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Differentiating Sodium-Glucose Cotransporter 2 Inhibitors from Live Biotherapeutic Products (Probiotics) as Novel Therapeutic Intervention to Slow CKD Progression

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Abstract

Chronic kidney disease (CKD) is a global public health problem with high morbidity and mortality, from cardiovascular complications. CKD is a progressive and irreversible deterioration of kidney function with complex pathophysiological and pathogenetic pathways due to diverse etiologies and risk factors. Progression of CKD has a common complex and interrelated immunological and metabolic pathway resulting in inflammation and oxidative stress processes. This progression manifests clinically as irreversible functional and structural damage. The primary aim of therapeutic intervention in CKD management is delay progressive loss of function, and to prevent and manage complications. Recent approaches to slowing CKD progression include therapy with sodium-glucose cotransporter 2 inhibitor (SGLT2) and gut microbiome modulation with probiotics, based on beneficial clinical outcomes of metabolic, immunological, inflammatory, and hemodynamic changes associated with CKD progression. Despite comparable mechanisms of action in slowing CKD progression, these two classes of medications differ in their safety profile, treatment effect on CKD stages, and patient population group. The focus of this review is how to differentiate SGLT2 from probiotics as novel therapeutic agents targeting CKD progression from the perspective of CKD severity, patient group and safety profile. This may be a valuable guide for future strategic planning and decision making in clinical development programs of therapeutic interventions in CKD progression.

Keywords: CKD progression • SGLT2 inhibitors • Probiotics

Introduction

Chronic kidney disease (CKD) is a leading public health problem, with a USA prevalence of 15% and globally about 13%, associated with high morbidity and mortality mainly from cardiovascular complications [1]. CKD is characterized by progressive and irreversible decline of renal function measured as GFR less than 60ml/min/1.73m2 or evidence of kidney damage markers (proteinuria, abnormal urinary sediments, electrolyte abnormalities, histological and imaging abnormalities, etc.), and more than three months duration irrespective of underlying cause [2]. The NKF-KDOQI classification of CKD severity is based on GFR and albuminuria changes from diverse pathophysiological and pathogenetic pathways, etiologies and risk factors [2,3]. The major risks for CKD are hypertension and diabetes, followed by chronic glomerulonephritis, polycystic kidney disease, tubulo-interstitial disease, and obstructive uropathies. Irrespective of underlying causes, CKD is a gradual, progressive, irreversible structural nephron loss and hyperfiltration with renal tissue inflammation, sclerosis, and fibrosis. This common pathway for CKD progression consists of complex and interrelated immunological and metabolic changes leading to inflammatory and oxidative stress, manifesting as irreversible functional and structural damage [3,4]. The primary aim of CKD therapeutic intervention is to delay progressive loss of kidney function, and to prevent and manage complications.

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In the last few decades, several experimental and approved therapeutic interventions have shown clinical efficacy in retarding CKD progression, notably renin-angiotensin-aldosterone system (RAS) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonist (MRA), anti-inflammatory/fibrotic agents and proinflammatory cytokines [4-6]. The hit targets conferring renal benefits of these medication classes include reduced intraglomerular pressure and proteinuria, modulation of immune function, and inflammatory process in CKD. Based on this understanding of cellular, molecular, and complex pathophysiological mechanisms, more novel therapeutic agents are at various stages of clinical development as multi-approaches to address these pathways in CKD progression. It has been consistently demonstrated that people with CKD have altered gut flora, impacting CKD progression and complications [7]. Restoring intestinal flora balance has shown favorable and significant benefits in general health and renal outcomes [6,7]. These kidney health benefits are further illustrated in Figure 1. Recent data has shown that certain probiotic strains specifically utilize uremic toxins and, as a result, reduce cardiovascular complications. This data has confirmed the critical role gut microbiome modulation with LBP (probiotics) plays in addressing the inflammatory, immunological and metabolic disturbances in CKD progression [6,7].

The recent approval of the SGLT2 inhibitors class of drugs as an effective treatment of CKD with CVD indications has significantly changed the therapeutic approach to CKD progression. As a result, this has raised concerns among stakeholders about whether it will be a good clinical and business strategy to pursue current development of LBP class of probiotics to target CKD progression. These stakeholders' concerns may be valid, as the two therapeutic interventions compare favorably in their mechanistic explanations of slowing CKD progression and targeting the same group of patient population.

This short review article will focus on differentiating the roles of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and live biotherapeutic products (probiotics) as novel intervention therapies to slow CKD progression. A secondary focus is the utility of these differentiating factors in identifying categories of CKD patients that will clinically benefit either mutually or exclusively from the two drug classes. Finally, it will propose recommendations where probiotics may fit into CKD spectrum.

SGLT2 inhibitors therapy in CKD progression

The main goals of CKD management are early diagnosis and treatment, delaying progression, identifying and treating complications, and timely intervention of long-term renal replacement therapy [3,6]. Most CKD risks and underlying diseases are irreversible and progressive, so the central focus is on identifying novel therapies that delay progression, especially the underlying risk factors; targeted control of hypertension, hyperlipidemia, and hyperglycemia; and avoiding nephrotoxic agents. Current standard recommended interventions are ACE inhibitors/ARB in glomerular proteinuria and recently with selective non-steroidal mineralocorticoid receptor antagonist (MRA) and SGLT2 inhibitor as novel therapeutic agents, which impressively and significantly reduced the poor renal and cardiovascular outcomes in Type 2 diabetes mellitus (T2DM) and CKD [6,8].

Most significant is the intervention with the SGLT2 inhibitors class, which has led to recent recommendations as an add-on therapy for retarding CKD progression [9]. This was based on major cardiovascular outcome trials of EMPA-REG OUTCOME (Empagliflozin), CANVAS program (Canagliflozin), DECLARE-TIMI 58 (Dapagliflozin), VERTIS CV (Ertugliflozin) which demonstrated a significant reduction in both renal and CV events in T2DM and CKD [9,10]. The CREDENCE and DAPA-CKD studies designed to investigate treatment effects on CKD progression showed significant renal benefit of primary endpoints of doubling in serum creatinine or reduced 40% decline of eGFR, ESKD, or renal death [11]. These treatment effects of SGLT2 inhibitors in CKD patients were summarized in a meta-analysis of 27 studies involving 7363 patients, clearly showed significant risk reduction for renal composite outcomes (doubling of serum creatinine, renal death, ESKD), uric acid, and mean decline of eGFR [10,11]. Most of these favorable hard renal outcomes and other clinical benefits were reported chiefly in patients with early stages of CKD (>60 ml/min/1.73m^2), those with overt albuminuria/macroalbuminuria (high UACR) and those with relatively preserved GFR [10]. No report of treatment effect on blood uremic toxins, in spite of the data from credence study that enrolled patients in advanced stages of CKD [11].

The mechanistic explanations for improved renal outcomes by SGLT2 inhibitor include reduced blockade of proximal tubular glucose reabsorption by serum-glucose cotransporter 2 receptors which cause natriuresis and osmotic diuresis. As a result, they decreased intraglomerular pressure and hyperfiltration, reduced proinflammatory and profibrotic processes, and reduced cellular toxicity and oxidative stress. SGLT2i are also known to reduce abdominal and subcutaneous fat associated with insulin resistance. SGLT2i promote lipolysis with production of ketones serving as an efficient energy substrate for renal and cardiac mitochondrial cells. SGLT2 intervention has been shown to restore erythropoietin production with an increase in hematocrit level. This increases oxygen delivery to renal interstitial and myocardial cells and may explain the improved renal and cardiac functional indices of SGLT2i in both CKD and CVD patients [9-12].

Despite these clinical benefits of SGLT2, there were reported safety concerns among intervention groups, like acute decline of eGFR in the early treatment phases, higher kidney failure rates, and dose dependent rapid GFR decline with increased risks in patients at advanced stages of CKD. Other reported adverse events included genital and urinary tract infections, frequent dehydration, hypotension, and hypovolemia episodes in elderly patients [10,11]. Fractures, limb amputation, and scrotal necrotizing fasciitis were also noted in some patients [10]. These SGLT2 risks in elderly populations and advanced stages of CKD indicate there is still unmet need for safe and effective therapy to slow progression in some category of CKD patients [10-12].

Gut microbiota in CKD progression

It has been established from animal and human CKD models that gut flora or microbiome changes are associated with CKD progression characterized by decrease in the number and activities of healthy microbiota of gastrointestinal tract referred to as gut dysbiosis [13]. Various risk factors are associated with CKD-associated gut dysbiosis, including low dietary fiber; uremic toxin retention products; prolonged colonic transit time; poor protein assimilation; drugs such as antibiotics, phosphate binders, and iron supplements; and the many co-morbidities [14]. In CKD-associated gut dysbiosis, there is increased activity of pathogenic proteolytic bacteria species of the family Enterobacteriaceae (especially Enterobacter Klebsiella and Escherichia), Enterococci, Clostridium perfringens, and Pseudomonas and concomitant decrease activity of healthy saccharolytic bacteria family of Bifidobacteriaceae (especially Bifidobacterium, Lactobacillaceae, and Prevotellaceae) [13-15].

This gut bacteria imbalance explains the increased production of gut-derived uremic toxins like Indoxyl sulfate, p-cresyl sulfate, indole acetic acid, and phenols, known to trigger inflammatory and immunological processes attributable to CKD progression. This gut dysbiosis leads to decreased production of short-chain fatty acids (SCFA) such as butyrate, acetate, and propionate by disrupting gut endothelial integrity, inducing endotoxemia, and increasing cytokine production, culminating in syndrome of CKD progression [16,17]. This explains the complex bidirectional relationship between gut microbiota and kidney ('Gut-Kidney' axis) in CKD, with ongoing renal dysfunction contributing to gut dysbiosis, while dysbiosis exacerbates renal inflammation, proinflammatory cytokines and mediators, ROS, endotoxemia, and uremic toxins [18].

These metabolic products reach the systemic circulation through the disrupted gut barrier ("leaky gut syndrome") due to increased pathogenic proteolytic bacteria overproducing cardiorenal uremic toxins and metabolites, thus triggering local and systemic inflammation, direct cellular toxicity, and immunological responses seen in CKD progression and cardiovascular complications [18,19]. Restoring healthy gut flora through gut microbiome modulation using selected strains of Probiotic microorganisms such as Streptococcus thermophilus, Lactobacillus acidophilus, Bifidobacterium longum demonstrated to utilize urea, uric acid, creatinine results in decreases of uremic toxins, restore gut barrier function, improve systemic immune function, reduce inflammation and improve quality of life CKD patients [13,19] (Figure 1).

Differentiating SGLT2 inhibitors from probiotics as therapeutic interventions to slow CKD progression

These therapeutic interventions belong to two different medication classes but comparable in their mechanism of action targeting CKD to slow progression. However, they differ in reported safety profiles and clinical benefits in various CKD patients. This will largely guide in developing future selection criteria of these medication classes for better treatment options in CKD progression. Having a safety and CKD stage criteria, preferred options for elderly and advanced CKD stages 3-4 patients will be probiotics intervention in comparison to SGLT2i. Considering the complex pathogenesis of CKD progression, combination therapy at minimal doses of individual classes may be another approach worth considering in future clinical study and perhaps lead to even better clinical outcomes [12,20,21]

SGLT2 inhibitors are primarily indicated as add-on therapy for T2DM and CKD (with and without diabetic kidney disease) with CV risks [9]. The renal benefits were reported mainly in patients with early CKD stages (>60 ml/min/1.73 m^2), macroalbuminuria with high urine albumin creatinine ratio

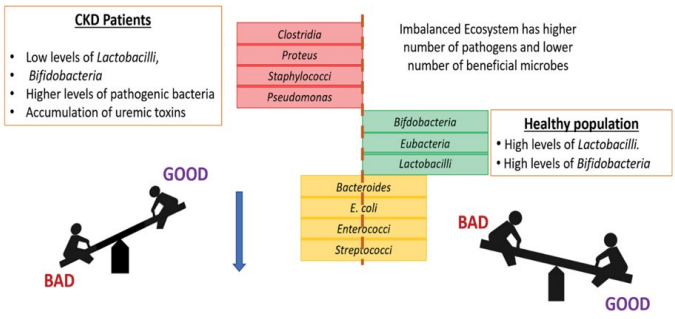

Figure 1. Intestinal flora composition in healthy individuals and changes that occur in CKD patients. Probiotic therapeutic intervention for CKD-associated gut dysbiosis increases beneficial bacterial while lowering number of pathogenic strains to restore healthy gut microbiome balance [23].

Table 1. Summary of SGLT2i vs probiotics in therapeutic intervention to reduce CKD progression.

Characteristics	SGLT2 Inhibitors	Probiotics
Product class	Blocks proximal tubule reabsorption of glucose-(empagliforin, canagliflozin, dapagliflozin, ertugliflozin), drug class	Oral Live Biotherapeutic bacterial organisms to correct the colonic dysbiosis in CKD biologic class.
Target patient population	Type 2 diabetes with CKD. Diabetic kidney disease in early stages (1-3)	All CKD stages 1-5 both DKD/non-DKD
Mechanism of action	Glucose control, albuminuria reduction, uric acid reduction, eGFR stabilization, proinflammatory factors, reduces cell toxicity, lipolysis, cellular oxygenation	Removes uremic toxins, reduces local and systemic inflammation, reduces proinflammatory cytokines, improves lipid, glucose metabolism and nutrition, Improves quality of life, reduces renal infections/hospitalization
Safety profile	Kidney failure/impairment Genito-urinary infections (UTI), fractures, amputations, scrotal gangrene, dehydration, hypotension in elderly patients. Not recommended in eGFR<60 ml/min	Mild GIT symptoms, Generally regarded as safe (FDA classification) Safe in elderly CKD 1-5

(UACR), and those with preserved or stable eGFR. SGLT2i reduced serum uric acid levels, but no report of treatment effect on other uremic toxins despite the inclusion of patients with advanced CKD stages (CKD 3-4) in the CREDENCE CT study [10,11]. Beyond the observed renal and cardiovascular benefits, no reported effect of the SGLT2i class on CKD-associated gut dysbiosis [11,12]. The SGLT2 safety profile limited clinical use in late stages of CKD (CKD 4 & 5) and elderly patients (>75 years).

In contrast, probiotic intervention in CKD and specifically at late stages (CKD 3-5) showed a good safety profile and significant decreases in serum uremic toxins, endotoxemia, and oxidative stress markers with improved antioxidant capacity. Clinical benefits in CKD patients include improved quality of life, slowed decline of GFR, reduced infectious complications, and cardiorenal uremic toxins [13-16]. The adverse events profile with probiotics were mainly mild to moderate gastrointestinal symptoms [15]. No reported adverse effect on acute GFR decline or kidney failure (Table 1). Probiotics are generally regarded as safe (GRAS) under USA-FDA classification due to their safety profile and widely used in the food and pharmaceutical industries [22]. The beneficial effects of LBP probiotics are seen even beyond the gut-kidney axis, and there is emerging evidence about the link between most organ dysfunctions and gut microbiome changes [22]. Restoration of a healthy gut microbiome has become an area of great interest in precision medicine projects and one of the platforms for developing specific therapy for prevention and interventions in various medical conditions [22,23].

Conclusion

In summary, SGLT2 inhibitors clinically indicated for T2DM, and CKD with CV risks is a blocker of SGLT2 receptor at the proximal tubule and secondarily modulate the metabolic, inflammatory, and immunological changes associated with CKD progression. However, SGLT2i indications and recommendations will benefit more patients with T2DM in the early stages of CKD (eGFR >60 ml/min/1.73 m^2) and DKD with high UACR. Despite SGLT2i clear benefits outweighing their risks, the safety profile has raised concerns in certain categories of CKD patients. Probiotics as LBP act primarily to reverse the underlying gut dysbiosis using selected strains of healthy bacteria to address the complex pathophysiology and pathogenesis of CKD progression. CKD progression has a complex pathophysiology, interrelated molecular processes, and co-morbidities, which require multifaceted therapeutic approaches and selection of specific therapies based on criteria on their safety profiles, target patient populations, and CKD stages.

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