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Role of Empagliflozin and Linagliptin Combination in Diabetic Kidney Disease

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Abstract: ***Chronic kidney disease (CKD) isa common comorbidity in type 2 diabetes mellitus (T2DM). It has been documented that CKD is associated with an increased risk of CVD and this further increases the mortality rate in T2DM by 2-3-fold. The current need is of a comprehensive approach to T2DM with concomitant renal disease. Scientific literature recommends early use of combination therapy in T2DM patients with a high risk of renal impairment. Considering the recent guidelines and published data on renal benefits with empagliflozin and linagliptin, combination therapy with these two agents may be a promising option in preventing and delaying the progression of renal impairment in T2DM patients. This review highlights the clinical evidence and the possible mechanisms for renal benefits with empagliflozin and linagliptin.***

Keywords: T2DM, CKD, combination therapy, Empagliflozin, Linagliptin

1. Introduction

Type 2 diabetes mellitus (T2DM) has become a global health concern, with its prevalence ranging from 6.9 to 10.2% in developed countries and more than 7% in the developing countries. [1] It is anticipated that the prevalence of diabetes will rise up to 124 million in India, and more than 640 million globally by 2040. [1] Macro-vascular and micro-vascular complications are the chief reasons for mortality and morbidity associated with T2DM. One such microvascular complication is diabetic nephropathy or chronic kidney disease (CKD) associated with diabetes which is related to different stages of renal impairment. It is characterized by microalbuminuria, which progresses into macro albuminuria, leading to blatant nephropathy. [1], [2] There is a significant deterioration of the glomerular filtration rate (GFR). If this condition is not managed medically at the earliest, nephropathy advances into CKD. [1]

CKD remains an inadequatelytackled complication of T2DM, affecting almost 2 of every 5 patients. Concurrent occurrence of CKD and T2DM characterizes a subset of patients, who are at noticeably higher risk of mortality. Furthermore, CKD associated with T2DMis significant risk factors for CVD. [3] Documented data suggests that presence of CKD has been linkedto nearly 1.5-fold higher risk of major vascular events, stroke, and CHD, eventually a 2-fold increased risk of mortality. [2], [3]According to an Indian database, most physicians agreed that 20-40% of their patients of T2D had CKD, the point-prevalence of CKD was found to be 64.7%. Approximately 43% of the patients with T2DM demonstrated ‘early CKD’, diagnosed by either moderate-grade albuminuria or eGFR ranging between 89-60 mL/min/1.73m^2. [3]To sum up, almost one-third of the patients revealedco-existence of CVD, and around half of the patients had CKD, in an out-patient setting in Indian scenario.

Figure 1 depicts different pathways and networks involved in the initiation and progression of diabetic kidney disease. Significant changes in the metabolic pathways that alter renal hemodynamics and stimulate inflammation and fibrosis in early stages ofT2DMconsists of hyperaminoacidemia, which leads to glomerular hyperfiltration and hyperperfusion, and hyperglycemia concomitantly, increased local production of angiotensin II at the efferent arteriole causes vasoconstriction. The net result is raised intraglomerular pressure along with glomerular hyperfiltration. [4], [5], [6]

2. Current Guidelines for Diabetic Kidney Disease

According to the recent consensus by European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA), there was a paradigm shift in management of T2DM where patient factors were of prime importance. It suggested that if chronic kidney disease predominates and if the eGFR is favorable, then sodium glucose co-transporters (SGLT2-I) are the class of choice owing to the documented renal benefits followed by glucagon like receptor analog (GLP1-RA). If the HbA1c is above target, then addition of dipeptidyl peptidase-4 inhibitor (DPP4-I) is recommended as one of the second line drug. [7] These recommendations are further endorsed by recently published ADA 2019 guidelines. [8]

Need to Fill the Treatment Gap:

The present-day need is to find a therapeutic measure which is not only fast acting but also provides sustained and durable beneficial effects on hyperglycemia thereby suspending the onset and progression of CKD. [9], [10], [11] Current literature suggests the use of fixed dose combinations with agents demonstrating complementary mechanisms of action to reduce complications. One of thecombinations is empagliflozin and linagliptin. [12] Linagliptin enhances thesecretion of postprandial insulin along with decreasedsecretion of glucagon. [12], [13]This action is glucose-dependent, thereby reducing the possibility of hypoglycemia. [12]Furthermore, current literature suggests that it is weight neutral. [12]

On the other hand, empagliflozin exerts a non-insulin dependentaction on blood glucose by inhibiting renal glucose reabsorption thereby leading to glucosuria. However, plasma glucagon levels are increased following treatment with empagliflozin, which subsequently is associated with an increasedhepatic glucose production. [12]This further rationalizes the addition of linagliptin, which inhibits glucagon secretion by inhibiting alpha cell activity in pancreas. This may have the potential to reducehepatic glucose production thus,enhancing the glucose-lowering ability of empagliflozin. [12]

Renal Benefits with Empagliflozin

A relative risk reduction of 46% in the composite of renal outcomes was noted in the EMPA-REG renal outcome trial. [14]The results of this study confirmed that in patients with T2DM and at high risk of developingCVD, empagliflozin benefitted by delaying the progression of kidney disease with lower rates of clinically significant renal events as compared to placebo. [14]

Figure 2 denotes the postulated changes in renal fuel metabolism before and after treatment with empagliflozin. It is hypothesized that T2DM is associated with increased renal oxygen consumption secondary to increased Na+ reabsorption through the proximal convoluted tubule. The researchers further thought that the diabetic kidney needs higher renal blood flow to meet the higher oxygen demand.[15]The theory of tubular hypothesis suggests that the GFR increase in the diabetic kidney is primarily due to hyper-reabsorption in the proximal tubularwhich is a result ofaugmented SGLT activity and tubular growth. Consequently, empagliflozin administrationmay lower renal oxygen consumption in T2DM by lowering GFR (and the tubular Na+ load) and by directly inhibiting SGLT2-facilitated Na reabsorption in the early proximal convoluted tubule. [15], [16] Thus, it can be concluded that empagliflozin treatment maydecrease renal oxygen consumption thereby reducing hypoxic stress on the diabetic kidney.Based on the assumption that CKD is linked with undesirable glomerular hyperfiltration in the remainder of intactnephrons; and enhanced glucose delivery to the early proximal tubule, SGLT2 inhibition by empagliflozinmay be expected to moderately lower tubular Na+ load and GFR in patients with CKD associated with T2DM. [15]

Another possible mechanism for impressive renal benefits with empagliflozin could be enhanced tubulo-glomerular feedback mechanism. An increase in delivery of sodium chloride to the macula densa as a result ofinhibition of sodium reabsorption with empagliflozin may activate tubule-glomerular feedback and this might lead to afferent renal arteriolar vasoconstriction, thereby a reduction in glomerular hyperfiltration and subsequent normalization of intraglomerular pressure. [17]This fact is further substantiated by the findings from empagliflozin trials, where it was noted that the drug demonstrated a statistically significant ($P \leq 0.01$) reduction in the urinary albumin-to-creatinine ratio (UACR). [17] Furthermore, the fact that empagliflozin mediated SGLT2 inhibition is also associated with minor decrease in eGFR over the initial 3-4 weeks' treatment proposes that reduction in intraglomerular pressure may contribute to the UACR-lowering effects. Additionally, the promising effects of empagliflozin on systemic and renal neurohormonal pathways, arterial stiffness, vascular resistance and serum uric acid levels may be responsible fora significant reduction in kidney disease progression in patients with T2DM. [17], [18], [19]

Renal Benefits with Linagliptin

The results from the exploratory analysis in the recently published CARMELINA trial support the hypothesis that linagliptin may reduce the progression of albuminuria as compared with placebo. [20]Another study demonstrated that linagliptin administered in addition to RAAS inhibitor therapy led to a clinically significant reduction in albuminuria in T2DM patients with associated renal dysfunction. [21] Current scientific literature suggests that linagliptin is well tolerated in mild, moderate and severe renal disease and also in those undergoing dialysis. [22], [23], [24], [25]The available evidence suggests that the albuminuria lowering effect of linagliptin may be due to prevention of damage of podocytes and myofibroblast transformation; besides improvement in renal inflammatory responses due to increased glucagon-like peptide-1 (GLP-1)activity or inhibition of tumor necrosis factor-αactivity. [21]

Renal Benefits with Combination:

Current evidence suggests that both empagliflozin and linagliptin have favorable renal safety data. Moreover, it has been studied that the treatment with combination of empagliflozin and linagliptin in drug naïve patients, [26] in metformin failure cases [27] and in patients where intensifying glycemic control is needed which cannot be achieved with dual therapy of metformin and empagliflozin or linagliptin only [28], [29] is efficacious and showed clinically significant reductions in HbA1c and FPG. Additionally, treatment with this combination further demonstrated significant BP and weight reduction which are known CKD risk factors. Also, the glycemic control with this combination was persistent for a period of 52 weeks thereby reducing the risk of glycemic variability. This in turn further reduces the chance of diabetes associated renal impairment.

To summarize, fixed dose combination of empagliflozin and linagliptin has animpressive potential to provide benefits beyond lowering blood glucose, such as improved and restored fuel metabolism in a diabetic kidney, BP and weight reduction, natriuretic and diuretic effects and prevention of progression of diabetic nephropathy. Hence, treatment with this combination may improve the renal status in a patient with diabetes. However, further well planned clinical trials are needed in this accord.

3. Conflict of Interest

The authors are employees of Lupin Ltd.

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inadequately controlled with linagliptin and metformin: a 24-week randomized, double-blind, parallel-group trial. Diabetes Care. 2017 Feb; 40(2): 201-9.

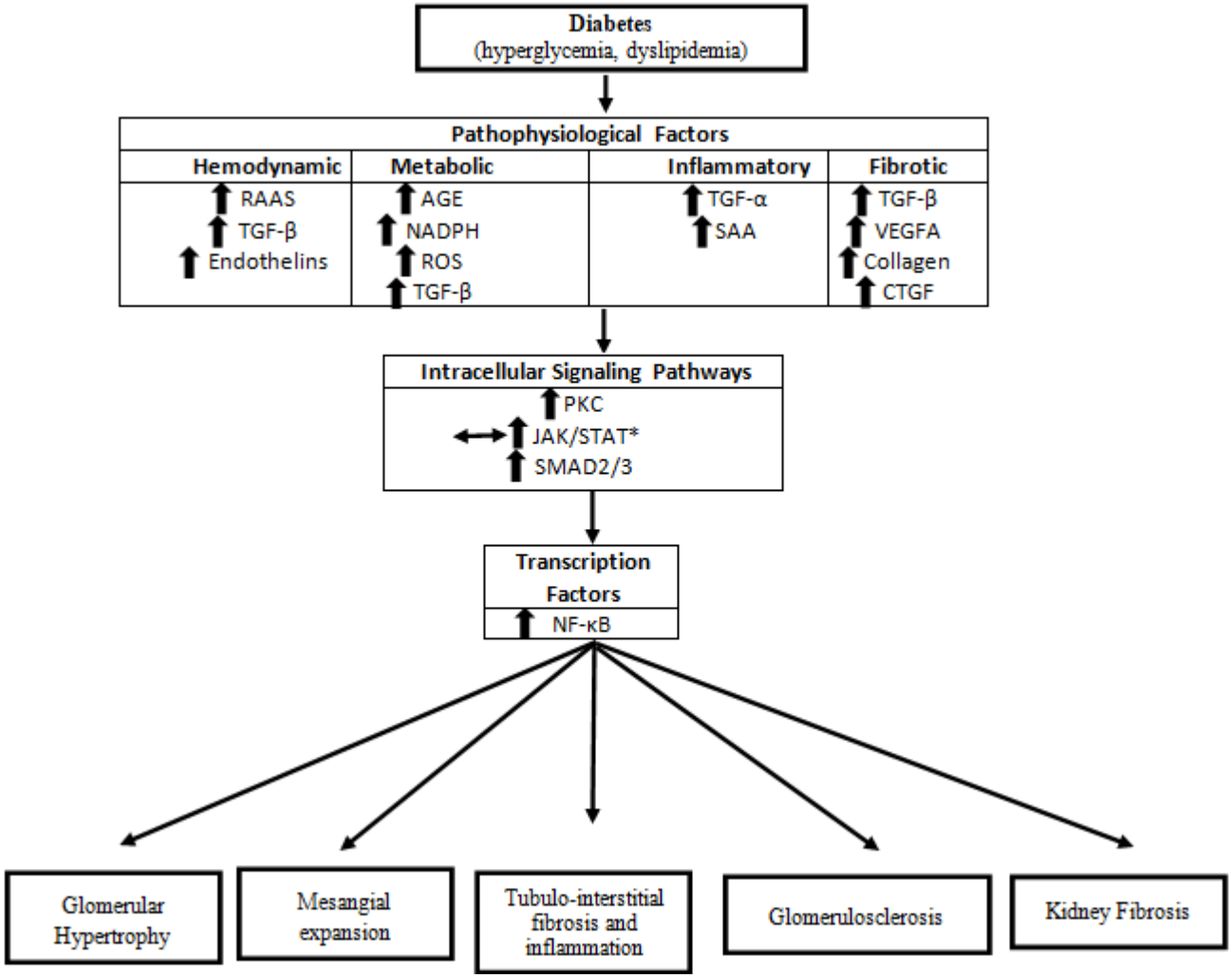
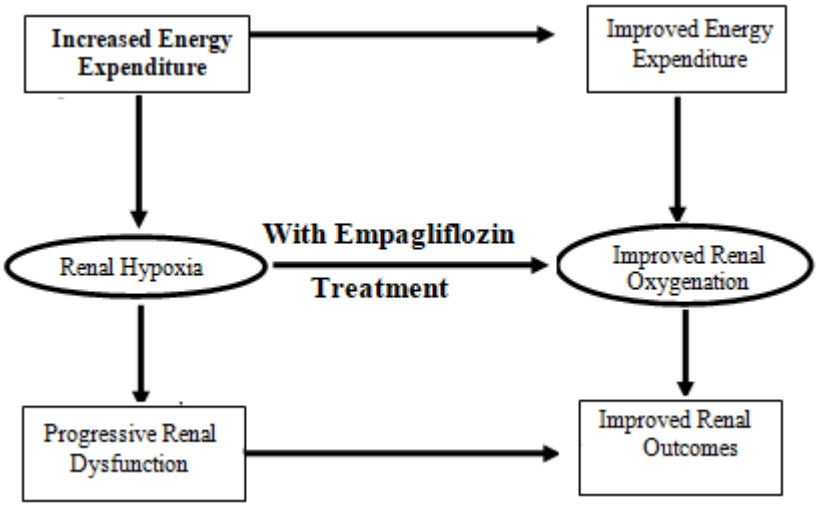


Figure 1: Different Pathways involved in Initiation and Progression of Diabetic Kidney Disease. [4]

AGE, advanced glycation end product; CTGF, connective tissue growth factor; JAKSTAT, Janus kinase/signal transducer and activator of transcription; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SAA, serum amyloid A; VEGF-A,vascular endothelial growth factor A. *JAK/STAT signaling can be unchanged (↔) or upregulated (↑) in early and later stages of diabetes, respectively.

T2DM Kidney	Preferred Substrate In	T2DM Kidney with Empagliflozin Therapy
Lactate/FFA Glutamate	S1/S2 Segments	↓ Lactate/FFA ↔ Glutamate
Lactate/FFA Glutamate/Glucose BHOB	S3 Segment	↓ Lactate/FFA ↓ Glutamate/Glucose ↑ **BHOB**
Lactate/FFA Glucose BHOB	Distal Collecting Tubules/Cortical Collecting Tubules	↓ Lactate/FFA ↓ Glucose ↑ **BHOB**

Figure 2: Suggested changes in renal fuel metabolism before and after empagliflozin therapy. [15]



FFA, free fatty acid; BHOB, beta-hydroxybutyrate