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Review Article

Restoring Eubiosis in Intestinal Microbiota as a Therapeutic Strategy for Chronic Kidney Disease

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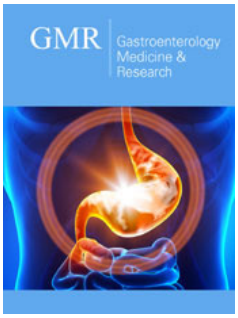

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Abstract

Chronic Kidney Disease (CKD) is associated with intestinal dysbiosis, especially when it is accompanied by arterial hypertension, metabolic disorder, sympathetic activation, and/or immune deregulation. One particularly common mechanism of pathogenesis triggered by dysbiosis is chronic inflammation. Recent research has highlighted the importance of the microbiota and its genes in health and disease. The aim of the current contribution is to review the possible advantages of certain innovative strategies for establishing eubiosis in CKD patients. A key advance in microbiota research took place in 2007 with the characterization of the human microbiome, finding billions of bacteria in the large intestine, which is 150cm long and has a surface area of 1.3m^2. Such bacteria are mainly of the phyla *Bacteroidetes* and *Firmicutes*. According to the review of the literature, the use of probiotics, prebiotics, synbiotics, postbiotics, parabiotics, and intestinal microbiota transplantation can be beneficial for CKD patients under certain conditions. When intestinal microbiota transplantation afforded a positive outcome for a patient with a *C. difficile* infection, the procedure was provided with greater validity because this infection is a frequent complication in CKD patients. Upon performing any procedure for reestablishing eubiosis, the recommendations of the U.S. FDA in regard to the crisis of COVID-19 must be considered.

Keywords: Chronic kidney disease; Intestinal microbiota; Intestinal microbiota transplantation; Probiotics; Prebiotics; Synbiotics

Introduction

The human microbiome was first defined by Joshua Lederberg in 2001 as the ecological community of commensal, symbiotic and pathogenic microorganisms that exists in the human organism. The microbiome had at that time largely been ignored as a determinant of health or disease, according to Lederberg [1]. The human microbiome currently refers to the set of microorganisms together with their genetic material that are found in the body. It has been given many names since 2001, including "our second genome" [2], "the invisible organ of the body" [3], "the forgotten organ" [4], "the super-organ" and "super-organism" [5], "the last human organ" [6], "the new systemic organ" [7], and "the human organ in research" [8]. In 2007, the human microbiome was characterized by the Human Microbiome Project, after an investment of ~170 million dollars. Its constitution, and more specifically that of the Intestinal (gut) Microbiota (IM), is an important factor in Chronic Kidney Disease (CKD). The latter is a grave public health problem that affects 350 million patients around the world, with deaths ranging from 0.5 to 1 million people annually [9]. Although the microbiota is

often confused with the microbiome, with the term "intestinal microbiome" used by some, they are not the same [10]. It is necessary to standardize the use of this terminology. The IM consists of over 100 billion bacteria, as well as fungi, viruses, protozoa, archaea, and other microorganisms [11]. This set of microorganisms in the intestine contains more vital genes than our own genome, evidence of its unique functions. Intestinal microorganisms aid the immune response to invasive pathogenic infections of mucous membranes and the skin. Without the IM, individuals would die from pathogens that normally cannot proliferate. Whereas eubiosis exists in healthy individuals, dysbiosis is present with many diseases, including CKD. Since each element of the IM performs specific and essential functions, dysbiosis leads to pathogenic conditions in the human organism. One particularly common mechanism of pathogenesis triggered by dysbiosis is chronic inflammation.

The gastrointestinal tract is considered the largest immune organ [12-14]. Within this context, the IM has various protective activities. It maintains intestinal homeostasis and an intact intestinal barrier, inhibits the proliferation of opportunistic pathogens (and thus the development of the corresponding diseases), modifies the microenvironmental conditions in the intestine through changes in pH, avoids the development of neoplasms, and stimulates the synthesis of vitamins and anti-inflammatory substances that our body alone cannot produce. Moreover, the IM participates in digestive functions, including the assimilation of nutrients, the production of digestive enzymes, the digestion of complex carbohydrates, the generation of certain compounds from food, the maintenance of energy balance, the supply of substrates for enterocytes, the degradation of indigestible plant polysaccharides and oxalates, and the elaboration of short-chain fatty acids derived from microbial fermentation of indigestible foods. In addition, it contributes to neurological function and development through the gut-brain axis and promotes endocrine activity (from the carbon cycle in the soil to the fermentation of food in the intestine). The IM also provides a supportive environment for pregnancy [15-24].

Many of the mechanisms of CKD tend to engender dysbiosis of the IM. For instance, the increase in urea with renal insufficiency causes a substantially greater number of bacteria [25], while changes in appetite stemming from renal failure may affect the abundance and diversity of the IM [26]. A difference was detected in the composition of the IM between CKD patients on hemodialysis and healthy controls [27]. In patients with CKD versus healthy individuals, moreover, there is a greater level of *Actinobacteria*, *Firmicutes*, and *Proteobacteria* phyla [28]. The colon becomes the main route for uric acid and oxalate secretion [29]. Among the possible mechanisms capable of accounting for the difference in the composition of the microbiome between patients with uremia and healthy controls is the decrease in the capacity to manage dietary fiber [30], leading to constipation in patients on hemodialysis and peritoneal dialysis [31].

Factors Involved in the Modification of the Intestinal Microbiota

The IM can be altered by stress (e.g., disease), the intake of antibiotics and some other drugs, diet, and the composition of the microbiota itself. Diet acts on the microbiota through the activity of macronutrients and micronutrients [32]. For example, polyphenols and vitamin D derived from red wine and tea modulate potentially beneficial bacteria [33]. Dietary fibers, including inulin, galactooligosaccharides, oligofructose, and arabinoxylans, promote beneficial bacteria and kill potentially harmful species [34]. In the intestine, the amount and type of fat modulate beneficial and potentially harmful microorganisms, as well as the ratio of *Firmicutes* to *Bacteroides* [35]. Meanwhile, the quantity and type of protein in the diet has a substantial and differential effect on the IM [36]. Although multiple antibiotics, with short and long-term use, generate a reduction in bacterial diversity in the IM, antibiotics have been postulated as possible adjuvant therapies in terminal CKD to diminish uremic solutes that are not effectively removed by dialysis. However, only orally administered vancomycin has shown promising results [37-39]. On the other hand, some antineoplastic drugs provide anti-carcinogenic activity by changing the composition of the microbiota [40].

Apart from diet and medications, the composition of the IM is influenced by the genetics and immune response of the host. It may also be modified by stress and at the same time contribute considerably to stress [41].

Dysbiosis (dysbacteriosis, an imbalance in the IM) participates in the genesis of many diseases [42], such as those involving inflammatory processes. It plays a major role in the mechanisms of CKD, frequently causing fatal outcomes by triggering cardiovascular events [43]. Whether with or without hemodialysis, CKD patients present dysbiosis of the IM and inflammation, usually accompanied by an increase in the level of uremic toxins, indoxyl sulfate, and p-cresyl sulfate [44]. Likewise, the prevalence of insulin resistance is higher when diabetic and obese patients exhibit a limited diversity in the IM [45]. A distinct profile of the IM has been observed in progressive IgA nephropathy, with patients displaying an elevated level of *Eubacteriaceae*, *Ruminococcaceae*, *Streptococcaeae*, and *Lachnospiraceae* [46]. In a healthy person, the fermentation of indigestible elements of food by the IM produces *Short-Chain Fatty Acids* (SCFA), known to protect the kidneys [47]. Apart from affecting this function, dysbiosis can alter the absorption of the intestinal barrier, leading to a series of health problems caused by greater exposure to endotoxins [48].

The composition of the IM plays a fundamental role in arterial hypertension, CKD, and the generation of nephrolithiasis [49-51]. In the case of arterial hypertension, it does so through communication with the endocrine system, the nervous system, and the immune system by regulating host homeostasis. Patients with high systolic pressure undergo changes in the composition of the IM (e.g., the

abundance of *Firmicutes* and *Bacteroidetes*) [52]. Additionally, fecal and urinary dysbiosis occur in the case of calcium oxalate nephrolithiasis, which gives rise to elevated levels of *Bacteroidetes spp.* and *Prevotella spp.* compared to healthy controls [53].

The Gut-Brain-Kidney Axis

The complex interaction between the brain, the IM, and the kidneys has attracted enormous interest in recent years [54] because two-way communication is able to influence many conditions, including CKD [55], by modifying the composition and metabolism of the IM [56]. As aforementioned, an imbalance in the IM is commonly found with arterial hypertension and CKD [49-51]. Through the autonomous regulation of the brain and the signals of the intestine and kidneys, the gut-brain-kidney axis makes connections between the organs [57]. For instance, uremic toxins originate in microbial metabolism [58]. An increase in the concentration of indoxyl sulfate and p-cresyl sulfate, produced in the colon, decreases renal function. This imbalance can lead to alterations in coagulation, damage to renal tubular cells, fibrosis and cardiac hypertrophy, endothelial dysfunction, and insulin resistance [59]. Some of these toxins are bound to proteins, making it very difficult to remove them with dialysis. Furthermore, gut bacteria convert choline and betaine to trimethylamine. A recently discovered metabolite, trimethylamine N-oxide (TMAO), is associated with atherosclerosis [60].

Therapeutic Strategies for CKD

The composition of the IM and the metabolites it produces are closely related to the existence of a healthy or diseased condition. Thus, the maintenance of homeostasis in the IM greatly helps patients suffering from CKD and arterial hypertension [61]. Possible therapeutic strategies for modulating the IM include a change in diet (e.g., an increase in fiber), the use of probiotics, prebiotics, and symbiotics, and intestinal microbiota transplantation [62,63]. Other important factors are exercise, stress management, and the avoidance of certain drugs (especially antibiotics as well as antineoplastic and anti-inflammatory drugs) [64]. Sedentarism, smoking, and inappropriate eating habits are risk factors for cardiovascular disease, which is associated with the progression of CKD.

Diet

Dietary changes as a therapeutic strategy for CKD are aimed at improving subclinical acidosis in order to preserve muscles and bones and decrease the glomerular filtration rate. The reduction of acid by increasing sodium in the diet helps to protect the kidneys [65], and the inclusion of base-inducing fruits and vegetables attenuates kidney injury [66]. However, these measures are insufficient. Monitoring urinary acid excretion may be helpful [67].

The best diet for CKD is plant-based, consisting of proteins, sodium, phosphorus, and potassium. A limited consumption of processed meats, refined sugar, and sodium is desirable, as is an elevated content of fibers and grains [68]. The Mediterranean diet usually provides benefits because of the comorbidities found with nephropathy [69]. The DASH-type diet of the Institutes of Health of the USA is also advantageous under certain conditions [70]. In addition to diet, exercise represents an essential and often overlooked therapeutic strategy [71]. Without adequate exercise, CKD patients experience a decline in the quality of life in daily activities.

Probiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" [72]. Some probiotics improve human health little by little, such as *Bifidobacterium longum*, prepared as an enteric capsule [73]. Probiotics possess antioxidant and anti-inflammatory properties in albino rats, probably by modulating the IM [74]. After administering *Lactobacillus acidophilus*, *Streptococcus thermophilus* and *Bifidobacterium longum* for 6 months, a decrease was observed in serum urea. The follow-up randomized controlled trial in 22 patients failed to reduce plasma uremic toxins [75]. It is suggested that persistent alloys due to uremia, dietary regimes, and the intestinal biochemical environment generate unfavorable conditions for the symbiotic microbiota [76]. To date, there has been a lack of quality in the intervention trials related to this new therapy [77]. Various probiotics stimulate an increase in the production of the intestinal mucus barrier, demonstrating a positive effect on the immune system [78]. Through goblet cells, probiotics can also enhance the synthesis of mucin, which has the first contact with invading bacteria [79]. Despite some good outcomes stemming from the intake of probiotics and prebiotics, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends the use of these products only for antibiotic diarrhea and gastroenteritis [80].

Prebiotics

The ISAPP defines prebiotics as "a substrate that is selectively utilized by host microorganisms to confer a health benefit" [81]. For instance, indigestible carbohydrates positively affect beneficial colonic bacteria [82]. Glucans and fructans appear to increase the level of *Lactobacillus* and *Bifidobacteria* [83]. Moreover, prebiotics diminish several factors, such as the serum concentration of uremic toxin and p-cresol, lipid levels, the concentration of oxidative stress indicators, systemic inflammation, and the inflammatory response in the early stages of CKD. They also improve the condition of kidney failure and prevent renal osteodystrophy [84]. Indoxyl sulfate is reduced by the oral administration of the prebiotic p-inulin or oligofructose-inulin in hemodialysis patients [85,86]. Both prebiotics and probiotics modulate the IM, promoting anaerobic bacterial metabolism and a decline in host solute production (e.g., bile salts and metabolic endotoxemia) [87]. When prebiotics are degraded by the IM, short-chain fatty acids are generated and released into the bloodstream, thus affecting distant organs. The

two most important groups of prebiotics in terms of human health are galactooligosaccharides and fructooligosaccharides [88].

Synbiotics

The ISAPP currently defines synbiotics as "a mixture comprising live microorganisms and substrate(s) selectively utilized by microorganisms to confer a health benefit to the host" [89]. For example, compounds resulting from the binding of probiotics and prebiotics decrease the level of plasma p-cresol [90]. Indoxyl sulfate and p-cresyl sulfate are attributed to dysbiosis in the IM, according to a randomized study. A two-month treatment with synbiotics diminished C-reactive protein, an inflammatory marker [91]. Moreover, synbiotic therapy was found to reduce the serum concentration of uremic toxins [92]. Although some doctors suggest that probiotics, prebiotics, and synbiotics should be further developed before being administered to CKD patients, others recommend their present use, adding them to control strategies [93].

Postbiotics and parabiotics

Postbiotics are defined by the ISAPP as "the preparation of inanimate microorganisms and their components to confer a health benefit to the host" [94-96]. They have afforded a better impact on health than their parent compounds, probiotics. Postbiotics mainly consist of enzymes derived from *Lactobacilli* and *Bifidobacteria* [97]. Their development in recent years as interesting tools to modulate the microbiota has not yet taken the place of intestinal microbiota transplantation [94,95]. Postbiotics produce antioxidant, antimicrobial, and immunomodulating agents, thus positively influencing the IM [98]. These agents inhibit pathogenic organisms, improve the microbial composition and inflammatory profile, and lead to weight gain [99]. They include enzymes (e.g., NADH-peroxidase and glutathione peroxidase), organic acids (e.g., propionic acid), proteins (e.g., glutathione and cell surface proteins), polysaccharides, and lipids [100].

Probiotics are a set of bacteria that are predecessors of postbiotics. The most common probiotics come from *Lactobacilli* and *Bifidobacteria* and give rise to the postbiotics *L. plantarum* RG14, RG11, and TL1, which are antioxidant agents [101,102]. Probably due in part to this characteristic, inflammatory processes seem to be attenuated by the use of postbiotics, especially if they is associated with dysbiosis [103]. According to various authors, bacteria must be alive in order to be effective because their activity is fundamentally metabolic [102]. Parabiotics, on the other hand, are inactive, unviable cells capable of conferring health benefits when taken in sufficient quantities. They have provided successful therapy in some cases of CKD [104].

Intestinal microbiota transplantation

A difference in the composition of bacterial phyla between healthy individuals and CKD patients has been observed. In 2020, for example, the first report was published on a decreased level of *Akkermansia muciniphila* in CKD patients, which led to a reduced production of interleukin (IL)-10 (an anti-inflammatory cytokine) [105-107]. New procedures have been sought that are able to modify the IM and attenuate chronic renal inflammation [106]. Intestinal microbiota transplantation seeks to restore eubiosis after CKD or other disorders have generated dysbiosis. It can be performed through various techniques, including esophagogastroduodenojejunostomy, jejunostomy, colonoscopy, naso-jejunal tube, and enema. The procedure requires an excellent donor, perfectly studied in order to avoid the spread of disease [105]. Many doctors who deal with CKD patients still consider intestinal microbiota transplantation as a controversial treatment. Additionally, it is not exempt from complications, even if they are minor. Nevertheless, the vital role of the microbiota in the human organism is well known. In the case of a kidney transplant, for instance, the microbiota regulates immunomodulation [108]. Since no cases of intestinal microbiota transplantation or sterile fecal filtration for CKD patients have been described in the literature, their use has been limited. However, when intestinal microbiota transplantation was utilized on a patient with a *C. difficile* infection, the positive outcome provided this procedure with greater validity because such an infection is a frequent complication in CKD patients [109]. Another factor in favor of the application of intestinal microbiota transplantation is that many of the conditions found in CKD patients are also associated with intestinal dysbiosis, including arterial hypertension, metabolic disorder, sympathetic activation, and immune deregulation [110]. Hence, intestinal microbiota transplantation is an important option to be taken into account in cases of CKD.

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Conflicts of Interest

The authors declare that they do not have any conflict of interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained written informed consent from the patients in order to develop this article.

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