AMP-activated protein kinase
[14] specificityprotein1
[15] Phosphoglycerate mutase family member 5
[16] high mobility group box-1
[17] toll-like receptor-4
[18] pyruvate kinase M2
[19] phosphorylated STAT3
[20] Transforming growth factor beta

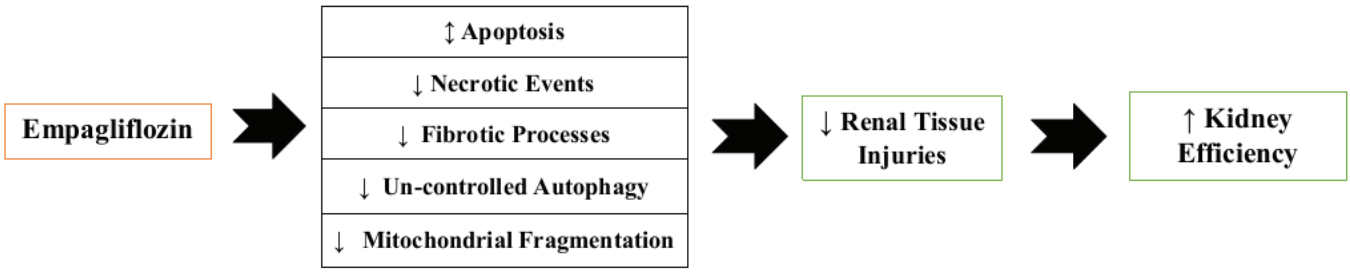

Fig 4; Empagliflozin improves kidney efficiency by lowering the tissue damages through damping injurious pathways in kidneys

Taken together, we suggest that empagliflozin can provide beneficial renal impacts demonstrated in the EMPA-REG OUTCOME trial at least partly via modulating injurious processes, restoring physiologic histology, and improving renal morphology and efficiency in T2DM (63).

5. Uric acid level

Hyperuricemia or increased serum levels of uric acid is an important sign of renal insufficiency which is one of the main predictors for the onset of CKD in most patients with T2DM CKD (95, 96). Also, hyperuricemia is itself a risk factor for further renal injuries by inducing pathophysiologic pathways involved in CKD (97). Uric acid acts as an independent risk factor for lowering eGFR and new-onset CKD and so, epidemiologic evidence demonstrates a negative relationship between uric acid level and renal sufficiency (98). Thus, prevent of hyperuricemia or normalizing uric acid levels may decrease the incidence of CKD especially in patients with T2DM (97, 99, 100).

An extensive systematic review and meta-analysis of clinical studies including 5781 patients in 12 randomized controlled trials with a follow-up of 28 ± 22 weeks reported that empagliflozin significantly reduces uric acid levels in patients with T2DM (101). Similarly, another systematic review and meta-analysis in 2019 found that empagliflozin decreases uric acid level compared with placebo in 31 studies including 13,650 patients with T2DM (102). Also, a recent post hoc analysis of the EMPA-REG OUTCOME trial demonstrated that empagliflozin reduces uric acid levels in patients with T2DM (103). Moreover, a recent clinical study on T2DM patients demonstrated that only four weeks of empagliflozin therapy make a significant reduction in serum uric acid levels (104). It may also provide beneficial effects for patients with gout, a disorder with increased levels of uric acid (105). The exact mechanism for this renal effect of empagliflozin is unclear. It could be through upregulating the uric acid transporter of ABCG2 in the ileum and kidney, or via AMPK/AKT/CREB signaling pathway increasing uric acid excretion (106). Also, it may be via Glut-9[21] activity which are the glucose-uric acid transporters located in the proximal tubule or urate transporter of URAT1, which is responsible for uric acid transport in the tubular system (107, 108). SGLT2 inhibition increases Glut-9 and urate transporter of URAT1 expression in animals (109). Increased levels of glucose in the proximal tubule stimulate Glut-9 dependent uric acid excretion and inhibit its reabsorption which both reduces uric acid level in plasma (108, 110).

[21] Glucose transporter-9

6. Other Effects

Empagliflozin may provide more beneficial effects in improving renal damage in patients with T2DM. For example, its well-known diuretic effect eliminates extra body fluids and re-adjust body fluid homeostasis and balance between intracellular and extracellular fluids which in turn provides cardio-renal benefits (111, 112). Also, it can induce osmotic diuresis by renal handling of sodium and glucose in patients with diabetes having cardiac failure which provide further cardio-protective benefits for these patients (113). Moreover, empagliflozin can suppress some pathophysiologic pathways involved in CKD development such as oxidative stress and inflammation (87). These pathogenic pathways have significant roles in histologic and cellular damages of CKD and so, agents attenuating them may prevent CKD development and improve renal efficiency (20, 114).

Kidney Effects of Empag. in T2DM	Details	References
Proteinuria	Ameliorates proteinuria via several possible pathways	(44, 45)
Glomerular Hyperfiltration	Improves glomerular hyperfiltration via hemodynamic interventions	(7, 48, 63, 64)
Hematopoiesis and Oxygenation to Renal Elements	Induce erythropoietin secretion and hematopoiesis and increases tissue oxygenation in kidneys	(70-72)
Uric Acid Level	Modulates serum uric acid level thru different suggested mechanisms	(101-110)
Renal Tissues Survival and Efficiency	Attenuates tissue injuries by suppressing pathophysiologic pathways	(83-93)

Table 1: Renal effects of empagliflozin in type 2 diabetes mellitus

Conclusion

Empagliflozin has pharmacologic effects which enable it to deal with renal functions in patients with T2DM (fig 5). It can induce urinary glucose excretion which is commonly followed by fat burning and more ketone body generation as the metabolic substrate that in turn provide renal benefits. Also, it reduces glomerular capillary hypertension and hyperfiltration via higher glycosuria and more water excretion, thus decreasing the physical stress on the glomerular filtration barrier, albuminuria, and the oxygen demand for renal tubular reabsorption which in turn improves cortical oxygenation and functions. It also improves systemic hypoxia and induces erythropoiesis, which stimulates hematopoiesis and improves oxygen delivery. Empagliflozin reduces diabetes-induced cellular injuries via damping pathophysiologic pathways as fibrosis, uncontrolled autophagy and apoptosis, and necrotic events. These events together with lesser tubular glucotoxicity and reduced oxidative stress (due to glucose excretion in urine) and inflammatory responses, preserve tubular function and improve eGFR in the long term in patients with T2DM.

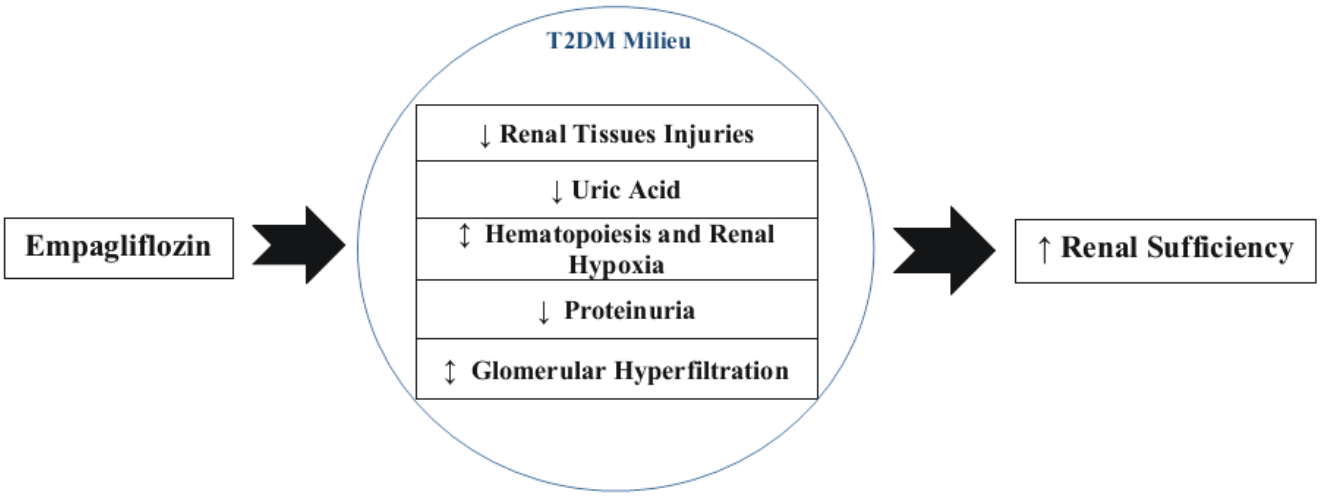

Figure 5; Empagliflozin improves renal sufficiency in T2DM via at least 5 pathways as reduction of renal tissue injuries, lowering the uric acid levels, modulating hematopoiesis and oxygenation, reduction in proteinuria and modulating glomerular filtration

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Conflict of Interests

The authors have no conflict of interest to declare in this study.

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