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Review Article

The Role of Microbiota in the Development and Progression of Chronic Kidney Disease

Kronik Böbrek Hastalığının Gelişmesinde ve İlerlemesinde Mikrobiyotanın Rolü

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ABSTRACT

Researchers related to micobiota have claimed that intestinal microbiome exerts an effect on development of disease in many organ systems. Fat tissue, kidneys, heart and vasculature, intestines and even brain tissue are affected by dysbiosis of gut flora. With the increasing number, and quality of the studies, the topics investigated have demonstrated variations from being focused solely on microbiome itself to metabolites of this flora penetrating into serum and immune response of the body to these metabolites. Metabolites released by intestinal flora trigger chronic inflammation in the body and lead to the development of metabolic syndrome, chronic renal disease or cardiovascular diseases. With such a vast gamut of diseases and pathologic conditions related to intestinal microbiome, it should come as no surprise that there have been attempts at treatment of dysbiosis with methods including flora transfer from healthy individuals. This review will focus on these disease states and how they are affected by dysbiosis of flora. The roles played by specific metabolites that increase during intestinal dysbiosis such as indoxyl sulfate, p-cresyl sulfate or trimethylamine N-oxide in chronic kidney disease and atherosclerosis will be discussed. Besides, increase in the permeability of intestinal barriers due to the evolvement of uremia as a result of chronic renal disease, ensuing development of dysbiosis, and the effects of these diseases on dysbiosis will be also dealt with.

Keywords: *Gut microbiota, chronic kidney disease, inflammation, proteinuria*

ÖZ

Mikrobiyota hakkındaki araştırmalar birçok sistemdeki hastalık gelişiminde bağırsak mikrobiyomunun etkisi olduğunu iddia ediyor. Bunlardan birkaçı; yağ doku, kalp, dolaşım sistemi, sindirim sistemi ve hatta santral sinir sistemidir. Bu konudaki araştırmaların sayısının ve kalitesinin artmasıyla birlikte üzerinde araştırılan konular; bağırsak mikrobiyomunun saf oluşumundan, bu floranın kana geçiş yapan metabolitleri ve vucüdun buna verdiği tepkiye kadar çeşitlilik göstermeye başladı. Bağırsak florasının salgıladığı metabolitler, vücutta kronik enflamasyonu tetikleyerek metabolik sendrom, kronik böbrek hastalığı ya da kardiyovasküler hastalıklar gibi hastalıklara yol açabilmektedir. Bunlar gibi geniş kapsamlı ve multi-sistemik hastalıkların bağırsak mikrobiyomuyla bağlantıları kurulması üzerine, bağırsak mikrobiyomunun bozulmasının flora aktarımı gibi yöntemlerle tedavi edilmeye çalışılması şaşırtıcı olmayan bir gelişme olmuştur. Bu makale, bazı hastalıkların flora disbiyozundan nasıl etkilendikleri üzerine yoğunlaşacaktır. Indoxil sülfat, p-krezil sülfat ya da trimetilamin N-oksit gibi bağırsak disbiyozu sırasında artan metabolitlerin kronik böbrek hastalığı ve ateroskleroz gibi hastalıklarda ne gibi roller oynadığı tartışılacaktır. Bağırsak bariyerlerinin permeabilitesinin kronik böbrek hastalığı sonucunda gelişen üremi nedeniyle artması ve bunun sonucunda gelişen disbiyoz gibi bu hastalıkların da disbiyoz üzerindeki etkilerine de değinilecektir.

Anahtar kelimeler: *Gut mikrobiyota, kronik böbrek yetmezliği, inflamasyon, proteinüri*

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INTRODUCTION

Human gut is populated with more than 100 trillion cells, reaching densities of 1011-1012 cells/ml in densest regions of colon[1]. Although crowded, when compared to the genus density of biosphere, gut population diversity is extremely limited, and can be tracked to two divisions of bacteria (Bacteriodites and Firmucites) and one of archea[2]. Numerous studies demonstrated that microbiome is affected by lifestyle and nutrition[3,4]. Gut microbiome affects the body habitus and health status of the individual[5] whereas change in gut microbiome diversity and species are also affected by age - as suggested by notable differences between old and very old patients[6,7]. In this article, the effect of gut microbiota on human health will be discussed, especially focusing on pro-inflammatory effect of microbiome due to immune dysregulation and how this affects the development and progression of chronic kidney (CKD) and cardiovascular disease (CVD).

Effects of microbiome dysbiosis and subsequent endotoxemia

Gut microbiome may be seen even in meconium[8], and it is sensible to think that this flora affects the host's life in ways not limited to the gastrointestinal tract[9]. Such effects can be tracked to fat cells in the body and how they react to ingested lipids. Even isocaloric diets can exert significant differences on body fat composition and energy expenditure of the organismi because diet promotes different species of gut microbiota[10]. Experiments have found that white adipose tissue inflammation is the main outcome of the diet induced Toll-Like Receptor (TLR) signaling activation, which will be further discussed. Substances related to accelerated atherosclerosis such as trimethylamine N-oxide (TMAO) have been found in the bloodstream of mice following fecal microbe implantation from mice which were prone to atherosclerosis due to innate increase in the production of TMAO[11]. Fermentation of ingested protein by gut microbiota also increases toxic substances such as p-cresol sulfate and indoxyl sulfate which are thought to have an effect on CKD[12]. Clerance of these toxins are more difficult in CKD patients and therefore they can build up leading to uremia[13]. Gut microbiota has been shown to have a role in the conversion of free choline and phosphatidylcholine to TMAO, and even with the same dietary choline supplementation, an intact gut flora seems to increase atherosclerotic rate up to threefold in healthy mice[14].

Effects of microbiome dysregulation on the course of chronic kidney disease

Gut microbiome is limited to the inside of intestinal lumen due to the barrier function of the intestinal epithelium. Antigens and pathogens have restricted passage through these tight junctions[15]. It is suggested that in uremic patients barrier function in intestinal mucosa is impaired[16,17] and prone to the inflammatory effects of circulating endotoxemia caused by the dysfunctional epithelial barrier and modified gut flora[18]. When intestinal barrier shows a normal physiologic behavior, circulating amounts of plasma endotoxins are quite small, while increased amounts of endotoxins are associated with atherosclerosis and cardiovascular disease[19,20]. Responses to microbiome and associated endotoxemia are quite diverse in origin and include immunologic response to toxins through TLRs that detect lipopolysaccharides (LPS) and other related molecules[15,21]. Synthesis of tryptophan and related serotonin[22] is also affected, which exerts an effect on the cardiovascular system (see below for more details).

However, endotoxemia resulting from dysfunctional epithelial barrier is not the only route of interaction between gut microbiome and kidneys, as short chain fatty acids produced by gut microbiome effect renin secretion by interacting with olfactory receptor 78 (Olfr 78), a G protein-coupled receptor expressed in juxtaglomerular apparatus with a consequent increase in RAAS activation[23-25]. Propionate secreted by gut microbiome has

a positive effect on renin secretion through this Olfr78 g protein-coupled receptor[23,24]. In a recent research, gut microbiome was shown to have an effect on enterochromaffin cells. These cells are responsible for serotonin synthesis. Increased plasma levels of serotonin and related physiological changes have been shown in mice with deficient gut microbiome[22,26]. Long-term elevated serum serotonin levels decrease blood pressure[27] which might be related to its cardioprotective effects[28]. Yet another metabolite of gut microbiome from serotonin precursor tryptophane is indoxyl sulfate, which is excreted through proximal tubules, but can build up in CKD patients[13].

Pathogen and antigen transition and effect of dysbiosis on development and progression of proteinuria

It is possible to draw a cause and effect relationship between gut dysbiosis and decreased renal functions. The main affector in this situation is the increased permeability of the intestinal epithelial barrier[32]. With overt uremia, due to decreased excretion from proximal tubules, intestinal epithelial barrier loses its effectiveness through loss of protein mass and thus, luminal endotoxins and related antigens are released into circulation. This results in a vicious cycle which increases morbidity in CKD patients.

Proteinuria is the outcome of another pathological association between microbiotal dysbiosis and kidney function. Dysbiosis is significantly related to obesity, and related metabolic syndromes[29,30]. Obesity in itself is a risk factor for CKD[31], due to obesity-related glomerulopathy. Dysfunctional energy metabolism is not the only way renal functions are also affected by dysbiosis. In a study based on rats with 5/6 nephrectomy, increased number of Lactobacillus was correlated with decreased systemic inflammation and proteinuria[32]. Levels of uremic toxins such as indoxyl sulfate and p-cresyl sulfate decrease in serum. Decreases in the levels of proteinuria, serum urea and related uremic toxins were suggestive of the nephroprotective function of Lactobacilli spp. The previously mentioned decrease in protein mass of intestinal tight junction barrier was more deeper in Lactobacillus- supplemented nephrectomized mice. This so- called protective effect seems to stem from TLR-2 activation via stimulation with Lactobacillus. TLR-2 expression was found to be lower in nephrectomized mice compared to control group, but increased with Lactobacillus supplementation. With this supplementation and subsequent rise in TLR-2 expression and intestinal epithelial barrier protein mass, serum indoxyl sulfate, LPS levels and urinary protein excretion decreased.

Another pattern recognition molecule is CD14, which functions in the pattern recognition cascade of endotoxin. High levels of CD14 are associated with increased proteinuria, and mortality in hemodialysis patients and inversely associated with eGFR[33]. CD14 count greatly increases monocyte response to LPS and endotoxemia in general resulting in both local and systemic inflammatory response. This was shown in a study focused on CD14 knockout mice that were grafted with two separate patches of fat, one from another CD14 KO mouse and one from a wild type. The patch from the wild type showed excess macrophage proliferation when compared to the CD14 KO graft, in response to endotoxemia resulting from LPS infusions[34]. Activation of CD14 as a result of endotoxemia can be a possible candidate for a decreased renal function in dysbiotic CKD patients with failing intestinal epithelial barrier.

Chronic Inflammation caused by microbiotal transition and subsequent effects on cardiovascular disease

Another potential morbidity related to gut microbiome is the chronic low-grade inflammation. The aforementioned deterioration of the intestinal barrier to endotoxins and related luminal pathogen-antigen transition into systemic circulation (aptly named leaky gut phenomenon)[35,36]

is related to chronic inflammation of the whole gastrointestinal system[37]. This event usually co-exists with CKD, both pathologies affecting the course of each other. It is being pointed out that altered immune response to the tight junctions of colonic mucosa in CKD leads to a marked decrease in protein content of tight junctions[38]. The resulting endotoxemia leads to a vicious cycle of immune recruitment of pro-inflammatory substances; IL1,6 and TNF-α[39]. This cycle is started by endotoxins activating cellular signaling pathways involving CD-14, TLR-4, LPS Binding Protein and MD-2[35,40]. With the activation of these pathways, significant low-grade inflammation ensues in the whole body. With atherosclerosis considered a chronic inflammatory disease[41] the origin of the inflammation is being tracked to the TLRs in myocardium. This was observed in a study that used TLR-4 knockout mice[42]. These TLR-4 knockout mice had decreased ischemia and reperfusion injury and also significantly less risk for myocardial infarction, compared to wild types[42]. In addition, this study showed that endotoxemia is a strong risk factor for early atherogenesis[19] and another pathway responsible for degenerative changes is thought to be related to activation of nuclear factor kappa-B[40] which is considered to be an atherogenic agent[43,44]. This nfk-B pathway is thought to be one of the triggering agents of specific TLR responses[45]. The subsequent endotoxemia and bacterial DNA translocation into body also increase insulin resistance and in this study bacterial DNA + subjects were shown to be significantly more resistant to insulin when compared to DNA - patients[45]. The same study points out that resolution of chronic inflammation is delayed in the bacterial DNA- positive subgroup of obese patients.

Effects of dysregulated gut microbiome on the development of type I and type II diabetes mellitus

Considering that microbiotal cell count outnumbers human cell count 10 to 1, it is no surprise that gut microbiome affects the energy harvesting efficiency of the host, and therefore the body habitus. This was shown in a study in which microbiome from obese mice was transferred to sterile mice, with a resultant consecutive increase in fat deposition[46]. It was found that a relative increase in Firmucites spp. and subsequent decrease in Bacteroides spp. resulted in a net increase in calorie intake[47]. It has also been pointed out that short chain fatty acids and their metabolites released by microbiome can alter regulation of appetite and adipogenesis in liver[48]. Considering body habitus and metabolic syndromes including diabetes, the effect of microbiome on development and progression of diabetes mellitus can hardly be underestimated. It was discovered that high fat consuming mice started to demonstrate signs of significant endotoxemia and strong intolerance to glucose and increased fasting insulinemia. During the same research, some of the high fat consuming group of mice was also introduced to non-digestible carbohydrates that showed prebiotic properties. Mice that received prebiotic treatment had lesser endotoxemia compared to high-fat consuming group[49]. Insulin sensitivity was shown to be increased in a metabolic syndrome-induced human patient group 6 weeks after they had an infusion of microbiome from lean donors[50]. This change in glycemic control has been addressed in another research using two genus of microbiome, namely Proteobacteria spp and Enterobacteriaceae spp. that induced an increase in insulin resistance. One of the main perpetuators of poor glycemic control related to microbiota is monosaccharides and short- chain fatty acids functioning both as signaling molecules and substrates for gluconeogenesis and lipogenesis in liver[51]. These molecules are derived from polysaccharises which are fermentated by gut microbiota[52]. The mammalian digestive tract is inherently unable to digest most of the complex polysaccharides, and these undigested complex molecules reach the distal gut and are hydrolyzed by the gut flora producing myriad of byproducts through fermentation[53]. One of these products is acetate, which, in an experiment performed with high-fat

consuming mice and chow-fed mice, intra-arterial acetate infusion to chow-fed mice showed similar increase in insulin secretion compared to high-fat fed mice due to their glucose-stimulated insulin secretion pattern[54]. From this finding it can be assumed that these short-chain fatty acids produced by microbiome can disrupt glucose metabolism via changes in both endocrine signaling and net energy balance of diet.

Another molecule that was under focus in a study was butyrate whose levels were shown to be increased in the presence of significant Roseburia intestinalis and Roseburia inulinivorans populations[55]. Infusion of these microbota was found to improve insulin sensitivity in a previous research[56]. Also seven microbiota that were found to be decreased in a study which evaluated 39 significant genuses in the microbiome of type 2 diabetes mellitus patients were found to be butyrate producing[55].

Endotoxemia due to LPS infusion in this study also showed decreased glycemic response in mice that were on a high fat diet[34]. Epithelial barrier dysfunction, due to dysbiosis, can trigger endotoxemia which can result in glucose intolerance.

In type 1 diabetes mellitus patients, dysbiosis is evident[57] with decreased numbers of phylum Firmucites and increased numbers of Bacteroidetes colonization. Another study has found that the short-chain fatty acid producing phyla, Bifidobacterium adolescentis, Faecalibacterium prausnitzii etc. were much less populous in four antibody- positive children (antibodies to insulin, glutamic acid decarboxylase and protein tyrosine phosphatase (IA2 or ICA512), which are the hallmark antibodies in type 1 diabetes mellitus)[58] when compared to controls[59]. It is possible to find contradicting evidence however, as another large-scale study[60] did not find significant effect of change in bacterial colonization diversity or dysbiosis in the progression of islet autoimmunity in type 1 diabetes mellitus patients.

Future aspects to consider and treatment of the diseases associated with microbiotal dysregulation

In the light of these researches it is possible to state that gut microbiome is host to numerous species that co-exist in balance inside the human body and have a significant effect on multiple organ and systems and on development of different disease states, through multiple pathways, including TLR signaling activation in myocardium, olfactory receptors in juxtaglomerular apparatus, and multiple other pro-inflammatory pathways. Through these pathways, microbiotal dysbiosis can worsen the course of chronic diseases like CKD or cardiovascular disease. Numerous studies have shown that when the integrity of the gut epithelium is broken, subsequent endotoxemia adversely affects the course of CKD and hastens atherogenesis. Gut microbiome has also fundamental effect on our energy metabolism, and certain strains are more suitable to proliferate in high fat diets, further increasing the metabolic load of excess dietary fat on body by further increasing energy harvest potential. Metabolic diseases and related systemic injuries such as glucose intolerance, diabetes mellitus type 1, and 2 have microbiotal changes before the onset of the disease and this could further affect disease progression. Early detection of certain diseases via fecal examination of microbiotal biomarkers could narrow diagnostic window after the onset of the aforementioned diseases and can decrease morbidity and mortality. Further research is needed if we want to reveal additional ways in which the microbiome affects the organ and systems and to control these effects. We may get to learn to cope with chronic diseases in a much more cost and time-efficient manner and also to keep the multisystemic adverse effects of diseases like CKD, diabetes mellitus and cardiovascular disease. Treatment of dysbiosis can decrease systemic effects related to these diseases and can be a part of a multisystemic approach that is usually necessary in the treatment of these type of chronic diseases.

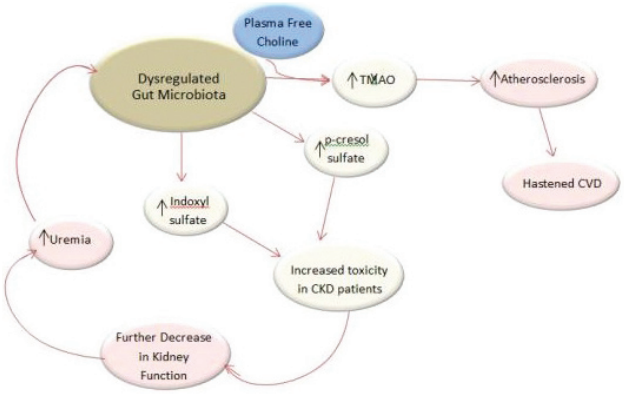

Figure 1. The chain of events in the vicious cycle that leads to dysbiosis in chronic kidney disease (CKD) patients. The pathological metabolites such as trimethylamine N-oxide (TMAO) tend to reach much higher serum values in CKD patients compared to control.

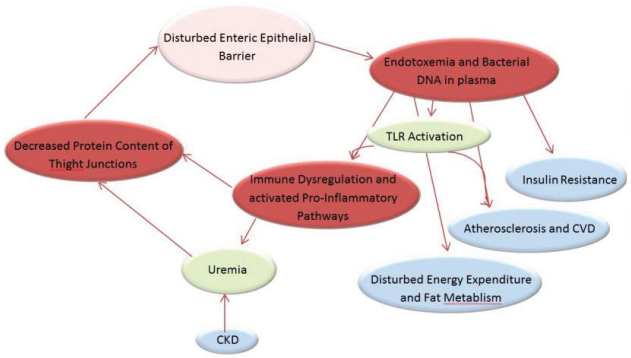

Figure 2. Endotoxemia and subsequent immune recruitment such as Toll-Like Receptor (TLR) signaling activation that leads to chronic low grade inflammation due to dysregulated pro-inflammatory pathways, affecting pathological course of multiple chronic diseases such as chronic kidney disease (CKD) and cardiovascular disease (CVD).

CONCLUSION

There is a crosstalk between gastrointestinal system and kidneys of which has a decisive role in the development of kidney disease, inflammation and proteinuria. Management of gut microbiota will create novel opportunities in the prevention and treatment of many previously undertreated conditions such as CKD.

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