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Review

Exploring the Role of Vitamin D and the Vitamin D Receptor in the Composition of the Gut Microbiota

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Abstract

The microbiome has a major impact on human physiology and plays a critical role in enhancing or impairing various physiological functions such as regulation of the immune system, metabolic activities, and biosynthesis of vitamins and hormones. Variations in the gut microbial community play a critical role in both health and disease. Regulation of calcium and bone metabolism, as well as cellular functions such as proliferation, apoptosis, differentiation, and immune modulation, are among the known effects of vitamin D. These biological functions are primarily carried out through the binding of vitamin D to the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. The immunomodulatory properties of vitamin D suggest that this molecule plays an important role in various diseases. Maintenance of immune homeostasis appears to occur in part through the interaction of the gut microbiota with vitamin D. Increasing evidence points to the central role of vitamin D in maintaining mucosal barrier function, as vitamin D deficiency has been associated with disruption of gut barrier integrity, translocation of bacteria into the bloodstream, and systemic inflammation. In parallel, a bidirectional interaction between vitamin D and the gut microbiota has been demonstrated as data show upregulation of intestinal VDR expression and downregulation of inflammatory markers in response to fermentation products. The aim of this review is to provide an overview of the evidence of a link between the gut microbiome and vitamin D, with a focus on data from experimental models and translational data from human studies related to vitamin D-induced changes in gut microbiota composition.

Keywords: microbiota; gut integrity; microbiome; vitamin D; vitamin D receptor

1. Introduction

The gut microbiota, also known as the intestinal flora, is a complex ecosystem of microorganisms such as bacteria, fungi, viruses, parasites, and archaea that live in symbiosis in the human intestinal lumen [1,2]. These microorganisms are mainly host–specific, and their composition and numbers vary depending on the host species and microenvironment [3]. The gut microflora plays an important direct and/or indirect role in a variety of physiological processes, including regulation of the immune system, modulation of neurotransmitters and hormones, and production of metabolites and antioxidants. Emerging evidence suggests that the gut microbiota plays a critical role in alleviating various systemic diseases [3]. The gut microbiome is considered a new active organ due to its ability to interact with host biology and integrate systemically [4,5]. Changes in the composition or number of the gut microbiota disrupt the commensal relationship with the host and have negative consequences for human health [6–8].

Vitamin D/vitamin D receptor (VDR) signaling contributes significantly to the immunological, genetic, environmental, and microbial aspects of human health and disease [8,9]. The human *VDR* is the first identified gene that functions as an essential host factor and genetically influences the modulation of the gut microbiome [10]. Several studies have demonstrated the crucial function of vitamin D and its receptor in maintaining a healthy gut [11,12].

The aim of this review is to provide an overview of the data linking the gut microbiome to vitamin D and VDR, with a focus on data from experimental models and translational data from human studies related to changes in gut microbiota composition caused by vitamin D.

2. Materials and Methods

2.1 Inclusion Criteria

Our review focused on quantitative studies published in peer-reviewed English language journals and available as full text online or through a library. We considered randomized controlled trials, comparative studies, multicenter studies, observational studies, clinical trials, review articles, systematic reviews, meta-analyses, and case reports.

2.2 Search Strategy

We performed a thorough search of the MEDLINE, COCHRANE, and PubMed databases to find relevant articles from the beginning of each database to February 28, 2023. We used Boolean operators (AND, OR, NOT) to combine search terms and narrow the search results because the topic included multiple keywords. Search terms included “vitamin D”, “vitamin D receptor”, “VDR”,

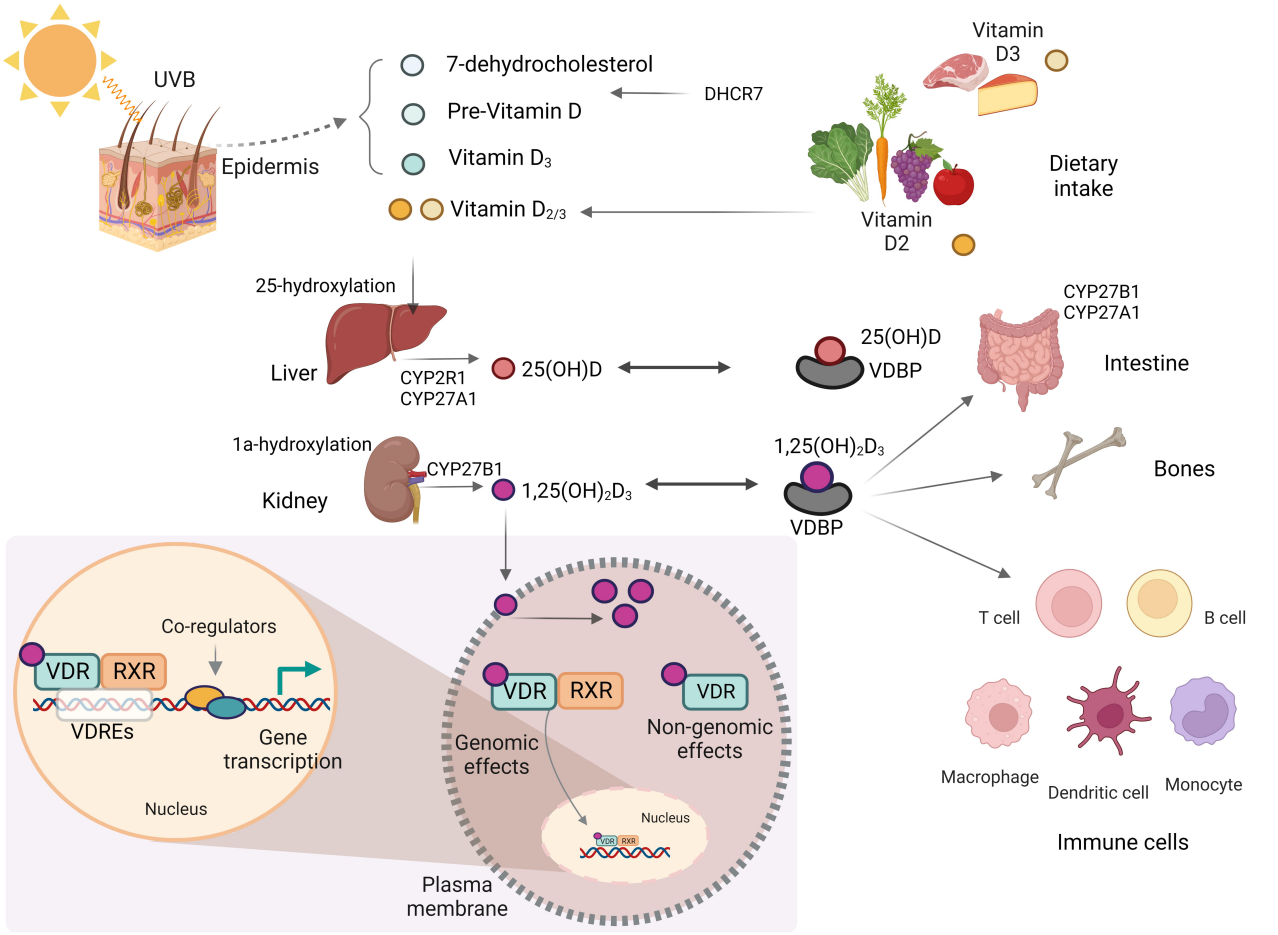

Fig. 1. Biosynthesis and metabolism of vitamin D. This figure was created using BioRender (https://biorender.com, accessed February 13, 2023). UVB, ultraviolet B; CYP2R1, cytochrome P450, family 2, subfamily R, polypeptide 1; CYP27A1, cytochrome P450, family 27, subfamily A, polypeptide 1; CYP27B1, cytochrome P450, family 27, subfamily B, polypeptide 1; VDR, vitamin D receptor; VDRE, vitamin D response element; RXR, retinoid X receptor; DHCR7, 7-dehydrocholesterol reductase; VDBP, vitamin D-binding protein.

"25(OH)D", "25 hydroxyvitamin D", "$1,25(OH)_2D_3$", "microbiota", "microbiome", "gut microbiota", "intestinal microbiota", and "dysbiosis" in various combinations. Three investigators (IA, EPT, and CT) independently screened and reviewed the titles and abstracts of eligible studies. In case of discrepancies, the research group was consulted for clarification. In parallel, additional articles were identified and included that were relevant and cited in other articles but were not originally included in the search.

3. Physiological Properties and Metabolism of Vitamin D

Vitamin D, a fat-soluble vitamin, occurs in two forms, ergocalciferol or vitamin D_2 and cholecalciferol or vitamin D_3, which are chemically distinguished by their side chains [13]. These forms are either formed in the skin by the photochemical conversion of 7-dehydrocholesterol to pre-vitamin D or are absorbed in the small intestine (Fig. 1) [14,15].

Until their enzymatic hydroxylation, these forms remain biologically inactive [16]. After vitamin D_3 binds to vitamin D-binding protein (VDBP), this complex is transported to the liver. The liver and other tissues are able to convert the vitamin D–DBP complex to 25-hydroxyvitamin D or 25(OH)D, the predominant circulating form of vitamin D. Several enzymes have a 25-hydroxylase function; however, the cytochrome P450, family 2, subfamily R, polypeptide 1 (CYP2R1) enzyme is most important [16,17]. Subsequently, 25(OH)D is further metabolized, mainly in the kidney, by the enzyme 1-α-hydroxylase cytochrome P450, family 27, subfamily B, polypeptide 1 (CYP27B1); this produces $1,25(OH)_2D_3$, the biologically active form of vitamin D responsible for most of its biological effects (Fig. 1) [16,17]. Synthesis of $1,25(OH)_2D_3$ in the kidney is a highly regulated process that is suppressed by calcium, phosphate, and fibroblast growth factor 23 (FGF23) [14] and activated by parathyroid hormone [18]. In addition to renal tissues, $1,25(OH)_2D_3$ synthesis by CYP27B1 also occurs in extrarenal tissues, such as intestinal macrophages and cells of the immune system [19].

In addition to the classical effects of vitamin D in regulating bone mineralization and maintaining systemic calcium homeostasis, non-classical effects such as regulation of cell proliferation and differentiation, hormone secretion, and immune system function have recently been reported [16,17].

4. VDR

The VDR acts as a transcription factor and controls the expression of genes involved in the biological effects of vitamin D. Binding of $1,25(OH)_2D_3$ to the VDR activates its transcription (Fig. 1) [20,21]. The VDR belongs to the superfamily of nuclear hormone receptors [22] and exerts its functions in various genes of mammalian cells and tissues [23]. Therefore, $1,25(OH)_2D_3$-induced changes in the transcriptome of VDR-expressing cells are closely related to the biological effects of vitamin D_3 [24]. After binding to $1,25(OH)_2D_3$, the VDR heterodimerizes with the retinoid X receptor and is transported to the nucleus. After binding to vitamin D response elements (VDREs) in the promoter region of target genes, this complex regulates their transcription (Fig. 1). Several additional factors, called coregulators, form complexes with the VDR to stimulate (coactivators) or repress (corepressors) the transcriptional activity of the VDR. These coregulators are specific for different genes, and different cells express these coregulators differently to ensure the specificity of vitamin D and VDR actions [13]. Healthy intestinal epithelial cells (IECs) show high VDR expression, especially in crypts [25] and the vast majority of immune cells [26]. Interestingly, the bacterial microbiome does not express the VDR gene, suggesting that vitamin D likely exerts its effects via VDR signaling in immune cells and IECs [27].

5. Composition of the Gut Microbiome

The protective barriers of the mucus layer and intestinal epithelium prevent bacteria and their products from entering the interstitial space, thus preventing the development of intestinal inflammation [28]. However, disruption of the homeostasis of the gut microbiota and the subsequent entry of immunogenic byproducts into the interstitial space can trigger an inflammatory response by activating the immune system [29].

In the human body, the total number of bacterial cells ranges from 10^{13} to 10^{14}, with a ratio of microbial cells to human cells of approximately 1:1 [30]. It is estimated that the gastrointestinal tract harbors between 200 and more than 1000 bacterial species [31,32]. The extent and composition of the gut microbiota vary widely throughout the gastrointestinal tract [2]. The colon is colonized by a large number of bacterial species that exhibit a variety of microbiological characteristics [33]. The predominant bacterial phyla in the gastrointestinal microbiota include Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria [34]. The phylum Firmicutes consists of aerobic and anaerobic Gram-positive bacteria, Bacteroidetes of Gram-negative bacteria, Actinobacteria of Gram-positive bacteria with beneficial effects, and Proteobacteria of Gram-negative bacteria commonly found in the family *Enterobacteriaceae* [2]. While the gut microbiota community is generally stable in adulthood, changes may occur over time-related to diet and general health [35,36]. It is estimated that the gut microbiome encodes approximately 3,000,000 genes, which is about 100 times more genes than in the host. In humans, the gut microbiome is relatively unique and stable but also constantly changes over time [37,38]. It also appears to be critical to human body functions, contributing to the breakdown of otherwise indigestible polysaccharides from the diet and to the synthesis of important amino acids and vitamins [39]. Gut dysbiosis leads to impaired immunoregulatory function of the intestinal mucosa, which may result in the development of various inflammatory and immune-mediated diseases [2,40]. Emerging evidence suggests that a modified diet has the potential to partially reverse dysbiosis, which may ultimately improve human health [41].

6. The Influence of Vitamin D on the Composition of the Gut Microbiota

6.1 Experimental Animal Studies

Vitamin D has been shown to alter the composition of the gut microbiome in several experimental animal models (Table 1, Ref. [42–44]) [45]. Genome-wide association studies have shown that variations in the human *VDR* gene are associated with changes in the gut microbiota [10], whereas, by contrast, the absence of VDR in the gut results in dysbiosis in mice [46]. Two VDR polymorphisms were significantly associated with changes in microbiota composition in a mixed cohort [10]. In this study, VDR genetic variants affected the genus *Parabacterioides* (phylum: Bacteroidetes), while examination of VDR knockout (KO) mice revealed higher levels of *Parabacteroides* compared to wild-type (WT) mice [10]. Vitamin D deficiency caused by dietary restriction, CYP27B1 depletion, or VDR depletion in experimental models resulted in an increase in the Bacteroidetes population and Proteobacteria phyla [42]. Vitamin D supplementation or hypovitaminosis had little effect on gut microbiota composition at the phylum level; however, significant differences occurred at lower taxonomic levels [44]. In CYP27B1 KO mice, deficiency of $1,25(OH)_2D_3$ resulted in a reduction in colon mucosal size and increased accumulation of *Akkermansia muciniphila*, leading to increased invasion of microbes into the intestinal mucosa and triggering inflammation in the colon [44]. Bioinformatics analysis has revealed differences between the functional modules in the microbiome of the cecum and feces of WT and VDR KO mice; data on the VDR KO mice suggest that the colon is more accessible to toxins and has a higher risk of cancer and infection, whereas the effects on the cecum are mainly limited to modules related to metabolism [43]. In parallel, in patients with inflammatory

Table 1. Effect of vitamin D on the composition of the gut microbiota—Animal studies.

Study [ref.]	Model used	Intervention/Parameter	Study duration	Outcomes	
				Microbial alterations	Other
Assa *et al*., 2014 [42]	Weaned C57BL/6 mice	Vitamin D dietary intake: sufficient *vs*. deficient	5 weeks	Vitamin D deficiency → - Increase in Bacteroidetes, Firmicutes, Actinobacteria, and *Gammaproteobacteria*	$1,25(OH)_2D_3$ → - Reduction of *Escherichia coli* O157:H7-induced decrease in transepithelial electrical resistance - Reduction of permeability - Barrier integrity preservation Vitamin D-deficient mice challenged with *Citrobacter rodentium* → - Increase in colonic hyperplasia - Epithelial barrier dysfunction
Jin *et al*., 2015 [43]	VDR KO and WT C57BL/6 mice	VDR KO *vs*. WT mice	NA	VDR KO mice - fecal stool → - Increase in *Clostridium* and *Bacteroides* Sphingobacteria-to-*Sphingobacteriaceae* Decrease in *Lactobacillus* VDR KO mice - cecal stool → - Increase in *Eggerthella* - Decrease in *Alistipes* and *Odoribacter*	VDR status affected NLR signaling
Zhu *et al*., 2019 [44]	WT and Cyp27b1 KO mice	Cyp27b1 KO mice fed a rescue diet (1.25% phosphorus, 2% calcium, 20% lactose) *vs*. CYP27B1 KO mice subcutaneously injected with $1,25(OH)_2D_3$ (1 μg/kg)	Rescue diet or $1,25(OH)_2D_3$ injection → - For 10–12 weeks or - Until mice reached 8–10 months of age	$1,25(OH)_2D_3$ deficiency → - Increase in *Akkermansia muciniphila*, *Solitalea Canadensis* - Decrease in *Bacteroides acidifaciens*, *Bacteroides plebeius* $1,25(OH)_2D_3$ supplementation → Decrease in *Akkermansia muciniphila* abundance	$1,25(OH)_2D_3$ deficiency → - Decrease in the colonic mucus layer - Increase in bacterial translocation to mesenteric lymph nodes

VDR, vitamin D receptor; KO, knockout; WT, wild-type; NA, not applicable; NLR, nucleotide-binding oligomerization domain-like receptor.

Table 2. Effect of vitamin D on the composition of the gut microbiota—Human studies.

Study [ref.]	Patients included (n)	Study design	Intervention/Parameter	Study duration	Outcomes	
					Microbial alterations	Other
Wu *et al*., 2012 [49]	98	Cross-sectional study	Vitamin D dietary intake	NR	Long-term vitamin D intake → - Increase in *Bacteroides* - Decrease in *Prevotella*	NR
Wang *et al*., 2020 [10]	1812	Genome-wide association cross-sectional	Genetic variants	NR	*VDR* gene and *POMC* gene were associated with β diversity Taxa significantly associated with VDR → - *Parabacteroides* - Unclassified *Enterococcaceae* - Unclassified *Ruminococcaceae* - Bacteroides	NR
Tabatabaeizadeh *et al*., 2016 [50]	50	Intervention study	Pre- *vs*. post-supplementation with 9 doses of 50,000 IU cholecalciferol pearls (1 dose/week)	9 weeks	Post-supplementation → - Increase in *Bifidobacterium*, Firmicutes - Decrease in *Lactobacillus*, Bacteroidetes	NR
Bashir *et al*., 2016 [51]	16	Interventional, open-label, pilot study	Pre- *vs*. post- supplementation → Weeks 1–4: Weekly vitamin D_3 dose of 980 IU/kg body weight Weeks 5–8: Weekly vitamin D_3 dose of 490 IU/kg body weight	8 weeks	Post-supplementation → - Increase in Bacteroidetes (gastric antrum & duodenum) - Decrease in Proteobacteria (gastric antrum & gastric corpus) and *Gammaproteobacteria* (upper GI tract)	Post-supplementation → - Increase in phylotype richness in the gastric antrum - Trend toward an increase in phylotype richness in the duodenum - Significant change in microbial composition in the upper GI tract
Luthold *et al*., 2017 [52]	150	Cross-sectional study	Vitamin D dietary intake (highest tertile *vs*. 1st & 2nd tertile combined) Serum 25(OH)D (highest tertile *vs*. 1st & 2nd tertile combined)	NR	Highest vitamin D intake tertile → - *Prevotella* is more abundant - *Haemophilus* & *Veillonella* aer less abundant Highest serum 25(OH)D → - *Megasphaera* is more abundant - *Haemophilus* & *Veillonella* are less abundant	- Inverse correlation lipopolysaccharides with 25(OH)D - Inverse correlation of CRP & E-selectin with 25(OH)D
Seura *et al*., 2017 [53]	28	Cross-sectional study	Vitamin D dietary intake	3 days	No association with *Bacteroides*, *Bifidobacterium*, and *Lactobacillales*	NR

Table 2. Continued.

Study [ref.]	Patients included (n)	Study design	Intervention/Parameter	Study duration	Outcomes	
					Microbial alterations	Other
Naderpoor *et al*., 2019 [54]	26	Double-blind, randomized clinical trial	Pre- *vs*. post-supplementation with cholecalciferol 100,000 IU dose at baseline followed by 4000 IU daily or matching placebo	16 weeks	Post-supplementation → - Increase in *Lachnospira* - Decrease in *Blautia* Individuals with 25(OH)D >75 nmol/L *vs*. individuals with 25(OH)D <50 nmol/L → - Increase in *Coprococcus* - Decrease in *Ruminococcus*	NR
Singh *et al*., 2020 [55]	80	Intervention study	Vitamin D responders *vs*. non-responders post-supplementation of a weekly oral dose of 50,000 IU vitamin D_3	12 weeks	Vitamin D supplementation → - Increase in Bacteroidetes to Firmicutes ratio - Increase in *Akkermansia* and *Bifidobacterium* - Increase in *Bacteroides/Prevotella* ratio - Decrease in *Ruminoccoccus* - Increase in *Bacteroides acidifaciens*, *Ruminococcus bromii*, *Bacteroides eggerthii*, and *Barnesiella intestinihominis* in responders - Decrease in *Bacteroides acidifaciens* in non-responders	NR
Singh *et al*., 2022 [56]	112	Pilot study	Vitamin D deficient *vs*. non-deficient children		Vitamin D deficient children → - Increase in Bacteroidetes/Firmicutes ratio Vitamin D deficient children → - Gut enterotypes dominated by *Prevotella* as opposed to *Bacteroides*	NR

NR, not reported; VDR, vitamin D receptor; POMC, proopiomelanocortin; GI, gastrointestinal; CRP, c-reactive protein.

bowel disease, both intestinal inflammation and bacterial translocation are significantly increased in association with a decrease in butyrate-producing species, effects that can be reversed by vitamin D supplementation [47]. In a model of type 2 diabetes, vitamin D supplementation improved gut dysbiosis and gut barrier function in rats fed a high-fat, high-sugar diet, which was supported by the observations of decreased serum levels of circulating lipopolysaccharides, peptidoglycans, and tumor necrosis factor alpha [48]. The observed improvement may be related to a decrease in cannabinoid receptor 1 in the colon and an increase in the expression of zonula occluden-1 (ZO-1) and occludin [48].

6.2 Human Studies

A significant correlation between gut microbiota composition and vitamin D has also been demonstrated in human studies (Table 2, Ref. [10,49–56]). In healthy individuals, high vitamin D intake resulted in increased levels of *Prevotella* and lower levels of *Haemophilus* and *Veillonella* in stool samples [52]. In addition, bacterial enrichment varied in individuals with high or low serum 25(OH)D concentrations, as higher vitamin D levels were associated with increased *Megasphaera* concentrations and lower *Veillonella* and *Haemophilus* concentrations [52]. By contrast, another study found that vitamin D supplementation was inversely related to *Prevotella* concentrations and strongly associated with *Bacteroides* in healthy individuals [49]. Singh *et al*. [55] demonstrated that vitamin D supplementation significantly increased the diversity of the gut microbiota, resulting in a higher proportion of Bacteroidetes compared to Firmicutes, in addition to an increase in the abundance of beneficial microorganisms such as *Bifidobacterium* and *Akkermansia*.

Administration of high-dose vitamin D supplements caused changes in the gut microbiome of female adolescents; specifically, a weekly dose of 50,000 IU cholecalciferol over a 9-week period resulted in a decrease in populations of Bacteroidetes and *Lactobacillus* and an increase in populations of Firmicutes and *Bifidobacterium* [50]. In parallel, vitamin D supplementation caused significant changes in *Bacteroides* and *Prevotella*, which showed a variation in enterotypes [55]. In a study by Bashir *et al*. [51], analysis of stool samples and endoscopy and colonoscopy biopsies demonstrated that 8 weeks of vitamin D_3 administration resulted in a decrease in Proteobacteria (especially Gamma Proteobacteria) and an increase in Bacteroidetes concentrations in the upper gastrointestinal tract. The lower gastrointestinal tract and fecal microbial composition did not show significant differences before and after vitamin D_3 supplementation, suggesting that fecal samples may not be suitable for analyzing the effects of vitamin D_3 on microbial populations [51]. Seura *et al*. [53] also failed to demonstrate a correlation between fecal microbial abundance and vitamin D supplementation. In another study, vitamin D supplementation was shown to have no significant effect on bacterial diversity in stool samples, but some changes at lower taxonomic levels (e.g., genera) were observed; in particular, a higher proportion of the genus *Lachnospira* and a lower proportion of the genus *Blautia* were found in the fecal microbiota [54].

A study conducted in a pediatric population in Qatar showed that the gut microbial community differed significantly between groups with and without vitamin D deficiency, with individuals with deficiency having lower microbial diversity [56]. In addition, significant differences were observed in phyla Firmicutes and Bacteroidetes, with individuals with deficiency having a higher ratio of Bacteroidetes to Firmicutes than those without deficiency [56]. The same study showed that children with vitamin D deficiency had a higher concentration of the genus *Prevotella* than *Bacteroides* in the gut [56].

On the other hand, a retrospective case-control study of adult women with irritable bowel syndrome compared with healthy controls examined plasma 25(OH)D levels and gut microbiome composition and found no association between plasma 25(OH)D levels and bacterial richness, measures of alpha diversity including Shannon and Simpson indices or bacterial abundance in either group [57].

A systematic review examined the role of vitamin D on the gut microbiome in animals and humans [45]. The results of animal studies showed an increase in Bacteroidetes in the vitamin D-deficient and VDR KO groups [42]. Human studies have mainly been observational; 12 of 14 studies reported an association between vitamin D and the gut microbiome but with differences among studies [45]. A recent systematic review of 25 human studies examining the role of vitamin D on gut microbiota composition found that vitamin D supplementation was associated with greater changes in the composition of phyla Firmicutes, Actinobacteria, and Bacteroidetes [58]. Regarding alpha and beta diversity, high dietary vitamin D intake promoted changes in bacterial composition and/or influenced the richness of different species [58]. Vitamin D supplementation and an increase in 25(OH)D levels led to a decrease in the families of *Veillonellaceae* and *Oscillospiraceae* [58]. Functional profiling of the bacterial communities in the gut using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUST) analysis showed that there are metabolic pathways involved in lipid metabolism and fatty acid biosynthesis that play an important role in the uptake of vitamin D in the gut lumen [55].

These results suggest that vitamin D has a major impact on the distribution of intestinal flora, considering that the effects depend on the dosage and duration of vitamin D supplementation, as well as on the origin of the tissue for microbiome analysis [51,54]. The question arises whether vitamin D has an effect on microbial richness either in the gastrointestinal tract or in stool samples, and caution should be exercised when collecting stool samples. In addi-

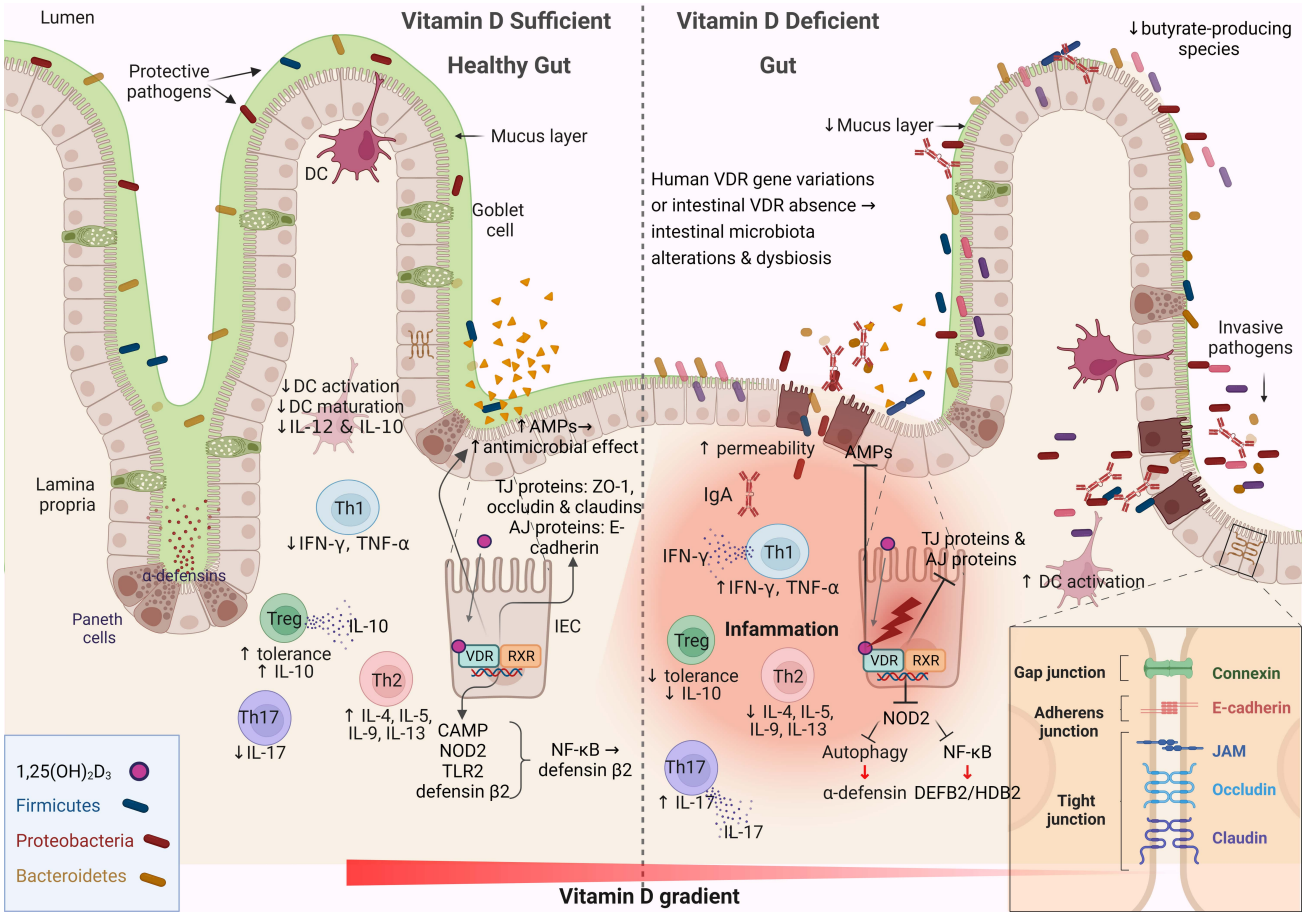

Fig. 2. Schematic representation of the changes associated with the intestinal barrier between a vitamin D-sufficient and vitamin D-deficient dysbiotic gut. This figure was created using BioRender (https://biorender.com, accessed February 13, 2023). DC, dendritic cell; IL-12, interleukin 12; Th, T helper; TNF-α, tumor necrosis factor alpha; IFN-γ; interferon gamma; Treg, regulatory T cell; TJ, tight junction; AMPs, antimicrobial peptides; AJ, adherent junction; ZO-1, zonula occluden-1; VDR, vitamin D receptor; RXR, retinoid X receptor; IECs, intestinal epithelial cells; NOD2, nucleotide-binding oligomerization domain protein 2; CAMP, cathelicidin antimicrobial peptide; TLR, Toll-like receptor; DEFB2/HBD2, antimicrobial peptide defensin β2/human beta-defensin-2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IgA, immunoglobulin A; JAM, junctional adhesion molecule.

tion, methodological differences in the assessment of vitamin D origin (ultraviolet B radiation, dietary intake, serum 25(OH)D, dietary supplements) may lead to conflicting results.

7. The Role of Bacteria in Vitamin D Metabolism

There is increasing evidence that bacteria play an important role in altering vitamin D metabolism. Several enzymes expressed by bacteria are involved in the hydroxylation of steroids; consequently, these enzymes can induce vitamin D in a similar manner as in humans [59]. The bacterial CYP105A1 (*Streptomyces griseolus*) is responsible for the conversion of vitamin D_3 to the biologically active form of vitamin D by two successive hydroxylations. This suggests that the bacterial function corresponds to the CYP27A1, CYP27B1, and CYP2R1 enzymes associated with vitamin D [60]. The National Center for Biotechnology Information BioSystems database showed the existence of homologous proteins for CYP27A1 and CYP27B1 in bacterial populations, and in particular, in *Ruminococcus torques* from the phylum Firmicutes and in *Mycobacterium tuberculosis*, respectively [61]. A patent (US5474923) describes a technique for incorporating hydroxyl groups into vitamin D compounds at the 1α-position in the kidney and/or at the 25-position in the liver in the presence of a cyclodextrin using a mixture containing a microorganism (Actinomycetales such as *Nocardia*, *Streptomyces*, *Sphinogmonas*, and *Amycolata*) capable of hydroxylating vitamin D compounds or an enzyme produced by a microorganism. In addition, factors such as FGF23, which play a crucial role in the regulation of vitamin D metabolism by the microbiota, are key elements for further studies to understand how they influence this process [62].

8. Influence of the Gut Microbiome on Immune Responses and Autoimmunity

The presence of dysbiosis and alterations in the gut microbiota in autoimmune diseases is becoming increasingly clear [63]. Nevertheless, the exact way in which the immune system and the gut microbiota interact in the development of disease is not yet fully understood. Although the extent of dysbiosis may vary among autoimmune diseases, there is evidence that certain bacteria may promote or inhibit immune responses in different ways, suggesting that the microbiota may have a multifaceted influence on inflammatory diseases [63].

9. The Role of Vitamin D in Gut Immunity

Commensal bacteria, toxins, and food antigens are involved in stimulating the immune response, which in turn leads to the initiation of inflammatory response; persistent inflammation can lead to the development of autoimmune diseases [64]. Recent evidence has shown that vitamin D signaling has a major impact on a variety of aspects of intestinal physiology and plays a critical role in maintaining intestinal homeostasis [65]. Vitamin D contributes to the activation and synthesis of pattern recognition receptors, various cytokines, and antimicrobial peptides (AMPs). It also plays an important role in modulating the gut microbiota, preventing bacterial overgrowth, and strengthening the integrity of the gut barrier [65]. In parallel, vitamin D positively affects intestinal tissues by promoting innate immune responses and attenuating T-cell-mediated inflammatory adaptive immunity, functions that are closely associated with the development of autoimmunity [66].

10. Vitamin D and Intestinal Mucosal Barrier

The intestinal mucosa serves as both a physical and functional barrier separating host cells from the microenvironment. It consists of several components that work together to fulfill its function, such as the commensal gut microbiota, an outer mucus layer, secretory immunoglobulin A (sIgA), and AMPs secreted into the mucus layer as immune-sensing molecules and regulatory proteins. The specialized epithelial cell layer and inner lamina propria also contribute to this function (Fig. 2) [67].

The IECs form a monolayer and are tightly connected by symmetrical structures called junctional complexes. The tight junctions (TJs) are located on the apical side of the cells and are responsible for ion transport and small molecule regulation (Fig. 2). The gut-associated lymphoid tissue is involved in both adaptive and innate immunity and consists of B cells, T cells, macrophages, and dendritic cells, which contribute critically to the immunological defense mechanisms of the gut barrier [68]. Immunoregulators such as sIgA and AMPs are secreted into the mucus layer to enhance the gradient separation of the microbiota from the epithelium to the lumen [69]. The sIgAs are produced by plasma cells, and their functions are diverse: they coat bacteria to facilitate their interaction with host immune cells, downregulate inflammation-associated epitopes, or neutralize toxins [70]. The composition of the mucus layer can influence the gut microbiota, and in parallel, the gut microbiota determines the properties of the mucus layer [71]. The IEC layer preserves the property of not being penetrated by pathogens and toxins through the function of TJs. Impairment of any aspect of the intestinal barrier, whether physical or functional, renders the host vulnerable to pathogen invasion, triggers a local immune response, and stimulates an inflammatory response in the gut (Fig. 2) [72].

Vitamin D–VDR signaling is critical for maintaining the integrity of the intestinal barrier by regulating apical junctions, adherent junctions, and proteins associated with TJs [73]. Defensin beta 4/human beta-defensin-2 (HBD-2) and cathelicidin antimicrobial peptide are stimulated directly and indirectly by vitamin D in human intestinal and monocyte cell lines through stimulation of the intracellular pattern recognition receptor nucleotide-binding oligomerization domain protein 2 (NOD2) [74,75]. Stimulation of NOD2 by its ligand muramyl dipeptide induces *HBD-2* gene expression (Fig. 2) [76]. These data support the hypothesis that AMPs have a major impact on the composition of the gut microbiota, whereas AMPs, in combination with IgAs, exert protective effects on the mucus layer [77].

Vitamin D–VDR signaling helps maintain intestinal barrier integrity by regulating myosin light chain kinase (MLCK) and provides protection by preventing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb)-mediated MLCK stimulation [78]. In VDR-deficient mice, ileal Paneth cell production of α-defensins and matrix metalloproteinase 7 is impaired, possibly leading to the development of dysbiosis (Fig. 2) [79]. VDR KO Paneth cells inhibit the growth of pathogenic bacteria and enhance the autophagic response [80]. Following infection with *Salmonella* increased inflammation and susceptibility to small intestinal damage were observed in this experimental model, suggesting that deficiency of VDR in Paneth cells may lead to decreased antibacterial activity and increased inflammation [80]. Vitamin D supplementation and the production of AMPs, such as α-defensins by Paneth cells and HBD-2 and cathelicidin by IECs, exert antimicrobial effects [81].

11. Conclusions and Future Perspectives

There is growing evidence that the microbiome plays an important role in both health and disease. Variations in the human microbiome are closely related to a variety of physiological functions. In parallel, new data show that the effect of vitamin D on health is mediated in part by the microbiome. Vitamin D exerts its modulatory effects on gastrointestinal health by either regulating the composition

and metabolic activity of the gut microbiome or modulating the functions of the physiological gut barrier and immune system. However, the effects of vitamin D on the gut microbiome are also closely related to VDR activation, as VDR is a crucial host factor that can influence the gut microbiome at the genetic level [82]. Several studies have demonstrated the association between vitamin D deficiency and the development of dysbiosis, while intervention studies have demonstrated vitamin D-induced changes in the composition of the microbiome, mainly through the induction of a health-promoting microbiota and the reduction of the Firmicutes/*Bacteroides* ratio.

Future research should focus on elucidating the mechanisms involved in the changes in gut microbiota composition associated with vitamin D status or supplementation and/or genetic impairment of VDR expression/activity. Thus, there is a great need for well-designed animal and human studies that allow consistent analyses of gut microbiota and assessment of vitamin D or VDR. In addition, the question of what dose of vitamin D supplementation results in specific changes in the gut microbiome that affect host health remains unresolved. Considering that the gut microbiome can provide valuable information to assess individual responses to vitamin D supplementation, future research should focus on intra- and inter-individual variability using multi-omics strategies. In parallel, the design of experimental animal studies is necessary to understand causality, as it is possible that microbial changes precede disease onset, suggesting a potential causal relationship or passive response to disease.

Abbreviations

VDR, vitamin D receptor; VDBP, vitamin D binding protein; CYP2R1, cytochrome P450, family 2, subfamily R, polypeptide 1; CYP27B1, cytochrome P450, family 27, subfamily B, polypeptide 1; FGF23, fibroblast growth factor 23; VDRE, vitamin D response elements; IEC, intestinal epithelial cell; KO, knock out; WT, wild type; ZO-1, zonula occluden-1; PICRUST, phylogenetic investigation of communities by reconstruction of unobserved states; AMP, antimicrobial peptide; sIgA, secretory immunoglobulin A; TJ, tight junction; NOD2, nucleotide-binding oligomerization domain protein 2; MLCK, myosin light chain kinase; NF-κb, nuclear factor kappa-light-chain-enhancer of activated B cells.

Availability of Data and Materials

Not applicable.

Author Contributions

IA and ET: conducting research and investigation process, specifically performing the data/evidence collection; contributing to the visualization preparation, creation and presentation of the published work; contributing to the preparation, creation and presentation of the published work, specifically writing the initial draft (including substantive translation) and AM and CT: contributing to conceptualization ideas; formulation and evolution of review aims; contributing to management and coordination responsibility for the research activity planning and execution; contributing to preparation, creation and presentation of the published work, specifically critical review, commentary and revision—including pre- or post-publication stages. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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