Vitamin D and The Gut Microbiota: a Narrative Literature Review

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ABSTRACT

Recently several studies have attempted to investigate the association between vitamin D and microbiota. However, studies have reported inconsistent results. This narrative review aimed to investigate the potential association between vitamin D and microbiota population in the gut by pooling together the results from observational studies and clinical trials. We considered animal and human studies in this field. Several studies have shown the correlation of vitamin D deficiency with microbiota. Furthermore, interventional studies were emerging that vitamin D change the microbiota composition in which leads to an increase in beneficial bacteria, such as Ruminococcaceae, Akkermansia, Faecalibacterium, and Coprococcus while decreases in Firmicutes. Vitamin D could change the microbiota toward decreasing in Firmicutes and increasing in Bacteroidetes. At genera level, vitamin D may connect to some genera of Lachnospiraceae family (e.g., Blautia, Rosburia, Dorea, and Coprococcus). It seems that adequate level of vitamin D is an important factor in improving the composition of the gut microbiota. More studies are needed to confirm possible underling mechanisms.

Keywords: Microbiome; Microbiota; Intestines; Vitamin D

INTRODUCTION

Vitamin D deficiency is described as a public health concern globally, which has health consequences in more than one billion people [1,2]. Vitamin D is known for its role in calcium-phosphorus homoeostasis and bone metabolism [2]. Recent evidences have shown the association between hypovitaminosis D and autoimmune disorders [3], cancers [4,5], cardiovascular disease [6], diabetes mellitus [7], and infections [8,9]. Furthermore, vitamin D deficiency is highly associated with gastrointestinal diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colon cancer [10,11]. The presence of vitamin D receptor (VDR) in almost every tissue highlights the importance of vitamin D in biological functions. VDR is expressed in many cells, including muscle, intestinal epithelium, kidney and also in the immune cells [12,13]. As VDR is widely expressed in various immune cells, including B cells, T cells and antigen presenting cells, it may demonstrate the immunomodulatory role of vitamin D in different organs such as gut [13].
Human gut is a host of numerous numbers of microorganisms (about $10^{13} - 10^{14}$) known as microbiota [14]. Evidence has supported the roles of microbiota in human’s immunity and metabolism [15]. The microbiota includes bacteria, fungi, archaea, protozoa and viruses that act in the human gut as symbiotic or pathogenic [15,16]. More than 1,000 different bacterial species have been determined in human gut. The 4 major phyla composed the gut microbiota are at first Bacteroidetes and Firmicutes and then Actinobacteria, and Proteobacteria [17]. The alteration in the diversity of gut microbiota, called dysbiosis, can negatively influence gut health. The change in the composition and diversity of gut microbiota depends on many factors like host genetics, environmental factors, diet, antibiotics, pregnancy, and infection [18-21]. Among these factors, dietary elements responsible for up to 57% changes in gut microbiota [22].

Considering that vitamin D deficiency can cause gastrointestinal disease through its immunomodulatory role, recently, a hypothesis has been suggested on an association between vitamin D and gut microbiota. Recent human and animal investigations have shown that vitamin D could alter microbiota composition through increasing the maintenance of gut homeostasis [23] and decreasing permeability [24]. However, it is not clear how vitamin D could shift gut microbial communities to achieve these goals. Therefore, the present study reviewed the association between vitamin D and gut microbiota composition. The characteristics of studies are presented in details in Tables 1 and 2.

## VITAMIN D AND MICROBIOTA: ANIMAL STUDIES

In a study by Assa et al. [26], a relatively high quantity of Bacteroidetes was found in vitamin D deficient mice. The researchers showed that vitamin D through preserving gut barrier homeostasis and tight-junction building reduces dysbiosis and adherent-invasive *Escherichia coli* colonization. Assa et al. [24] also reported the similar results in another study in which vitamin D deficient mice were more vulnerable to infectious and predisposed to epithelial barrier dysfunction that leads to increasing gut permeability. Jahani et al. [25] indicated supplementation with vitamin D, during pregnancy and lactation had different effects.

### Table 1. Summary of animal studies

| Author          | Population       | Sex | Intervention                     | Duration (day) | Microbiome identification       | Results                                                                                                                                 |
|-----------------|------------------|-----|----------------------------------|----------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Jahani et al.   | Female and male CD-1 mice | M/F | 5,000 IU D3/kg diet              | During pregnancy, lactation and 3-mon aged | qRT-PCR targeting 16S rRNA gene | VDR expression was 50% higher in the offspring in high vitamin D feeding group. Lower vitamin D levels was correlated with increased pro-inflammatory genes expression at 3-mon age, low vitamin D diet fed mice had lower *Bacteroides/Prevotella* ratio count at PND 21 although this difference disappeared at adulthood. Higher level of LPS concentration were seen in vitamin D deficient diet group at adulthood. |
| Assa et al.     | C57BL/6 mice     | F   | Vitamin D deficient diet         | 5 wk           | qPCR targeting 16S rRNA gene    | Higher relative quantities of Bacteroidetes, Firmicutes, Actinobacteria and Gammaproteobacteria: vitamin D deficient mice. After 10-day injection of *Citrobacter rodentium*, relative abundance of Gammaproteobacteria and Actinobacteria in vitamin D deficient group. |
| Assa et al.     | C57BL/6 mice     | F   | Vitamin D deficient diet         | 5 wk           | qPCR targeting 16S rRNA gene    | Higher abundance of Bacteroidetes: vitamin D deficient mice. Relative increase in Gammaproteobacteria was observed in infected mice with LFB2. |
| Ooi et al.      | Cyp KO & VDR KO C57BL/6 mice | Sex-matched | 1.25 mg/100 g diet | qRT-PCR targeting 16S rRNA gene | Higher abundance of Bacteroidetes and Proteobacteria and lower bacteria from *Firmicutes and Deferribacteres* phyla was reported in Cyp KO and VDR KO mice compared with wild-type. |

qRT-PCR, quantitative real time polymerase chain reaction; qPCR, quantitative polymerase chain reaction; VDR, vitamin D receptor; PND, postnatal days; LPS, lipopolysaccharides; KO, knockout; Cyp, cytochrome P; rRNA, ribosomal ribonucleic acid; NR, not reported.
| Author          | Country       | Study type     | Population                                                                 | Sex | Number | Dose (IU/day) | Duration (day) | Microbiome identification | Results                                                                 |
|-----------------|---------------|----------------|------------------------------------------------------------------------------|-----|---------|---------------|-----------------|----------------------------|-------------------------------------------------------------------------|
| Schäffler et al. [27] | Germany       | Interventional | Patients with Crohn’s disease                                                | M/F | 17      | 20,000 IU daily from day 1 to day 3, then every second day | 30   | PCR targeting 16S rRNA gene | Grater abundance of Alistipes, Barnesiella, unclassified Porphyromonadaceae, Roseburia, Anaerotruncus, Subdoligranulum and an unclassified Ruminococcaceae was seen after vitamin D supplementation. |
| Garg et al. [28]  | London        | Interventional | Patients with ulcerative colitis                                             | M/F | 25      | 40,000 IU D3 weekly                                    | 60   | PCR targeting 16S rRNA gene | Enterobacteriaceae increased significantly after vitamin D supplementation. |
| Kanhere et al. [29] | USA           | Interventional | Adults with cystic fibrosis                                                 | M/F | 41      | 50,000 IU D3 weekly                                    | 90   | PCR targeting 16S rRNA gene | Lactococcus was increased, while Veillonella and Erysipelotrichaceae were decreased. |
| Sordillo et al. [30] | USA           | Interventional | Infants 3–6 mos whose parents had allergies/asthma                           | M/F | 333     | 4,000 or 400 IU/day D3 + prenatal vitamins             | NR  | Sequencing of bacterial 16S rRNA gene | Greater levels of Lachnospiraceae/U. Clostridiales, higher frequency of Lachnobacterium, and lower frequency of Lactococcus. |
| Gominak et al. [31] | USA           | Interventional | Neurology patient                                                            | M/F | 90      | Individualized dose of vitamin D to guarantee a blood level of 60–80 ng/mL | Over 1,000 | NR                      |                                                                                   |
| Ciubotaru et al. [32] | USA           | Interventional | Prediabetes and hypovitaminosis                                             | M/F | 115     | 50,000 IU/week D3                                     | Over 365 PCR targeting 16S rRNA gene | Lower relative abundance of genera belonging to the Lachnospiraceae (e.g., Ruminococcus, Roseburia, Blautia, and Dorea). Lower abundance of members of Clostridia class. |
| Cantarel et al. [33] | USA           | Interventional | Women with or without relapsing-remitting multiple sclerosis                 | F   | -       | 5,000 IU/day D3                                       | 90   | PCR targeting 16S rRNA gene | Greater abundance of Faecalibacterium and Enterobacteriaceae, and lower abundance of Ruminococcus. MS patients (untreated): higher Akkermansia, Faecalibacterium, and Coprococcus genera. MS patients (treated by GA): higher Janthinobacterium, lower Eubacterium and Ruminococcus. |
| Talsness et al. [34] | The Netherlands | Observational | One month old infants                                                        | M/F | 913     | -                                                       | - | RT-PCR targeting 16S rRNA gene | A significant negative linear trend between maternal vitamin D supplementation and plasma 25(OH)D concentration and Bifidobacterium spp. was seen. There was a positive linear trend between quintile groups and Bacteroides fragilis group counts. In some breast-fed infants vitamin D supplementation leads to lower abundance of Clostridium difficile. |
| Luthold et al. [35]  | Brazil        | Observational | Healthy individual                                                           | M/F | 150     | -                                                       | - | PCR targeting 16S rRNA gene | Higher abundance of Proteotella and lower abundance of Haemophilus and Veillonella. Lower abundance of Coprococcus and Bifidobacterium. |
| Mandal et al. [36]  | Norway        | Observational | Pregnant women                                                               | F   | 60      | -                                                       | - | PCR targeting 16S rRNA gene | Increased Actinobacteria/Proteobacteria ratio, Actinobacteria/Bacteroidetes ratio, Proteobacteria/Firmicutes ratio, and other Bacteroides. |
| Thomas et al. [37]  | USA           | Observational | Older men                                                                   | M   | 567     | -                                                       | - | PCR targeting 16S rRNA gene | Higher levels of 1,25(OH)D, D were more related to butyrate producing bacteria that are associated with better gut microbial health. |
| Kassem et al. [38]  | USA           | Observational | Infants                                                                     | M/F | 580     | -                                                       | - | PCR targeting 16S rRNA gene | Prenatal and cord blood vitamin D levels were associated with early life (up to 1 mon) gut microbiota. |

PCR, polymerase chain reaction; rRNA, ribosomal ribonucleic acid; NR, not reported; RT-PCR, reverse transcription polymerase chain reaction.
on offspring at different life span. Lower vitamin D levels were related with increased pro-inflammatory genes expression, reduction in VDR at 3-month-aged offspring, lower Bacteroides/Prevotella ratio at day 21 and higher level of lipopolysaccharides (LPS) concentration in adults. In addition, lower bacteria count was reported in the mice received low vitamin D in comparison to high vitamin D diet. Dysbiosis and increasing of injury in gut following VDR or 1, 25(OH)\(_2\)D\(_3\) deficiency has been also reported by Ooi et al. [23]. They found that vitamin D could regulate the intestinal microbiota while Bacteroidetes and Proteobacteria were more abundant in fecal sample of cytochrome P (Cyp) knockout (KO) and VDR KO mice in comparison to wild-type mice. In contrast, Firmicutes were less abundant in Cyp KO and VDR KO mice. The results of Ooi et al. [23] is similar to Assa et al. [24] about the abundance of Bacteroidetes as Assa et al. [25] reported the relatively high quantity of Bacteroidetes, Firmicutes, Actinobacteria and Gammaproteobacteria observed in vitamin D deficient mice in one study and in another one higher relative abundance of Bacteroidetes.

**VITAMIN D AND MICROBIOTA: HUMAN STUDIES**

Cantarel et al. [3] conducted a clinical trial on women with or without relapsing-remitting multiple sclerosis (MS) who were vitamin D insufficient. They reported that after 3 months of vitamin D supplementation (5,000 IU/day), the relative abundance of Faecalibacterium and Enterobacteriaceae increased, while in overall the relative abundance of Ruminococcus decreased. Moreover, after supplementation with vitamin D, untreated MS participants had an increased abundance of Akkermansia, Faecalibacterium, and Coprococcus genera, in comparison with healthy controls and glatiramer acetate-treated MS subjects. Those treated with glatiramer acetate compared to other groups had increases in Janthinobacterium and decreases in Eubacterium and Ruminococcus after vitamin D supplementation [5]. In a 3-month uncontrolled trial, 1,000 neurological patients received individualized doses of vitamin D to guarantee a blood level of 60–80 ng/mL plus B100 (B complex of 100 mg of all B vitamins except 100 mcg of cyanocobalamin, 100 mcg of biotin, and 400 mcg of folic acid). The authors concluded that these patients did not experience the IBS symptoms during 3 years after stopping the supplementation. Supplementing vitamin D plus all 8 B vitamins led to a change in the intestinal microbiome to normal status in 3 months. This result showed the role of normal intestinal microbiome in reducing pain, sleep disorders, and IBS symptoms through increasing vitamin D and B vitamins level [17].

In another study, Ciubotaru et al. [31] conducted a double-blind placebo-controlled randomized trial in men with pre-diabetes and vitamin D deficiency for more than one year. Supplementation with 50,000 IU/week ergocalciferol reduced the relative abundance of several genera of the Lachnospiraceae (e.g., Ruminococcus, Roseburia, Blautia, and Dorea) in high vitamin D quartiles. Another clinical trial also investigated the association between vitamin D supplementation and gut microbiome composition on 333 infants 3 to 6-month-aged. After vitamin D supplementation in pregnant women in 2 different doses of 4,000 IU vitamin D + prenatal vitamins or 400 IU vitamin D + prenatal vitamins, fecal samples from infants were collected and analyzed. In infants with higher cord blood vitamin D levels, the relative abundance of Lachnospiraceae/U. Clostridiales and Lachnobacterium was higher, while the relative abundance of Lactococcus was lower [30].

According to the study recently published by Garg et al. [28] Enterobacteriaceae were significantly increased in patients with ulcerative colitis following 40,000 IU D3/week

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supplementation for 8 weeks. In another controlled trial on patients with Crohn’s disease, 20,000 IU D3 were given for one month. Greater abundance of Alistipes, Barnesiella, unclassified Porphyromonadaceae, Roseburia, Anaerotruncus, Subdoligranulum and an unclassified Ruminococcaceae was reported after vitamin D supplementation [27]. In a double-blind, randomized, placebo-controlled clinical trial on adults with cystic fibrosis, Lactococcus was increased, while Veillonella and Erysipelotrichaceae were decreased after 12-week supplementation with 50,000 IU D3/week [29]. In another study 62 fecal sample from healthy infants were collected that thirty-five of them were supplemented with 400 IU of vitamin D per day. Comparative metagenomic analysis was done to investigate the distribution and diversity of infant gut microbiota. The researchers found that vitamin D plays an important role in modifying the infant gut microbiota, especially increase the probiotics types [37].

Observational studies have also been conducted in this field. In a cross-sectional study designed on 150 healthy individuals, authors demonstrated that higher vitamin D intake was associated with higher abundance of Prevotella and lower abundance of Haemophilus and Veillonella. Moreover, the abundance of Coprococcus and Bifidobacterium was inversely related to the vitamin D intake [33]. Another study was conducted to find the correlation between some dietary nutrients and microbiota composition in 60 women, during the second trimester of pregnancy. Results showed that higher vitamin D intake is associated with increased ratio of Actinobacteria/Proteobacteria, Actinobacteria/Bacteroidetes, Proteobacteria/Firmicutes, and other Bacteroides in pregnant women [34]. Another cohort study by Talsness et al. [32] aimed to evaluate the effect of vitamin D supplementation of infant and maternal subject on microbiota composition. A significant negative linear trend between maternal vitamin D supplementation and plasma 25(OH) D concentration and Bifidobacterium spp. was seen. In some breast-fed infants, vitamin D supplementation leads to lower abundance of Clostridium difficile. In a cross-sectional study of 567 old men, higher levels of 1,25(OH)2 D were more related to butyrate producing bacteria that are associated with better gut microbial health [35]. In a birth cohort study, prenatal and cord blood vitamin D levels were associated with early life (up to 1 month) gut microbiota [36]. Recently, a review highlighted the therapeutic potential of vitamin D/VDR in the gut microbiota modulation and anti-inflammatory effects in IBD [38].

CRITICAL APPRAISAL OF EVIDENCE

Reviewing the studies showed that the normal microbiota makes up of 4 main phyla (Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria) [17] in which many factors including diet could change their balance [39]. Gut microbiota plays an important role in health and disease and now is considered as a separate human organ that affect the other organs [40]. The 2 main bacteria phyla in human feces are Bacteroidetes and Firmicutes. Other dominant phyla with less relative abundance are Proteobacteria, and Actinobacteria [17,41]. To make a better view about the results, we considered microbiota in the phylum to genus level. In this section of review, we discuss the probable effect of vitamin D on gut microbiome in the phylum to genus level.

In phyla level, one study has shown that supplementation with vitamin D may change the microbiota composition with reducing in phylum Firmicutes [31]. Two other interventional studies have reported inconsistence results in which Firmicutes genus increased in one study while, the population of Firmicutes decreased in the other study [3,30]. Although some studies showed increased Firmicutes genus, it has been reported that this genus is known as butyrate producers and anti-inflammatory [42]. In an observational study, Luthold et al. [33], have
shown a reduction in Firmicutes phyla while Mandal et al. [34], have reported an increase in Proteobacteria/Firmicutes ratio. However, in both studies, the population of phylum Bacteroidetes increased. There is a hypothesis in which changing in microbiota composition to higher level of Bacteroidetes and lower level of Firmicutes may leads to gut barrier dysfunction [43,44].

The other 2 dominant phyla are Proteobacteria, and Actinobacteria, which seems to present pro-inflammatory and anti-pathogenic properties. One study has reported increase in Proteobacteria after vitamin D supplementation [3] and the other showed increase in Actinobacteria/Proteobacteria, Actinobacteria/Bacteroidetes, and Proteobacteria/Firmicutes ratio with higher dietary intake of vitamin D [34] while Luthold et al. [33] showed inverse relationship between some Proteobacteria and Actinobacteria genus and serum levels of vitamin D. This controversy may be explained by differences in study design. Luthold et al. [33], conducted his study in a cross-sectional design which is not strong for identifying causal relationships.

In genus level, all genera that their changes have been reported in the studies were as follows: Lactococcus, Blautia, Rosburia, Ruminococcus, Dorea, Faecalibacterium, Coprococcus, Veillonella, Subdoligranulum, Erysipelotrichaceae, Eubacterium, Anaerotruncus, C. difficile (phylum Firmicutes), Provotella, Alistipes, Barnesiella, Porphyromonadaceae (phylum Bacteroidetes), Haemophilus, Jannichinobacterium, Enterobacteriaceae (phylum Proteobacteria), Bifidobacterium (phylum Actinobacteria), and Akkermansia (phylum Verrucomicrobia). Among these genera Blautia, Rosburia, Dorea, and Coprococcus are all from family Lachnospiraceae. One study showed significant reduction in abundance of Blautia, Rosburia, Ruminococcus, and Dorea after vitamin D supplementation [31] which all are associated with increasing gut permeability and inflammation [45]. In another study by Cantarel et al. [3] supplementation with vitamin D3 in MS women lead to increase in abundance of Akkermansia, Faecalibacterium, and Coprococcus (family Lachnospiraceae) which Coprococcus and Faecalibacterium have known as butyrate producers and may be anti-inflammatory [42]. Akkermansia, another increased genus is a mucin-degrading bacteria [46]. Sordillo et al. [30] concluded that higher vitamin D level is correlated with higher abundance of Lachnospiraceae U. Clostridiales. Multivariate analysis showed increasing Lachnospiraceae and decreasing Lactococcus abundance. According to this research, low vitamin D level is associated with dysbiosis and inflammation progression. Contrary to the results of this study about Lactococcus, 2 studies reported an increase in Lactococcus, which related to positive gut health, after supplementation with vitamin D [29,33]. On the other hand, based on Luthold et al. [33], the abundance of Bifidobacterium inversely related to the vitamin D intake. In line with this finding, the abundance of Bifidobacterium spp. was inversely related to maternal plasma 25(OH)D concentration in observational study by Talsness et al. [32]. Bifidobacterium and lactic acid bacteria like Lactococcus are both known for their potential probiotic effects. Although the results of this review are partly associated with the prebiotic properties of vitamin D, are not confirmed by the contradictory nature of the studies and there is a need for further studies focusing on probiotic bacteria.

Luthold et al. [33] showed higher abundance of Provotella and lower abundance of Coprococcus, Haemophilus and Veillonella in the highest vitamin D intake tertile which is consistent with Kanhere et al.’s study [47] on the Veillonella which was known as cause of many infections [47]. Results about Coprococcus are inconsistent with Cantarel study which could be due to its cross-sectional design or the other factors for example the probable effect of MS on intestinal microbiota. Moreover, results of this research showed the lowest tertile of vitamin D intake correlated with increasing in LPS level that likely due to increase in gram negative bacteria (Haemophilus & Proteobacteria) which have LPS in their outer membrane. As mentioned above,
in the Mandal et al.’s research [34], vitamin D intake was associated with increasing the Actinobacteria/Proteobacteria, Actinobacteria/Bacteroidetes, Proteobacteria/Firmicutes ratio, and other Bacteroides in pregnant women. On the other hand, higher vitamin D intake may decreases microbiome diversity. It has been known that reduction in microbiota variety is related to some diseases including IBD [48], obesity [20], autism [49], and allergy [50]. Besides higher intake of vitamin D changes the microbiome toward increasing Actinobacteria and Proteobacteria abundance at phyla levels. These 2 phyla presented anti-pathogenic properties [34]. To be noted that meat and other animal products are important sources of vitamin D and several publications have reported the effect of meat on microbiota [51]. These relationships may be explained with antimicrobial characteristics of vitamin D that encompass certain groups of bacteria. Therefore, higher intake of vitamin D might cause an increase in probable pathogens [34]. The observed contradiction in findings may be the result of inaccurate vitamin D assessment method (food frequency questionnaire) used in this research.

Suggested mechanisms for the role of vitamin D in gut health is shown in Figure 1. Generally, vitamin D effects are as follows: gene expression modulation of anti-microbial peptides like cathelicidin, β-defensin and angiogenin-4.
cathelicidin and β-defensin [52], gene expression modulation of tight junction proteins like zonulin occluden-1, zonulin occluden-2, claudin 2, and 12 [53], regulation of innate immune system via gene expression modulation of toll-like receptor 2 and nucleotide-binding oligomerization domain 2 and adaptive immune system via modulation of B- and T-lymphocyte function [52,54].

CONCLUSION

This study reviewed the data of literatures that investigated the association between vitamin D and gut microbiota. In observational studies, the association of vitamin D deficiency with dysbiosis has been reported. Furthermore, interventional studies were emerging that vitamin D change the microbiota composition in which leads to increase in beneficial bacteria, such as Ruminococcaceae, Akkermansia, Faecalibacterium, Lactococcus, and Coprococcus while decreases in some genera from Firmicutes.

There is scarcity of research on the association between vitamin D and microbiota composition. It seems appropriate dose of vitamin D can alter the gut microbiota with increase in Bacteroidetes and decrease in Firmicutes. At genera level, vitamin D may connect to some genera of Lachnospiraceae family (e.g., Blautia, Roshuria, Dorea, and Coprococcus). Therefore, maintaining the appropriate amount of vitamin D in the body seems to have beneficial effects on the composition of the gut microbiota.

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