Chapter

The Vitamin D- Microbiome Axis: Mechanistic Insights into Gut Immunity and Health

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Abstract

The gastrointestinal tract is both the largest immune organ and the primary interface between the host and trillions of commensal microbes. Vitamin D, through its active metabolite calcitriol ($1,25(OH)_2D_3$), and the Vitamin D receptor (VDR), exerts critical regulatory roles in maintaining gut homeostasis. It strengthens epithelial barrier integrity, modulates antimicrobial peptide production, and fine-tunes immune tolerance to prevent chronic inflammation. Emerging evidence shows that Vitamin D deficiency is linked to dysbiosis, increased intestinal permeability ("leaky gut"), and heightened risk of inflammatory bowel disease (IBD), colorectal cancer, and metabolic endotoxemia. On the flip side, optimal Vitamin D signaling promotes microbial diversity, dampens excessive Th17-driven inflammation, and favors regulatory T-cell (Treg) responses. This chapter explores the multidimensional role of Vitamin D in gut health, spanning cellular mechanisms, microbiota interactions, and clinical implications, while also addressing translational opportunities in supplementation and precision medicine.

Keywords: Vitamin D, microbiota, gut, immunity, intestinal health

1. Introduction

The gastrointestinal tract once initially found as a site of digestion and absorption. However, in recent decades, it has emerged as a complex and integrated system, functioning not only as the major interface with the external environment but also as an integrative hub that fine-tunes immune regulation and metabolic homeostasis [1]. This dual role positions the gut at the crossroads of health and disease, with profound implications for systemic physiology and susceptibility to disorders ranging from infections and autoimmune conditions to metabolic syndrome and neuropsychiatric diseases [2].

The gut harbors the most extensive immune network in the body, with an estimated 70% of immune cells strategically positioned within the gut-associated lymphoid tissue (GALT) [3]. This expansive immune infrastructure serves as a dynamic sentinel, constantly discriminating between harmless dietary antigens and

commensal microbes on one hand, and invasive pathogens on the other. Intestinal epithelial cells, reinforced by mucus layers and antimicrobial peptides, constitute a crucial first line of host defense, creating a selective barrier that is both physical and biochemical [4]. Beneath this barrier lies a sophisticated immune network comprising Peyer's patches, isolated lymphoid follicles, mesenteric lymph nodes, and a rich network of innate and adaptive immune cells.

The immune functions of the gut extend beyond pathogen defense. A defining hallmark of the intestinal immune system is its capacity to actively promote immune tolerance. Commensal bacteria and food-derived antigens are generally tolerated, a process mediated by regulatory T cells (Tregs), secretory IgA, and anti-inflammatory cytokines [5]. At the same time, the system retains the capacity to mount rapid inflammatory responses when microbial breaches occur. Maintaining a finely tuned equilibrium between immune acceptance and protective responses is essential, as its breakdown can precipitate persistent inflammation, including conditions like inflammatory bowel disease and broader autoimmune disorders [6]. Thus, the gut is not simply a passive digestive organ but an immune command center with broad systemic relevance.

Parallel to its immune functions, the gut plays a decisive role in regulating host metabolism. Beyond the absorption of macronutrients and micronutrients, the gut-microbiota contributes substantially to host energy balance through the fermentation of indigestible fibers, yielding short-chain fatty acids (SCFAs) such as propionate, acetate, and butyrate [7]. These microbial metabolites provide fuel for colonocytes, regulate gluconeogenesis and lipogenesis, and offer anti-inflammatory effects by enhancing Treg differentiation [8].

The metabolic influence of the gut extends further through bile acid modification and tryptophan catabolism [9]. Primary bile acids are enzymatically transformed by the gut microbiota into structurally and functionally distinct secondary bile acids, which engage receptors such as FXR and TGR5 to regulate lipid metabolism, glucose homeostasis, and innate immunity [10]. Similarly, tryptophan-derived microbial metabolites influence serotonin biosynthesis and aryl hydrocarbon receptor (AhR)-mediated immune responses [11]. Endocrine communication between the gut and peripheral organs is also central to metabolic regulation. Hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and ghrelin, secreted by enteroendocrine cells, modulate appetite, insulin secretion, and systemic energy balance, reinforcing the concept of the gut as a master regulator of whole-body metabolism [12].

A notable hallmark of the gut is the close and dynamic interaction between immune control mechanisms and metabolic processes. Microbial metabolites serve as immunomodulators, linking dietary inputs to host immune tone. For example, SCFAs not only support energy metabolism but also condition dendritic cells and macrophages toward tolerogenic phenotypes, while bile acids regulate inflammasome activation and antimicrobial peptide production[13]. Conversely, immune activity shapes metabolic outcomes, pro-inflammatory cytokines can alter insulin signaling, disrupt lipid metabolism, and impair nutrient absorption. Disruption of this immune–metabolic crosstalk contributes to a range of chronic conditions, such as obesity, type 2 diabetes, nonalcoholic fatty liver disease, and cardiovascular disease [14].

This bidirectional communication highlights the gut as a central hub where nutrition, microbial ecology, immunity, and systemic physiology converge. The health of this hub depends on the integrity of the epithelial barrier, the composition of the microbiota, and

the fine-tuned balance of mucosal immune responses. Disturbances at any point in this system can ripple far beyond the gut, highlighting the growing recognition of intestinal homeostasis as a key driver of overall health and lifespan [15].

Vitamin D is now recognized as a pivotal modulator of gut health, extending beyond its traditional functions in calcium balance and bone physiology to strongly influence mucosal immune responses, epithelial barrier function (**Figure 1**), and gut microbial composition [16]. Vitamin D receptor (VDR) signaling influences tight junction protein expression, antimicrobial peptide production, and T-cell differentiation, thereby integrating immune and metabolic functions at the mucosal interface [17]. Growing evidence further indicates that insufficient Vitamin D levels are linked to microbial imbalance, compromised intestinal barrier integrity (**Figure 1**), and an increased vulnerability to inflammatory diseases [18].

Against this backdrop, the present chapter explores the multifaceted relationship between Vitamin D and gut health, with a particular focus on the microbiota, barrier function, and mucosal immunity. Understanding how Vitamin D intersects with the gut's dual identity as an immune and metabolic hub may provide novel insights into preventive and novel therapeutic avenues across a broad spectrum of diseases.

2. Vitamin D and the gut barrier

2.1 Regulation of epithelial tight junction proteins

The intestinal epithelium serves as the primary physical barrier separating luminal contents from the host's internal milieu [19]. Its functional integrity is primarily

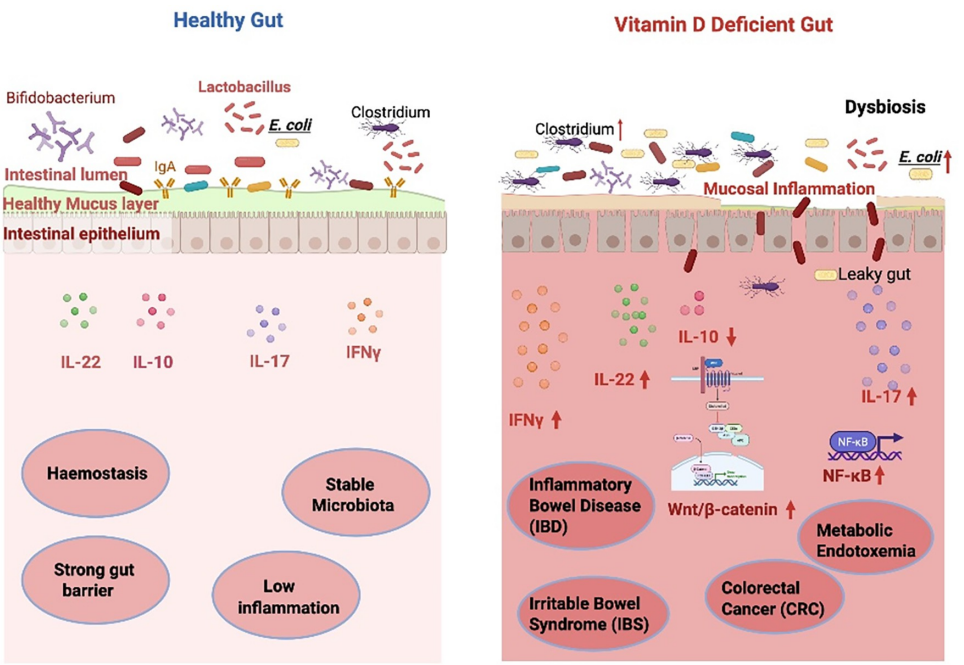

Figure 1.
Contrasting features of a healthy gut versus a Vitamin D-deficient gut.

governed by the regulated expression and spatial arrangement of tight junction proteins, notably occludin, claudins, and zonula occludens-1 (ZO-1). Vitamin D, through activation of the Vitamin D receptor (VDR), has been shown to regulate the transcription and assembly of these critical proteins [20]. Experimental studies demonstrate that VDR signaling enhances occludin expression and stabilizes ZO-1 localization at the apical junctional complex, thereby strengthening intercellular adhesion. Specific claudin family members are also modulated by Vitamin D, contributing to the fine-tuning of barrier selectivity [18]. These effects collectively reinforce the epithelial interface against paracellular leakage, ensuring that the mucosa can accommodate nutrient absorption while restricting pathogen entry.

2.2 Prevention of increased permeability and microbial translocation

A key consequence of impaired barrier function is the phenomenon of "leaky gut," characterized by increased paracellular permeability and translocation of luminal antigens, endotoxins, and microbial products [21]. Such breaches can trigger aberrant immune activation and low-grade systemic inflammation, linking intestinal dysfunction to disorders ranging from inflammatory bowel disease (IBD) to metabolic syndrome. Vitamin D plays a protective role by maintaining barrier tightness and reducing permeability. VDR-deficient models exhibit increased intestinal leakiness and elevated translocation of bacterial components into systemic circulation [16]. Conversely, supplementation with Vitamin D reduces permeability, preserves mucosal architecture, and limits systemic exposure to microbial antigens [22]. This barrier-protective function positions Vitamin D as a critical determinant in preventing the escalation of mucosal disturbances into systemic immune dysregulation.

2.3 Role in mucosal wound healing and epithelial regeneration

Beyond barrier maintenance, Vitamin D contributes to the repair and regeneration of damaged mucosa. Injury to the intestinal epithelium, whether due to infection, inflammation, or mechanical stress, necessitates rapid wound-healing processes that involve epithelial proliferation, migration, and differentiation [23]. Vitamin D promotes these processes by modulating growth factor signaling pathways, enhancing epithelial cell proliferation, and facilitating restitution of the monolayer. Furthermore, VDR activation stimulates antimicrobial peptide expression, such as cathelicidin and defensins, which not only limit microbial burden but also support epithelial recovery [24]. Evidence from experimental colitis models indicates that Vitamin D supplementation accelerates mucosal healing, reduces ulceration, and restores villus architecture [25]. This reparative capacity highlights the critical role of sufficient Vitamin D availability in preserving intestinal resilience, especially in the setting of persistent injury or inflammatory stress.

3. Vitamin D and the gut microbiota

3.1 VDR signaling in shaping microbial composition

The gut microbiota represents a dense and diverse microbial ecosystem whose composition is intimately linked to host immunity, metabolism, and overall health.

Vitamin D, acting via the Vitamin D receptor (VDR), exerts an important regulatory role in shaping this ecosystem. Intestinal epithelial and immune cells are not the only sites of VDR expression but also influences the luminal environment indirectly by modulating antimicrobial peptide production, mucin secretion, and epithelial barrier function. These host-generated cues impose selective constraints that promote the expansion of beneficial commensals while limiting the outgrowth of opportunistic pathogens. VDR deficiency in animal models has been associated with altered microbial profiles, reduced microbial diversity, and a shift toward dysbiosis, underscoring the receptor's central role in maintaining microbial homeostasis [26].

3.2 Influence on beneficial vs. pathogenic species

Vitamin D status has been shown to influence the relative abundance of major microbial taxa, particularly the balance between Firmicutes and Bacteroidetes, which is a key marker of gut microbial health [27]. Robust VDR signaling fosters the growth of health-promoting commensals like Lactobacillus and Bifidobacterium while restraining the overrepresentation of pathogenic or pro-inflammatory taxa such as Enterobacteriaceae. Deficiency states, on the other hand, often correlate with a reduction in beneficial taxa and an overrepresentation of potentially pathogenic microbes, a shift that predisposes the host to inflammatory responses (**Figure 1**). By modulating immune tone and barrier function, Vitamin D indirectly creates a gut environment where symbiotic interactions are sustained and pathogenic overgrowth is suppressed. This ecological regulation has direct implications for conditions such as inflammatory bowel disease, metabolic disorders, and infections, where microbial imbalance is a hallmark feature [28].

3.3 Impact on short-chain fatty acid (SCFA) production and microbial metabolites

Vitamin D's impact on the gut microbiota encompasses not only shifts in community structure but also functional consequences, notably the generation of microbial metabolites such as short-chain fatty acids (SCFAs). SCFAs, including butyrate, acetate, and propionate, are central to colonic health, fueling epithelial cells, reinforcing barrier integrity, and regulating immune responses through effects on Treg differentiation and cytokine production [29]. Vitamin D sufficiency has been associated with enhanced SCFA production, likely mediated by its ability to support SCFA-producing bacteria within the Firmicutes phylum. Moreover, VDR activation directly modulates host responses to microbial metabolites by influencing signaling pathways such as GPR41/43 and histone deacetylase inhibition, thereby amplifying the immunoregulatory effects of SCFAs. In contrast, Vitamin D deficiency diminishes SCFA production, reducing the anti-inflammatory and barrier-supportive functions of the microbiota. These functional consequences highlight the role of Vitamin D in shaping microbial ecology and also in sustaining the metabolic dialog between microbes and the host [30].

4. Vitamin D and innate mucosal defense

The innate immune system of the gut represents the first line of host defense against the dense and diverse microbial community residing in the lumen. While

adaptive responses provide specificity and memory, it is the innate mucosal machinery that ensures rapid recognition and neutralization of microbial threats, thereby maintaining tissue homeostasis. Vitamin D, primarily through signaling via the VDR, plays an important role in orchestrating these innate defenses. By regulating antimicrobial peptide production, influencing specialized secretory cells, and enhancing the activity of innate immune sentinels, Vitamin D strengthens the gut's capacity to contain microbial insults while preserving tolerance to commensals [31].

4.1 Induction of antimicrobial peptides

The regulation of antimicrobial peptides (AMPs) is one of the most extensively studied mechanisms linking Vitamin D to innate immunity. Among these, cathelicidins (notably LL-37 in humans) and defensins form the cornerstone of mucosal defense. The gene encoding cathelicidin antimicrobial peptide (CAMP) contains a Vitamin D response element (VDRE) in its promoter region. VDR activation directly upregulates LL-37 transcription, leading to enhanced secretion into the intestinal lumen. LL-37 exhibits broad-spectrum antimicrobial activity, disrupting bacterial membranes, neutralizing lipopolysaccharides (LPS), and inhibiting viral entry [32]. Within the intestinal environment, LL-37 further shapes immune responses by recruiting immune cells to sites of microbial challenge and by dampening excessive inflammatory responses, thereby linking antimicrobial activity with immune regulation. Vitamin D also influences defensin production, particularly human β-defensins (hBDs). These peptides not only kill bacteria, fungi, and viruses but also act as chemoattractants for dendritic cells and T cells through CCR6 signaling. Paneth cells are the primary source of α-defensins (cryptdins in mice) in the small intestine, which are vital for controlling microbial density in the crypts. Evidence suggests that Vitamin D signaling enhances the expression of certain defensins, thereby contributing to localized microbial control at the epithelial surface.

The induction of AMPs by Vitamin D provides a powerful mechanism for direct microbial killing, thereby sculpting the gut microbial landscape and impeding the establishment of pathogenic organisms [33].

4.2 Effects on paneth cells and mucus production

Vitamin D also exerts regulatory effects on specialized epithelial cell subsets that are essential for innate mucosal defense. Situated at the base of intestinal crypts, Paneth cells release α-defensins, lysozyme, and RegIIIγ, collectively establishing a microbicidal gradient that safeguards the stem cell niche [34]. VDR is expressed in Paneth cells, and studies in VDR-deficient mice reveal impaired Paneth cell function, altered antimicrobial peptide secretion, and susceptibility to dysbiosis. Vitamin D signaling ensures optimal Paneth cell differentiation and activity, reinforcing the epithelial barrier at its most vulnerable regenerative sites.

4.3 Goblet cells and mucus layer

Goblet cells produce mucins (predominantly MUC2 in the intestine), which form the mucus gel layer that separates luminal microbes from the epithelial surface.

Vitamin D contributes indirectly to mucus production by maintaining epithelial health, reducing oxidative stress, and modulating goblet cell function. In deficiency states, thinning of the mucus barrier has been observed, facilitating closer microbial-epithelial interactions and increasing infection risk [35]. By preserving mucus integrity, Vitamin D enhances the spatial compartmentalization that is central to gut homeostasis. Collectively, the Paneth and goblet cell populations underscore Vitamin D's crucial role in preserving both chemical and physical defenses against microbial invasion [36].

4.4 Enhancement of innate immune surveillance in the gut

Beyond epithelial and secretory functions, Vitamin D modulates the activity of innate immune cells residing within the gut mucosa. These cells act as surveillance units that constantly sample luminal antigens and orchestrate downstream immune responses. Vitamin D modulates dendritic cell (DC) maturation and activity, fostering a tolerogenic state marked by lower co-stimulatory molecule expression and enhanced IL-10 production. In the gut, this results in dampened inflammatory responses to commensals while maintaining the ability to respond to pathogens [37]. DCs exposed to Vitamin D also show enhanced antimicrobial activity through AMP induction, further strengthening innate defense. Intestinal macrophages represent a large fraction of innate immune sentinels in the lamina propria. Vitamin D enhances their phagocytic capacity, promotes bacterial clearance, and induces AMP expression. Importantly, Vitamin D polarizes macrophages to an M2 anti-inflammatory phenotype, reducing excessive tissue damage while preserving microbial control. Group 3 ILCs (ILC3s) are central to gut barrier defense via secretion of IL-22, which stimulates epithelial cells to produce AMPs and proliferate. Evidence suggests Vitamin D modulates ILC activity, indirectly supporting IL-22 production and epithelial protection [38]. Vitamin D has been shown to modulate Toll-like receptor (TLR) signaling pathways in innate cells. For example, TLR activation can enhance local VDR expression, creating a feed-forward loop in which microbial sensing boosts Vitamin D-mediated AMP production. This cross-talk underscores Vitamin D's role in fine-tuning the recognition–response balance of innate immune surveillance [39].

4.5 Integrative role in innate mucosal defense

By simultaneously promoting AMP production, supporting specialized secretory cells, and enhancing immune cell surveillance, Vitamin D creates a multi-layered defense system in the gut. These actions are not isolated; they reinforce one another. For instance, LL-37, produced under VDR influence, not only kills microbes but also promotes epithelial wound healing, while Paneth cell-derived defensins synergize with macrophage activity to shape microbial communities [40]. In conditions of Vitamin D deficiency, this synergy collapses: AMP levels decline, Paneth cell function is impaired, mucus layers thin, and innate immune surveillance becomes dysregulated, culminating in barrier dysfunction, dysbiosis, and heightened infection risk.

Collectively, the integration of Vitamin D into innate mucosal defense emphasizes its indispensable role in maintaining gut homeostasis. The Vitamin D–VDR axis connects gut barrier integrity, microbiota balance, and immune regulation,

explaining how deficiency increases the risk of infections and inflammatory diseases [41].

5. Vitamin D and adaptive gut immunity

The adaptive immune system of the intestine is critical for distinguishing between harmless antigens derived from food and commensals, and harmful pathogens that pose a genuine threat. This task requires finely tuned regulation, as inappropriate activation leads to autoimmunity or chronic inflammation, while inadequate responses allow infection and dysbiosis. Vitamin D, acting predominantly through the VDR, has a central function in guiding adaptive immune responses in the gut. Its influence extends across T cell differentiation, antigen presentation by dendritic cells (DCs), and the establishment of oral tolerance [42]. Collectively, these actions explain why Vitamin D status has profound consequences for susceptibility to chronic inflammatory and autoimmune diseases.

5.1 Regulation of Th17/Treg balance in the lamina propria

The gut lamina propria harbors abundant CD4 T cells, where Th17 and regulatory T (Treg) subsets create a pivotal axis that orchestrates intestinal immune balance [43]. Th17 cells produce pro-inflammatory cytokines like IL-17A, IL-17 F, and IL-22, crucial for defending against extracellular microbes, including fungi and specific bacterial species [44]. However, uncontrolled Th17 activity promotes inflammation, epithelial barrier disruption, and pathology in disorders such as IBD and multiple sclerosis. Treg cells, characterized by FoxP3 expression, are indispensable for maintaining tolerance to commensals and dietary antigens. They suppress effector T cell activity through IL-10 and TGF-β production, thereby preserving gut homeostasis.

Vitamin D strongly influences the Th17/Treg balance. VDR activation inhibits naïve T cell differentiation into Th17 cells by repressing RORγt, the key transcription factor driving Th17 lineage development. Simultaneously, Vitamin D promotes the expansion and stability of FoxP3 Tregs [45]. The net effect is a shift toward immune tolerance and away from pathological inflammation. Experimental colitis models show that Vitamin D supplementation reduces Th17-mediated inflammation while enhancing Treg-mediated regulation, providing mechanistic insight into its therapeutic potential [46].

5.2 Effects on dendritic cell function and oral tolerance

Dendritic cells are the principal cells in the gut, sampling luminal antigens via trans-epithelial dendrites or through the uptake of microbial products transported across M cells and epithelial cells. Their functional phenotype largely dictates the outcome of adaptive responses.

Vitamin D skews DCs toward a tolerogenic phenotype characterized by reduced expression of co-stimulatory molecules (CD80, CD86), increased secretion of IL-10, and reduced secretion of IL-12 [47]. Such tolerogenic DCs favor Treg

differentiation over Th1/Th17 effector responses, thereby maintaining mucosal immune tolerance.

Oral tolerance refers to the systemic unresponsiveness induced by the oral administration of antigens, an essential process for preventing unnecessary immune responses to dietary proteins and commensals. Vitamin D supports this process by reinforcing tolerogenic DC function and enhancing Treg induction in the mesenteric lymph nodes. In states of Vitamin D deficiency, oral tolerance mechanisms are impaired, leading to exaggerated immune responses against otherwise harmless antigens.

Through its regulation of dendritic cell biology, Vitamin D ensures that the adaptive immune system remains appropriately restrained in the intestinal environment, preventing overzealous activation that could trigger pathology [42].

5.3 Implications for autoimmunity and chronic inflammation

Vitamin D's regulation of T cell differentiation and dendritic cell activity profoundly influences systemic immunity, with disruptions linked to autoimmunity and chronic inflammation. Insufficient Vitamin D signaling is associated with higher rates of autoimmune diseases, including type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and celiac disease. In the gut, weakened Treg function alongside hyperactive Th17 responses fosters loss of tolerance and self-reactivity; murine studies show that Vitamin D deficiency worsens autoimmune diabetes by destabilizing Tregs and amplifying pathogenic Th17 activity.

In IBD, dysregulation of the Th17/Treg axis is a central pathogenic feature. Supplementation with Vitamin D has been shown to reduce disease severity, partly by restoring this balance and dampening mucosal inflammation [48]. Furthermore, on dendritic cells, the tolerogenic effects of Vitamin D mitigate excessive antigen-driven T cell activation, a mechanism increasingly recognized in Crohn's disease and ulcerative colitis. Vitamin D sufficiency thus supports not only mucosal tolerance but also systemic immune homeostasis, potentially reducing the risk of widespread chronic inflammatory states [49].

5.4 Integrative role in adaptive gut immunity

Taken together, Vitamin D functions as one of the key regulators of adaptive immunity in the gut. By suppressing pathogenic Th17 responses, stabilizing Treg populations, and promoting tolerogenic antigen presentation by dendritic cells, Vitamin D ensures that the immune system remains balanced, protective yet restrained [50]. The failure of this regulation in deficiency states presents a compelling explanation for the associations between low Vitamin D levels, increased susceptibility to IBD, impaired oral tolerance, and higher risk of autoimmunity. Thus, adequate Vitamin D status represents a cornerstone of adaptive immune resilience in the gut.

6. Clinical links

The physiological roles of Vitamin D in gut barrier function, mucosal immunity, and microbial homeostasis translate directly into clinical outcomes [36]. A growing

body of evidence suggests that Vitamin D status influences the onset, progression, and therapeutic responsiveness of several gastrointestinal and systemic diseases. The following sections highlight key clinical contexts where Vitamin D–gut interactions are of particular relevance.

6.1 Inflammatory bowel disease (IBD)

Vitamin D deficiency is prevalent in IBD patients, especially those with Crohn's disease and ulcerative colitis. Contributing factors include malabsorption from intestinal inflammation, limited sunlight exposure during flares, and systemic inflammation disrupting Vitamin D metabolism. Observational data consistently link low serum 25-hydroxyVitamin D levels with heightened disease activity, more frequent relapses, and increased risk of hospitalization or surgical intervention [51].

Clinical trials of Vitamin D supplementation in IBD have shown promising outcomes, including lower relapse rates, improved mucosal healing, and better quality of life in certain patient groups. Mechanistically, Vitamin D's ability to restore epithelial tight junctions, promote antimicrobial peptide production, and rebalance Th17/Treg responses provides a plausible explanation for its therapeutic benefit (**Table 1**). While the ideal dosing regimen is still being refined, keeping serum 25(OH)D above 30–40 ng/mL is increasingly advocated in IBD care. In adults, daily supplementation with 2,000 IU of cholecalciferol for approximately 12 weeks safely raised serum levels into the insufficient-to-sufficient range and maintained them through winter, with higher 25(OH)D concentrations linked to better disease outcomes in meta-analyses of randomized trials [52]. In Crohn's disease, a 24-week regimen of 5,000 IU/day Vitamin D_3 elevated serum 25(OH)D beyond 40 ng/mL, coinciding with lower CDAI scores and enhanced patient-reported quality of life [53]. Pediatric IBD data also demonstrate that 2,000 IU/day over six months significantly increases the proportion of subjects achieving ≥30 ng/mL compared with lower dosing, though effects on disease activity varied [54].

6.2 Irritable bowel syndrome (IBS)

Unlike IBD, IBS is not driven by overt mucosal inflammation but rather by visceral hypersensitivity, altered gut-brain signaling, and low-grade immune activation. Emerging evidence indicates that Vitamin D levels may influence the severity of IBS symptoms [58]. Patients with IBS are more likely to be Vitamin D deficient compared with healthy controls, and supplementation has been associated with improvements in abdominal pain, bloating, and quality of life (**Table 1**).

The mechanisms remain incompletely understood but may involve modulation of serotonin pathways, stabilization of mast cells, and reduction in visceral hypersensitivity. Vitamin D's ability to reinforce epithelial barrier function and reduce dysbiosis-driven immune activation may also mitigate post-infectious forms of IBS. While more randomized controlled trials are needed, Vitamin D supplementation represents a promising, low-cost adjunct in IBS management [67]. For example, in IBS populations, randomized trials and meta-analyses have investigated a range of dosing strategies. Weekly doses of 50,000

Clinical entity	Pathophysiological association to Vitamin D	Mechanistic insights	Clinical studies
Inflammatory Bowel Disease (IBD)	Microbial dysbiosis, impaired epithelial barrier function, and unregulated immunological activation against gut flora and chronic intestinal inflammation [55].	Vitamin D-increases Vitamin D receptor (VDR) signaling to lower proinflammatory cytokines, enhance regulatory T-cell activity, promote antimicrobial peptides, and restore gut microbial balance and epithelial barrier [56].	Supplementation of Vitamin D enhanced patients' quality of life, encouraged mucosal healing, and reduced relapse rates [57].
Irritable Bowel Syndrome (IBS)	Increased intestinal permeability,immunological dysregulation, and altered gut-brain axis communication, which can cause visceral hypersensitivity [58].	Vitamin D alleviates intestinal dysfunction and IBS severity by regulating serotonin, suppressing proinflammatory cytokines, reinforcing epithelial barrier integrity, and restoring gut microbiota balance [59].	Vitamin D supplementation has been linked to the relief of IBS symptoms, including bloating, gas, constipation, abdominal pain, and enhanced overall quality of life [60].
Colorectal Cancer (CRC)	Tumor development and higher metastatic potential are all associated to low Vitamin D levels [61].	In colonic epithelial and immunological cells, Vitamin D interacts with the VDR, modifying gene expression to prevent the development of tumors. Wnt/β-catenin signaling is inhibited, cell cycle arrest and cell death are induced, proinflammatory cytokines are decreased, and DNA repair and immune surveillance are improved [62].	Clinical records show that having enough Vitamin D lowers the risk of recurrent adenomatous polyps and is positively correlated with overall survival rates [63].
Metabolic Endotoxemia	Lipopolysaccharides (LPS) can enter the circulation in metabolic endotoxemia due to increased intestinal permeability caused by Vitamin D deficiency. This leads to obesity-related metabolic dysfunction, insulin resistance, and systemic low-grade inflammation [64].	When Vitamin D stimulates the VDR in immune and gastrointestinal epithelial cells, tight junctions are reinforced, and LPS translocation is reduced. It also reduces the effects of metabolic endotoxemia by lowering systemic cytokines, improving insulin sensitivity, and inhibiting TLR4/NF-κB signaling [65].	Vitamin D supplementation has been shown to enhance metabolic profiles and insulin sensitivity, while reducing inflammatory cytokines and circulating lipopolysaccharides [66].

Table 1.
Role of Vitamin d and its mechanisms in intestinal inflammatory diseases.

IU (~7,000 IU/day) over 6–9 weeks raised mean serum 25(OH)D from ~ 21 to ~ 36–40 ng/mL, improving IBS-SSS and quality-of-life scores versus placebo [68]. Meta-analyses of RCTs using daily or intermittent Vitamin D (≈3,000–3,500 IU/day) show consistent increases in serum 25(OH)D in IBS patients, with overall trends toward symptom relief and better quality of life, though effect sizes differ across studies [69].

6.3 Colorectal cancer

Epidemiological, genetic, and mechanistic evidence links Vitamin D to colorectal cancer, with low serum levels correlating with higher incidence and worse survival outcomes [70]. One mechanistic axis involves Vitamin D receptor (VDR) polymorphisms, which influence both cancer susceptibility and disease outcomes. Specific VDR alleles have been correlated with altered risk for CRC, suggesting that genetic variability modifies individual responsiveness to Vitamin D signaling.

Beyond tumor initiation, Vitamin D modulates tumor immunity and the tumor microenvironment. VDR activation enhances cytotoxic T cell function, reduces pro-tumorigenic inflammation, and upregulates antimicrobial peptides that may counter microbial carcinogens [43]. Importantly, Vitamin D also regulates microbiota composition, thereby limiting dysbiosis-driven carcinogenesis (**Table 1**). For example, the expansion of Fusobacterium nucleatum, a microbe linked to CRC progression, has been shown to be restricted under adequate Vitamin D/VDR signaling. Clinical trials exploring Vitamin D supplementation in CRC prevention and adjuvant therapy are ongoing, with preliminary results indicating reduced polyp recurrence and improved survival in patients with sufficient Vitamin D status.

6.4 Metabolic endotoxemia

Metabolic endotoxemia, a low-grade systemic inflammation from microbial products like lipopolysaccharides (LPS) entering the bloodstream, is increasingly seen as a contributor to obesity, insulin resistance, and NAFLD [71]. Vitamin D plays a central role in limiting this process by maintaining gut barrier integrity and microbial balance.

Deficiency states are associated with increased intestinal permeability, overgrowth of LPS-producing bacteria, and heightened systemic inflammation. In obese individuals, low Vitamin D status correlates with elevated circulating LPS and inflammatory cytokines such as TNF-α and IL-6 [72]. Supplementation studies have shown that Vitamin D can reduce markers of endotoxemia, improve insulin sensitivity, and modulate the gut microbiota toward a healthier profile (**Table1**). These findings suggest that adequate Vitamin D not only protects against local intestinal dysfunction but also reduces systemic metabolic inflammation linked to cardiometabolic disease.

7. Integrative perspective

Collectively, clinical evidence underscores the translational importance of Vitamin D in gut health. From chronic inflammatory conditions such as IBD, to functional syndromes like IBS, to malignancies such as CRC, and metabolic disorders driven by dysbiosis, Vitamin D emerges as a unifying factor that influences disease risk and outcomes [73]. Although larger clinical trials are needed to optimize treatment, maintaining sufficient Vitamin D levels offers a practical and broadly applicable approach to supporting gut and overall systemic health.

8. Therapeutic and translational implications, future directions, and conclusion

Expanding evidence base linking Vitamin D to gut barrier integrity, mucosal defense, and host–microbe crosstalk is reshaping therapeutic perspectives in gastroenterology and systemic health [30]. Beyond its classical skeletal functions, Vitamin D is now recognized as a cornerstone of gut–immune homeostasis, opening new avenues for translational interventions.

8.1 Therapeutic and translational implications

Vitamin D supplementation strategies are increasingly tailored not only to restore systemic sufficiency but also to maximize gut-specific benefits. Studies in IBD, IBS, and metabolic endotoxemia show that keeping serum 25(OH)D above 30–40 ng/mL promotes epithelial healing, curbs dysbiosis-related inflammation, and enhances clinical outcomes [74]. The therapeutic potential of Vitamin D is further amplified when combined with microbiota-directed strategies such as probiotics, prebiotics, and dietary modulation. These synergies reflect complementary mechanisms: Vitamin D reinforces barrier function and regulates immune tone, while microbiota-directed interventions shape the ecological context in which Vitamin D signaling unfolds.

Precision medicine approaches are emerging as critical in this field. Genetic variation in the Vitamin D receptor (VDR), coupled with individual microbiome configurations, modulates responsiveness to supplementation [75]. For instance, specific VDR polymorphisms influence colorectal cancer risk and treatment response, while microbial enzymes may regulate Vitamin D metabolism. Integrating host genetics, microbiome profiles, and nutritional data could enable stratified supplementation strategies that deliver greater therapeutic efficacy.

8.2 Future directions

The emerging perspective frames Vitamin D not just as a nutrient but as a key regulator of the gut–immune–brain axis. Preclinical studies already link Vitamin D status to neuroimmune interactions and visceral sensitivity, raising the prospect of novel interventions for disorders such as IBS, depression, and cognitive decline. However, current evidence is limited by short study durations and underpowered cohorts. Large-scale, longitudinal clinical trials incorporating microbiome sequencing and immune phenotyping are urgently needed to capture dynamic cause–effect relationships.

The integration of systems biology and artificial intelligence offers a transformative opportunity. Computational models could assimilate genomics, metabolomics, microbiome, and clinical datasets to predict individualized Vitamin D needs and outcomes. Such approaches would move beyond “one-size-fits-all” recommendations toward adaptive, precision-guided supplementation, with implications extending from gastrointestinal disorders to systemic metabolic and neuroimmune diseases.

9. Conclusion

Vitamin D is increasingly recognized as a central regulator of gut health, shaping microbial communities and modulating immune homeostasis. Its deficiency contributes to inflammatory, functional, neoplastic, and metabolic disorders, while supplementation holds promise for restoring homeostasis [30]. The path forward lies in integrating Vitamin D into a broader therapeutic framework that encompasses microbiota modulation, immune regulation, and personalized nutrition. By linking molecular insights to clinical practice, Vitamin D emerges not merely as a supportive nutrient but as a potential therapeutic cornerstone for preventing and managing complex gut-related disorders [76].

Vitamin D deficiency has become increasingly associated with early menopause, an important moderator of calcium homeostasis and overall menopausal health. The reduction in estrogen levels during the menopausal transition has negative effects on both Vitamin D metabolism and bone integrity and, therefore, directly relates Vitamin D status to the severity of menopausal symptoms, particularly in terms of bone loss. A 2-year prospective study found that postmenopausal women with Vitamin D deficiency (<20 ng/mL) experienced delayed menopause, lower estrogen, higher FSH, worse symptoms, reduced BMD, increased inflammation, and poorer quality of life compared with those sufficient in Vitamin D (>30 ng/mL) [77].

Furthermore, Vitamin D metabolism and its downstream effects on the immune system and gut ecology are modulated by sex hormones and age, factors of particular relevance for postmenopausal women and personalized medicine strategies [78]. Vitamin D has widespread physiological effects during menopause, which include maintaining skeletal integrity, cardiovascular health, immune regulation, and mental well-being. Despite its relatively low dose requirements for correction, Vitamin D insufficiency remains extremely prevalent among postmenopausal women and strongly predisposes individuals to osteoporosis and fracture risk. The major components of Vitamin D metabolism, at the molecular level, are significantly controlled through estrogen, including the activating enzyme CYP27B1 (1α-hydroxylase), the inactivating enzyme CYP24A1, and the Vitamin D receptor (VDR). This bidirectional interaction between estrogen and Vitamin D pathways contributes to sex- and age-specific immune and metabolic responses [79]. These components act within the major target tissues essential for the maintenance of calcium balance and skeletal homeostasis: the intestine, the bone, and immune cells. Following menopause, impaired VDR expression and responsiveness, resulting from reduced estrogen levels, most notably in the intestines, compromise calcium absorption and skeletal health, with further disturbance of immune function.

Moreover, estrogen deficiency after menopause leads to significant changes in gut microbiota composition, observed by a decrease in microbial diversity and a loss of specific beneficial genera, including Lactobacillus and Bifidobacterium. These microbiome alterations could further cause disruption to the Vitamin D-VDR signaling axis, since gut microbes influence Vitamin D bioavailability, intestinal barrier function, and immune modulation. The estrogen decline, impaired Vitamin D signaling, and gut dysbiosis thus creates an environment that biologically predisposes postmenopausal women to accelerated bone loss, heightened inflammation, metabolic disturbances, and diminished quality of life.

Menopause itself can lead to shifts in gut microbiota composition and diversity, associated to lower estrogen levels and increased intestinal permeability factors that can promote low-grade inflammation and dysbiosis [80]. These microbial changes may further influence estrogen metabolism through the "estrobolome," an accumulation of microbial genes which modulate estrogen recirculation, suggesting a complex feedback loop between hormones, the microbiome, and host metabolism [81].

Meta-analyses further show that age and sex influence the gut microbiome–Vitamin D relationship in immune-mediated conditions, with aging and declining sex hormones linked to higher inflammation and lower microbial diversity [79]. These findings highlight the importance of personalized Vitamin D supplementation in postmenopausal women, considering hormonal status, age-related metabolic shifts, immune function, and microbiome composition to maximize clinical outcomes [82].

Cumulatively, in the postmenopausal setting, these findings emphasize the clinical relevance of ensuring adequate levels of Vitamin D. In addition, Vitamin D adequacy may favorably preserve hormonal status, bone and immune health, reduce symptom severity during menopause, and mitigate microbiome-driven inflammatory changes [83]. Such interactions underscore the necessity of tailored Vitamin D supplementation strategies for postmenopausal women, taking into account hormonal status, age-related changes in Vitamin D metabolism, immune function, and microbiome composition to optimize clinical benefit [84].

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Abbreviations

AMPs	Antimicrobial peptides
CAMP	Cathelicidin antimicrobial peptide
CRC	Colorectal cancer
DC	Dendritic cells
GALT	Gut-associated lymphoid tissue
GLP-1	Glucagon-like peptide-1
hBDs	Human β-defensins
IBD	Inflammatory bowel disease
IBS	Irritable Bowel Syndrome
LPS	lipopolysaccharides
NAFLD	nonalcoholic fatty liver disease
SCFAs	Short-chain fatty acids
TJ Treg	Tight junction Regulatory T-cell
TLR	Toll-like receptor
VDR	Vitamin D receptor

VDRE	Vitamin D response element
ZO-1	zonula occludens-1

Conflict of Interest

"The authors declare no conflict of interest."

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References

[1] Chen K, Wang H, Yang Y, Tang C, Sun X, Zhou J, Liu S, Li Q, Zhao L, Gao Z. Common mechanisms of Gut microbe-based strategies for the treatment of intestine-related diseases: Based on multi-target interactions with the intestinal barrier. Cell Communication and Signaling. 2025;**23**:288. DOI: 10.1186/S12964-025-02299-5

[2] Park JC, Chang L, Kwon HK, Im SH. Beyond the gut: Decoding the gut–immune–brain axis in health and disease. Cellular & Molecular Immunology. 2025;**22**(11):1287–1312. DOI: 10.1038/s41423-025-01333-3

[3] Bemark M, Pitcher MJ, Dionisi C, Spencer J. Gut-associated lymphoid tissue: A microbiota-driven hub of B cell immunity. Trends in Immunology. 2024;**45**:211–223. DOI: 10.1016/j.it.2024.01.006

[4] Thoo L, Noti M, Krebs P. Keep calm: The intestinal barrier at the interface of peace and war. Cell Death & Disease. 2019;**10**(11):849–. DOI: 10.1038/s41419-019-2086-z

[5] Traxinger BR, Richert-Spuhler LE, Lund JM. Mucosal tissue regulatory T cells are integral in balancing immunity and tolerance at portals of antigen entry. Mucosal Immunology. 2022;**15**:398–407. DOI: 10.1038/s41385-021-00471-x

[6] Shao T, Hsu R, Rafizadeh DL, Wang L, Bowlus CL, Kumar N, Mishra J, Timilsina S, Ridgway WM, Gershwin ME, Ansari AA, Shuai Z, Leung PSC. The gut ecosystem and immune tolerance. Journal of Autoimmunity. 2023;**141**:103114. DOI: 10.1016/j.jaut.2023.103114

[7] Jyoti P. Dey, Mechanisms and implications of the gut microbial modulation of intestinal metabolic processes. Npj Metabolic Health and Disease. 2025;**3**(1):24–. DOI: 10.1038/s44324-025-00066-1

[8] Liu J, Tan Y, Cheng H, Zhang D, Feng W, Peng C. Functions of gut microbiota metabolites. Current Status and Future Perspectives, Aging Disease. 2022;**13**:1106. DOI: 10.14336/AD.2022.0104

[9] Golubeva AV, Joyce SA, Moloney G, Burokas A, Sherwin E, Arboleya S, Flynn I, Khochanskiy D, Moya-Pérez A, Peterson V, Rea K, Murphy K, Makarova O, Buravkov S, Hyland NP, Stanton C, Clarke G, Gahan CGM, Dinan TG, Cryan JF. Microbiota-related changes in bile acid & tryptophan metabolism are associated with gastrointestinal dysfunction in a mouse model of autism. EBioMedicine. 2017;**24**:166–178. DOI: 10.1016/j.ebiom.2017.09.020

[10] Kiriyama Y, Nochi H. Physiological role of bile acids modified by the gut microbiome. Microorganisms. 2021;**10**:68. DOI: 10.3390/MICROORGANISMS 10010068

[11] Li S. Modulation of immunity by tryptophan microbial metabolites. Frontiers in Nutrition. 2023;**10**. DOI: 10.3389/FNUT.2023.1209613

[12] Martin AM, Sun EW, Keating DJ. Mechanisms controlling hormone secretion in human gut and its relevance to metabolism. Journal of Endocrinology. 2019;**244**:R1–R15. DOI: 10.1530/JOE-19-0399

[13] Zhang W, Mackay CR, Gershwin ME. Immunomodulatory effects of microbiota-derived short-chain fatty acids in autoimmune liver diseases. The Journal of Immunology. 2023;**210**:1629–1639. DOI: 10.4049/JIMMUNOL.2300016

[14] Wan M, Zhao W, Cai Y, He Q, Zeng J. Role of gut-brain axis dysregulation in the pathogenesis of non-alcoholic fatty liver disease: Mechanisms and therapeutic implications. American Journal of Translational Research. 2025;**17**:3276. DOI: 10.62347/ZWSR4476

[15] Shabani M, Ghoshehy A, Mottaghi AM, Chegini Z, Kerami A, Shariati A, Taati Moghadam M. The relationship between gut microbiome and human diseases: Mechanisms, predisposing factors and potential intervention. Frontiers in Cellular and Infection Microbiology. 2025;**15**:1516010. DOI: 10.3389/FCIMB.2025.1516010/FULL

[16] Wang J, Mei L, Hao Y, Xu Y, Yang Q, Dai Z, Yang Y, Wu Z, Ji Y. Contemporary perspectives on the role of vitamin D in enhancing gut health and its implications for preventing and managing intestinal diseases. Nutrients. 2024;**16**. DOI: 10.3390/NU16142352

[17] He L, Liu T, Shi Y, Tian F, Hu H, Deb DK, Chen Y, Bissonnette M, Li YC. Gut epithelial Vitamin D receptor regulates microbiota-dependent mucosal inflammation by suppressing intestinal epithelial cell apoptosis. Endocrinology. 2018;**159**:967–979. DOI: 10.1210/EN.2017-00748

[18] Sun J, Zhang YG. Vitamin D receptor influences intestinal barriers in health and disease. Cells. 2022;**11**:1129. DOI: 10.3390/CELLS11071129

[19] Kagnoff MF. The intestinal epithelium is an integral component of a communications network. Journal of Clinical Investigation. 2014;**124**:2841–2843. DOI: 10.1172/JCI75225

[20] Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Yan CL. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2008;**294**:G208–G216. DOI: 10.1152/AJPGI.00398.2007

[21] Dmytriv TR, Storey KB, Lushchak VI. Intestinal barrier permeability: The influence of gut microbiota, nutrition, and exercise. Frontiers in Physiology. 2024;**15**:1380713. DOI: 10.3389/FPHYS.2024.1380713/FULL

[22] Cantorna MT, Snyder L, Arora J. Vitamin A and vitamin D regulate the microbial complexity, barrier function, and the mucosal immune responses to ensure intestinal homeostasis. Critical Reviews in Biochemistry and Molecular Biology. 2019;**54**:184–192. DOI: 10.1080/10409238.2019.1611734

[23] Neurath MF, Artis D, Becker C. The intestinal barrier: A pivotal role in health, inflammation, and cancer. The Lancet Gastroenterology & Hepatology. 2025;**10**:573–592. DOI: 10.1016/S2468-1253(24)00390-X

[24] Scheenstra MR, van Harten RM, Veldhuizen EJA, Haagsman HP, Coorens M. Cathelicidins modulate TLR-activation and inflammation. Frontiers in Immunology.

2020;**11**:540919. DOI: 10.3389/FIMMU.2020.01137/FULL

[25] Wu Z, Liu D, Deng F. The role of Vitamin D in immune system and inflammatory bowel disease. Journal of Inflammation Research. 2022;**15**:3167. DOI: 10.2147/JIR.S363840

[26] Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. Medicine. 2018;**97**. DOI: 10.1097/MD.0000000000012662

[27] Han XQ, Jiang HH, Chen ML, Han DY, Zhou SF, Wang JW, Ji SS, Wang LY, Lou JW, Li MQ. Gut microbiota interacting with vitamin D but not anandamide might contribute to the pathogenesis of preeclampsia: A preliminary study. Frontiers in Cellular and Infection Microbiology. 2024;**14**:1469054. DOI: 10.3389/FCIMB.2024.1469054/XML

[28] Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: Current status and the future ahead. Gastroenterology. 2014;**146**:1489–1499. DOI: 10.1053/J.GASTRO.2014.02.009

[29] Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016;**7**:189–200. DOI: 10.1080/19490976.2015.1134082

[30] Akimbekov NS, Digel I, Sherelkhan DK, Lutfor AB, Razzaque MS. Vitamin D and the host-gut microbiome: A brief overview. ACTA Histochemica ET CYTOCHEMICA. 2020;**53**:33–42. DOI: 10.1267/AHC.20011

[31] Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiology. 2009;**4**:1151–1165. DOI: 10.2217/FMB.09.87

[32] Nell MJ, Tjabringa GS, Wafelman AR, Verrijk R, Hiemstra PS, Drijfhout JW, Grote JJ. Development of novel LL-37 derived antimicrobial peptides with LPS and LTA neutralizing and antimicrobial activities for therapeutic application. Peptides. 2006;**27**:649–660. DOI: 10.1016/J.PEPTIDES.2005.09.016

[33] Ostaff MJ, Stange EF, Wehkamp J. A ntimicrobial peptides and gut microbiota in homeostasis and pathology. EMBO Molecular Medicine. 2013;**5**:1465–1483. DOI: 10.1002/EMMM.201201773

[34] Wallaeys C, Garcia-Gonzalez N, Libert C. Paneth cells as the cornerstones of intestinal and organismal health: A primer. EMBO Molecular Medicine. 2023;**15**. DOI: 10.15252/EMMM.202216427

[35] Vemulapalli V, Shirwaikar Thomas A. The role of Vitamin D in gastrointestinal homeostasis and gut inflammation. International Journal of Molecular Sciences. 2025;**26**:3020. DOI: 10.3390/IJMS26073020

[36] Fakhoury HMA, Kvietys PR, AlKattan W, Anouti FA, Elahi MA, Karras SN, Grant WB. Vitamin D and intestinal homeostasis: Barrier, microbiota, and immune modulation. The Journal of Steroid Biochemistry and Molecular Biology. 2020;**200**:105663. DOI: 10.1016/j.jsbmb.2020.105663

[37] Adorini L, Penna G, Giarratana N, Uskokovic M. Tolerogenic dendritic cells induced by vitamin D receptor

ligands enhance regulatory T cells inhibiting allograft rejection and autoimmune diseases. Journal of Cellular Biochemistry. 2003;**88**:227–233. DOI: 10.1002/JCB.10340

[38] Nowarski R, Jackson R, Flavell RA. The stromal intervention: Regulation of immunity and inflammation at the epithelial-mesenchymal barrier. Cell. 2017;**168**:362–375. DOI: 10.1016/j.cell.2016.11.040

[39] Gambhir V, Kim J, Siddiqui S, Taylor M, Byford V, Petrof EO, Jones G, Basta S. Influence of 1,25-dihydroxy vitamin D3 on TLR4-induced activation of antigen presenting cells is dependent on the order of receptor engagement. Immunobiology. 2011;**216**:988–996. DOI: 10.1016/j.imbio.2011.03.011

[40] Ridyard KE, Overhage J. The potential of human peptide LL-37 as an antimicrobial and anti-biofilm agent. Antibiotics. 2021;**10**. DOI: 10.3390/ANTIBIOTICS10060650

[41] Ullah H. Gut-vitamin D interplay: Key to mitigating immunosenescence and promoting healthy ageing. Immunity & Ageing. 2025;**22**(1): 20–. DOI: 10.1186/S12979-025-00514-Y

[42] Bscheider M, Butcher EC. Vitamin D immunoregulation through dendritic cells. Immunology. 2016;**148**:227–236. DOI: 10.1111/IMM.12610

[43] Xie M, Li X, Lau HCH, Yu J. The gut microbiota in cancer immunity and immunotherapy. Cellular & Molecular Immunology. 2025;**22**:1012. DOI: 10.1038/S41423-025-01326-2

[44] Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008;**28**:454–467. DOI: 10.1016/j.immuni.2008.03.004

[45] Chang SH, Chung Y, Dong C. Vitamin D suppresses Th17 cytokine production by inducing C/EBP Homologous Protein (CHOP) expression. Journal of Biological Chemistry. 2010;**285**:38751. DOI: 10.1074/JBC.C110.185777

[46] Hu Y, Yang Y, Li Y, Zhang Q, Zhang W, Jia J, Han Z, Wang J. Th17/Treg imbalance in inflammatory bowel disease: Immunological mechanisms and microbiota-driven regulation. Frontiers in Immunology. 2025;**16**:1651063. DOI: 10.3389/FIMMU.2025.1651063/FULL

[47] Garcia AM, Bishop EL, Li D, Jeffery LE, Garten A, Thakker A, Certo M, Mauro C, Tennant DA, Dimeloe S, Evelo CT, Coort SL, Hewison M. Tolerogenic effects of 1,25-dihydroxyvitamin D on dendritic cells involve induction of fatty acid synthesis. The Journal of Steroid Biochemistry and Molecular Biology. 2021;**211**:105891. DOI: 10.1016/J.JSBMB.2021.105891

[48] Daryabor G, Gholijani N, Kahmini FR. A review of the critical role of vitamin D axis on the immune system. Experimental and Molecular Pathology. 2023;**132–133**. DOI: 10.1016/j.yexmp.2023.104866

[49] Yin K, Agrawal DK. Vitamin D and inflammatory diseases. Journal of Inflammation Research. 2014;**7**:69–87. DOI: 10.2147/JIR.S63898

[50] Farias AS, Spagnol GS, Bordeaux-Rego P, Oliveira COF, Fontana AGM, de Paula RFO, Santos MPA, Pradella F, Moraes AS, Oliveira EC, Longhini ALF, Rezende ACS, Vaisberg MW,

Santos LMB. Vitamin D 3 induces IDO + tolerogenic DC s and enhances treg, reducing the severity of EAE. CNS Neuroscience & Therapeutics. 2013;**19**:269–277. DOI: 10.1111/CNS.12071

[51] Wang C, Zeng Z, Wang B, Guo S. Lower 25-hydroxyvitamin D is associated with higher relapse risk in patients with relapsing-remitting multiple sclerosis. Journal of Nutrition, Health and Aging. 2018;**22**:38–43. DOI: 10.1007/s12603-017-0894-3

[52] Kojecky V, Matous J, Kianicka B, Dite P, Zadorova Z, Kubovy J, Hlostova M, Uher M. Vitamin D levels in IBD: A randomised trial of weight-based versus fixed dose vitamin D supplementation. Scandinavian Journal of Gastroenterology. 2020;**55**:671–676. DOI: 10.1080/00365521.2020.1774921

[53] Yang L, Weaver V, Smith JP, Bingaman S, Hartman TJ, Cantorna MT. Therapeutic effect of vitamin D supplementation in a pilot study of Crohn's patients. Clinical and Translational Gastroenterology. 2013;**4**:e33. DOI: 10.1038/CTG.2013.1

[54] Rigterink T, Appleton L, Day AS. Vitamin D therapy in children with inflammatory bowel disease: A systematic review. World Journal of Clinical Pediatrics. 2019;**8**:1–14. DOI: 10.5409/WJCP.V8.I1.1

[55] Cantorna MT, McDaniel K, Bora S, Chen J, James J. Vitamin D, immune regulation, the microbiota, and inflammatory bowel disease. Experimental Biology and Medicine (Maywood). 2014;**239**(11):1524–1530. DOI: 10.1177/1535370214523890

[56] Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: Antibacterial, antiviral, anti-inflammatory. JBMR Plus. 2020;**5**:e10405. DOI: 10.1002/JBM4.10405

[57] Gill A, Orji C, Reghefaoui M, Peresuodei TS, Thota P, Palacios MSS, Franchini APA. The effectiveness of Vitamin D Intake in improving symptoms and relapses of multiple sclerosis: A systematic review. Cureus. 2024;**16**:e68565. DOI: 10.7759/CUREUS.68565

[58] Aggeletopoulou I, Geramoutsos G, Pastras P, Triantos C. Vitamin D in irritable bowel syndrome: Exploring its role in symptom relief and pathophysiology. Nutrients. 2025;**17**:1028. DOI: 10.3390/NU17061028

[59] Li X, Yuan Q, Huang H, Wang L. Gut microbiota in irritable bowel syndrome: A narrative review of mechanisms and microbiome-based therapies. Frontiers in Immunology. 2025;**16**:1695321. DOI: 10.3389/FIMMU.2025.1695321

[60] Qi S, Zhao M, Sun Y, Boro S, Arora B, Rastogi S. Impact of vitamin D supplementation on symptom severity and quality of life in patients with irritable bowel syndrome: A meta-analysis. Advances in Clinical and Experimental Medicine. 2025;**34**:1091–1104. DOI: 10.17219/ACEM/191463

[61] Hassanshahi M, Anderson PH, Sylvester CL, Stringer AM. Highlight article: Current evidence for vitamin D in intestinal function and disease. Experimental Biology and Medicine. 2019;**244**:1040–1052. DOI: 10.1177/1535370219867262;WGROUP:STRING:PUBLICATION

[62] Ferrer-Mayorga G, Larriba MJ, Crespo P, Muñoz A. Mechanisms of action of vitamin D in colon cancer. The Journal of Steroid Biochemistry and Molecular Biology. 2019;**185**:1–6. DOI: 10.1016/j.jsbmb.2018.07.002

[63] Ghazy B, Eltawil M, Nemer N, Abdelazim O, Patil JD, Fredericks S. Vitamin D deficiency, supplementation, and colorectal cancer outcomes: Interactions with obesity and risk profiles. Frontiers in Medicine. 2025;**12**:1657534. DOI: 10.3389/FMED.2025.1657534/BIBTEX

[64] Lee P, Campbell L. Vitamin D deficiency: The invisible accomplice of metabolic endotoxemia? Current Pharmaceutical Design. 2009;**15**: 2751–2758. DOI: 10.2174/138161209788923895

[65] Oku Y, Noda S, Yamada A, Nakaoka K, Goseki-Sone M. Vitamin D restriction and/or a high-fat diet influence intestinal alkaline phosphatase activity and serum endotoxin concentration, increasing the risk of metabolic endotoxemia in rats. Nutrition Research. 2023;**112**:20–29. DOI: 10.1016/j.nutres.2023.02.002

[66] Argano C, Mirarchi L, Amodeo S, Orlando V, Torres A, Corrao S. The role of Vitamin D and its molecular bases in insulin resistance, diabetes, metabolic syndrome, and cardiovascular disease: State of the art. International Journal of Molecular Sciences. 2023;**24**:15485. DOI: 10.3390/IJMS242015485

[67] Dell'Anna G, Fanizzi F, Zilli A, Furfaro F, Solitano V, Parigi TL, Ciliberto A, Fanizza J, Mandarino FV, Fuccio L, Facciorusso A, Donatelli G, Allocca M, Massironi S, Annese V, Peyrin-Biroulet L, Danese S, D'Amico F. The role of Vitamin D in inflammatory bowel diseases: From deficiency to targeted therapeutics and precise nutrition strategies. Nutrients. 2025;**17**:2167. DOI: 10.3390/NU17132167

[68] Jalili M, Vahedi H, Poustchi H, Hekmatdoost A. Effects of Vitamin D Supplementation in patients with irritable bowel syndrome: A randomized, double-blind, placebo-controlled clinical trial. International Journal of Preventive Medicine. 2019;**10**. DOI: 10.4103/IJPVM.IJPVM_512_17

[69] Cara KC, Taylor SF, Alhmly HF, Wallace TC. The effects of vitamin D intake and status on symptom severity and quality-of-life in adults with irritable bowel syndrome (IBS): A systematic review and meta-analysis. Critical Reviews in Food Science and Nutrition. 2025;**65**:4994–5007. DOI: 10.1080/10408398.2024.2400603

[70] Na S-Y, Kim KB, Lim YJ, Song HJ. Vitamin D and colorectal cancer: Current perspectives and future directions. Journal of Cancer Prevention. 2022;**27**:147. DOI: 10.15430/JCP.2022.27.3.147

[71] Jian E, Wang M, Zhang Z, Heng Y, Zhang C, Chen Q, Yu X, Zhu Y, Cai P. The metabolic endotoxemia and gut microbiota: Research trajectories and hot trends across the centuries (1999–2024). Frontiers in Microbiology. 2025;**16**:1634803. DOI: 10.3389/FMICB.2025.1634803/EPUB

[72] Calton EK, Keane KN, Newsholme P, Soares MJ. The impact of Vitamin D levels on inflammatory status: A systematic review of immune cell studies. PLoS One. 2015;**10**: e0141770. DOI: 10.1371/JOURNAL.PONE.0141770

[73] Raman M, Milestone AN, Walters JRF, Har AL, Ghosh S. Vitamin D and gastrointestinal diseases: Inflammatory bowel disease and colorectal cancer. Therapeutic Advances in Gastroenterology. 2011;**4**:49. DOI: 10.1177/1756283X10377820

[74] Ghosh S, Whitley CS, Haribabu B, Jala VR. Regulation of intestinal barrier function by microbial metabolites. Cellular and Molecular Gastroenterology and Hepatology. 2021;**11**:1463. DOI: 10.1016/J.JCMGH.2021.02.007

[75] Sun J. Dietary vitamin D, vitamin D receptor, and microbiome. Current Opinion in Clinical Nutrition and Metabolic Care. 2018;**21**:471. DOI: 10.1097/MCO.0000000000000516

[76] Jain W, Khaliq M, Wahab A, Laghari M. Evaluating vitamin D deficiency-linked digestive issues by bridging endocrinology with gastrointestinal disorders. Cureus. 2025;**17**. DOI: 10.7759/CUREUS.89598

[77] Muho KH. Impact of vitamin D status on age at menopause: A prospective cohort study. Journal of Advanced Pharmaceutical Technology & Research. 2025;**16**:190. DOI: 10.4103/JAPTR.JAPTR_52_25

[78] Min J, Jo H, Chung Y-J, Song JY, Kim MJ, Kim M-R. Vitamin D and the immune system in menopause: A review. Journal of Menopausal Medicine. 2021;**27**:109. DOI: 10.6118/JMM.21011

[79] Murdaca G, Tagliafico L, Page E, Paladin F, Gangemi S. Gender differences in the interplay between Vitamin D and microbiota in allergic and autoimmune diseases. Biomedicines. 2024;**12**:1023. DOI: 10.3390/BIOMEDICINES12051023

[80] Kverka M, Stepan JJ. Associations among estrogens, the gut microbiome and osteoporosis. Current Osteoporosis Reports. 2024;**23**. DOI: 10.1007/S11914-024-00896-W

[81] Lephart ED, Naftolin F. Estrogen action and gut microbiome metabolism in dermal health. Dermatology and Therapy. 2022;**12**:1535. DOI: 10.1007/S13555-022-00759-1

[82] Pérez-López FR, Chedraui P, Pilz S. Vitamin D supplementation after the menopause. Therapeutic Advances in Endocrinology and Metabolism. 2020;**11**. DOI: 10.1177/2042018820931291

[83] Mei Z, Hu H, Zou Y, Li D. The role of vitamin D in menopausal women's health. Frontiers in Physiology. 2023;**14**. DOI: 10.3389/FPHYS.2023.1211896

[84] Kalra S, Kalra S. Vitamin D and menopause. Journal of the Pakistan Medical Association. 2024;**74**:815–817. DOI: 10.47391/JPMA.24-27