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Microbiome and the kidney

Mikrobiom w chorobach nerek

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Summary

The human gut is home to a very complex environment comprising of tremendous amount of microbes (mainly bacteria but also archaea, viruses and eukaryotes). In the few recent years there has been a growing interest in the role of gut bacteria in health and disease. This has resulted in linking gut microbiome with a variety of disorders, kidney diseases among others. Indeed, recent studies have discovered a potential impact of colonic bacteria on development and/or progression of multiple renal diseases, including hypertension, IgA nephropathy, acute kidney injury, chronic kidney disease and nephrolithiasis. Moreover due to its importance in the modulation of immune system, microbiome plays a role in kidney transplantation. The discovery of relationship between colonic bacteria and renal pathophysiology create a potential therapeutic target. Novel strategies to rebuild intestinal symbiosis involve prebiotics, probiotics and synbiotics. Recent studies have provided encouraging data that these new opportunities may have a therapeutic role in improving outcome of patients with kidney diseases. Further investigation is needed to entirely elucidate the functions of the microbiome and assess efficacy of microbiome oriented interventions.

This review will focus on the potential role of gut microbiome in nephrology and discus the new emerging concept of microbiome targeted therapeutic intervention in management of renal diseases.

Streszczenie

Jelito człowieka jest zasiedlone przez ogromną ilość mikroorganizmów wywierających wpływ m.in. na metabolizm oraz odporność organizmu gospodarza. W ostatnich latach pojawiają się coraz liczniejsze doniesienia o roli zaburzeń flory jelitowej w różnorakich schorzeniach, w tym także w chorobach nerek. Badacze sugerują udział mikrobiomu w patogenezie i/lub progresji takich chorób jak nadciśnienie, nefropatia IgA, ostre uszkodzenie nerek, kamica nerkowa czy też przewlekła choroba nerek. Ponadto modulacja układu odpornościowego przez bakterie jelitowe prawdopodobnie ma znaczenie wśród pacjentów po przeszczepieniu nerki. Istnienie związku pomiędzy mikrobiomem a chorobami nerek stwarza potencjalne nowe możliwości terapeutyczne przy wykorzystaniu m.in. prebiotyków, probiotyków czy też synbiotyków. Badania z ostatnich lat sugerują korzystny wpływ takiej interwencji na zahamowanie dalszego rozwoju chorób dzięki odbudowaniu fizjologicznej mikroflory bakteryjnej. Ze względu na nieliczne dane konieczne są dalsze badania oceniające skuteczność takiej interwencji.

W niniejszej pracy przedstawiamy aktualne doniesienia o roli mikrobiomu w nefrologii oraz omawiamy nowe potencjalne możliwości terapeutyczne w chorobach nerek uwzględniające jego zaburzenia.

Conflict of interest
Konflikt interesów
None
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INTRODUCTION

The gut microbiota exist in a symbiotic relationship with the human organism. Under physiologic conditions, interactions between the gut microbiome and the host contribute to maintain normal nutrition, metabolism and immune function (1, 2). Great progress in characterizing the structure of microbiome has led to highlight the role of colon bacteria in health and in

disease. Disturbances in normal gut microbiota is called dysbiosis and growing evidence is linking dysbiosis with pathogenesis of multiple diseases, including kidney diseases. In this review we will focus on the potential role of gut microbiome in nephrology and discus the new emerging concept of microbiome targeted therapeutic interventions in management of renal diseases.

HUMAN MICROBIOME IN HEALTH

The human gut is home to a very complex environment comprising of approximately 1 kg of microbes (mainly bacteria but also archaea, viruses and eukaryotes). Genes within those organisms are termed the microbiome.

In the few recent years there has been a tremendous interest in the role of gut bacteria in health and disease. This has resulted in two large projects aiming to characterize the human microbiome: the European Metagenomic of the Human Intestinal Tract (MetaHIT) (3) and the Human Microbiome Project (HMP) (4). MetaHIT catalogued 3.3 million microbial genes (from a cohort of 124 European individuals) – 150-fold more than the human gene complement (3), HMP obtained samples from 300 American individuals (4). In 2014 the aforementioned data were combined with that from a Chinese project resulting in an integrated gene catalogue comprising of more than 9 million genes (5). Findings from these studies suggest that each and every person harbours a unique ecosystem of microbes which has the potential to change adaptively to our needs (depending on the surrounding environment, diet) and greatly influences our well-being. On average we host a few hundred species, mainly bacterial, with the predominant ones being Bacteroidetes, Firmicutes and Actinobacteria (6).

At birth the colon (where the microbiome is most abundant) is largely sterile (although some bacteria can be transmitted from the mother during pregnancy (7)). Bacterial colonization occurs during birth (especially vaginal) and continues afterwards depending on many factors (antibiotic treatment, mode of feeding etc.). The microbiome resembles that of an adult before the third year of age, remains relatively stable (8) and plays an important role in the development of the nervous system and immune response. It also participates in the synthesis of vitamins (vitamin K), degradation of dietary oxalates (*Oxalobacter formigenes*), indigestible plant polysaccharides, metabolism of bile acids (9).

HUMAN MICROBIOME AND KIDNEY DISEASE

The impact of gut microbiome on kidney diseases is a novel area of interest – PubMed search reveals 77 publications with the keywords gut microbiome and kidney disease, of which only 3 are older than 5 years. The impact of colonic bacteria on renal pathophysiology seems to be ubiquitous as suggested by more and more data each day.

Hypertension

Hypertension is probably also influenced by the composition of the human microbiome through gastrointestinal sodium handling (10), modification of expression of hypertensive phenotype (11) and other mechanisms. Recent studies have shown that both in rat models of hypertension and in a small sample of patients there is a decrease in the microbial abundance, diversity and an increased Firmicutes/Bacteroidetes ratio. A microbiome-oriented intervention (minocycline in this case) reduces blood pressure suggesting a therapeutic possibility (12). Another new study reveals a relationship between gut dysbiosis and blood pressure in obstructive sleep apnea-induced hypertension (13).

IgA nephropathy

IgA nephropathy (IgAN) has also been associated with intestinal immunity (IgA is present in mucosal secretions – gastrointestinal fluid). Studies show that the microbiome composition is different in patients with IgA nephropathy and healthy controls and also in patients in which disease progresses and non-progressors (14). In animal models B-cell activation factor transgenic mice were shown to exhibit IgA mesangial deposition which did not occur without the presence of specific gut microbiota and circulation of specific IgA antibodies (15). Genome-wide association studies suggest a tight link between IgAN and inflammatory bowel diseases (16) therefore strengthening the hypothesis for a strong intestine-kidney connection possibly mediated by the gut microbiome.

Acute kidney injury

In animal models of kidney ischemia-reperfusion injury the extent of damage differs between germ-free and control mice being more severe in "sterile" animals and becoming equivalent after addition of bacteria to diet suggesting a potential therapeutic intervention (17).

Another acute kidney injury (AKI) study evaluated the relationship between short-chain fatty acids (SCFAs) and the extent of renal dysfunction. In health SCFAs are fermentation end products (derived from dietary fiber) of gut microbiota which exhibit anti-inflammatory properties. Mice subjected to ischemia-reperfusion injury treated with butyrate, propionate and acetate 30 minutes before ischemia and at the moment of reperfusion which modulated the inflammatory process, ameliorated the effects of hypoxia and improved outcomes (18).

Chronic kidney disease

The emerging role of gut bacteria in chronic kidney disease (CKD), which has been termed "kidney-gut axis" or "microbiome-centric theory of CKD progression" (19, 20), has been gaining importance in recent years. The fact that some of the uremic toxins are of colonic origin and that in the face of disease the gut excretes some metabolites e.g. potassium has been known for years.

With the loss of kidney function the gut microbiome changes. There is an increase in the colonization

of the duodenum and jejunum (21), a higher number of aerobic bacteria and an abundance of proteolytic bacteria (22, 23). The resulting dysbiosis is both a consequence of uremia and contributes to it. In kidney disease generation of many metabolites such as ammonia (by urease producing bacteria), guanidine (from creatinine metabolism), phenols (para (p)-cresol), amines, indoles (especially indoxyl sulfate), thioles, trimethylamine-N-oxide (TMAO) (a metabolite of dietary choline, lecithin and L-carnitine) takes place in the colon (24). The pathogenesis of this is complex starting with histologic changes in the gastrointestinal system (reduction of villous height, elongation of the crypts, infiltration of lamina propria with inflammatory cells, disruption of colonic epithelial tight junction) resulting in increased intestinal permeability (25), slower intestinal passage (26), but also dietary changes (lower fiber intake) (27), more frequent hospitalizations, use of antibiotics (28) and possibly concomitant medications (phosphate binders, iron supplements) (29) are probable culprits. Toxins generated in the colon not only "leak" through the wall and appear in plasma but (as proposed in the protein metabolite hypothesis) may be taken up by organic anion transporters in the tubules and may damage them (30) thereby contributing to CKD progression. In a large cohort with minimal renal function decline levels of indoxyl sulfate, p-cresyl sulfate and phenylacetylglutamine were early markers of CKD and were associated with changes in the gut microbiome suggesting a causal relationship (31). Another culprit is endotoxin (phospholipid from the outer wall of Gram-negative bacteria). Its translocation from the colon is postulated to promote inflammation in kidney disease but also plays a role in atherosclerosis progression, obesity, insulin resistance and diabetes (32, 33).

CKD related comorbidities

As written above obesity, insulin resistance and type 2 diabetes are also linked to a dysbiotic microbiome (a decrease in Bacteroidetes/Firmicutes ratio and presence of some opportunistic pathogens) (34). The infectious pathogenesis of atherosclerosis has been present in science for many years. Apart from endotoxin and TMAO, a new player is hydrogen sulfide produced by sulfate reducing bacteria. Recent findings suggest that it can be cardioprotective (35) and its levels are reduced in animal models of CKD (36) and hemodialysis patients (37). Depression, anxiety, disruption of the circadian rhythm and some other neuropsychiatric disorders found in CKD patients are also associated with dysbiosis. In fact the gut-brain axis has been characterized long before the gut-kidney axis with the microbiome referred to as the "brain peacekeeper" (38).

Kidney transplantation

The microbiome also influences greatly the immune system of its host (it promotes regulatory T cells (Tregs), regulates CD4+ induction and many others (39)) therefore it seems prudent to think that it must play a great role in kidney transplantation. Indeed, there are pilot studies showing how gut microbe population changes after allograft placement and that these changes correlate with the development not only of post-transplant diarrhea and *Enterococcus* urinary tract infection but also with acute rejection (5). Research in the area of drug metabolism (namely tacrolimus) also implicates colonic bacteria as an important player in achieving adequate immunosuppression (40).

Kidney stones

A small study from 2016 suggests that also kidney stone formers (independent of stone composition) have a distinct gut microbiome (both *Bacteroides* and *Prevotella* abundance were associated with nephrolithiasis) (41).

POTENTIAL THERAPEUTIC INTERVENTIONS

Prebiotics

A prebiotic is a indigestible food ingredient that exerts its favorable effect by selective stimulation of the growth or activity of some bacteria in the colon. The most common substances include inulin, fructo-oligosaccharides, galacto-oligosaccharides etc. Oligofructose-enriched inulin and oligosaccharides reduces p-cresyl sulfate serum concentrations in hemodialysis patients (42). Acarbose as an inhibitor of α-glucosidase prevents hydrolysis of oligosaccharides and in that mechanism also reduces the concentration of p-cresol in healthy persons (43). High dietary fiber intake is also associated with lower risk of inflammation and reduced mortality of kidney disease patients (44).

Probiotics

Probiotics are natural or genetically modified microorganisms expressing specific exogenous enzymes that when consumed in adequate amounts offer health benefits to the host (45). The concept is to use probiotics in CKD to slow progression of the disease, control chronic inflammation, remove uremic toxins and relieve some of the gastrointestinal complications (e.g. chronic constipation).

Prakash and Chang used living urease-producing *Escherichia coli* to lower blood urea nitrogen levels in uremic rats (46), while Ranganathan et al. went a step further and proved that similar animals had a slower progression of kidney disease and longer life expectancy when fed *Bacillus pasteurii* (47). A few small studies in humans (CKD stage 3-4) show significant decrease in urea levels (48, 49). Studies in maintenance hemodialysis and peritoneal dialysis patients report reductions in serum levels of endotoxin, proinflammatory cytokines, p-cresol concentration, C-reactive protein (50, 51), however a randomized study of a specific probiotic formulation Renadyl (Kibow Biotech) in dialysis patients failed to demonstrate any efficacy (52).

Synbiotics

Synbiotic is the combination of both prebiotic and probiotic. SYNERGY (synbiotics easing renal failure by improving gut microbiology) – a placebo-controlled randomized cross-over trial of a synbiotic (*Lactobacillus*, *Bifidobacterium* and *Streptococcus thermophilus* together with high molecular weight inulin, fructo-oligosaccharides and galacto-oligosaccharides) in CKD patients showed a decrease in serum p-cresyl sulfate levels, no change in indoxyl sulfate levels and a favorable modification of the stool microbiome (53).

Eubiotics

Rifaximin is a non-absorbable antibiotic which has been demonstrated to increase the concentrations of Lactobacilli and help in keeping a stable gut environment (the effect persists after a 10-day treatment). It is widely used in many intestinal diseases and has been named an eubiotic (instead of an antibiotic because of it's favorable effect on the microbiome) (54). Studies on rifaximin therapy are lacking, although there is a currently recruiting trial from the Kansas Medical University (55) which aims to determine if this antibiotic/eubiotic decreases serum and urine levels of bacterial waste products (namely TMAO) and inflammatory markers and evaluate the microbiome of these patients.

Fecal transplantation

Human fecal transplantation has been proven effective in recurrent *Clostridium difficile* infection (56) and it seems prudent to think that it might be effective both in kidney disease and kidney transplantation maybe. Trials to examine those hypotheses are needed.

Adsorption of uremic toxins

Sevelamer is not only a phosphate binder but also binds endotoxin in the gut of hemodialysis patients (57). A new compound – AST-120 is an oral adsorbent that decreases serum levels of indoxyl sulfate and slowed the progression of kidney disease in rats (22), in a retrospective study of 560 patients with CKD delayed the time to dialysis initiation with no influence on survival (58) but unfortunately did not alter the course of disease, mortality or quality of life in a large randomized trial of 579 patients with advanced CKD (stage 3 or 4) (59).

Other

Lubiprostone is a chloride channel activator used in the treatment of constipation that in an animal model of kidney failure changed the gut microbiome, reduced blood urea nitrogen levels and protected against tubulointerstitial damage, renal fibrosis, inflammation (60). Studies in humans are lacking.

CONCLUSIONS

Recent advances in our understanding of gut microbiome have contributed to a new concept of kidney-gut axis and helped to explore the potential role of colon bacteria in renal disorders. Many data point that microbiome plays a critical role in pathogenesis and/or progression of several renal diseases. Interestingly, the introduction of that physiological pathway has opened possible novel therapeutic interventions including such agents as prebiotics or probiotics. Those uncomplicated treatment opportunities may be actually incredibly beneficial since studies suggest their relationship with improved patients' outcome. Unfortunately, studies undertaken so far have not brought answers to numerous microbiome related questions and many aspects of kidney-gut interaction are unknown. Thus, further investigation are needed to entirely elucidate the functions of the gut bacteria and assess efficacy of microbiome oriented interventions.

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