ISSN NO: 2770-0003
Date of Publication: 08-09-2023

The Relation Between Vitamin D and Gut Microbiota: A Systematic Review

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Abstract: Vitamin D enhances calcium absorption in the gut and ensures proper levels of calcium and phosphate in the bloodstream, which are necessary for normal bone formation and the prevention of hypocalcemic tetany. The gut microbiota is often referred to as an "extra organ" of the body as it performs vital functions for overall well-being. However, emerging research suggests that Vitamin D might impact the gut microbiota as well as anti-inflammatory and immune-modulatory. This systematic review aims to conduct an in-depth analysis of the research on the relationship between vitamin D and gut microbiota, which was published between 2018 and 2023. The most current articles were identified by conducting a comprehensive search on PubMed, Google Scholar, and Web of Science, focusing on articles published between 2018 and 2023. The phrases "vitamin D" and "gut microbiota" (sometimes referred to as "intestinal microbiota" or "microbiome") are the main components of this meta-analysis which presents the findings from twelve separate investigations. The study demonstrated that the structure and functions of the gut microbiota were impacted by vitamin D deficiency. Additionally, a lack of vitamin D resulted in higher levels of Escherichia coli and lower levels of Bifidobacterium, Lactobacillus, and Akkermansia muciniphila. On the other hand, Vitamin D supplements have improved gut flora composition and function. Recent research suggests that vitamin D plays a role in regulating the makeup of the gut microbiota. Recent discoveries have indicated that vitamin D can influence the composition of the microbial communities residing in the gastrointestinal tract. These findings highlight the potential impact of vitamin D on shaping the diversity and balance of the gut microbiota and underscoring the importance of understanding this relationship for overall health and well-being.
Keywords: Vitamin D, 25-OH vitamin D, Microbiome, Gut microbiota, Vitamin D deficiency.

1. Introduction

In recent years, vitamin D, a fat-soluble vitamin mainly recognized for its function in bone health, has gained much attention due to the possibility that it may impact various physiological processes beyond skeletal health (Charoenngam and Holick, 2020). Vitamin D is primarily known for its involvement in bone health. In addition to its traditional function in calcium and phosphate homeostasis, new evidence suggests that vitamin D may also play a vital role in modifying the structure and function of the gut microbiota (Pignolo *et al.*, 2022).

The term "gut microbiota" refers to the diverse population of microorganisms that reside in the gastrointestinal system (Anwar *et al.*, 2021). These microorganisms might be bacteria, viruses, fungi, archaea, or others. It is now widely recognized as a crucial element in determining both the state of the host's health and the progression of the disease (Barcik *et al.*, 2020). Vitamin D receptors (VDRs) are widely distributed throughout the human body, including the colon, where they are discovered (Bikle, 2021). Studies conducted on animals have shown that a lack of vitamin D can change gut microbiota (Dipasquale *et al.*, 2022). These changes are characterized by a reduction in microbial diversity and noticeable shifts in the composition of specific taxa within the gut microbiota (Jackova *et al.*, 2023).

Several studies have found a relationship that goes in both directions between the vitamin D level and the gut microbiota makeup (Rinninella *et al.*, 2022). They affect gene expression involved in innate immunity and host-microbe interactions (Chaiyapechara *et al.*, 2022). The microbiota in your stomach can affect the metabolism and absorption of vitamin D, which may, in turn, affect the bioavailability of vitamin D and its physiological consequences (Giustina *et al.*, 2023). In addition, there is accumulating evidence to show that the interaction between vitamin D and the microbiota in the gut may extend beyond the effects

ISSN NO: 2770-0003
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that are localized to the intestines and have consequences that are systemic to the health of the host (Cong *et al.*, 2022).

Changes in the composition of the microbiota found in the gut have been linked to a wide range of diseases, including metabolic disorders (Boscaini *et al.*, 2022), autoimmune conditions (Miyauchi *et al.*, 2023), and mental health disorders (Tsamakis *et al.*, 2022). Given the potential impact that both of these factors could have on these diseases, understanding the relationship between vitamin D and the microbiota in the gut should provide important insights into the development of novel therapeutic strategies and prevention measures. This systematic review aims to conduct a comprehensive analysis of the research on the relationship between vitamin D and the microbiota in the gut, which was carried out and published between 2018 and 2023.

2. Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct this review (Liberati *et al.*, 2009). The most recent articles were selected by performing a deep search on PubMed, Google Scholar, and Web of Science, focusing on publications released between 2018 and 2023. The keywords "vitamin D" and "gut microbiota" (sometimes referred to as "intestinal microbiota" or "microbiome") are the main components of this review, which presents the findings from twelve separate investigations. Our comprehensive study includes data on the impact of vitamin D on either human or animal gut flora. Our preliminary search across all three databases produced a total of 1033 matches. After eliminating the duplicates with Endnote, we reviewed the titles and abstracts of the 322 papers from Google Scholar, the 204 papers found on PubMed, and the 507 papers discovered on Web of Science. Studies that failed to meet our inclusion criteria or did not directly address our research question were not selected. This systematic review included twelve separate research studies, each exploring the connection between vitamin D and the microbiota present in the digestive systems of either humans or animals.

3. Results

According to the findings, a deficiency in vitamin D was connected to changes in the structure and the activity of the bacteria that live in the gut. These bacteria are responsible for maintaining a healthy gut environment. A deficiency in vitamin D has been associated with an increase in harmful bacteria like Escherichia coli and a decrease in beneficial bacteria like Bifidobacterium spp., Lactobacillus spp., and Akkermansia muciniphila (Table 1).

In addition, many studies have demonstrated that taking vitamin D supplements may improve both the makeup and function of the colony of bacteria that lives in the gut. One study, for instance, discovered that healthy adults who took vitamin D supplements had a microbiota that included more Bifidobacterium spp. and Lactobacillus spp. compared to people who did not take the supplement. Moreover, based on the results of another study, the utilization of vitamin D supplements was found to augment the performance of the intestinal barrier and reduce the inflammation linked to colitis.

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Table 1. A presentation of the key findings of eligible studies included in this review.

Authors	Research Objective	Methodology	Key Findings
(Villa *et al.*, 2018)	To examine the possible association between the maternal intake of vitamin D through diet and the prevalence of Bacteroides and Prevotella in offspring and to investigate the potential effects of this correlation on the bone mineral content, density, and structure of male and female adult participants who were provided with an obesogenic diet.	Female C57BL/6J mice were fed either a high or low vitamin D AIN93G diet from pre-mating to weaning. After weaning, the male and female offspring remained on their vitamin D regimens or were transferred to a high-fat, high-sugar diet until they were sacrificed at seven months. Bacteroides and Prevotella were quantified in the dam's and offspring's feces.	Bacteroides were only found in male adult offspring and were found to have a negative correlation with systemic inflammation in the body. Bacteroides were also found to have a positive association with the bone's strength and structure. This may affect maternal nutritional practices and guidelines tailored to specific genders.
(Naderpoor *et al.*, 2019)	To examine the effects of vitamin D supplementation on fecal microbiota, hs-CRP, and calprotectin in vitamin D-deficient and overweight or obese people likely to have subacute chronic inflammation.	A double-blind, randomized clinical study. Stool samples were collected before and after a 100,000-IU loading dose of cholecalciferol and 4000 IU daily or placebo for 16 weeks.	Vitamin D supplementation is associated with various unique impacts on the microbiota found in the feces.
(Wang *et al.*, 2020)	To determine whether vitamin D supplementation could reduce the plasma TMAO level in mice by regulating gut microbiota.	16-week-old C57BL/6J mice were fed standard chow (C) or a high-choline diet (HC) without or with vitamin D3 supplementation (CD3 and HCD3) or with vitamin D3 and antibiotics (HCD3A).	The HC group had higher plasma levels of trimethylamine (TMA) and TMAO, a less diverse intestinal microbiota, and more Firmicutes and fewer Bacteroidetes than the C group. In addition, Vitamin D treatment significantly decreased plasma TMA and TMAO in mice fed a high-choline diet. Vitamin D reduced the ratio of Firmicutes to Bacteroidetes and the gut microbiota composition. Also, Spearman correlation analysis revealed a negative association between Bacteroides and Akkermansia and plasma TMAO in HC and HCD3 groups.
(Kassem *et al.*, 2020)	To analyze the correlations between	The levels of 25(OH)D in the cord blood of the	The gut microbiota in early life is associated with cord blood

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	maternal and newborn plasma 25-hydroxyvitamin D (25[OH]D) and gut microbiota.	mothers and their infants were measured. The gut microbiota composition of the infants and toddler offspring was analyzed using race-adjusted techniques.	25(OH)D levels in the mother before conception.
(Charoenngam *et al.*, 2020)	To examine the effects of vitamin D3 supplementation on the diversity and composition of the gut microbiota.	Twenty adults with 25(OH)D concentrations of less than 30 ng/ml were recruited for the study. Participants were given 600, 4,000, or 10,000 IUs of vitamin D3 orally per day. Amplification and sequencing of the 16S rRNA gene were used to detect the gut microbiota in feces at the beginning and eight weeks afterward.	The relative abundance of Akkermansia and Porphyromonas increased and decreased with initial serum 25(OH)D levels ($p<0.05$). After the intervention, Bacteroides increased dose-dependently, with a statistically significant difference between the 600 IU and 10,000 IU groups ($p=0.027$). The abundance of Parabacteroides varied between 600 and 4,000 IUs ($p=0.039$).
(Bellerba *et al.*, 2022)	To examine the potential function of the microbiome as a modulator of 25(OH)D levels by analyzing microbiota changes in response to vitamin D supplementation.	After standard treatment (surgery with or without chemotherapy and/or radiotherapy as required), CRC patients were randomly assigned to receive 2000 IU of vitamin D3 per day or a placebo for one year. Moreover, treatment (adjuvant /neoadjuvant) versus no treatment was stratified. Furthermore, using logistic regression, relationships between taxa/pathways and vitamin D were investigated. A mediation analysis was conducted to determine whether treatment-associated taxa mediated the effect of supplementation on 25(OH)D levels.	Vitamin D supplements may potentially influence the composition of the gut microbiota. Additionally, the microbiota may serve as a partial mediator of the impact of Vitamin D supplementation on 25(OH)D. The observed sex-specific differences demonstrate the importance of including sex/gender as a variable in microbiome research.

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(Konstanti *et al.*, 2022)	To evaluate the intervention's effect on intestinal inflammatory and barrier markers and determine whether the intervention improved gut microbiota composition and function.	Participants' faces were examined in a double-blind, placebo-controlled nutritional intervention study. At T1, 25 elderly females were divided into two groups: one receiving nutritional intervention (n = 12) and the other receiving placebo (n = 13) for nine weeks. The experimental group consumed 1 gram of bovine lactoferrin (bLF) per day for 21 days (T2).	The proportion of the Holdemanella genus at T1 was significantly higher in the intervention group (p 0.01). The intervention group experienced a statistically significant (p 0.01) increase in Bifidobacterium during T2 compared to the placebo group. This statistically significant increase persisted throughout the study. On the other hand, T3 had minimal impact. The SCFAs, calprotectin, zonulin, and alpha-1-antitrypsin concentrations remained stable throughout the intervention. In contrast, the zonulin levels of the placebo group increased significantly in the conclusion.
(Singh *et al.*, 2022)	To understand the relationship between vitamin D status and host genetics, and the gut microbiome composition in a pediatric population from Qatar.	Blood and stool samples were collected from healthy 4–14-year-old participants. The serum metabolite of vitamin D, 25-hydroxycholecalciferol 25(OH)D, was measured using blood. Sequencing of the 16S rRNA gene was performed on fecal samples. 97% of the subjects in our study had vitamin D concentrations below 75 nmol/L.	ANOVA revealed that vitamin D deficiency increased the CT genotype at rs12512631, a GC gene SNP (p = 0.0356). Deficient (D) and non-deficient (ND) groups had significantly different gut microbiomes (Bray Curtis dissimilarity p = 0.049), with deficient participants having a lower number of gut microorganisms. Firmicutes (F) and Bacteroidetes (B) differed significantly between patients with and without deficiencies (p = 0.0097). Prevotella, not Bacteroides, governed vitamin D-deficient children's gut enterotypes. -It is suggested that vitamin D deficiency in children has a substantial effect on the gut microbiota. In addition, it emphasizes the significance of considering host genetics and baseline gut microbiome composition when interpreting clinical outcomes related to vitamin D deficiency and designing more personalized therapeutic interventions.

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(Albedewi *et al.*, 2022)	To examine the relationships between 25-hydroxyvitamin D [25(OH)D] levels, pulmonary function, and fecal microbiota in pediatric patients with cystic fibrosis.	The current cross-sectional investigation involved 35 children with CF (mean age 8.7 2.83 years) and 24 healthy controls without CF (mean age 9 2.7 years). Using the Elecsys vitamin D total II assay, the status of Serum 25(OH)D was determined. Real-time PCR was employed to evaluate the gut microbiota composition in the CF cohort. To quantify pulmonary function exams (PFTs), spirometry was utilized.	The results suggested the importance of investigating the manipulation of the gut and the use of microbiota to improve respiratory function in individuals with cystic fibrosis.
(Lin *et al.*, 2023)	To investigate the relationship between plasma 25(OH)D, the prevalence/ incidence of metabolic syndrome (MetS), and the role of the gut microbiota and bile acid axis in mediating this relationship.	The study involved 3,180 patients with baseline plasma 25(OH)D measurements. In addition, the nine-year follow-up consists of 2,966 people.	The research results suggest that the gut microbiota-bile acid axis influences the association between plasma 25(OH)D and the likelihood of persistent MetS and incident MetS.
(Al-Khaldy *et al.*, 2023)	To find the connection between serum vitamin D, gut microbiota, and obesity in Saudi females.	This case-control study encompasses a sample of 92 female participants aged between 18 and 25 years, comprising 48 individuals with normal weight and 44 individuals with obesity. The study involved collecting and analyzing anthropometric, biochemical, lifestyle data, and fecal samples. Shotgun metagenomic sequencing was employed to analyze the microbial communities present in stool samples.	The regulation of gut microbiota composition could be impacted by vitamin D status, as it has the potential to impede the proliferation of pathogenic bacteria and promote the growth of beneficial strains.

4. Discussion

Vitamin D is a crucial micronutrient that plays a pivotal role in various physiological processes, including maintaining skeletal integrity, maintaining the immune system's homeostasis, and regulating inflammation (Fantini *et al.*, 2023). It is predominantly acquired through cutaneous syntheses via sunlight exposure and dietary intake (Huang *et al.*, 2023). Bacteroides, which are anaerobic bacteria, are present in the gastrointestinal tract and contribute to the fermentation of complex carbohydrates and the synthesis of short-chain fatty acids (Fan *et al.*, 2023). Although there are indirect connections between vitamin D and Bacteroides, the precise nature of their relationship is not fully understood.

The regulation of the immune system has been independently linked to vitamin D and Bacteroides through immune modulation (Aggeletopoulou *et al.*, 2023). Research has demonstrated that Vitamin D can regulate immune responses and exhibit antimicrobial properties (Johnson and Thacher, 2023). Bacteroides, among other intestinal microbiota, assume a crucial function in modulating the maturation and operation of the immune system (Maciel-Fiuza *et al.*, 2023). There is a plausible hypothesis that alterations in the gut microbiota, particularly in relation to Bacteroides levels, may indirectly affect the metabolism of vitamin D or vice versa, thereby influencing the immune system's function (Li *et al.*, 2023)

Vitamin D absorption is contingent upon dietary fat intake and gut health due to its fat-soluble nature, resulting in dietary interactions (Sharma *et al.*, 2023). Numerous studies have examined the relationship between vitamin D administration and the gut microbiome. Vitamin D administration has been linked to changes in the proportional representation of specific bacterial taxa in the gastrointestinal tract (Sasso *et al.*, 2023). The administration of vitamin D was associated with an increase in the prevalence of Bifidobacterium species (F. Zhao *et al.*, 2023), which are beneficial microorganisms linked to improved gastrointestinal health.

Vitamin D supplementation has been associated with an augmentation in microbial diversity within the gastrointestinal tract (Banerjee *et al.*, 2023). Increasing microbial diversity is commonly viewed as beneficial due to its association with a more robust intestinal ecosystem and improved general health (Mady *et al.*, 2023). Thus, it is essential to observe that the precise mechanisms by which vitamin D supplementation affects the gut microbiota are not entirely comprehended. Existing research has frequently employed small sample sizes and exhibited inconsistencies in experimental methodology, making it challenging to reach definitive conclusions (Chmiel *et al.*, 2023).

The effect of vitamin D supplementation on the gut microbiota is subject to inter-individual variation (X. Zhao *et al.*, 2023), which can be attributed to several factors, including the initial composition of the microbiota, dietary behaviors, lifestyle, and general health status. (Santa *et al.*, 2023). However, more research is needed to get a more comprehensive knowledge of these effects, which include the long-term effects of vitamin D supplementation on the microbiota of the gastrointestinal tract and their possible implications on human health.

Several studies have reported variations in vitamin D levels among males and females. According to some, it has been observed that females have relatively lower vitamin D levels compared to males (Md Isa *et al.*, 2022). The observed difference can be caused by various factors, including but not limited to discrepancies in dietary patterns, hormonal effects, clothing preferences that impact sunlight exposure, and differences in body makeup. Current evidence suggests that vitamin D plays a crucial role in the pathogenesis of inflammatory bowel disease (IBD), as a deficiency in vitamin D is inversely associated with the severity of the disease (Vernia *et al.*, 2022). Concurrently, evidence suggests that the signaling of vitamin D receptor (VDR) is associated with regulating immunity against gastrointestinal pathogens and preserving gut barrier integrity, suggesting a plausible role in the pathogenesis of inflammatory bowel disease. (IBD) (Vernia *et al.*, 2022; Damoiseaux and Smolders, 2018). As a result, this topic has attracted considerable attention (Triantos *et al.*, 2022).

The significance of the microbiome lies in its association with autoimmune responses through the concept of molecular mimicry. This phenomenon occurs when microbial peptides exhibit a comparable structure and sequence to self-antigens, leading to auto reactivity of immune cells (Yamamoto and Jorgensen, 2019). Increasing evidence suggests that the vitamin D/VDR signaling pathway benefits both experimental and clinical inflammatory bowel disease (IBD). An association between mucosal inflammation

and injury in IBD patients with impaired VDR signaling has been established. Nevertheless, the relationship between impaired VDR signaling and inflammatory bowel disease (IBD) remains ambiguous (Aggeletopoulou *et al.*, 2023).

5. Conclusion

Recent findings indicate that vitamin D modulates the composition of the gut microbiota. This phenomenon can potentially influence the spread of harmful bacteria and promote the development of beneficial strains. Moreover, several studies have indicated that consuming vitamin D supplements could enhance the composition and performance of the microbiota living in the gastrointestinal tract. However, further research is required to better understand the fundamental mechanisms, the effects of vitamin D supplementation, and the clinical relevance of these discoveries concerning human health and pathology.

Acknowledgements

The authors thank the members of Imam AL-Kadhum College for their thoughtful review of this manuscript.

Competing interests

The author declare that he has no competing interests.

Funding

Not applicable.

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