

# The Role of Vitamin D in Immune System and Inflammatory Bowel Disease

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**Abstract:** Inflammatory bowel disease (IBD) is a nonspecific inflammatory disease that includes ulcerative colitis (UC) and Crohn's disease (CD). The pathogenesis of IBD is not fully understood but is most reported associated with immune dysregulation, dysbacteriosis, genetic susceptibility, and environmental risk factors. Vitamin D is an essential nutrient for the human body, and it not only regulates bone metabolism but also the immune system, the intestinal microbiota and barrier. Vitamin D insufficiency is common in IBD patients, and the abnormal low levels of vitamin D are highly correlated with disease activity, treatment response, and risk of relapse of IBD. Accumulating evidence supports the protective role of vitamin D in IBD through regulating the adaptive and innate immunity, maintaining the intestinal barrier and balancing the gut microbiota. This report aims to provide a broad overview of the role vitamin D in the immune system, especially in the pathogenesis and treatment of IBD, and its possible role in predicting relapse.

**Keywords:** vitamin D, immune system, inflammatory bowel disease, IBD treatment, relapse of IBD

## Introduction

Vitamin D was first classified as a vitamin and then as a steroid hormone and can be further classified into two isoforms in the human body, vitamins D2 and D3. Vitamin D2 can only be obtained from food while vitamin D3 can be obtained from food and also synthesized from sunlight through the skin. Supplementation with vitamin D3 is more effective at increasing 25(OH)D levels than vitamin D2.<sup>1</sup> The inactive form of vitamin D can be transformed into its active form (ie 1,25(OH)2D) through sequential hydroxylation in the liver and kidneys. Many studies have reported the mechanism by which active vitamin D maintains the balance of calcium and phosphorus metabolism, while its role in regulating the immune system and maintaining homeostasis of the intestinal barrier and microbiota has received increasing focus in recent decades.<sup>2,3</sup>

The vitamin D receptor (VDR) was discovered on immune cells about 30 years ago and has since been found on almost every human immune cell type.<sup>2</sup> While the relationship between vitamin D and the immune system remains unclear, existing evidence indicates that vitamin D plays an important role in both innate and adaptive immune modulation.<sup>2</sup> Vitamin D regulates the innate immune response by directly impacting the function of monocytes, macrophages, and dendritic cells (DCs), as well as the secretion of related cytokines. Vitamin D impacts the adaptive immune response, including the development and progression of many autoimmune diseases, by modulating T and B cell activation, proliferation, and differentiation.<sup>4,5</sup>

The incidence of IBD is increasing worldwide. Despite the advanced development of drugs for treatment, IBD still remains a complex issue for clinical healthcare, millions of patients suffer from this disease and its complications. A more comprehensive and effective therapeutic strategy is urgently needed. It has been brought out that there might be a positive feedback loop within vitamin D deficiency, inflammation process and IBD,<sup>6</sup> and supplying vitamin D is obvious the most convenient and effective way to break the loop. IBD pathogenesis is associated with genetic

susceptibility, immune disorders, intestinal dysbiosis, and environmental risk factors.<sup>7</sup> Recent studies have demonstrated a protective role for vitamin D in the development of IBD through its impact on the immune system and gut microbiota. In addition, vitamin D deficiency is prevalent in IBD patients<sup>8–11</sup> and low vitamin D levels are negatively correlated with disease activity and related complications.<sup>8,11–22</sup> All those findings support a promising role of vitamin D in treating IBD, which is convenient, safe and effective. This review aims to provide a broad overview of vitamin D and its role in regulating immune responses, especially those associated with the pathogenesis, treatment, and relapse of IBD.

## Vitamin D: Molecular Structure and Metabolism

### Sources and Existing Forms of Vitamin D

Natural vitamin D comes from two major sources, food and sunlight. When obtained from food, vitamin D is mixed with the bile and absorbed by the intestine through passive diffusion with partial involvement from some cholesterol transporters.<sup>23</sup> The dietary source of vitamin D includes fish, eggs, red meat, fatty foods, and dairy products,<sup>24–27</sup> of which fish is a dominant source.<sup>24</sup> Vitamin D obtained from sunlight is synthesized by the skin following exposure to ultraviolet B (UVB). Of note, exposure to sunlight can provide up to 90% of the vitamin D that humans need.<sup>28</sup>

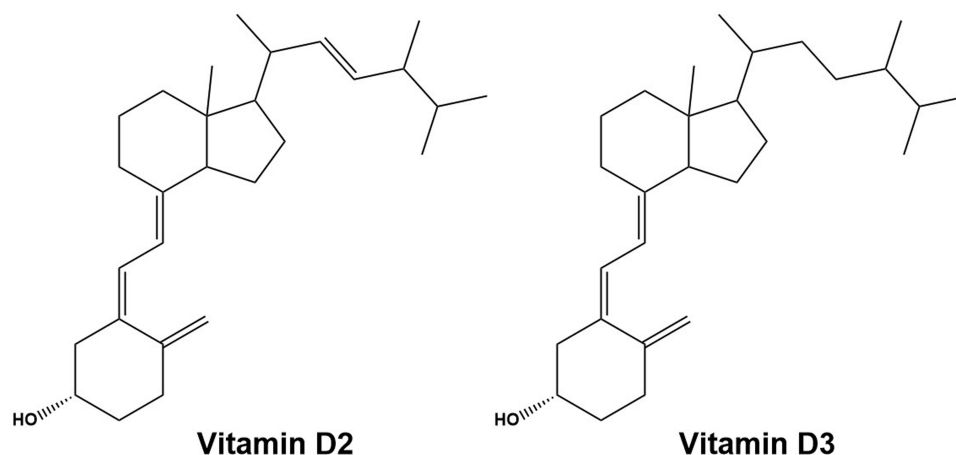
Vitamin D has several metabolites which can be separated into two main types, vitamin D3 or cholecalciferol, and vitamin D2 or ergocalciferol. D3 mainly includes 25-Hydroxyvitamin D3 [25(OH)D3] and 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] and can be obtained from both food and sunlight, while D2 primarily includes 25-Hydroxyvitamin D2 [25(OH)D2] and 1,25-dihydroxyvitamin D2 [1,25(OH)2D2] and can only be obtained from food. Of all types of vitamin D, 1,25(OH)2D3 is universally acknowledged as the bioactive form.

### Structure of Vitamin D and the Vitamin D Receptor

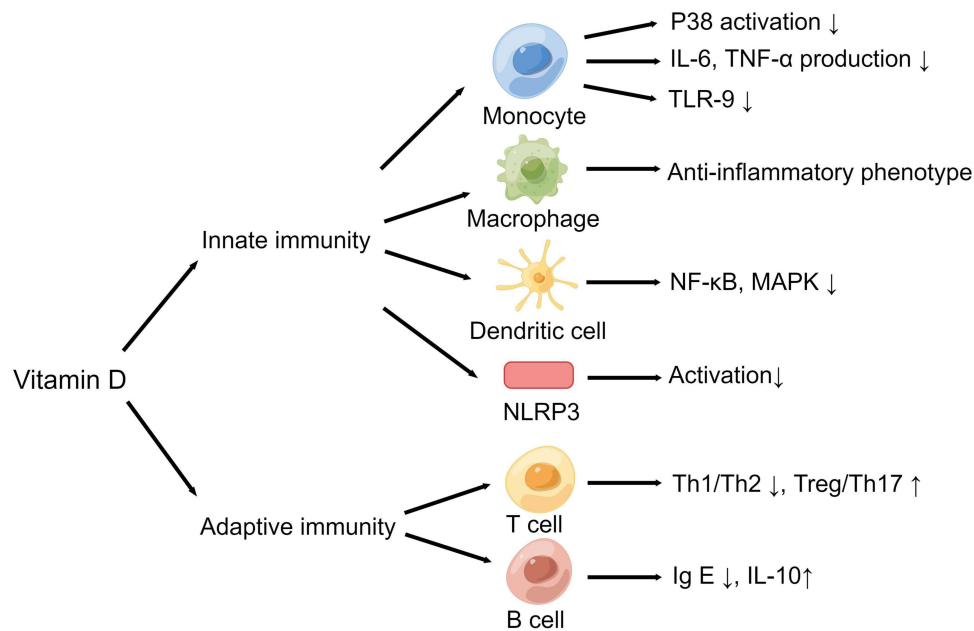
Unlike other vitamins, vitamin D has long been considered a steroid hormone, both structurally and physiologically.<sup>29</sup> The structures of 25(OH)D and 1 $\alpha$ -25(OH)2D have been revealed previously.<sup>30,31</sup> The basic structure of vitamin D2 and D3 contain four different parts and differ by the side chain (Figure 1).<sup>29</sup> Vitamin D receptor (VDR) is a ligand-activated transcription factor that regulates gene expression. VDR is activated by the binding of 1,25(OH)2D3, and is expressed in many tissues, including high levels in the intestine.<sup>32</sup> VDR regulates hundreds of myeloid cell genes to mediate susceptibility to latitude-dependent autoimmune diseases.<sup>33</sup> The VDR gene polymorphism plays a critical role in its structure and function and affects the immunomodulatory function of vitamin D.

### Vitamin D and the Immune System

Vitamin D is increasingly viewed as an immune modulator capable of directly impacting both innate and adaptive immune responses (Figure 2). Given that almost all immune cells express VDR,<sup>2</sup> it is not surprising that vitamin D is closely correlated with immunomodulation and the development of immune-related diseases including IBD.



**Figure 1** The chemical structure of vitamin D2 and vitamin D3.



**Figure 2** Vitamin D impacts the innate and adaptive immunity (By Figdraw ([www.figdraw.com](http://www.figdraw.com))).

**Notes:** In innate immunity, vitamin D inhibit LPS-induced p38 activation and IL-6 and TNF- $\alpha$  production by monocytes, and downregulate TLR-9 expression after stimulated with TLR-9 agonist in monocytes. Vitamin D also favors a anti-inflammatory phenotype of macrophages, inhibits the innate NF- $\kappa$ B and MAPK signaling in monocyte derived dendritic cells that have been stimulated with LPS. The activation of NLRP3 inflammasome is downregulated by vitamin D. In adaptive immunity, vitamin D downregulates Th1/Th2 while upregulates Treg/Th17, and decreases the production of IgE while increases IL-10 production. “ $\uparrow$ ” = increase/upregulated; “ $\downarrow$ ” = decrease/downregulated.

**Abbreviations:** IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; NF- $\kappa$ B, nuclear factor  $\kappa$ B; MAPK, mitogen activated protein kinase; NLRP3, NOD-like receptor protein 3; Th1, T helper 1; Th2, T helper 2; Treg, regulatory T cell; IL-10, interleukin-10.

## Vitamin D and Innate Immunity

Vitamin D differentially modulates monocyte, macrophage, and dendritic cell molecular responses to innate immune stimulation.<sup>34</sup> Almost a quarter of primary vitamin D targeted genes in monocytes are related to immune modulation.<sup>35</sup> In vitamin D deficient individuals (defined as 25(OH)D3<26ng/mL in this study), VDR expression in monocytes was decreased in a concentration-dependent manner in spite of an increase in monocyte adhesion to the endothelium.<sup>36</sup> Monocyte-platelet aggregates (MPA), markers for platelet activation, were elevated in vitamin D deficient individuals suggesting a pro-inflammatory monocyte phenotype in vitamin deficiency.<sup>36</sup> In addition, normal vitamin D levels (defined as 30–50ng/mL here) are enough to inhibit LPS-induced p38 activation and interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) production in human monocytes.<sup>37</sup> Besides, vitamin D could downregulate the expression of Toll-like receptor 9 (TLR-9) and inhibit its subsequently secreted IL-6 after stimulated with a TLR-9 agonist in monocytes.<sup>38</sup>

Macrophage function and gene expression are affected by vitamin D in a variety of ways. Vitamin D deficient rats show decreased macrophage chemotaxis.<sup>39</sup> In murine macrophages, the active form of vitamin D inhibits the expression of cyclooxygenase-2 (COX-2) in a dose-dependent manner, which play important role in promoting inflammation.<sup>40</sup> In addition, 1,25(OH)2D3 exerts an anti-inflammatory and anti-proliferation effect on murine macrophages by inducing vitamin D receptor interaction with the p50 subunit of nuclear factor  $\kappa$ B (NF- $\kappa$ B).<sup>41</sup> However, a study on human mononuclear phagocytes showed that vitamin D cannot inhibit innate NF- $\kappa$ B activation in monocyte-derived macrophages.<sup>34</sup> Moreover, 1,25(OH)2D3 stimulation results in dose-dependent increase of IL-1 production in monocytes or macrophages.<sup>42</sup> Thus, further research is required to explore the exact relationship between vitamin D and the regulation of signaling and cytokine secretion by macrophages.

Vitamin D not only inhibits DC differentiation and maturation<sup>43</sup> but also represses inflammation-related signaling pathways in DCs. This includes the inhibition of innate NF- $\kappa$ B and p38 mitogen activated protein kinase (MAPK) signaling in monocyte derived DC (MDDC) that have been stimulated with LPS.<sup>34</sup>

NOD-like receptor protein (NLRP) inflammasomes are an important component of innate immunity. The NLRP3 inflammasome is critical in many inflammatory and autoimmune diseases. The 1,25(OH)<sub>2</sub>D<sub>3</sub> form can prevent activation of the NLRP3 inflammasome and inhibit caspase-1 activation and IL-1 $\beta$  secretion by combining with VDR, thereby alleviating dextran sodium sulphate (DSS)-induced colitis in mice.<sup>44</sup> In general, vitamin D affects the innate immune response by modulating different immune cells. Maintaining normal vitamin D levels may be beneficial to the treatment of many immune-related diseases by inhibiting inflammation-related signaling and the production of pro-inflammatory cytokines.

## Vitamin D and Adaptive Immunity

Vitamin D not only affects innate immunity but also plays a critical role in regulating adaptive immune responses. Production of 1,25(OH)<sub>2</sub>D<sub>3</sub> by macrophages can inhibit DC differentiation and lymphocyte activation in a paracrine way and thereby suppress the adaptive immune response.<sup>45</sup>

### Vitamin D and B Cells

B cells are fundamental to the development of autoimmune diseases because of their key role in antigen presentation, antibody production, and pro-/anti-inflammatory cytokine secretion. Since activated B cells can express VDR, vitamin D has the potential to impact B cell activation and function thereby influencing adaptive immune responses.<sup>46</sup>

Vitamin D affects the activation, proliferation, and differentiation of activated but not initial B cells. Activated B cell proliferation is suppressed by culture with vitamin D and cell apoptosis is increased, while the division of initial B cells remained unaffected.<sup>47</sup> CD38 is a molecule that regulates B cell differentiation and the response to inflammation.<sup>48</sup> An *in vivo* study in humans showed that when the serum 25(OH)D concentration was increased to >70 nmol/l, the number of CD38 positive B cells also increased,<sup>49</sup> indicating that 25(OH)D can accelerate B cell differentiation and increase their response to inflammation.

Vitamin D also impacts the production of antibodies such as immunoglobulin E (IgE) and IL-10 from B cells and modulates adaptive immune responses. After binding to VDR, bioactive vitamin D can reduce IgE production from B cells.<sup>50</sup> The bioactive form of vitamin D may inhibit IgE production in anti-CD40 and IL-4 stimulated human peripheral B cells by causing the VDR to inhibit NF- $\kappa$ B p65 and p105 activation.<sup>51</sup> IL-10 is an anti-inflammatory cytokine that suppresses T cell activation by inhibiting antigen presentation by DCs, monocytes, and macrophages.<sup>52,53</sup> James et al showed that vitamin D can promote IL-10 production by B10 cells thereby preventing the secretion of IgE.<sup>50</sup> Bioactive vitamin D promotes IL-10 production more than threefold in activated B cells by recruiting the VDR to the IL-10 promoter and modulating 1,25(OH)<sub>2</sub>D<sub>3</sub>-dependent signaling.<sup>54</sup>

### Vitamin D and T Cells

Vitamin D also performs an important immunomodulatory role in T helper 1 (Th1), Th2, regulatory T (Treg), and Th17 cells, and suppresses both Th1 and Th2 dominant diseases.<sup>55</sup> Low vitamin D levels are also associated with the progression of Th1 mediated autoimmune diseases.<sup>56</sup>

Vitamin D affects T cell activation and proliferation. Vitamin D-VDR binding delays T cell activation when the T cell antigen receptor (TCR) is already activated, thus preventing immunopathology caused by the explosive proliferation of T cells by buying time for innate immune system to control infection and reduce antigen.<sup>57</sup> Unlike in acute infection, chronic-activated T cells play an important role in immune-mediated diseases, and vitamin D can turn off the chronic-activated T cells (including Th1 and Th17 cells) through its binding with VDR.<sup>58</sup> In addition, vitamin D and VDR are adequately involved in inhibiting T cell proliferation and cytokine production.<sup>58</sup>

Vitamin D also impacts Th cell differentiation and polarization, resulting in a more anti-inflammatory profile. The 1,25(OH)<sub>2</sub>D<sub>3</sub> form can regulate Treg/Th17 cell differentiation through the VDR/PLC- $\gamma$ 1/TGF- $\beta$ 1 signaling pathway. When vitamin D binds to VDR, phospholipase C gamma 1 (PLC- $\gamma$ 1) is upregulated, inducing transforming growth factor-beta 1 (TGF- $\beta$ 1) expression, causing a rise in Treg cell differentiation and inhibition of Th17 cell differentiation.<sup>59</sup> Palmer et al reported that 1,25(OH)<sub>2</sub>D<sub>3</sub> impairs the development of Th17 cells by inhibiting the key transcription factor, ROR $\gamma$ t.<sup>60</sup> Vitamin D also suppresses JAK/STAT, ERK/MAPK, and PI3K/Akt/mTor signaling to inhibit T cell activation

and differentiation into Th1 and Th17 cells.<sup>61</sup> In addition, 1.25(OH)2D3 increases the ratio of anti-inflammatory Th2 cells to pro-inflammatory Th1 and Th17 cells by activating the SIRT6/GAT3 signaling pathway.<sup>62</sup> Of note, a mouse study using the Bacille Calmette-Guerin (BCG) vaccine showed that 1.25(OH)2D3 could reduce the inflammatory response by inhibiting Th1 cell differentiation and related cytokine production through the JAK/STAT signaling pathway.<sup>63</sup> Thus, vitamin D can regulate Th cell differentiation through different signaling pathways, primarily leading to an anti-inflammatory Th cell phenotype.

Vitamin D has a critical impact on the immune function of Th cells, manifesting in the altered production of related cytokines. Treatment with 1.25(OH)2D3 can push pro-inflammatory memory CCR6+ Th cells which normally produce pro-inflammatory cytokines such as IL-17A, IL-17F, IL-22, and IFN- $\gamma$  to an anti-inflammatory phenotype that suppresses the proliferation of CD3+ T cells.<sup>64</sup> Bruce et al found that CD4+ T cells produce more IL-17 in the absence of vitamin D, and production can be inhibited by 1.25(OH)2D3 treatment.<sup>65</sup>

## Vitamin D and IBD Pathogenesis

### Pandemic of Vitamin D Insufficiency

Insufficient vitamin D status in humans is becoming more common worldwide.<sup>66</sup> Studies on African, European, American, and Brazilian populations support a high prevalence of vitamin D deficiency,<sup>67–70</sup> and this is more common in urban than rural areas, and in newborns than their mothers.<sup>67</sup> Studies indicate that vitamin D prevalence is latitude-related given that serum vitamin D levels are higher in the northern regions of Brazil and the southern regions of China.<sup>70,71</sup> In addition, serum 25(OH)D levels are not significantly related to gender and age worldwide.<sup>72,73</sup>

Vitamin D insufficiency is very common among IBD patients,<sup>8–11</sup> with studies indicating that at least half of patients are vitamin D deficient.<sup>20,74</sup> IBD patients have a 64% higher odds of having vitamin D deficiency than healthy individuals,<sup>75</sup> and 68% of patients are deficient at diagnosis.<sup>76</sup> Low vitamin D status is particularly common among IBD patients with active disease.<sup>77</sup>

### Definition of Vitamin D Status

The serum concentration of 25(OH)D is not significantly impacted by the metabolism so can reliably reflect vitamin D status in the human body.<sup>78</sup> In clinical practice, total 25(OH)D is usually measured to represent the bioactive vitamin D status of humans.<sup>66,79</sup> While there is no standard definition for vitamin D status, it is universally acknowledged that a sufficient level is >75 nmol/l (or >30 ng/mL), a deficient level is <50 nmol/l (or <20 ng/mL), and an insufficient level is between 50 and 75 nmol/l.<sup>66,80</sup>

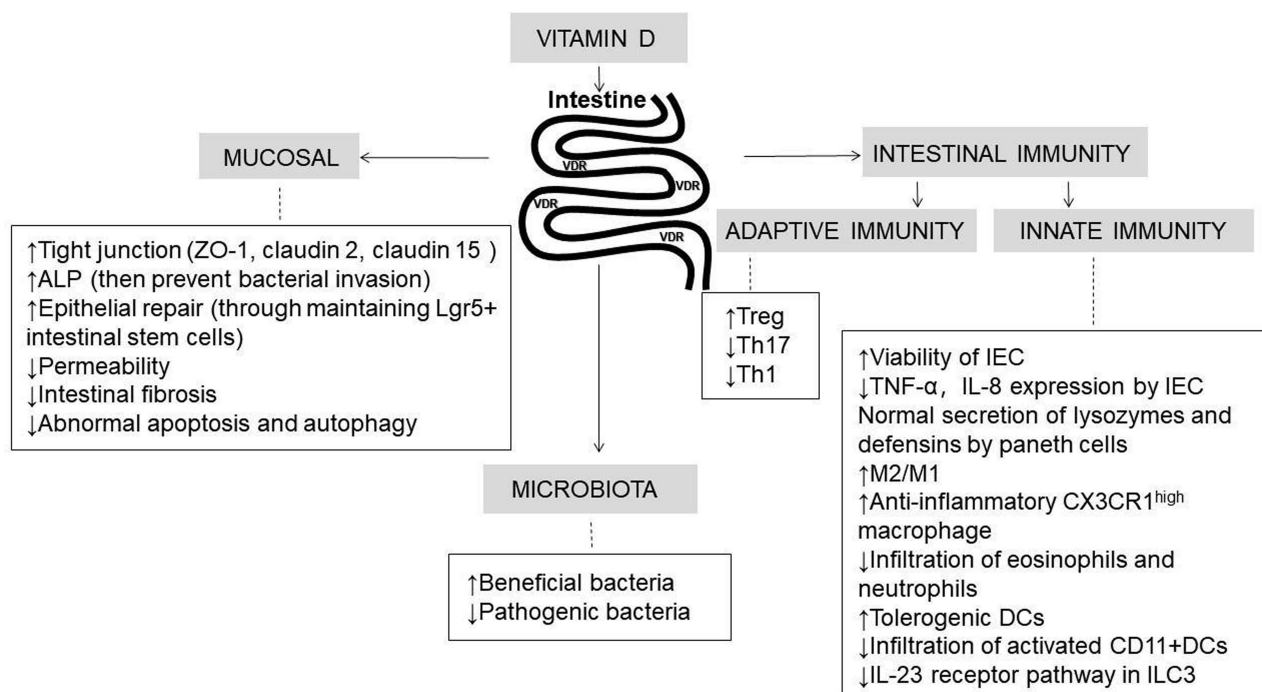
## IBD Pathogenesis

While IBD incidence is high and has remained stable in the western world since the 1990s, it has increased in newly industrialized countries in recent years.<sup>81</sup> IBD is a chronic gastrointestinal inflammatory disease, that includes ulcerative colitis (UC) and Crohn's disease (CD). While the pathogenesis of IBD is not fully understood, genetic susceptibility, immune dysregulation, dysbacteriosis and environmental risk factors are associated with disease development and progression<sup>7</sup> (Figure 3).

### Vitamin D and Intestinal Adaptive Immunity

Immune dysfunction is important for IBD pathogenesis. Prior studies have shown that while Th cells play an essential part in IBD development and progress,<sup>82</sup> their biological features and functions differ.<sup>82,83</sup> Recent studies have demonstrated that IBD pathogenesis is related to an imbalance in the ratio of regulatory T (Treg) cells to Th17 cells. The ratio of these cells is reduced in CD patients with vitamin D deficiency,<sup>18,19</sup> Notably, Treg cells are shown to decline in UC and non-smoking CD patients with vitamin D deficiency,<sup>19</sup> and are lower in the colon mucosa of IBD patients.<sup>84</sup> Vitamin D induces Treg cell differentiation while inhibiting Th17 differentiation.<sup>85</sup> Mice with a VDR deletion in the gut epithelial cells had severe clinical colitis after 2,4,6-trinitrobenzene sulfonic acid (TNBS) induction, characterized by enhanced Th1 and Th17 responses and increased IFN- $\gamma$ +, IL-17+ and IFN- $\gamma$ +IL17+ T cells in the mucosa.<sup>86</sup> In rat CD models, disease activity was also considerably lower in a vitamin D treated group than the control group. This was accompanied





**Figure 3** Vitamin D influence the development of IBD by directly impacting intestinal immunity, microbiota and the intestinal mucosal barrier.

**Notes:** "↑" = increase/up-regulated; "↓" = decrease/down-regulated.

**Abbreviations:** VDR, vitamin D receptor; ZO-1, zonula occludens-1; ALP, alkaline phosphatase; Treg, regulatory T cell; Th17, T helper 17; Th1, T helper 1; IEC, intestinal epithelial cells; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-8, interleukin-8; M2, Macrophages 2; M1, Macrophages 1; DC, Dendritic cell; IL-23, interleukin-23; ILC3, innate lymphoid cell 3.

by lower levels of IL-17, IL17R, and Th17 cells in the colonic mucosa, suggesting that vitamin D may alleviate CD-induced inflammation by inhibiting the IL-17/IL-17R pathway, thus improving immune function and reducing disease severity.<sup>87</sup> Interestingly, a randomized controlled trial (RCT) showed that treating pregnant women with 2000 IU vitamin D daily can increase regulatory T cell immunity by enhancing the percentage of Treg and IL-10<sup>+</sup>CD4 T cells in the peripheral blood.<sup>88</sup> In addition, vitamin D can enhance Treg function by increasing IL-10, TGF- $\beta$ , FoxP3, and CTLA4 production thereby suppressing inflammation.<sup>83,89</sup> Moreover, replenishing vitamin D in UC patients can increase CTLA4 expression and inhibit T cell activation.<sup>90</sup>

Abnormal Th1/Th2 function also contributes to IBD pathogenesis. While CD is highly associated with elevated Th1 cytokine production, UC correlates with a modified Th2 response.<sup>91</sup> In both diseases, vitamin D can help to regulate the Th1/Th2 balance.<sup>91</sup> Treatment with the low calcemic analog of calcitriol, ZK1916784, decreased expression of the Th1-specific transcription factor, T-beta, in DSS treated mice.<sup>92</sup> In CD patients, vitamin D inhibits Th17 and Th1 cytokine production,<sup>19</sup> while in UC patients, 1.25(OH)2D3 supplementation reduces the Th1 response and production of TNF- $\alpha$ , IFN- $\gamma$ , and IL-12p70.<sup>93</sup> In addition, 1.25(OH)2D3 downregulated Th1 and Th17 related cytokine production in a murine model of UC.<sup>94</sup>

Therefore, increasing the ratio of Th1 to Th2 cells and Th17 to Treg cells contributes to IBD pathogenesis, and altering these imbalances may help to alleviate inflammation in IBD patients. Vitamin D supplementation may be beneficial for IBD treatment by increasing the percentage of Treg cells and decreasing the proportion of Th1 and Th17 cells.

### Vitamin D and Intestinal Innate Immunity

Dysregulation of the innate immune response also plays an important role in intestinal inflammation associated with IBD. Aberrant innate immune responses such as antimicrobial peptide production, innate microbial sensing, and autophagy are particularly associated with IBD development.<sup>95</sup> Vitamin D has a significant regulatory effect on the innate immune system in IBD patients. Vitamin D can induce the antimicrobial peptide cathelicidin in human colonic epithelial cells and

is also associated with UC outcomes.<sup>96</sup> 1.25(OH)2D3 and VDR help to maintain innate immunity and protect the colon from chemical injury.<sup>97</sup>

The innate immune response is the first line of defense against pathogens. The anti-inflammatory activity of vitamin D occurs through modulating innate immunity in both intestinal epithelial and local immune cells. Lee et al found that vitamin D can increase the viability of intestinal epithelial cells (IEC-18) and alleviate inflammation by downregulating TNF- $\alpha$  and IL-8 expression.<sup>98</sup> The protective role of vitamin D was also confirmed in intestinal organoids where TNF- $\alpha$  expression was reduced in epithelial cells following vitamin D treatment.<sup>98</sup> Moreover, TNF- $\alpha$  and IL-8 expression in epithelial cells increased when the serum vitamin D level was <20 ng/mL.<sup>21</sup>

In addition to intestinal epithelial cells, a normal intestinal innate immune response requires functioning intestinal immune cells, including Paneth cells, macrophages, DCs, and lymphoid cells. Paneth cells are secretory cells of the small intestine and dysfunction of these cells contributes to the onset and progression of IBD,<sup>99</sup> an effect which may be associated with vitamin D and the vitamin D/VDR axis. Paneth cells with deficient VDR expression have decreased lysozyme secretion, weakened anti-pathogenic ability, and reduced autophagic responses. Paneth cell-specific VDR knockout mice are highly susceptible to small intestinal injury induced by indomethacin.<sup>100</sup> Wu et al also reported that antibacterial peptide including defensins and lysozymes produced by Paneth cells were reduced in intestinal VDR conditional knockout mice.<sup>101</sup> After administering a high-fat-diet plus vitamin D deficient feeding in mice, Paneth cell-specific alpha-defensins such as  $\alpha$ -defensin5 (DEF5) and MMP7, were suppressed in the ileum, resulting in increased gut permeability, dysbiosis, and systemic inflammation.<sup>102</sup> A reduction in normal Paneth cells and an increase in abnormal Paneth cells (including disordered, depleted, and diffuse Paneth cells) were also observed in conditional VDR epithelial knockout mice.<sup>103</sup>

The vitamin D/VDR axis performs a critical role in regulating monocyte/macrophage activation in the intestine. Macrophages are generally classified as having an M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotype following stimulation with different environmental cues. Vitamin D can induce the macrophage phenotype transition, favoring M2 over M1 polarization. Wang et al reported that DSS induced more severe body weight loss and mucosal inflammation in mice with VDR deletion from nonepithelial intestinal cells mice than in mice with VDR deletion from colon epithelial cells.<sup>104</sup> In addition, vitamin D treatment induced a switch in macrophage phenotype from M1 to M2, which is consistent with decreased production of pro-inflammatory cytokines.<sup>104</sup> This indicates that vitamin D exerts a protective role during colitis by modulating macrophage biology. Vitamin D can also help to restore normal villus structure in the intestinal epithelium of IEC-specific Rab11a knockout mice and reduce macrophage infiltration into the mucosa after chronic intestinal inflammation.<sup>105</sup> Oral delivery of 1.25(OH)2D3 to the colon of mice can increase infiltration of anti-inflammatory CX<sub>3</sub>CR<sub>1</sub><sup>high</sup> macrophages and decrease infiltration of eosinophils and neutrophils.<sup>106</sup> Moreover, loss of the VDR on macrophages and granulocytes mildly affects colitis symptoms in DSS-induced mice but greatly enhances expression of pro-inflammatory cytokines in the inflamed colon.<sup>107</sup> These results demonstrate that vitamin D-macrophages signaling plays a prominent role in controlling intestinal inflammation and suggests that vitamin D treatment can induce M2 polarization and reduce inflammation in the gut microenvironment.

DCs establish the connection between innate and adaptive immune response. Vitamin D favors tolerogenic DCs such as CD103<sup>+</sup> DCs. The number of CD11c/CD103<sup>+</sup> tolerogenic DCs is lower in the lamina propria of mice that cannot produce 1.25(OH)2D3, causing dysbiosis and severe gut inflammation.<sup>108</sup> In addition, since CD11b<sup>+</sup>CD103<sup>+</sup>DCs can drive the Th1 and Th17 activation and differentiation, TNBS-induced colitis in gut epithelial VDR deficient mice activates CD11b<sup>+</sup>CD103<sup>+</sup>DCs, dramatically increasing Th1 and Th17 cell populations in the mucosa.<sup>86</sup> Interestingly, an analog of calcitriol, ZK191784, can modulate intestinal DC numbers and phenotype, reducing activated CD11<sup>+</sup>DC infiltration into the colon and pro-inflammatory cytokine production by primary mucosal DCs.<sup>92</sup> However, in contrast to this finding, Bak et al has found that high dose vitamin D3 supplementation decreases the proportion of CD103<sup>+</sup>DC in the lamina propria mononuclear cell population and creates a more tolerogenic milieu in healthy individuals, accompanied by higher TGF- $\beta$ , PD-L1, and TNF- $\alpha$  production.<sup>109</sup> These findings suggest that vitamin D/VDR may induce a DC shift toward a more tolerogenic and less activated phenotype, thus reducing Th1 and Th17 responses and controlling gut inflammation. The function of CD103<sup>+</sup> DCs is not yet completely understood and more studies are needed to explore how vitamin D regulates DCs.

Innate lymphoid cells (ILCs) are lymphocytes with phenotypes that are distinct from T and B cells, functioning more like innate immune cells. Group 3 innate lymphoid cells (ILC3) are a subtype of ILCs that generally reside in the gut lamina propria and play a prominent role in regulating intestinal homeostasis. Vitamin D/VDR signaling regulates ILC3 proliferation and affects ILC3-related innate immunity.<sup>110</sup> IL-22 is an important anti-inflammatory cytokine which can be produced by ILC3, that relieves inflammation and promotes mucosal healing. Vitamin D is shown to be indispensable for early IL-22 production following intestinal infection with *Citrobacter rodentium* (*C. rodentium*).<sup>111</sup> In vitamin D or VDR deficient mice, mucosal ILC3 levels are decreased, impairing the immune response to *C. rodentium* infection, and replenishing 1.25(OH)2D3 rescues the ILC3 deficiency.<sup>110</sup> Interestingly, in VDR knockout mice, more IL-22 producing ILCs were detected in the small intestine, indicating that VDR deficiency has a cell-autonomous effect on ILC frequency.<sup>112</sup> Vitamin D also downregulates IL-23 receptor signaling, a pathway essential to IBD pathogenesis and its downstream mediators, including RORC, IL-17Fm and IL-26 in the human mucosal ILC3, alleviating IBD-associated inflammation.<sup>113</sup> Thus, the anti-inflammatory effect of vitamin D on IL-22 production and IL-23 signaling in mucosal ILC3 may help to relieve gut inflammation and aid in the treatment of IBD.

The human and animal studies described above demonstrate that vitamin D affects the function of intestinal epithelial and immune cells through distinct patterns. The anti-inflammatory effect of vitamin D on intestinal innate immunity is important for controlling gut inflammation and could be considered for IBD treatment.

### Vitamin D and Gut Microbiota

Gut microbiota and the metabolites they produce constitute an important part of the mucosal barrier,<sup>114–116</sup> but the relationship between disturbance of the gut flora and the development of IBD is not fully understood.<sup>117</sup> Serum vitamin D levels affect the distribution of fecal microbiota, and elevated vitamin D levels are generally associated with higher levels of beneficial bacteria and reduced levels of pathogenic bacteria.<sup>118</sup> Gut microbiota help to maintain gut immunity<sup>119</sup> and are essential for protection against pathogens. In addition, several recent studies demonstrated that fecal microbiota transplant favors mucosal remission in mild-to-moderate UC patients<sup>120</sup> and CD patients in remission,<sup>121</sup> and induces remission in active UC patients.<sup>122</sup> These findings raise questions about the interaction between vitamin D, gut microbiota and IBD.

Existing mice studies have indicated that vitamin D deficient leads to disturbance of gut microbiota, impaired ability against bacterial infiltration. Naderpoor et al reported that vitamin D-deficient adults who receive vitamin D supplementation had a richer abundance of genus *Lachnospira*, and lower abundance of genus *Blautia* in the faecal microbiota.<sup>123</sup> Bashir et al showed that while vitamin D supplements can modulate the microbiome of the upper gastrointestinal tract by reducing the number of opportunistic pathogens such as  $\gamma$ -proteobacteria, and increasing abundance of bacterial genus, similar changes do not occur in the lower gastrointestinal tract.<sup>124</sup> These two studies showed that vitamin D affects the distribution of intestinal flora in different ways, potentially due to differences in the dosage and duration of vitamin D supplementation or different regions of tissue taken for microbiome analysis; however, both studies concluded that vitamin D could significantly affect distribution of the gut microbiome. Vitamin D is also found to benefit IBD therapy by altering the gut microbiome. There was a dose-dependent increase in beneficial bacteria and decrease in pathogenic bacteria in stool samples from healthy adults after vitamin D3 supplementation, and bacteria associated with lower IBD disease activity like *Bacteroides* and *Parabacteroides* were also found to be higher.<sup>118</sup> These bacteria were identified as being suppressed in active IBD patients.<sup>125,126</sup> In addition, vitamin D had a specific influence on bacterial communities in CD, and replenishing vitamin D in CD patients altered the composition of intestinal bacteria by increasing the abundance of potentially beneficial bacterial strains.<sup>127</sup>

Mice IBD model have provided clues on how vitamin D impact IBD through its influence on gut microbiota. Vitamin D deficient mice exhibit dysbiosis and impaired antimicrobial activity, and are more susceptible to DSS-induced colitis.<sup>108,128</sup> And vitamin D can also affect mice susceptibility to DSS-induced colitis by regulating the gut microbiota and the amount of ROR $\gamma$ t/FoxP3+ regulatory T cells in the colon.<sup>129</sup>

These results indicate that vitamin D may alleviate intestinal inflammation and reduce IBD disease activity by modulating gut microbiota, resulting in an increase in beneficial bacteria and a decrease in pathogenic bacteria.



## Vitamin D and the Intestinal Mucosal Barrier

The intact structure of the intestinal barrier primarily consists of enterocytes and the connection between them (eg tight junction). The epithelial barrier not only moderates the absorption of nutrition and transmits signals, but also has an extremely important role in providing protection against pathogenic agents. An impaired barrier can induce a local immune response and activate inflammatory responses in the gut. Vitamin D plays a critical role in maintaining intestinal epithelial integrity and regulating intestinal epithelial cell function by preserving epithelial cell tight junction protein expression and preventing cytokine-induced epithelial cell apoptosis. Studies have shown that vitamin D deficiency in mice may weaken the defensive function of the intestinal epithelial barrier and increase susceptibility to DSS-induced colitis.<sup>130</sup>

Vitamin D can enhance the tight junction (TJ) formed by colon epithelial cells and maintain the structural integrity of TJs following exposure to DSS.<sup>130</sup> In mice that cannot produce 1.25(OH)2D3, E-cadherin expression is reduced on the gut epithelium.<sup>108</sup> Vitamin D can also help maintain the structural integrity of TJs by upregulating TJ-related mRNA and protein expression in mice.<sup>131</sup> These findings were supported by in vitro studies showing that vitamin D could preserve the integrity of rat intestinal epithelial cells (IEC-18) by reducing permeability and restoring expression of the TJ proteins, zonula occludens-1 (ZO-1) and Claudin 2.<sup>98</sup> The positive role of vitamin D in restoring ZO-1 has also been confirmed in injured organoids.<sup>98</sup> Moreover, IBD patients with serum vitamin D levels <20ng/mL have decreased expression of VDR, E-cadherin, occludin, and ZO-1.<sup>21</sup> Vitamin D deficient CD patients had lower expression of TJ proteins such as occludin, Claudin-1, ZO-1, and JAM-1.<sup>18</sup> In addition, overexpressing VDR protected mice from chemical- and bacterial-induced colitis by upregulating expression of the TJ protein, Claudin-15 and colonic Claudin-15 was reduced in VDR knockout mice.<sup>132</sup> Bioactive vitamin D induces TJ expression and function in part through binding with VDR.<sup>130</sup> VDR enhanced Claudin-2 promoter activity using a functional vitamin D response element (VDRE) in a Caudal-Related Homeobox (Cdx) 1 binding site-dependent manner, and the absence of VDR decreased Claudin-2 expression by abolishing VDR/promoter binding.<sup>133</sup> In VDR knockout mice, there was a decrease in claudin-2 mRNA and protein expression.<sup>134</sup> These studies suggest that vitamin D/VDR signaling enhances the tight junction and maintains epithelial barrier integrity by upregulating TJ-related proteins.

Vitamin D/VDR signaling in epithelial cells plays a critical role in maintaining the mucosal barrier.<sup>135</sup> Yu et al showed that the genetic deletion of VDR in the intestinal epithelium was closely related to the incidence of intestinal fibrosis in DSS- or TNBS-induced mice and vitamin D restored VDR expression and inhibited fibroblast activation.<sup>136</sup> Deletion of VDR in mouse intestinal epithelial cells results in fecal dysbiosis, metabolic dysfunction, and increased risk of infection.<sup>137</sup> Sun et al also demonstrated that intestinal epithelial VDR knockout mice had abnormal Paneth cell function, impaired autophagy, and dysbiosis, along with downregulation of ATG16L1, a regulator of autophagy, and are susceptible to colitis.<sup>138</sup> In addition, intestinal epithelial VDR deficiency increases epithelial cell apoptosis and impairs cell autophagy by decreasing ATG16L1 and Beclin-1 expression.<sup>103,139</sup> MiR-142-3p, which suppresses autophagy, was increased in the intestinal tissues of mice and patients with IBD, and Paneth cells in the intestinal epithelium had early markers of autophagy dysregulation in response to vitamin D deficiency.<sup>140</sup> When VDR was deleted in gut epithelial cells, intestinal epithelial cells apoptosis increased and was accompanied by impaired mucosal barrier permeability.<sup>86</sup> Intestinal type alkaline phosphatase (ALP), a brush-border protein that hydrolyzes monophosphate esters, is a component of the gut mucosal defense system.<sup>141</sup> Bioactive vitamin D enhances expression of intestinal ALP and prevents bacterial invasion across the gut mucosal barrier to maintain gut homeostasis.<sup>142</sup> In addition, because bioactive vitamin D is necessary to maintain Lgr5+ intestinal stem cells, delivery of high 1.25(OH)2D could be a promising strategy to accelerate intestinal epithelial repair in IBD patients.<sup>143</sup> These findings indicate that vitamin D/VDR signaling may maintain the integrity of the intestinal mucosal barrier by regulating epithelial cells, which exert a profound effect on Paneth cells, autophagy, defensins, and the microbiome.

## Vitamin D and IBD Treatment

### Vitamin D as a Treatment for IBD

Given that vitamin D supplements help to maintain the integrity of the intestinal mucosal barrier and regulate the gut microbiota and the intestinal immune response, we suggest that it could also have a therapeutic effect on IBD. Higher concentrations of vitamin D in the plasma and vitamin D supplements are associated with a decreased risk of IBD in

women.<sup>144</sup> It is suggested that 2000 IU/day or 50,000 IU/week doses of vitamin D, which are higher than the recommended doses for healthy adults, should be used to correct vitamin D deficiency in IBD patients.<sup>76,145</sup> In addition, receipt of 300,000 IU bioactive vitamin D has the same safety and effectiveness as the 50,000 IU/week used at 12 weeks of follow-up in vitamin D deficient (<30ng/mL) IBD children.<sup>146</sup> However, the replenishment of vitamin D based on weight is not superior to the fixed dose of 2000 IU/day.<sup>147</sup> Thus, 2000 IU/day of bioactive vitamin D supplementation should be recommended for the treatment of IBD patients.

Maintaining or normalizing vitamin D status in IBD patients not only helps to alleviate disease activity but also improves the long-term prognosis of patients including the quality of daily life and mental disorders (Table 1). The normalization of vitamin D status is highly correlated with a lower risk of surgery in IBD patients.<sup>148</sup> In addition, vitamin D treatment of IBD patients who are suffering from vitamin D deficiency can alleviate disease activity at both the clinical and biochemical levels,<sup>149,150</sup> decreasing the need for additional healthcare.<sup>13</sup> Meanwhile, supplementation with 2000IU/day vitamin D can significantly increase the quality of life in UC patients with vitamin D deficiency and reduce disease activity.<sup>151</sup> Vitamin D intervention can also improve the psychological state. After vitamin D treatment, anxiety and

**Table 1** Vitamin D as a Therapeutic Strategy for IBD

Study	Patients Included	Intervention/Control Group	Vitamin D Dose in the Intervention Group vs Control Group	Follow Up	Outcomes (Adverse Events; Vitamin D Level)	Study Type
Guzman-Prado <sup>149</sup> 2020	/	/	/	/	↑Vitamin D level ↓Harvey Bradshaw Index ↓Hs-CRP	Meta analysis
Ahamed <sup>150</sup> 2019 India	Active UC (UCDAI≥3) and vitamin D <40 ng/mL	30/30	Oral nano liquid formulation of vitamin D3 60,000IU daily for 8 days/placebo	4 weeks	↑Vitamin D level ↑ 3-point reduction in UCDAI ↓Severity grade ↓ CRP	RCT
Kabbani <sup>13</sup> 2016 U.S.A	IBD patients with similar condition (subgroup analysis)	/	/	/	↓ Health-care utilization	Longitudinal study
Karimi <sup>151</sup> 2019 Iran	Mild to moderate UC patients with vitamin D deficiency	25 /25	2, 000 IU vitamin D daily / 1000 IU vitamin D daily	12 weeks	↑Vitamin D level ↓ SCCAI score ↑ IBDQ-9	Randomized clinical trial
Narula <sup>152</sup> 2017 Canada	CD patients in remission	18 /16	10,000 IU vitamin D3 daily/ 1000 vitamin D daily	12 months	↓ HADS score (in both group)	RCT
Sharifi <sup>153</sup> 2019 Iran	Mild to moderate UC patients	46 /44	A single injection of 300,000 IU vitamin D3/1 mL normal saline	3 months	↑Vitamin D level ↓ BDI score	RCT
Arihiro <sup>154</sup> 2019 Japan	IBD patients	108 /115	500 IU vitamin D daily/ placebo	6 months	↑Vitamin D level ↑ Lichtiger clinical activity index score	RCT

**Notes:** The table includes representative studies and their outcome of using vitamin D as a therapeutic strategy. “↑” = increase; “↓” = decrease.

**Abbreviations:** CRP, C-reactive protein; hs-CRP, high sensitivity C-reactive protein; RCT, randomized controlled trial; HBI, Harvey Bradshaw Index; UCDAI, ulcerative colitis activity index; IBDQ-9, inflammatory bowel disease questionnaire-9; SCCAI, simple clinical colitis activity index questionnaire; HADS, hospital anxiety and depression scale; BDI, beck depression inventory.

depression scores improved in CD patients in remission,<sup>152</sup> and vitamin D reduced the Beck Depression Inventory score in mild to moderate UC patients.<sup>153</sup> Thus, higher serum vitamin D levels may be needed for its antidepressant effect.<sup>153</sup> Of note, there is controversial finding on the use of vitamin D as a treatment for IBD. Supplemental vitamin D at 500IU/day during the winter and early spring reduced the incidence of influenza and upper respiratory infections in patients with IBD but increased disease activity according to the Lichtiger Clinical Activity Index in UC patients.<sup>154</sup> This may be the result of insufficient sunshine exposure and vitamin D absorption in winter.

Since bioactive vitamin D represses IBD in multiple ways, a relatively high dose in the intestine is required to achieve a therapeutic effect. A new pharmaceutical preparation of vitamin D has been constructed recently. This consists of a nanostructured lipid carrier (NLC) that encapsulates 1.25(OH)<sub>2</sub>D<sub>3</sub> for colonic delivery by oral administration. This mechanism maintains a high concentration of 1.25(OH)<sub>2</sub>D<sub>3</sub> in the colonic tissue for at least 12 hours,<sup>106</sup> reducing the infiltration of polymorphonuclear leukocytes and the production of inflammatory cytokines, and may serve as a new option for IBD therapy.<sup>106</sup>

## Biologicals Improve Vitamin D

Biologicals like anti-TNF- $\alpha$  antibodies are found to modulate the serum level of vitamin D. Higher levels of inflammatory markers are associated with lower 1.25(OH)<sub>2</sub>D concentrations, and the serum level of 1.25(OH)<sub>2</sub>D in CD patients increased after a 10-week infliximab treatment.<sup>22,155</sup> In pediatric patients with moderate to severe CD, treatment with infliximab for one year diminished the seasonal variability in vitamin D levels.<sup>156</sup>

## Vitamin D Enhances the Efficacy of Biologicals

Anti-TNF $\alpha$  biologicals, which primarily include infliximab and adalimumab, are widely used in IBD treatment. Recent studies have demonstrated that biologicals have a positive effect on vitamin D levels, but it is unclear whether vitamin D also impacts the efficacy of biologicals.

While anti-TNF- $\alpha$ -trough concentrations are closely associated with clinical and biochemical remission during IBD, serum vitamin D level may also be a predictive marker of remission.<sup>9</sup> Vitamin D supplement has been reported to enhance the efficacy of infliximab in CD patients, especially for those with vitamin D deficiency in a retrospective study, and the positive effect might be due to the upregulation of IL-10.<sup>157</sup> In IBD patients receiving infliximab during the maintenance phase, the trough infliximab concentration is positively related to vitamin D levels; however, this association is not seen during adalimumab treatment.<sup>9</sup> In addition, while CD patients receiving high dose vitamin D (a 5 mg bolus followed by 0.5 mg/day for 7 weeks) and infliximab (5 mg/kg) had the same level of clinical disease as those receiving infliximab and placebo-vitamin-D, they had a reduced need for later infliximab dose-escalation and lower expression of inflammatory markers.<sup>158</sup> Moreover, combined use of vitamin D decreases the number of adverse dermatological events associated with the use of biologicals in these patients.<sup>10</sup> The unsatisfactory outcome of biological use in vitamin D insufficient patients further supports a role for vitamin D in enhancing biological efficacy during IBD therapy. IBD patients with low vitamin D levels are less likely to achieve clinical remission regardless of anti-TNF- $\alpha$  therapy with infliximab or adalimumab.<sup>159</sup> In addition, pediatric IBD patients with vitamin D insufficiency frequently have a poor clinical response to anti-TNF $\alpha$  treatment.<sup>160</sup> However, a few studies showed contradictory results about the impact of vitamin D on biological efficacy. For example, a lower vitamin D level in patients with moderate to severe CD receiving infliximab therapy more often had infliximab-induced clinical remission at week 14 than patients with normal vitamin D levels.<sup>161</sup> The small sample sizes in this study may explain this finding. In summary, supplementation of vitamin D may enhance the efficacy of biologicals in IBD patients, especially among vitamin D insufficient patients.

## Vitamin D Analogue Treatment

Vitamin D analogues have also shown outstanding efficacy in IBD treatment. The analogue, KH 1060, inhibits PBMC proliferation, downregulates TNF- $\alpha$ , and synergizes with anti-TNF- $\alpha$  biologicals to treat IBD.<sup>162</sup> Intracellular adhesion molecules (ICAM) and matrix metalloproteinases (MMPs) are up-regulated in the mucosa of IBD patients and play an important role in recruiting leukocytes to sites of inflammation. In addition, inflammatory cytokines such as TNF- $\alpha$  and IL-1 can induce ICAM-1. The vitamin D analogue, ZK 156979, reduces MMP production and ICAM-1 and LFA-1 levels

in PBMCs from IBD patients and could serve as a potential IBD treatment strategy.<sup>163</sup> The vitamin D form, 1.25(OH) 2D3, and its analogue, EB 1089, inhibit PBMC proliferation, induce apoptosis of PBMC from healthy individuals and IBD patients, and downregulate ICAM-1 expression.<sup>164</sup> These results demonstrated that vitamin D analogues play a critical role in suppressing mucosal inflammation during IBD likely by inhibiting the recruitment of leukocytes and production of pro-inflammatory cytokines at sites of inflammation.

## Predictive Role for Vitamin D During IBD

### Ability of Vitamin D to Predict IBD Disease Activity and Relapse

Given the strong association between vitamin D and mucosal inflammation, it is possible that vitamin D may act as a predictor of IBD disease activity. Vitamin D deficiency (defined as 25(OH)D levels <9 ng/mL) was associated with a longer duration of disease in CD but not UC patients.<sup>165</sup> In addition, Ko et al found a negative correlation between disease activity and vitamin D levels in CD but not in UC patients,<sup>74</sup> and Rasouli et al showed that patients with active disease are more likely to have low vitamin D levels than those in UC remission.<sup>77</sup> Moreover, serum bioactive vitamin D status was inversely correlated with fecal calprotectin (FC) during IBD, but not with systemic inflammation markers such as CRP, white cell count, and platelet count, indicating that vitamin D correlated negatively with intestinal but not systemic inflammation.<sup>166</sup> Other studies have also shown a highly inverse correlation between vitamin D concentration and disease activity (Table 2).<sup>8,11–22,113</sup>

Several studies have also demonstrated that low levels of vitamin D in IBD patients is strongly associated with poor quality of life,<sup>8,13,20</sup> increased levels of systemic and intestinal inflammatory markers such as ESR, CRP, FC,<sup>11</sup> increased

**Table 2** Vitamin D as a Predictor of IBD Disease Activity

Study	Patients Included	Vitamin D Deficiency/Insufficiency and Disease Activity in UC	Vitamin D Deficiency/Insufficiency and Disease Activity in CD	Study Type
Kabbani <sup>13</sup> 2016 U.S.A	965 IBD patients with 5-year follow-up	↑Disease activity (UCAI scores)	↑Disease activity (HBI)	Longitudinal study
Ko <sup>74</sup> 2019	87 IBD	=Disease activity (Mayo score)	↑ Disease activity (HBI)	Retrospective study
Rasouli <sup>77</sup> 2020 Iran	153 IBD	↑ Disease activity (Truelove score in ulcerative colitis)	=Disease activity (CDAI)	Epidemiological-analytical research
Scolaro <sup>11</sup> 2018 Brazil	60 IBD	↑Disease activity (partial Mayo score)	↑Disease activity (HBI)	Cross-sectional descriptive study
Hausmann <sup>14</sup> 2019 German	470 IBD	= Disease activity (SSCAI)	↑Disease activity (HBI)	Retrospective study
Torki <sup>16</sup> 2015 Iran	133 IBD	↑Disease activity (SSCAI)	↑Disease activity (CDAI)	Cross-sectional study
Yang <sup>18</sup> 2021 China	198 CD	↑Disease activity (CDAI)	/	Cross-sectional study
Schardey <sup>19</sup> 2019 German	200 IBD	↑Disease activity (partial Mayo score)	= Disease activity (HBI)	Prospective study
Ulitsky <sup>20</sup> 2011 U.S.A	504 IBD	= Disease activity (UCAI)	↑Disease activity (HBI)	Retrospective study
Meckel <sup>21</sup> 2016 U.S.A	230 UC	↑Disease activity (total Mayo score)	/	Prospective study

**Notes:** The table includes representative studies concerning vitamin D status and IBD disease activity. “↑” = increase; “↓” = decrease; “=” = no significant change.

**Abbreviations:** HBI, Harvey Bradshaw Index; UCAI, UC disease activity index; CDAI, crohn's disease activity index; SCCAI, simple clinical colitis activity index.

pain,<sup>13</sup> and a higher incidence of hospital admission,<sup>12,148</sup> emergency treatment,<sup>13</sup> and surgery.<sup>13,148</sup> Of note, vitamin D deficient UC patients were more likely to have a longer disease duration and more severe disease symptoms than patients with normal vitamin D levels.<sup>167</sup> Importantly, vitamin D directly correlated with IBD disease severity; the worse the disease, the lower the serum vitamin D level.<sup>168</sup> Vitamin D levels were also decreased in UC patients, and the mean vitamin D level was lowest in patients with extensive UC (E3), suggesting a close relationship between disease progression and serum vitamin D level.<sup>169</sup> Furthermore, during periods of clinical UC remission, serum vitamin D levels <35mg/mL could predict the risk of relapse.<sup>170</sup> The ability of low vitamin D status to predict poor IBD outcomes is clarified in a review by Gubatan et al.<sup>171</sup> A retrospective study found that 27.5 ng/mL is the optimal cut-off value for vitamin D to define the active and remission phases of IBD.<sup>14</sup>

Taken together, these findings suggest that there is a strong relationship between vitamin D and IBD disease activity and the risk of relapse. This indicates that vitamin D status can be reliably used to predict disease activity and relapse in patients with IBD, helping to inform the most appropriate treatment and reducing cost.

## Role for Vitamin D in Predicting the Therapeutic Efficacy of Biologicals

The positive correlation between Vitamin D levels and the trough concentration of anti-TNF- $\alpha$  antibody, particularly infliximab, during IBD indicates that vitamin D can reliably predict the therapeutic efficacy of biologicals.<sup>9</sup> Vitamin D levels can also influence the initial response to anti-TNF- $\alpha$  medication in patients with IBD.<sup>159</sup> In addition, some vitamin D related genetic variants have already been reported associated with the remission after adalimumab treatment in CD patients,<sup>172</sup> which potentially supports that vitamin D might affect the efficacy of adalimumab. Moreover, as gut-tropic integrin  $\alpha 4\beta 7$  is another IBD immune treating target, vitamin D can downregulate gut-tropic integrin,  $\alpha 4\beta 7$ , expression on immune cells, and higher 25(OH)D is associated with lower  $\alpha 4\beta 7$  positive PBMC levels and  $\alpha 4\beta 7$  positive intestinal leukocytes.<sup>173</sup> Low vitamin D (<25ng/mL) is associated with higher vedolizumab (anti- $\alpha 4\beta 7$ ) primary non-response during induction and failure at 1-year follow-up in IBD patients.<sup>173</sup> These results indicate that vitamin D levels can influence the therapeutic efficacy of particular biologicals. However, despite the potentially promising role vitamin D acts in IBD biological treating efficacy, there exist only a limited amount of study concerning both vitamin D and biologicals in IBD treatment, more investigations into the relationship between vitamin D and the efficacy of biologicals are urgently needed.

In conclusion, in addition to maintaining bone health, vitamin D also plays a prominent role in regulating innate and adaptive immunity. Vitamin D is closely associated with IBD pathogenesis, which includes a distinct effect on intestinal immunity, and maintenance of the intestinal mucosal barrier and the gut microbiome. Vitamin D treatment could reduce inflammatory cytokine production and alleviate intestinal inflammation, and benefit for IBD patient with reduced disease activity and improved prognosis of disease. Most importantly, vitamin D can affect the therapeutic efficacy of biologicals, and predict IBD disease activity and relapse risk. Assessing disease activity and IBD relapse by monitoring the vitamin D levels may provide a novel strategy to treat IBD, helping to guide the most appropriate treatment for IBD patients and reducing medical costs. More researches concerning vitamin D and IBD biological treatment especially in the underlying mechanism behind them are urgently needed.

## Data Sharing Statement

No new data were generated or analysed in support of this research.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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