International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Vitamin D and GUT Microbiota: A Review

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ARTICLE INFO

Keywords:
Gut microbiota
Vitamin D
Inflammatory diseases

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Received: December 20, 2019
Revised: March 14, 2020
Accepted: March 22, 2020

ABSTRACT

Vitamin D plays an important role in the body. Beyond its role in bone metabolism, this vitamin is involved in regulating immune and hormonal responses, antioxidant activity, cell proliferation and differentiation, and the prevention of various diseases. Vitamin D deficiency was shown to decrease the risk of inflammatory diseases including multiple sclerosis (MS) and inflammatory bowel disease (IBD). Vitamin D can affect the diversity and composition of the gut microbiota, which can be associated to a wide range of physiological processes, and disruption of gut microbiota was shown to be related to inflammation, metabolic disorders, excessive fat accumulation, and loss of insulin sensitivity. Some of the anti-inflammatory effects of vitamin D may be related to the changes in the composition of the intestinal microbiota. This study aimed to review the relationship between vitamin D and gut microbiota.

Please cite this article as: Shahsavani Z, Sohrabi Z, Karamizadeh M, Akbarzadeh M. Vitamin D and GUT Microbiota: A Review. Int J Nutr Sci. 2020;5(2):54-60.

Introduction

Vitamin D is a fat-soluble steroid hormone that is produced in the skin after exposure to sunlight. This vitamin, also known as sunlight vitamin, is found in a limited number of foods; therefore, the main way to receive this vitamin is through direct exposure of the skin to the sun light (1, 2). Vitamin D deficiency was demonstrated to affect approximately 50% of the world's population, and based on the global estimates, regardless of age and gender, more than one billion people suffer from vitamin D deficiency worldwide (2). Various factors such as low consumption of food resources, lack of sufficient access to sunlight, air pollution, latitude, and season, are the major reasons mentioned as factors related to vitamin D deficiency. Adequate access to sunlight is affected by many variables that influence the amount of sunlight (type B ultraviolet, UVB) that reaches the skin and also its efficiency (3). Vitamin D deficiency is mainly caused by increased time spent indoors and increased use of sunscreen to reduce the risk of skin cancer (4).

Vitamin D and Its Physiological Roles

Vitamin D plays an important role in several physiological processes, including calcium-phosphorus metabolism, bone regeneration, and muscle contraction (5, 6). In addition to skeletal roles, vitamin D has other activities, including prevention of cardiovascular diseases, cancer, diabetes mellitus (type 1 and type 2), autoimmune and inflammatory diseases (7-9). Vitamin D is a powerful molecule of the immune system and is involved in many innate immune processes. Vitamin D, as a strong antioxidant, also neutralizes free radicals through nitric oxide synthase and gamma-glutamyl transpeptidase (10) . Besides, the anti-inflammatory effects of vitamin D in various acute and chronic inflammatory conditions such as obesity, diabetes, and inflammatory bowel disease

(IBD) have been extensively investigated (11-14).

Chronic inflammatory diseases such as multiple sclerosis (MS) and IBD have become a problem in developed countries, while the prevalence of these diseases is increasing in developing countries too. Most likely, the interaction between genetic and environmental factors may be responsible for pathogenesis of these diseases (15, 16). The environmental factors include limited exposure to UVB and thus a reduction in serum hydroxyl vitamin D, the Western diet, and the widespread use of antibiotics. It is noteworthy that the last two factors affect the arrangement and function of the intestinal microbiota (15, 16).

Gut Microbiota

The human gut is the home for 100 trillion different microbial organisms, including bacteria, viruses, fungi, and protozoa, which make up the microbial flora or gut microbiota (17). Molecular methods have shown that more than 1000 species of bacteria live in the gastrointestinal tract (18). The cloning process of these microbes begins with the transmission of the microbe from mother to fetus. Colonization of the human gut is started after birth and is regulated by factors such as gestational age, delivery (normal or cesarean section), diet (breast feeding or formula), hygiene, and exposure to antibiotics. The environment and diet in the first 3 years of life are very important to receive the future adult microbiota and to create coexistences that affect the development of the immune and nervous systems (19).

The number and variation of the bacteria vary in different parts of the digestive tract. A small number of species live in the stomach and upper part of the small intestine, while the number of bacteria gradually increases in the large intestine (20). More than 99% of intestinal bacteria belong to the four species of Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria (21). Bacteroidetes and Firmicutes are the dominant intestinal microbial species in healthy adults .(22) The intestinal microbiota is involved in key functions such as digestion of indigestible foods, activation of immune system such as differentiation of T helper 1 (Th1) cells, proliferation of regulatory T cells, activation of tolerogenic dendritic cells, and maturation of the host's innate and acquired immune system (23, 24).

Intestinal microbiota provide the necessary energy and nutrients for the host, including Bifidobacterium that can synthesize and supply vitamins such as vitamin K and water-soluble vitamins, including B vitamins. Intestinal bacteria also produce short-chain fatty acids (SCFAs; C2-C6) by fermenting resistant starches or indigestible carbohydrates known as dietary fibers (25). Intestinal microbiota also activates drug-signaling molecules that interact with the host's metabolism, including short-chain fatty acids (SCFAs) that can interact with G protein-coupled receptors (GPCR) and can alter insulin sensitivity in fat cells and peripheral organs, and thus can regulate energy metabolism (19) .

SCFAs including acetate, propionate, and butyrate are the major anions in the large intestine, and butyrate is the main source of energy for colonial epithelial cells. *Fyli firmicutes* and Bacteroidetes, in collaboration with oligosaccharide fermentation species including Bifidobacteria, produce SCFAs from indigestible carbohydrates. In IBD, SCFA levels are significantly reduced, which may be a key factor in compromising intestinal homeostasis and immunity (25).

Mutual coexistence between human hosts and microbiota is essential for maintaining human health (25). Transient changes that occur in the intestinal ecosystem over a lifetime can, in some cases, lead to disruption of host and microbial coexistence. Due to the fundamental role of the intestinal ecosystem in maintaining host physiology, its alteration can cause a wide range of physiological disorders such as inflammation, metabolic disorders, excessive fat accumulation and loss of insulin sensitivity, which further increases the incidence of metabolic diseases (19).

Seasonal changes in the gut microbiota coincide with changes in vitamin D throughout the year, while seasonal changes in the microbiota do not significantly affect people health, but it can have an important role for people with immunodeficiency. For example, the recurrent and destructive nature of IBD and MS is strongly associated with vitamin D levels (16). A change in the composition and function of the gut microbiota is called dysbiosis (dysbacteriosis). It has been hypothesized that the cause of chronic inflammatory diseases is that dysbiosis kills beneficial microbes and their metabolic products (16).

It is clear that determining the basis for these changes, as well as identifying new ways to promote beneficial microbiota, is essential to maintain the overall health (26, 27). The intestinal microbiota creates an anti-inflammatory and protective environment that can inhibit the growth of pathogenic microorganisms (10). Recently, intestinal microbiota has been linked to chronic and inflammatory diseases (28), however in humans, no direct causal relationship has been found between intestinal microbiota change and IBD (25).

Studies on Vitamin D and Intestinal Microbiota

Animal Studies

In vitro and *in vivo* studies supported the association between vitamin D and intestinal microbiota (29, 30). Studies on vitamin D receptor (VDR)-knockout rats indicated that a lack of VDR in these animals would lead to disruption of intestinal microbiota in comparison to the control rats (31, 32). Also in VDR-knockout rats with vitamin D deficiency, there was a decrease in alpha defensin secretion and a decrease in ileal Paneth cells, as well as a decrease in the frequency of *Akkermansia muciniphila*. In contrast, an increase in the frequency of *Helicobacter hepaticus* has also been illustrated in the control rats (33). Vitamin D activates the expression of defensins and cathelicidins antimicrobial peptide (CAMP) genes, which are expressed by epithelial and immune cells and have antimicrobial properties (34).

In knock-out rats that lack the enzymes needed to produce the active form of vitamin D, treatment with 25-hydroxy vitamin D [25(OH)D] was demonstrated to reduce the severity of IBDs. This fact suggests that vitamin D can play an important role in the regulation of intestinal microbiota, and vitamin D deficiency may lead to microbial dysfunction and intestinal sensitivity to inflammatory processes (32). Several studies showed that VDR, by activating NFKB, negatively regulated the response to intestinal infections caused by bacteria (33). Also, vitamin D was shown to reduce the penetration of bacteria into the epithelium of the colon and to decrease the inflammation caused by bacteria in animal models (4, 35).

Human Studies

Observational studies have shown that serum concentration of 25(OH)D was associated with an abundance in various bacterial colonies (4). Vitamin D deficiency causes an inflammatory environment that would lead to biological disruption in intestinal microbiota, even in clinically healthy individuals (16, 36). In a study that searched for relationship between vitamin D and intestinal microbiota, they found that baseline vitamin D levels were positively associated with presence of Akkermansia bacterial population (37).

Increased Akkermansia population is associated with a reduced risk of cancer, obesity, and atherosclerosis, as well as improved fasting plasma glucose, plasma triglycerides, and body fat composition (37). After treatment with vitamin D for 8 weeks, regardless of the dose, a significant reduction in the ratio of Firmicutes to Bacteroidetes populations was observed. The high Firmicutes to Bacteroidetes ratio was associated with obesity and poor blood sugar control. This may be a mechanism for expressing a possible relationship between vitamin D deficiency and obesity, insulin resistance, and metabolic syndrome (37).

This study also found an inverse relationship between 25(OH)D and the relative abundance of Porphyromonas species that can indicate an association between vitamin D deficiency and gingivitis, as well as the benefits of vitamin D in the treatment of gingivitis (37). Few studies have examined the interaction between vitamin D and intestinal microbiota (4). Oral vitamin D supplementation is helpful for people suffering from chronic inflammatory diseases (11, 12). Oral supplements in people with vitamin D deficiency can have a significant effect on their microbial variations. In a study of 3,188 patients with IBD, higher serum concentration of 25(OH)D was shown to be associated with a lower risk of *Clostridium difficile* infection (4).

Vitamin D can also correct the intestinal bacterial flora having beneficial effects on microorganisms and can enhance the proliferation of microorganisms with the ability to produce substances with anti-inflammatory function (10). A double-blind randomized clinical trial study of vitamin D supplementation among people with vitamin D deficiency (less than 25 nmol/L) who were overweight or obese (body mass index above 25 kg/m^2) showed that vitamin D supplementation could increase serum concentration of 25(OH)D, as well as a change in the frequency of some bacterial species. So the frequency of Lachnospira population increased and Blautia population decreased (4). It was shown that Lachnospira is less common in obese people than in thin individuals (38). This evidence could show the positive effect of Lachnospira on body mass index (BMI) and the immune system (39).

Coprococcus was illustrated to decrease in children with autism (40) and HIV (41). It is also more common in elderly people living in senior houses, when compared to the older people living in the society, as well as in children living with their pet animals indicating the beneficial effect of Coprococcus on health status (4). Also, Blautia and Ruminococcus were reported to be associated with insulin resistance, higher HbA1c, and inflammatory diseases (4, 42). Decreased levels of Balutia and Ruminococus populations after vitamin D supplementation have been seen in overweight and obese people, demonstrating the positive effect of blood sugar control in this population .(4)

Another study found that the incidence of *Ruminococcus gnavus* decreased in mucosal biopsies in patients with active ulcerative colitis (UC). Besides,

the frequency of *R. gnavus* decreased slightly in all patients after vitamin D supplementation. In another study, the overall diversity of the intestinal microbiota did not change following vitamin D supplementation among people with IBD (33). However, a high increase in Enterobacteriaceae was observed following vitamin D supplementation in patients with UC. Enterobacteriaceae contain a large proportion of harmless, as well as potentially pathogenic bacteria in the human gut; so the significance of such a change is still unclear (33).

In another study, after nine weeks of vitamin D supplementation in adolescent girls, Firmicutes was shown to increase and Bacteroidetes was demonstrated to decrease (43). Bifidobacterium has also been increased after taking vitamin D supplements (40). Bifidobacterium is a gram-positive bacterium that acts as a treatment in patients with IBD and reduces symptoms in these patients and is useful for maintaining recovery in patients with UC (43).

Also, exposure to the sun's UVB light can affect the gut microbial populations. A study measuring the sun's UVB effect on the gut microbiota of 23 healthy women revealed that people who did not get enough vitamin D had at least 10% increase in their vitamin D levels after a week of exposure to sunlight, which was accompanied by an increase in microbial diversity too. Participants with insufficient levels of vitamin D had lower microbial diversity in comparison to the group with adequate levels of vitamin D at the beginning of the study, which increased the microbial diversity to the same level as those with adequate levels of vitamin D, when exposed to UVB (16) .

Not only does vitamin D affect microbial population in the gastrointestinal tract, but also the association could be vice versa. The microbial state of the body can affect the state of vitamin D level. In a clinical trial, the oral supplement of *Lactobacillus reuteri* (NCIMB30242), which is a probiotic, could increase the serum concentrations of 25(OH)D. This increase in mean serum levels of 25(OH)D was independent of oral intake and intervention season. Probiotics have also been shown to enhance VDR expression and activity (34, 44).

The Association between Vitamin D and the Intestinal Microbiota

The microbial population was shown to be formed directly by vitamin D, but under control of VDR transcription genes (45). Also, the intestinal microbiota was demonstrated to affect vitamin D metabolism and expression of vitamin D receptors in the colonic epithelium (4, 30). Some bacteria can also reduce VDR activity, which may be due to a bacterial capnine mechanism. Decreased VDR expression may lead to an increase in Proteobacteria population and such changes in microbial variation might lead to intestinal inflammation (43). Besides, vitamin D can exert regulatory effects on antimicrobial peptide secretion and therefore the population of mucosal microbiota (33).

Vitamin D regulates nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and protects against IBD due to antibacterial responses (by antimicrobial peptides such as cathelicidin). Therefore, increased inflammation in the gut can lead to presence of pathogens competing with beneficial bacteria of the gut (43). In an animal study in mice with colitis, vitamin D was able to have protective effects by regulating the intestinal microbiota. In this study, it was shown that increased inflammation in the intestine led to the competition of pathogens with beneficial bacterial species (43). In this study, a deficiency of 1'25$(OH)_2D_3$ or VDR led to dysbiosis and caused inflammation and severe intestinal damages (32). Similar to the results of this study, in another study, VDR-knockout mice developed dysbiosis and changes in the intestinal microbiota, in which the Bacteroidetes increased, and Lactobacillus had a decreasing trend (31).

Monocytes express the enzyme 1α hydroxylase (CYP27B1), which converts 25(OH)D to active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), which causes macrophages to produce antimicrobial peptides leading to destruction of the bacteria. $1,25(OH)_2D$ also modifies T cell functions by inhibiting T cell proliferation, inducing changes from Th1 to Th2 development, suppressing Th17 cell growth, and facilitating regulatory T cells. Therefore, it is possible that vitamin D, by modulating the host's immune response to certain bacteria, may affect the intestinal microbial composition (37).

Conclusion

Vitamin D is effective on controlling the population and the species of gut microbiota, and anti-inflammatory effects of vitamin D may be related to changes in the composition of the intestinal microbiota. Therefore, vitamin D can be used to prevent or treat inflammatory disorders such as IBD. Also, gut microbiota can affect vitamin D related reactions. Further studies are needed a better understanding of the interaction between vitamin D and gut microbiota.

Conflict of Interest

None declared.

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