Mini Review
Volume 14:01, 2024

Journal of Nephrology & Therapeutics

ISSN: 2161-0959 Open Access

Targeting Inflammation to Slow CKD Progression- Role of Gut Microbiome Based Therapy

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Abstract

Chronic Kidney Disease (CKD) is a worldwide public health problem associated with high morbidity, mortality, and socioeconomic burden. Despite recent advances in pathogenesis and effective Standard of Care (SOC) therapy, the incidence of end stage renal disease remains high, attributed to the complex and diverse pathophysiological pathways in progression of CKD. Among the many pathogenetic pathways, inflammation plays the most central role in disease progression and related complications. Current SOC treatment to slow CKD progression has not adequately addressed these complex processes as a result of persistence of low-grade inflammation occurring at all stages of CKD. Previous attempts to address the inflammatory pathway with specific anti-inflammatory agents were, in certain cases discontinued for reasons ranging from drug safety to efficacy concerns, and business development decisions. Recent research findings demonstrating direct correlation between systemic inflammation associated gut microbiota changes and CKD progression, provided a potential novel therapeutic approach to target the inflammatory pathways. Exploring current scientific knowledge of modulating gut microbiome with microbiome-based therapies provides options in addressing these complex pathogenetic mechanisms of CKD-induced inflammation.

The purpose of this minireview is to discuss the role of inflammation associated with gut microbiome changes in CKD progression and gut microbiome-based therapeutic options to slow CKD progression.

Keywords: CKD progression • Inflammation • Gut microbiome

Introduction

Chronic Kidney Disease (CKD) is a worldwide public health problem associated with high morbidity, mortality and disproportionately higher healthcare expenditure compared to other disease conditions [1]. CKD has been projected to be among leading top five causes of death worldwide attributed to elderly population and high prevalence of cardiovascular complications from diabetes [2]. CKD progression is characterized by persistent low-grade systemic inflammation typifies by presence of proinflammatory markers, similar to what obtains in other chronic inflammatory conditions such as metabolic syndrome, Non-Alcoholic Fatty Liver Disease (NAFLD), Cardiovascular Disease (CVD), malignancy and Diabetes Mellitus (DM) [3]. The inflammatory process is initiated by tissue injury or presence of foreign particles which triggers production of proinflammatory markers culminating in inflammatory cascade. This physiological proinflammatory process is controlled or abated by counter regulatory production of anti-inflammatory molecules and any residual and persistent low-grade inflammation is either due to failure to discontinue the inflammatory cascade or there is a continued generation of ongoing pro-inflammatory markers [3,4].

This persistent inflammatory phenomenon was also found in conditions associated with poor nutritional status, gut microbiota dysbiosis, infections, dyslipidemia, and stress [4]. Inflammation plays significant components in uremic toxemia, oxidative stress, infections, dyslipidemia, malnutrition, volume overload and dialysis treatment, which are well known contributing factors to CKD progression and related cardiovascular complications [4,5]. Targeting inflammatory pathway plays a key role in therapeutic approach in CKD progression such as Renin-Aldosterone Angiotensin System (RAAS) blockers, Sodium Glucose Co-transporter 2 inhibitor (SGLT2i), Mineralocorticoid Receptor Antagonist (MRA) and other anti-inflammatory agents undergoing clinical development [6]. Despite evidence of clinical benefits of these medications as Standard Of Care (SOC) therapy, risk for disease progression persists, necessitating further search for a safe novel therapy targeting inflammation in high-risk patients for CKD progression.

Recent evidence of systemic inflammation in CKD-associated gut dysbiosis has provided further mechanistic insight into the complex relationship between inflammation and molecular, immunological, and metabolic pathways in CKD progression [7,8]. Exploring gut microbiota modulation targeting inflammatory process to slow CKD progression is a pivotal intervention central to these complex and interrelated pathophysiological phenomena [9]. The purpose of this review is to briefly summarize the key roles of inflammation and gut microbiome changes in CKD progression and discuss gut microbiome-based therapy options to slow CKD progression.

Inflammation and CKD progression

Recent reviews on therapeutic options to retard progression of kidney diseases highlighted the central role of inflammation in initiation and outcome of CKD, including its significant relationship with pathophysiological pathways of hemodynamic, metabolic, and immunologic factors [4,6,10]. Potential therapy to slow CKD progression would, therefore, be multi-approach, preferably combination therapies to target the complex pathways addressing the various incompletely understood pathogenetic mechanisms [10]. The need for novel multi-approach to inflammation of CKD was further supported by recent findings that despite available effective agents such as RAAS blockers, SGLT2 inhibitors and MRA as standard of care therapy for kidney protection, a significant proportion of patients still develop ESRD [6,11,12]. This points to the fact that treatment gaps exist and significant limitations of clinical benefits by current SOC therapy in CKD. The unmet needs in high-risk patients for CKD progression necessitate discovery and development of novel therapies targeting inflammatory pathways.

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Received: 01 January, 2024; Manuscript No. jnt-23-118437; **Editor Assigned:** 02 January, 2024; PreQC No. P-118437; **Reviewed:** 17 January, 2024; QC No. Q-118437; **Revised:** 23 January, 2024, Manuscript No. R-118437; **Published:** 31 January, 2024, DOI: 10.37421/2161-0959.2024.14.481

Inflammation is a well-recognized pathway in CKD pathogenesis as demonstrated by reduced disease progression in response to intervention with anti-inflammatory agents [13,14]. Despite the potential benefits, clinical development of some of these anti-inflammatory agents were discontinued for reasons ranging from drug safety concerns to uncertain future investment returns and recent approval of SGLT2i and MRA in CKD treatment, raised the required standard for potential pipeline products in treatment of kidney disease progression [6,15]. Recent advances in gut microbiome-based therapy approaches provides additional opportunity to explore safe and effective novel anti-inflammatory to curb the high CKD and ESRD incidence [16,17].

The principle of inflammation is based on detection and elimination of harmful pathogens through interaction of resident renal parenchymal cells and various immune cells, a process initiated through either stress or injury, leading to irreversible tissue damage and organ dysfunction [10,18]. In the kidneys, the initial cellular interactions are between resident parenchymal immune cells (macrophages, dendritic cells) and circulating immune cells (monocytes, lymphocytes, neutrophils) [19]. The exact mechanistic process involved in inflammation of CKD progression is not well understood, but is known to include contribution from hemodynamic, immunologic, and metabolic etiological factors [20].

Further findings showed that even CKD that is not immune mediated in etiology, has inflammation playing a significant pathogenetic role in disease progression [21]. Initiation of inflammatory process depends mainly on resident immune cells whose key responsibility is to maintain tissue homeostasis between the Dendritic Cells (DC), macrophages, regulatory T cells (Tregs), CD8, NK lymphocytes, who are closely in contact and interact with renal parenchymal cells [22]. Once these cells are triggered by kidney injury from external or internal agents (microbial antigens, toxins, hyperglycemia, proteinuria) produce inflammatory mediators, initiating inflammatory cascade that sets the process of kidney disease progression. As a result of initiation of inflammatory process, a counter-regulatory physiological response is triggered to control inflammation, repair tissue damage, and restore homeostasis [23].

This key initiating step involve activation of DC, leading to enhance in activity of CD8+T, CD4+T and TH2 causing glomerulopathy with infiltrations by macrophages thereby amplify repeated processes of repair and fibrotic changes [4,10,23,24]. The onset of glomerulopathy and proteinuria triggers RAAS which further increased production of several proinflammatory factors, cytokines, chemokines, and growth factors (Figure 1). These secondary responses activate innate immunity and signaling transcription factors particularly NK-kB, NLRP3 inflammasome, TLR, NrF2.

The activated transcriptomes regulate proinflammatory and senescence factors (IL-6, TNFα, CCR2, CCR5, JAK-STAT2, MCP1, klotho-α), thereby setting a vicious cascade of aggravated inflammation and renal fibrosis [23,25] (Figure 1). Further insight in recent Acute Kidney Injury (AKI) and CKD models showed the inflammatory process in AKI persists and continues to CKD, even after the renal function was restored, confirming strong association between low-grade inflammation and slow development of disease progression and fibrosis [26,27]. Mechanistic studies of how the activation of these cells and receptors and outcomes measures are potential targets for novel therapeutic agents in CKD progression. Clear understanding of inflammatory pathways triggered by uremic toxins forms the basis to explore benefits of Live Biotherapeutic Products (LBP) as gut microbiome-based therapy in CKD progression [28].

Gut microbiome in CKD progression

The human gastrointestinal tract harbors complex commensal microorganisms of bacteria, archaea, small eukaryotes, and viruses called microbiomes. The human microbiome is predominantly located in the colon consisting mainly of diverse bacteria, whose cell composition is 10 times greater than human cells [29]. Factors affecting gut microbiota composition and function include host factors such as mode of birth delivery, gestational age, breastfeeding, age, diet, geographical location, antibiotic use, sanitation [28]. Various studies showed microbiome-host interactions modulate many vital functions in healthy human host such as metabolism, immunity, cardiovascular and neurological functions [30]. The gut microbiota and host

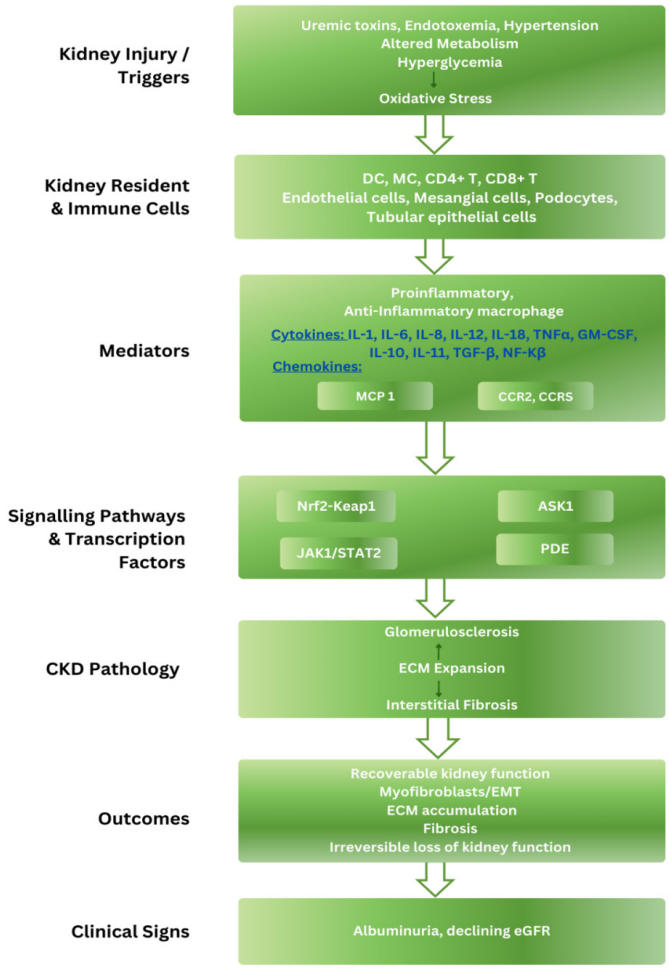

Figure 1. Summary of key roles of inflammation in initiation and progression of chronic kidney disease. Abbreviations: DC: Dendritic Cells; MC: Macrophages; IL: Interleukins; TNF: Tumor Necrosis Factor; GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor; TGF: Transfer Growth Factor; NF-KB: Nuclear Factor-Kappa B; MCP1: Monocyte Chemoattractant Protein1; CCR2/CCR5: CC-Chemokine Receptor; NrF2-Keap1: Nuclear Factor-(erythroid -derived 2)- Like 2; Keap 1: Kelch-Like ECH-Associated protein 1; ASK1: Apoptosis Signal-regulating Kinase 1 , JAK-STAT2:Janus Kinase/Signal Transducers and Activators of Transcription; PDE: Phosphodiesterase; ECM: Extracellular Matrix; EMT: Epithelial-to-Mesenchymal Transition.

are in a mutualistic relationship with microbiota utilizing host nutrients in a conducive environment and at same time modulating large vital functions of host immunity and metabolic process [31]. Additionally, these bacteria encode enzymes to produce metabolites essential to host health, such as vitamins, bile acids, choline, and Short Chain Fatty Acids (SCFA).

The SCFA are fermentation products of non-digestible dietary carbohydrate by gut microbiota consisting mainly of butyrate, propionate, and acetate whose main functions are provision of energy source for colonocytes, maintain integrity of intestinal barrier, regulates glucose and lipid metabolism, and regulates immune system [32]. Specific aspects of immune regulation involve attenuation of NF-kB activation and inhibition of proinflammatory cytokine production through activity of Tregs cells, protecting against sustained activation of immune system [33,34]. In addition, SCFA inhibits histone deacetylases through their action on G-Protein Coupled Receptors which includes GPR41 (FFAR3), GPR43 (FFAR2) and GPR109a responsible for regulating various functions and metabolic effects of adipocytes, immune and vascular endothelial cells [35]. Persistent and low-grade inflammation is a known process associated with many chronic diseases like CKD, cardiovascular, metabolic syndrome, neurological and allergic disorder [36].

The initiation of inflammation starts with gut microbial-host interaction, resulting in functional and compositional changes of the four main microbiota phyla, namely Actinobacteria, Proteobacteria, Firmicutes and Bacteriodetes

[37]. Evidence indicates that changes in microbiota composition and function (gut dysbiosis) causes gut inflammation and disruption of intestinal barrier integrity, ("leaky bowel") results in activation of NF-kB pathway and eventual development of systemic inflammation [38]. Consequences of disrupted intestinal barrier includes translocation of bacterial toxins, Lipopolysaccharide (LPS), uremic toxins and endotoxemia with increased production of proinflammatory cytokines and gut-derived uremic toxins (IS, PCS, TMAO) which further worsens inflammation, increases proinflammatory cytokines and Reactive Oxygen Species (ROS) production [39,40]. High levels of uremic toxins have been implicated in pathogenesis of renal fibrosis and cell senescence through mechanistic reduction of klotho expression [41,42].

The relationship between kidney dysfunction and gut dysbiosis is bidirectional, termed "Gut-kidney axis" in which CKD causes gut microbial changes (dysbiosis) and in turn worsens CKD, aggravated by complications of metabolic acidosis, hypervolemia, prolonged colonic transit time, antibiotic use, intestinal wall edema and poor dietary fiber intake [10,43-45]. The systemic inflammation induced by gut dysbiosis is characterized by increased composition of colon bacteria families possessing enzymes that generate uremic toxins compared to dietary fiber degraders that produce beneficial SCFA metabolite, given rise to reduced SCFA production, accumulation of harmful metabolites and endotoxemia prior to systemic inflammation [46,47] (Figure 2).

Targeting inflammation with gut microbiome-based therapy

Previous interventions in CKD progression directly targeting various specific inflammatory markers have not significantly reduced high CKD burden [48]. Various mechanistic studies have shown that current recommended RAAS blockers, SGLT2i, MRA and GLP-1 receptor agonist anti-inflammatory benefits were attributed to secondary reduction of glomerular hyperfiltration and proteinuria [49-51]. Additionally, there are ongoing clinical development of various therapeutic agents targeting specific inflammatory markers such as NrF2 activators, Endothelin-1 Receptor Agonist (ERA), Soluble Guanyl Cyclase Activator(sGC), Anti-inflammatory cytokines (anti-TNF, IL-6, CCL2, NF-kB) and cell therapy [52-54].

Several studies have reported that CKD -associated gut microbiome changes have a direct relationship with disease progression and live biotherapeutic interventions to restore colonic bacteria balance (eubiosis) are known to improve biochemical and clinical outcomes in CKD [55,56]. Targeting CKD- induced inflammation with microbiome-based therapy addresses pathways that reduce uremic toxins, increase beneficial SCFA metabolites, restores epithelial barrier, regulates immune system, and decreases persistent low-grade inflammation [57].

The dietary approach is well known cost-effective approach to modulate gut microbiome with recommendation that support plant-based diets and low animal protein to decrease bacterial proteolytic fermentation while promoting and increasing saccharolytic bacterial composition. This dietary regime affects microbiota composition that reduces inflammation and uremic toxin production associated with CKD progression and CVD complications [58,59]. The goal of gut-based microbiome intervention primarily is normalization of CKD-associated dysbiosis by reducing composition and activity of proteolytic bacterial species while increasing that of saccharolytic species, classified as prebiotics, probiotics and synbiotics [60]. Prebiotics are non-digestible carbohydrate fibers selectively used as substrates by host microorganisms to confer a health benefit (examples of dietary fiber are inulin, resistant starch, fructo- and galacto-oligossacharide) [61].

Probiotics are live microorganisms, which when administered in adequate amounts confer a health benefit on the host (examples of probiotic strains include, Bifidobacterium, Lactobacillus and Streptococcus species) [62]. Several studies reported probiotics significantly reduce gut derived uremic toxins, inflammatory markers and proinflammatory cytokines in all CKD stages. These clinical benefits corresponded to changes in colonic bacteria taxa providing further proof of gut-kidney involvement in CKD progression. Synbiotics is a combined therapy of prebiotics and probiotics synergistically reduce the effect of uremic toxins and ameliorate gut dysbiosis in CKD progression [63]. Intervention studies in advanced CKD using combination prebiotic (Inulin, fructo-oligosaccharide, galacto-oligossacharide) and probiotic (lactobacilli, streptococci, Bifidobacterium) showed altered composition of fecal microbiome with increased Bifidobacterium, and while pathogenic Ruminococaeceae were reduced [64,65]. In addition, various synbiotic interventions were reported to decrease protein bound uremic toxins such as

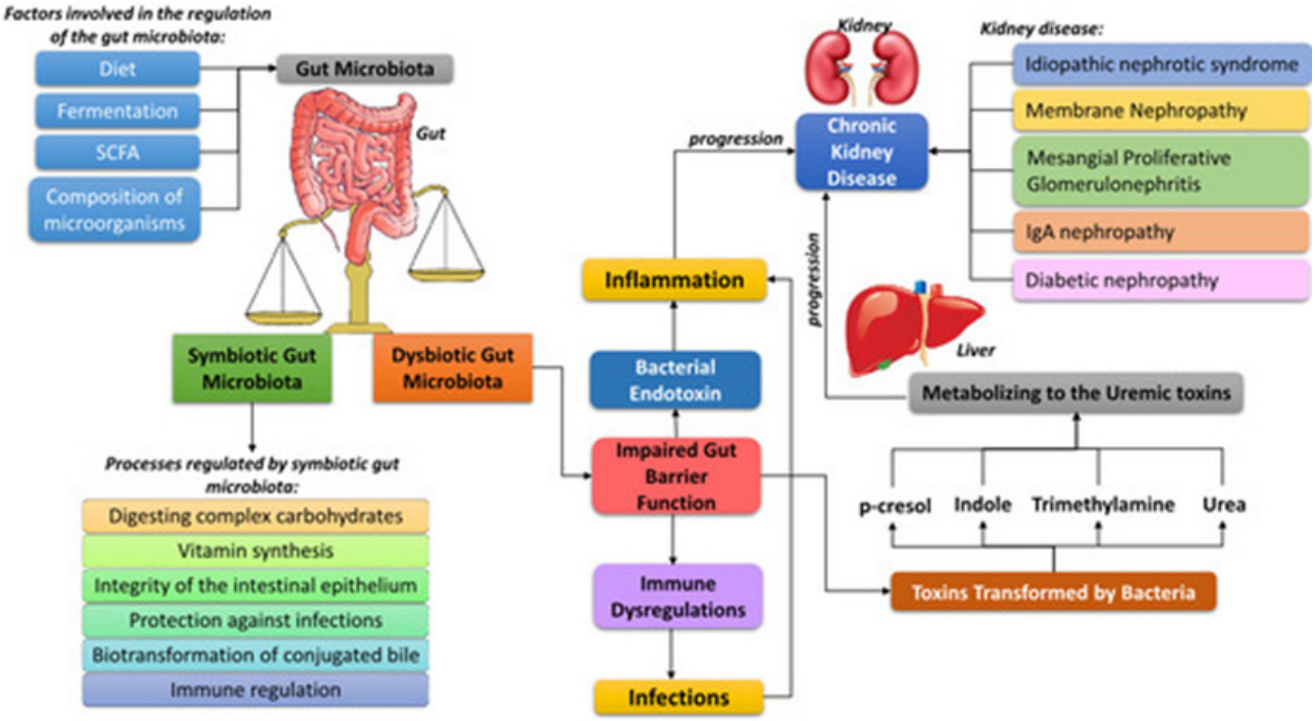

Figure 2. Graphic illustration demonstrating complex relationship between CKD-associated gut microbiome changes (Dysbiosis) and Inflammation in development of chronic kidney disease progression. Adapted with Permission from: Mertowska P, Mertowski S, Wojnicka J, et al (2021). Link between Chronic Kidney Disease and Gut Microbiota in Immunological and Nutritional Aspects. Nutrients.; 13(10):3637. https://doi.org/10.3390/nu13103637

p-cresol in Pre-dialysis and dialysis CKD populations [66].

A new concept of postbiotic as adjunctive or alternative therapeutic approach in gut homeostasis and immune modulation was recently proposed and the term postbiotic refers to products of non-viable bacteria or metabolites of probiotic organisms such as vitamins, SCFA, cell surface proteins and enzymes that have demonstrated positive effect on gut microbiome and host [67]. In contrast to synbiotic products, postbiotics have pharmacokinetic properties of absorption, distribution, metabolism, and excretion raising concerns on dosage and systemic toxic effects. An experimental postbiotic SCFA treatment demonstrated reduction of inflammation and oxidative stress in ischemia-reperfusion animal model of kidney injury [68].

Another Live Biotherapeutic Product (LBP) approach is fecal microbiota transplantation, as capsules or through colonoscopy, normally sourced from healthy donors with preclinical data showing potential benefits in CKD patients. This mode of therapy has recently gotten approval for recurrent *Clostridium difficile* infection and clinical benefits have equally been reported in metabolic syndrome, autism, IBS, and ESRD-associated bacteremia [69].

In comparison to drug therapy, some of the microbiome-based therapy is cheaper with well tolerated fewer side effects across spectrum of CKD /ESRD patients.

Conclusion

Inflammatory process plays a central role in the initiation and sustenance of CKD progression. The persistence of low-grade systemic inflammation in CKD is partly a reason partly given for the high burden of CKD and related CVD complications. Despite decades of available effective standard of care therapy to slow CKD progression such as RAAS blockers, SGLT2 inhibitor, MRA and GLP-1 agonist, the high incidence of CKD/ESRD still persists. The inability to reduce CKD public health burden showed that current interventions are inadequate to address the complex and interrelated pathogenetic pathways, particularly the key and central role of inflammation in initiation and progression of kidney disease. Hence, further clinical studies to identify novel therapies targeting inflammation will bridge scientific gap and address unmet needs of patients who are high risk for CKD progression. Gut dysbiosis is associated with systemic inflammation in CKD and hence microbiome modulation through microbiota-based therapy is a potential anti-inflammatory therapeutic product in retarding disease progression.

Acknowledgement

Sumanth Narayana helped with graphical and digital illustrations of Figures 1 and 2.

Disclosures

No conflict of interest.

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Data Sources

NA.

Funding

None.

IRB Approval

NA.

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How to cite this article: Anteyi, Emmanuel, Natarajan Ranganathan and Usha Vyas. "Targeting Inflammation to Slow CKD Progression- Role of Gut Microbiome Based Therapy." *J Nephrol Ther* 14 (2024): 481.