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The gut microbiome, diet, and chronic kidney disease

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Abstract

The human gut consists of many microorganisms. The exact components of bacteria are undetermined, but studies based on molecular analysis have revealed that there are two main of phyla, Firmicutes and Bacteroidetes. The gut microbiota has been appeared to participate in specific metabolic activities. Disruption of normal gut microbiota (dysbiosis) is associated with systemic and metabolic disease, such as chronic kidney disease (CKD). Recent studies revealed quantitative and qualitative changes in gut microbiota in patients with CKD. In addition, dysbiotic gut microbiome may participate in progression CKD and CKD associated complications. Investigation determined dietary habit in short- or long-term is one of the most important factors that influence the diversity and constitution of the human intestinal microbiota thus, affecting host metabolism and disorder risk or progress. In addition, increased interest has created in using probiotics, and prebiotics to decrease the risk of dysbiosis in the intestinal to prevent or cure the human illnesses. In this review we summarized the gut microbiota composition, the relation between gut microbiota and CKD, and dietary factors that influence on gut microbiota and finally we concluded that the Mediterranean diet with probiotic, prebiotic or symbiotic direction are ideal and innovative method for CKD patients.

Introduction

The adult gut consists of more than 100 trillion microorganisms with 160 such species from a group of 1000 to 1150 common bacterial species called the microbiota. The number of genes from these microbes (microbiome) has been approximated 150-fold more than the host genome (1,2).

The exact components of bacteria are undetermined, but studies based on molecular analysis have revealed that there are two main of phyla, Firmicutes and Bacteroidetes. Firmicutes (e.g. Enterococcus, Clostridium, Ruminococcus and Lactobacillus) that contain gram-positive bacteria and constitute 60% of the gut microbiota classified as the main producers of butyrate which specially degrade indigestible polysaccharides. The gram-negative Bacteroidetes (e.g. Bacteroides and Prevotella) constitute 15% phylum categorized as propionate producers that utilize a broad kind of substrates. The rest of bacteria include Verrucomicrobia, Actinobacteria and Proteobacteria have influence on health status (2,3).

The composition of the gut bacteria alters considerably between individuals, but it is also impressionable to alteration in every individual and it influenced by host age, medication use specially antibiotics, diet, genetics, immunological factors, general lifestyle, geography, health and disease status (4,5).

The gut microbiota has been appeared to participate in specific metabolic activities such as synthesis of some vitamins, dissection of indigestible plant polysaccharides, transformation of conjugated bile acids, break down of dietary oxalates, energy homeostasis, lipid metabolism, fat storage regulation, toxin neutralization, promotion of the immune system and defense against pathogens (4).

Core tip

It has been detected that toxins produced by gastrointestinal dysbiosis may contribute to chronic kidney disease progression and complications. Thus the Mediterranean diet, that shifts gut microbial metabolism towards saccharolytic pathway and decreases colonic transit time, with probiotic, prebiotic or symbiotic direction, which may be useful in lessening gut derivative uremic toxins, are ideal and innovative method for chronic kidney disease patients.

The gut microbiota in a state of "normobiosis" in healthy circumstances affects the health of the host and in dysbiosis condition (disruption of normal gut microbiota) associates with systemic and metabolic disease, such as obesity, insulin resistance, inflammatory bowel disease, Crohn's disease, colorectal cancer, cardiovascular disease, autoimmune disease, allergy, chronic kidney disease (CKD), and non-alcoholic fatty liver disease (2,6).

Materials and Methods

For this mini-review we searched PubMed, EBSCO, directory of open access journals (DOAJ), Google Scholar, and Web of Science with key words chronic kidney disease, gut microbiota, gut bacteria and end-stage renal disease.

Chronic kidney disease and gut microbiota

As mentioned in the gastrointestinal and systemic disorders similarly in CKD, a gut microbiota dysbiosis is present. Recent studies reveal quantitative and qualitative changes in gut microbiota in patients with CKD and end-stage renal disease (ESRD). Also dysbiotic gut microbiome may participate in progression CKD and CKD-associated complications. This bilateral relationship is not exactly determined (7).

The change of gut microbiota in CKD patients

Investigations have shown an increase in both aerobic and anaerobic organisms in the duodenum and jejunum and decreases in both Lactobacillaceae and Prevotellaceae families in ileum of uremic CKD/ESRD patients; also there are higher number of aerobic bacteria and *Clostridium perfringens* (anaerobic bacteria) and a lower amount of Bifidobacteria (anaerobic bacteria) in hemodialysis patients (1).

The intestinal dysbiosis in CKD patient may be due to several factors such as uremia, dietary factor, and iatrogenic reasons. Uremia, a term referred as reducing of glomerular filtration rate causes increasing in urea concentration in the body fluid compartments that enter into the gastrointestinal tract and microbial urease produces a large quantity of ammonia, which is converted to ammonium hydroxide. Ammonium hydroxide increases the luminal fluid's pH that affects on mucosal irritation. The second factor that causes uremia is reduction in uric acid and oxalate excretion by renal and so adaptively secretion considerable amounts of them by colonic epithelium.

Decreased ingestion of dietary fiber, probably oral iron consumption, intestinal wall edema, metabolic acidosis, slow colonic transit, and frequent usage of antibiotics are other causative factors in uremia. In addition, these factors can destroy the mechanical wall of the gut, which causes bacterial translocation to blood and micro-inflammation (8).

Dietary factor: Dietary alterations and medical interventions can impact on the biochemical environment of the intestinal tract in progressive CKD patients. The limitation of fruits and vegetables, which contain lots of potassium, to prevent hyperkalemia causes low intake of indigestible compound carbohydrates that are the main source of nutrients for the gut microbiome thus change the metabolism and composition of the microbiome (8).

Iatrogenic factors such as antibiotic therapy and a number of phosphate binding compounds including calcium carbonate, calcium acetate, iron-based products, aluminum hydroxide that are commonly eaten by patients with progressive CKD can exert significantly effects in shaping the intestinal microbiome (7).

The role of gut microbiota in CKD progression

It has been suggested that toxins produced by gastrointestinal dysbiosis may contribute to CKD. These toxins including phenols, indoles and p-cresol generate of protein fermentation by gut microbiota. Indoxyl sulfate, indoxyl glucuronide, p-cresyl glucuronide, p-cresyl sulfate, phenyl glucuronide and phenyl sulfate that is due of metabolizing these compounds in the liver, is predictor of CKD progression. These molecules biologically stimulate pro-inflammatory responses, leukocyte stimulus, and endothelial dysfunction. Systemic inflammation and oxidative stress have a key role in progress of CKD and its complications. Thus, dysbiotic causes the systemic distribution of these molecules that increases the possibility of a uremic toxin load for the kidneys and may cause CKD.

Gut microbiota is a key factor, regulating primary events to activate, the inflammation related with various diseases. Certain microbial components up-regulate immune receptors, such as Toll-like receptors (TLRs) in the tissue. This activates some signaling transduction pathways (e.g. JNK and IKKβ/NF-κB), which produce inflammatory chemokine and cytokine (TNF-α, IL-1, MCP1) and lead to inflammatory changes. It is proved that systemic inflammation and oxidative stress have a key role in progress of CKD and its complications (9).

Diet and gut microbiota

Investigation determined dietary habit in short- or long-term is one of the most important factors that influence the diversity and constitution of the human intestinal microbiota thus affecting host metabolism and disorder risk or progress. Food components supply substrates for the intestinal microorganism (3). Diverse group of bacteria ferment specific substrate so complicated diets can provide factors to promote or inhibit special phylotypes.

The dietary exerts effects on microbial metabolism and immune functions throughout some pathways include increasing intestinal permeability, changing the bacterial fermentation of nutrients, disturbances intestinal function by triggering both native- and adaptive-immune responses, and overexpression of genes (10).

Gut bacteria contributes in food digestion via two major catabolic way including proteolytic and saccharolytic. Proteolytic and saccharolytic pathway containing bacterial species that dominantly fermenting proteins and bacteria are predominantly carbohydrates fermenters respectively.

Studies have revealed that a balanced, healthy colonic microbiota is mainly saccharolytic with the dominance of Lactobacilli and Bifidobacteria, which hydrolyze complex polysaccharides to short-chain fatty acids (SCFAs), mostly acetate, butyrate, propionate. They have a positive immune-modulating and protective activity either by promoting intestinal barrier integrity or by prompting direct transcriptional responses in immunity cells. Proteolytic fermentation produces polyphenols that stimulate anti-oxidative, anti-inflammatory, anti-ageing effects, also generate SCFA by amino acid fermentation. On the other hand, in anaerobic condition proteolytic bacteria (putrefaction) ferment proteins to branched, SCFAs, phenols, thiols, indoles, ammonia, and amines (11).

Both macronutrients and micronutrients shape the gut microbial environment. The study about micronutrient is rare in human and as regard the percentage of one macronutrient to total energy intake naturally influences the proportion of other macronutrients to the energy intake and their biological effects result from the mixed impact of all macronutrients. Although determination of pure effect of them is difficult. In this review, we summarize the study about the effect of macronutrient and dietary pattern on gut microorganism.

Dietary carbohydrates

Carbohydrate intake is a main determinant of microbial composition. Dietary carbohydrates that do not digest and so reach the colon are mainly resistant starches (RS), oligosaccharides, and non-starch polysaccharides (NSP) even though a number of di- and mono-saccharides may also reach the colon. Carbohydrate fermentation causes the production of SCFAs including butyrate, propionate, and acetate. Butyrate is the main energy resource for the colonocytes; propionate involves gluconeogenesis in the liver; and acetate is used up in lipogenesis. They also affect cell difference and proliferation, vitamin production, ion absorption and participate to the provide amino acids (12,13).

Dietary fiber

Dietary fibers with different chemical components motivate the activity and growth of producing butyrate bacteria such as *Eubacterium rectale*, Roseburia, and *Faecalibacterium prausnitzii* that promote the health, increase lactobacilli and Bifidobacteria, decrease Firmicutes/Bacteroidetes ratio and produce phenolic compounds with antitumoral and antioxidant activities. Bacterial metabolism of plant cell walls causes releasing and transformation of phytochemicals that have antioxidant and anti-inflammatory activities (14).

Dietary proteins

Protein fermentation produces diverse metabolite. The chief pathway of amino acid fermentation is deamination, causing the construction of SCFA and ammonia. Also bacteria deaminate aromatic amino acids and produce the phenolic compounds p-cresol, phenylacetate (from phenylalanine), phenylpropionate (from tyrosine), and indole acetate and indole propionate (from tryptophan) that some of them are potentially toxic (15).

Dietary fats

Quantity and quality of dietary fat by its impression on bile acid composition and secretion modifies intestinal microbiota composition and initiates microbial dysbiosis, inflammation, and intestinal permeability. High fat diets independently of fatty acid composition reduce total fecal microbiota and Bacteroidetes/Firmicutes ratio however, it is not obvious this resulted of elevated fat or reduced carbohydrate content. Studies have indicated that a high fat diet causes elevated intestinal permeability and a rise in plasma LPS levels that can activate TLRs and the nucleotide-binding oligomerization domain containing 1 (NOD1) receptor and lead to inflammation and insulin resistance (16).

Dietary pattern

The study in this field is rare and there is only a little study about Mediterranean and Western dietary pattern.

Mediterranean dietary pattern

This diet is rich in complex carbohydrates, vitamins, fibers, and poor in fats and animal proteins and shift the gut microbiota metabolism to a saccharolytic profile and as mentioned above promote general health (17).

Western dietary pattern

This diet is rich in animal proteins and fats that shift gut microbiota metabolism to proteolytic and increase chronic systemic disorders (18).

Prebiotics

A prebiotics are food ingredient resistance to hydrolysis by enzymes in the upper segment of the gastrointestinal tract and selectively motivate the proliferation or action of one or a partial number of bacteria in the gut with constructive impressions on host health. Prebiotics have been categorized primarily into two groups, based on their chemical compositions, the galacto-oligosaccharides (GOS) and the inulin-type fructans (ITF). They elevate the growth of useful gut bacteria, predominantly Bifidobacterium and Lactobacillus and reduce destructive proteolytic and putrefactive microorganisms. Mechanisms have been proposed for protective effect of prebiotic including improving the production of SCFAs, improvement of the gut barrier, alterations in the intestinal bacteria and control of the systemic and mucosal immune response (19).

Probiotics

Probiotics, as identified by the World Health Organization (WHO), are "live microorganisms which when administered in adequate amounts present a health benefit on the host". Probiotics comprise living bacteria,

for instance lactobacilli, Bifidobacteria species, and streptococci, which can modify intestinal microbiota and influence health state. The health-promoting effects of probiotics may be associated to their ability to produce anti-bacterial combinations, modulate pH, produce antioxidants, vitamins, and compete with pathogens (20,21).

Symbiotic

Symbiotics are a construction of both probiotics and prebiotics, with a synergic and incorporated influence on gut flora stability and health elevation (6,22).

Conclusion

Gut microbiota has been detected as a novel and general target for non-pharmacologic therapies in pathological situations. It is necessary to be noted that this field is in initial stages and has not yet been identified and described the composition and function of bacterial in detail. Microbial composition appears to be personalized and microbiome function can alter considerably among persons.

Primary dietary research presents provision for diet, as a possible goal for microbial alteration, but more high quality study involving randomized controlled trials seems necessary to understand the impression of diet quality on compound and function of microbiota. In addition, elevated interest has created in applying probiotics, and prebiotics to decrease the risk of dysbiosis in the intestinal and modify the gut microbiota to prevent or even cure the human illnesses.

It has been detected that toxins produced by gastrointestinal dysbiosis may contribute to CKD progression and complications. Thus the Mediterranean diet, that shifts gut microbial metabolism towards saccharolytic pathway and decreases colonic transit time, with probiotic, prebiotic or symbiotic direction, which may be useful in lessening gut derivative uremic toxins, are ideal and innovative method for CKD patients.

Author's contribution

MK was the single author of the manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

The author of this manuscript declares that he has followed the ethical requirements for this communication. Also, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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