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Role of in vitamin D in Irritable Bowel Syndrome

Abstract

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder affecting 10-22% of adults. Its development is closely related to the gut microbiota, and the inflammatory and immune responses triggered by the gut microbiota can lead to IBS. Vitamin D (VD) effectively treats IBS with fewer side effects by improving gut microbiota, immune regulation, and anti-inflammatory effects. In the future, it is necessary to carry out epidemiological studies on the relationship between VD and IBS, clinical studies on the efficacy of supplementing VD to improve IBS, and animal studies on the mechanism of VD improving IBS. Therefore, this paper discusses the relationship between VD and IBS.

Key Words: Irritable bowel syndrome; Vitamin D; Gut microbiota; Immune response; Mental status

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Core Tip: Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder affecting 10-22% of adults. Its development is closely related to the gut microbiota, and the inflammatory and immune responses triggered by the gut microbiota can lead to IBS. Vitamin D (VD) is effective in treating IBS with fewer side effects by improving gut microbiota, immune regulation and anti-inflammatory effects. In the future, it is necessary to carry out epidemiological studies on the relationship

between VD and IBS, clinical studies on the efficacy of supplementing VD to improve IBS, and animal studies on the mechanism of VD improving IBS. This paper discusses the relationship between VD and IBS.

INTRODUCTION

⁴ Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder characterized by abdominal pain, bloating, urinary urgency, voiding incontinence, and altered bowel habits associated with structural and biochemical abnormalities^[1], which affects 10-22% of the adult population^[2]. ² According to Rome IV criteria, IBS is divided into four types: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed constipation and diarrhea (IBS-M), and IBS unclassified^[3].

In the census statistics of the Albanian adult samples, the prevalence of IBS in the study population was 8.6%. There was no gender difference, age differences and regional differences. IBS-C is a common type^[4]. However, in Western countries, the ratio of males to females with IBS is 2:1^[5]. The disease is mild for most people but can be severe and even life-threatening in 1 in 20^[6]. Although the etiology of IBS is unknown, current research suggests that it is related to host and environmental factors. Host factors include the gut-brain axis, serotonin (5-HT) pathway, and gut microbiota, and environmental factors include psychological stress, infection, antibiotic use, diet, and eating habits^[7].

Vitamin D (VD) is a fat-soluble steroid that is a key regulator of calcium and phosphorus metabolism^[8]. Two forms of vitamin D play a major role in humans, D2 and D3, which are ergocalciferol and cholecalciferol, respectively, and they are similar in function. However, studies in recent years have shown that biochemical indicators show that vitamin D2 seems to be cleared from the tissue faster than vitamin D3. At the same dose, the efficacy of D2 is 1/3 to 1/2 of D3, so when supplementing vitamin D, we generally tend to choose vitamin D3^[9]. Studies have found a strong correlation between VD and type 1 diabetes mellitus^[10, 11] and obesity^[12]. The main source of VD is sunlight, and very little is obtained from food. 7-Dehydrocholesterol (7-DHC) is converted in the

skin to vitamin D₃ precursor upon exposure to ultraviolet (UV) B (UVB, 280-310nm). It isomerizes to vitamin D₃, which binds to vitamin D-binding protein (DBP). In the liver, vitamin D₃ attached to DBP is hydroxylated by 25-hydroxylase (CYP2R1) to 25-hydroxyvitamin D₃ (25(OH)D₃), the main circulating form of VD. Later 25(OH)D is hydroxylated in the kidney and eventually converted to 1,25-dihydroxy vitamin D₃ (1,25-(OH)₂D₃)^[13, 14]. Therefore, the main cause of VD deficiency is insufficient sun exposure^[15], such as excessive indoor activity time and sun protection habits ^[16]. The Institute of Medicine (IOM) defines vitamin D deficiency as 25(OH)D below 20 ng/mL and vitamin D deficiency as 25(OH)D below 21-29 ng/mL^[17]. Literature shows that VD can regulate calcium and phosphorus metabolism^[18], inhibit inflammation^[19], regulate immune response^[13], affect the intestinal barrier^[20], and play an important role in the pathogenesis of diabetes^[11], obesity, and IBS. This article provides an overview of research progress on the link between vitamin D supplementation and the pathogenesis of IBS. See Figure 1.

PATHOGENIC RELATIONSHIP BETWEEN VD LEVELS AND IBS

VD deficiency is closely related to IBS's occurrence, development, and complications. Experiments by Nwosu^[21], Cho^[22], and Khayyat^[23] showed that children and adults with IBS had insufficient or inadequate vitamin D levels. Observational studies have also demonstrated that the prevalence of VD deficiency in IBS patients is as high as 82%^[24]. Between April 2015 and April 2017, a prospective randomized controlled trial evaluated 112 VD-deficient adolescents aged 14 to 18 years with IBS. Compared with the placebo, the clinical status of adolescents with IBS who took VD was significantly improved. This study suggests that vitamin D supplementation effectively treats adolescent irritable bowel syndrome ^[25].

Furthermore, a systematic review and meta-analysis assessed the efficacy of vitamin D supplementation in improving IBS. Four randomized controlled trials found that vitamin D supplementation improved symptoms and quality of life in people with IBS^[26]. Nevertheless, Williams *et al* conducted a randomized, double-blind, placebo-controlled study that demonstrated that there were no improvements in the IBS

symptom severity and quality of life (QOL) between the trial (Vit-D supplementation) and placebo groups^[27]. However, the current research has not confirmed the clear pathogenesis of IBS. Many experimental results only prove a link between vitamin D and IBS, but there is no definite explanation. Most of the guesses shown in the literature tend to be VD's intestinal flora adjustment, inflammation inhibition, and mental relief in IBS patients.

VD IMPROVES IBS BY MODULATING GUT MICROBES

Gut microbial diversity maintains intestinal homeostasis, among which Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria are the most important phyla. Disturbances in this microbial balance can lead to many diseases, including IBD^[28]. However, VD supplementation may treat IBS by improving patients' type and abundance of gut microbes. A comprehensive systematic review of the gut microbiota and IBS revealed the presence of *Enterobacteriaceae* (phylum *Proteobacteria*), family *Lactobacillaceae* and genus *Bacteroides* (phylum *Bacteroidetes*) in patients with IBS compared with normal individuals. In addition, IBS patients had potentially harmful microbiota, such as the family *Lactobacillaceae* and genus *Bacteroides* which caused bloating and diarrhea^[29]. VD is an essential hormone to maintain gut barrier function, along with many other roles in the gut^[30]. Intervention studies in IBD have shown that VD alters the gut by increasing the relative abundance of beneficial bacteria (e.g., *Ruminococcus*, *Akkermansia*, *Faecalibacterium*, *Lactococcus*, *Coprococcus*, *Bifidobacteria*) and decreasing the Firmicutes phylum microbial composition^[28].

IMMUNOMODULATORY EFFECT OF VD IN IBS

Vitamin D may play an immunomodulatory role by improving the gut microbiota. The intestinal epithelial barrier (IEB) is the primary interface between the *in vitro* and the *in vivo* environments^[31]. In addition to absorbing water and nutrients, it is also responsible for defending against harmful substances. The IEB secures mucus, and substances are exchanged through intercellular and paracellular pathways. Meanwhile, in addition to

secreting short-chain aliphatic hydrocarbons such as acetate, propionate, and butyrate, specific gut microbes can also regulate the permeability of IEB^[32]. Dysbiosis of gut microbes leads to a decrease in the abundance of short-chain aliphatic hydrocarbon-producing *Akkermansia*, *Phaecococcus*, and *Coprococcus* and an increase in the quantity of LPS-producing *Enterobacteriaceae* so that pro-inflammatory responses outweigh anti-inflammatory responses and cause intestinal inflammation^[33]. Furthermore, *Faecalibacterium prausnitzii* increases butyrate production stimulates Treg maturation, and better balances intestinal inflammation^[33].

As an immunomodulator, VD can not only improve the gut microbiota ^[34] but also increase the production of antimicrobial peptides, improve the intestinal barrier, regulate the integrity of intestinal epithelial cells, inhibit Th1/Th17 cells, relieve Treg cells, and benefit adaptive immune system^[35]. The vitamin D receptor (VDR) is a ligand-dependent transcription factor that could recognize 1,25-(OH)₂D₃^[36]. Vitamin D requires the mediation of VDR to exert its biological actions^[37]. The VD/VDR signaling pathway plays an inhibitory role in infection by activating the transcription of genes related to innate immunity^[38], such as inducing and regulating autophagy^[39], so VD/VDR axis may be an important inhibitor of inflammatory response. Under the influence of vitamin D, macrophages can increase the secretion of IL-10 while reducing the secretion of TNF- α ^[40]. At the same time, studies have shown that the expansion of ILC3 requires vitamin D, and the IL-22 secreted by ILC3 regulates epithelial tight junction proteins to enhance gut epithelial integrity and regulates the intestinal microbiota^[41]. See Figure 2.

VD IMPROVES MENTAL STATUS IN IBS PATIENTS

Growing evidence suggests that the underlying pathophysiological mechanism of IBS is a disruption of brain-gut interactions. Up to 94% of IBS patients have been demonstrated to have psychiatric disorders^[42], of which anxiety and depression are the most common^[43]. Psychological stress alters gut motility and permeability, visceral sensitivity, immune response, and gut microbiota composition, leading to IBS^[44]. Although research on VD and psychiatric disorders has not been well defined, there is evidence that adequate levels of VD are required for normal brain neuropsychiatric

function and that VD regulated through brain cells differentiation, axonal growth, and calcium signaling, as well as neurotrophic factors, affect the brain^[45]. In addition, VD can induce the expression of the tryptophan synthesis gene tryptophan hydroxylase 2 while inhibiting the expression of tryptophan hydroxylase 1, thereby preventing depression by maintaining normal serotonin levels^[46]. Therefore, VD positively affects anxiety and depression in IBS patients.

FUTURE OUTLOOK FOR VD SUPPLEMENTATION

Compared with the side effects of eating disorders and other drugs, vitamin D supplements are significantly more effective, with only mild side effects. Long-term excessive vitamin D intake is relatively rare. If the amount of VD supplementation is well-controlled, side effects can be effectively avoided^[24]. It is also more convenient and efficient to get VD outdoors in sunlight. More research is needed to determine whether oral vitamin D intake increases indoor exposure to ultraviolet (UV) B (UVB, 280–310 nm) in people who work indoors for long periods.

CONCLUSION

IBS is a chronic gastrointestinal functional disorder whose etiology may be mainly relevant to gut microbiota and immune regulation. At the same time, VD can increase the number of beneficial bacteria in the gut, inhibit the inflammatory response, inhibit Th1/Th17 cells, stimulate Treg cells, and relieve the mental state of patients. However, the experiment of VD on IBS in the community population is more complicated, which increases the difficulty of the investigation and reduces the accuracy of the results. Hence, the treatment of VD on IBS is still controversial. In the future, it is necessary to carry out epidemiological studies on the relationship between VD and IBS, clinical studies on the efficacy of supplementing VD to improve IBS, and animal studies on the mechanism of VD improving IBS.

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