NCPD 2.5 ANCC Contact Hours

Sarah W. Matthews, DNP, MN, BSN, APRN, FNP-BC
Margaret M. Heitkemper, PhD, MN, BSN, RN, FAAN
Kendra Kamp, PhD, BSN, RN

Early Evidence Indicates Vitamin D Improves Symptoms of Irritable Bowel Syndrome

Nursing Implications and Future Research Opportunities

ABSTRACT

Irritable bowel syndrome (IBS) affects approximately 11.2% of the population. Yet, full understanding of its etiology and optimal treatment remains elusive. Understanding of the underlying pathophysiology of IBS has been limited. However, research is beginning to identify the cause as multifactorial (e.g., low-grade local mucosal inflammation, systemic immune activation, altered intestinal permeability, intestinal hypersensitivity, altered central nervous system processing, changes in intestinal microbiota). Understanding of the role of vitamin D in intestinal inflammation, immunity, and gastrointestinal conditions is increasing but is not yet fully understood. Growing evidence has linked vitamin D deficiency with a variety of gastrointestinal disorders, including inflammatory bowel disease, diverticulitis, colorectal cancer, and IBS. Several studies have demonstrated that individuals with IBS are more likely to have vitamin D deficiency than healthy controls. Recent vitamin D supplementation studies have shown improvement in quality of life and reduction in IBS symptoms (including abdominal pain, distention, flatulence, constipation, and visceral sensitivity) but the mechanism remains unclear. Nurses are well positioned to educate patients about the importance of sufficient vitamin D for overall health in individuals with IBS as well as participate in well-designed therapeutic studies to explore whether enhanced vitamin D status will ultimately help treat IBS more effectively.

IBS Epidemiology, Clinical Features, and Pathophysiology

Irritable bowel syndrome (IBS) is a disorder of gut–brain interaction (DBGI) affecting approximately 11.2% of the population (Lovell & Ford, 2012). Yet, full understanding of its etiology and optimal treatment remains elusive. Irritable bowel syndrome is chronic and potentially debilitating due to abdominal pain, bloating, and altered bowel patterns of diarrhea (IBS-D), constipation (IBS-C), or a combination of the two (IBS-mixed) (Drossman, 2016). It is associated with significant costs to individuals (Canavan, West, & Card, 2014) and society due to healthcare utilization and lost productivity (Tana et al., 2010). Currently, diagnosis is made using the Rome Criteria, which is symptom-based (Drossman, 2017).

Understanding of the underlying pathophysiology of IBS has been limited due to its heterogeneity. However, research is beginning to identify the causes of DBGI, such as IBS, as multifactorial (Drossman, 2016; Holtmann, Shah, & Morrison, 2017). Mechanisms may include low-grade local mucosal inflammation, systemic immune activation, altered intestinal permeability, intestinal hypersensitivity,

Received May 19, 2021; accepted July 12, 2021.

About the authors: *Sarah W. Matthews, DNP, MN, BSN, APRN, FNP-BC, is Assistant Professor, Department of Child, Family, and Population Health Nursing, University of Washington, School of Nursing, Seattle; and Nurse Practitioner, Kaiser Permanente Washington, Bellevue.*

Margaret M. Heitkemper, PhD, MN, BSN, RN, FAAN, is Professor and Chairperson, Department of Biobehavioral Nursing and Health Informatics, University of Washington, School of Nursing, Seattle.

Kendra Kamp, PhD, BSN, RN, is Assistant Professor, Department of Biobehavioral Nursing and Health Informatics, University of Washington, School of Nursing, Seattle.

The authors declare no conflicts of interest.

Correspondence to: *Sarah W. Matthews, DNP, MN, BSN, APRN, FNP-BC, University of Washington, School of Nursing, 1959 NE Pacific St, Seattle, WA 98195 (sarahm09@uw.edu).*

DOI: 10.1097/SGA.0000000000000634

altered central nervous system processing, and changes in the intestinal microbiota. In addition, environmental factors, such as diet, have an effect.

Vitamin D

Our understanding of the role of vitamin D in intestinal inflammation, immunity, and gastrointestinal conditions is growing but is not yet fully understood. Vitamin D is a lipid-soluble vitamin that functions like a hormone. It occurs in two forms in the diet, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) (Nair & Maseeh, 2012). Because vitamin D occurs naturally in a limited number of foods, it is often added to foods (e.g., breakfast cereals and milk) to increase its availability in the diet (Table 1).

Vitamin D_2 is present only in a small number of plants and is not found in animals. Vitamin D_3 is found in a limited number of animals. Both are similar in structure and referred to as provitamins. They are absorbed from the upper small intestine and the presence of bile is essential for absorption.

Vitamin D is also produced in the skin through exposure to ultraviolet B rays from the sun. When ultraviolet rays contact the skin, humans synthesize vitamin D_3, whereas plants, such as sun-exposed mushrooms, synthesize vitamin D_2 (Nair & Maseeh, 2012).

Vitamin D, from either ultraviolet-exposed skin or the diet, is biologically inert and must go through hydroxylation in the liver and then the kidneys to become active. The active form is 1,25-dihydroxycholecalciferol and is also called calcitriol or 1,25-dihydroxyvitamin D (25(OH)D). Testing of serum vitamin D relies on immunoassay techniques that use antibodies that target both 25-OH vitamin D_2 and D_3 and is reported as the "total vitamin D" (i.e., the sum of D_2 and D_3 levels).

Vitamin D is best known for its important role in skeletal health (e.g., prevention of osteoporosis) but recently there has been a growing appreciation of its wide range of biological functions mediated through vitamin D receptors throughout the body.

TABLE 1. Dietary Sources of Vitamin D (USDA, 2020; Yamamoto & Jørgensen, 2019)

Sources of vitamin D_2
Sun-exposed mushrooms
Sun-exposed yeast
Sources of vitamin D_3
Fish (e.g., mackerel, wild salmon, catfish, tuna, cod liver oil)
Egg yolks
Liver
Fortified foods (inconsistent standards therefore important to check ingredients to verify)
Breakfast cereal
Milk
Cheese
Tofu
Soy milk
Nut milk
Orange juice
Yogurt
Energy bars

Vitamin D and Gastrointestinal Conditions

Many tissues possess vitamin D receptors, including the intestines, indicating that vitamin D affects the body in a variety of ways, many of which are becoming clearer as research increases. Interest in the effect of dietary and ultraviolet-related vitamin D on intestinal health is growing because of recent studies identifying its important role in immune regulation, inflammation, and direct and indirect effects on the microbiome, which, in turn may positively influence intestinal health (Aranow, 2011; Bakke, Chatterjee, Agrawal, Dai, & Sun, 2018; Battistini, Ballan, Herkenhoff, Saad, & Sun, 2020; Dimitrov & White, 2016; Fakhoury et al., 2020; Kong et al., 2008; Li, Chen, & Du, 2015; Sun, 2018; Waterhouse et al., 2019; Yamamoto & Jørgensen, 2019; Yuk et al., 2009).

Vitamin D receptors, a member of the nuclear hormone receptor superfamily, are expressed in the gut epithelial cells and play a role in maintaining the mucosal barrier and regulating mucosal inflammation (Kong et al., 2008; Li et al., 2015). Vitamin D helps regulate immune homeostasis, specifically the intestinal immune system, which must differentiate pathogens versus normal microbiota and produce a well-orchestrated immune response without damaging normal tissues (Cantorna, Rogers, & Arora, 2019). The innate immune system's first response in the intestinal epithelium depends on vitamin D. This is illustrated by mouse colitis models in which the vitamin D receptor gene is knocked out. The mice exhibit loss of intestinal epithelial tight junctions, loss of their epithelial integrity, increased bacterial infiltration, and increased susceptibility to epithelial injury (He et al., 2018; Kong et al., 2008).

Animal and human studies indicate that epithelial vitamin D receptor signaling likely suppresses intestinal inflammation by protecting the mucosal barrier in multiple ways—by inhibiting inflammation-induced apoptosis of intestinal epithelial cells (Li et al., 2015), influencing intestinal bacterial composition through regulation of antimicrobial peptides (Dimitrov & White, 2016; Waterhouse et al., 2019) and autophagy (Yuk et al., 2009), and initiating other immune responses (Aranow, 2011; Cantorna et al., 2019).

Growing evidence has linked vitamin D deficiency in humans with a variety of gastrointestinal disorders

affected by these processes, including inflammatory bowel disease (Kojecký et al., 2019; Li et al., 2015; Tan et al., 2018), diverticulitis (Maguire, Song, Strate, Giovannucci, & Chan, 2013) and colorectal cancer (Protiva et al., 2016). A meta-analysis found that patients with inflammatory bowel disease had 64% higher odds of vitamin D deficiency (≤20 ng/ml) when compared with healthy controls (Del Pinto, Pietropaoli, Chandar, Ferri, & Cominelli, 2015). Nevertheless, despite the clear significance of vitamin D in intestinal immune homeostasis and its association with clinical inflammatory bowel disease, it is unclear whether the association reflects cause or effect, and may be bidirectional (Myint, Sauk, & Limketkai, 2020). For example, it is common for people with inflammatory bowel disease to be on self-imposed restrictive diets, which can lead to insufficient macro- and micronutrients including vitamin D (Holick et al., 2011; Lim, Kim, & Hong, 2018).

In a meta-analysis of inflammatory bowel disease observational studies, low vitamin D was a biomarker for disease activity, mucosal inflammation, clinical relapse, low quality of life, and predictor of poor clinic outcomes (Gubatan, Chou, Nielsen, & Moss, 2019). Another meta-analysis reviewed the efficacy of vitamin D in the treatment of IBD in 18 randomized controlled trials (RCTs) which involved 908 patients and concluded that vitamin D supplementation can improve the serum level of vitamin D in individuals with inflammatory bowel disease and control the relapse rate of the disease (studies examined 3-, 6-, and 12-month time frames). Thus, the authors recommended that vitamin D be used for the treatment of inflammatory bowel disease, at least as an adjunct therapy (Li, Chen, Wang, Zhang, & Gong, 2018).

Still, the association between vitamin D status and the success of various inflammatory bowel disease treatments has been variable. Several studies have found it to augment treatment with biologics (Winter et al., 2017; Zator et al., 2014) but others have not seen a clear association between the therapeutic effects of biologics and vitamin D. One study found that normal vitamin D levels at the start of biologic therapy (anti-tumor necrosis factor [TNF]) were associated with 2.64 increased odds of staying in remission at 3 months (Winter et al., 2017). In contrast, another prospective cohort study found that vitamin D deficiency was not associated with anti-TNF failure (Santos-Antunes, Nunes, Lopes, & Macedo, 2016).

To date, there has been a clear association between vitamin D and inflammatory bowel disease in animal knockout models but in human studies, it is less clear. Given the contradictory results and lack of clarity of cause and effect in humans, the potential role of vitamin D in the treatment of inflammatory bowel disease warrants further research.

Vitamin D and IBS

Several studies have also demonstrated that individuals with IBS are more likely to have vitamin D deficiency (≤20 ng/ml) than healthy controls (Abbasnezhad et al., 2019; El Amrousy, Hassan, El Ashry, Yousef, & Hodeib, 2018; Khayyat & Attar, 2015; Nwosu, Maranda, & Candela, 2017; Tazzyman et al., 2015) (Table 2). Khayyat and Attar (2015) studied vitamin D levels in 60 individuals with IBS and 100 healthy controls identifying vitamin D deficiency (<20 ng/ml) in 82% of the IBS group compared with 31% of healthy controls. Nwosu et al. (2017) studied a pediatric population and found significantly lower vitamin D concentrations in children with IBS compared with a healthy control group, with 53% of those with IBS in the deficient range (<20 ng/ml) versus 27% of the healthy controls despite having similar body mass index (BMI) values. The researchers did not investigate the cause of low vitamin D levels but noted that previous studies showed a combination of lifestyle choices (limited sunlight), and restrictive diets that limited dairy, as well as other micronutrients, may be factors.

Vitamin D deficiency/insufficiency can occur because of malabsorption and metabolism in some conditions (e.g., liver or kidney disease and gastric bypass), dietary restrictions (e.g., avoiding dairy due to lactose intolerance), or reduction of skin synthesis (e.g., sun avoidance, sunscreen utilization, decreased outdoor activities, clothing choices) (Bikle, 2007; Holick et al., 2011). Dietary restrictions and reduction of vitamin D synthesis in the skin may be factors in the development or exacerbation of IBS. Malabsorption and dysfunction of vitamin D metabolism have not yet been identified as a cause of vitamin D deficiency in individuals with IBS. Although vitamin D deficiency appears common in IBS, much is unknown about its exact cause, which is likely to be multifactorial.

Because of the role of vitamin D in many of the physiologic processes associated with IBS (immune modulation, inflammation, and microbiome composition), it has been suggested that vitamin D supplementation may improve symptoms of IBS (Ghaly, Hart, & Lawrance, 2019; Shang & Sun, 2017). Recent studies on supplementation with vitamin D in IBS have shown improvement in quality of life and reduction in IBS symptoms (abdominal pain, distention, flatulence, constipation, visceral sensitivity, and overall gastrointestinal symptoms) (Abbasnezhad et al., 2016; El Amrousy et al., 2018; Jalili et al., 2016; Khalighi Sikaroudi et al., 2020), but the mechanism of this effect is unclear and the optimal dosing and length of treatment are not known (Table 2). In these few available studies, there is a wide range of vitamin D dosing (ranging from 2,000 IU/day to 50,000 IU/week) and variable length of treatment (6 weeks to 6 months). In

TABLE 2. Summary of Studies Examining Vitamin D Status and Effect on Symptoms in IBS (Observational and Interventional Studies in Order of Publication)

Study, Year	Study Design	Sample	Length of Study	Intervention	Outcomes
Observational					
Khayyat and Attar (2015)	Prospective comparative case control	60 IBS patients 100 HC (79% female) 42 ± 5 years	N/A	N/A	82% of IBS patients were VD deficient. 31% of HC were VD deficient.
Nwosu et al. (2017)	Retrospective case-controlled study	55 IBS patients (73% female) 16.5 ± 3.1 years 116 HC (58% female) 14.6 ± 4.3 years	N/A	N/A	53% of IBS deficient 27% of HC deficient (deficiency <20 ng/ml)
Interventional					
Tazzyman et al. (2015)	Double-blind, randomized placebo controlled, stratified study	51 IBS participants (92% female) 20–51 years No HC	12 weeks	3 groups G1: Placebo G2: 3,000 IU of VD alone G3: 3,000 IU of VD and probiotic	80.4% IBS deficient (<20 ng/ml) Increased VD levels after intervention in all groups Significant association between QoL and VD levels observed.
Abbasnezhad et al. (2016)	*Double*-blinded, randomized, placebo-controlled study Intervention	90 IBS patients (64% female) 18-70 years	6 months	2 groups G1: 50,000 IU VD weekly G2: placebo	Treatment showed effectiveness to reduce overall GI symptoms (abdominal pain, rumbling, bloating, abdominal distention, and dissatisfaction with bowled habits, improvement of QoL) Improvements started at the 4th month of supplementation.
Jalili et al. (2016)	Blinded randomized clinical trial	100 IBS female patients 18–75 years	6 weeks	4 groups G1: placebo of VD and soy isoflavone (SI) G2: placebo of VD and SI (20 mg biweekly) G3: VD (50,000 IU biweekly) and placebo SI G4: VD and SI	50,000 IU of VD biweekly significantly reduced the severity and duration of abdominal pain, life disruption, and improved QoL. SI and VD promoted significant improvement in total IBS score. Coadministration of SI and VD did not improve symptom severity scores and QoL but improved the total scores for IBS.
El Amrousy et al. (2018)	Prospective randomized clinical trial	112 adolescents with IBS and VD deficiency 14–18 years	6 months	2 groups G1: VD 2,000 IU/day G2: placebo	Patients supplemented with VD had significant improvement in vitamin D level (increased from 17.2 ± 1.3 to 39 ± 3.3 ng/ml) and significant improvement in IBS symptom severity scores and QoL when compared with placebo group.

(*continues*)

TABLE 2. Summary of Studies Examining Vitamin D Status and Effect on Symptoms in IBS (Observational and Interventional Studies in Order of Publication) *(Continued)*

Study, Year	Study Design	Sample	Length of Study	Intervention	Outcomes
Khalighi Sikaroudi et al. (2020)	Blinded, placebo controlled randomized clinical trial	88 males and females with IBS-D 18–65 years	9 weeks	2 groups G1: 50,000 IU VD weekly G2: placebo	Total score of IBS severity score system was significantly improved in both groups compared with baseline ($p < .001$) but the VD group was significantly higher ($p < .001$). Comparing groups, abdominal pain severity, abdomen pain duration, bowel habit satisfaction, and life disruption significantly improved in the VD group compared with the control group. QoL significantly improved in both groups but VD group showed more improvement.

Note. GI = gastrointestinal; HC = healthy controls; IBS = irritable bowel syndrome; N/A = not applicable; QoL = quality of life; VD = vitamin D.

addition, these studies did not account for dietary sources of vitamin D or seasonal differences in sun exposure that may have affected their results.

Because of the relatively small number of studies and variations in study design, a cause-and-effect relationship between vitamin D and symptoms is still not completely understood and warrants further investigation. One area for further investigation is vitamin D's influence on IBS through the gut microbiome.

Microbiome and IBS

The human microbiome is a term used to name the array of bacteria, viruses, and fungi present in and on the body, including the gastrointestinal tract. Twelve different bacterial phyla have been identified, with 93.5% of phyla classified as bacteroidetes, proteobacteria, firmicutes, actinobacteria, or euryarchaeota (Yamamoto & Jørgensen, 2019). These microbiotas play a critical role in synthesis of some vitamins (vitamin K and most water-soluble B vitamins), intestinal barrier integrity, renewal of epithelial cells, and immune health (LeBlanc et al., 2013; Sun, 2018).

Dysbiosis, or disruption of the gut microbiome composition, is a risk factor for the development of several conditions such as inflammatory bowel disease, diabetes, asthma, allergies, and IBS (Bakke et al., 2018; Fakhoury et al., 2020; Klem et al., 2017). A systematic review and meta-analysis found that more than 10% of patients with infectious enteritis later developed IBS (Klem et al., 2017). The risk of IBS was fourfold higher than in individuals who did not have infectious enteritis. Women were at even higher risk, especially those with severe enteritis. Also, those who used antibiotics during the enteritis were at significantly higher risk for the development of IBS.

Research in the last decade has accelerated our understanding of the role of the microbiota in the pathogenesis of IBS and several other intestinal disorders, but knowledge of how to manipulate it is limited (Distrutti, Monaldi, Ricci, & Fiorucci, 2016; Harris & Baffy, 2017; Hollister et al., 2020). Many IBS treatments specifically target the microbiome, such as prebiotics, probiotics, antibiotics, and fecal microbiota transplant, but the results are variable and the ability for these treatments to influence the microbiome and maintain desired changes over time is still not well established. Vitamin D seems to be a potentially important adjunct treatment to help promote gut microbiota homeostasis in inflammatory bowel disease management (Battistini et al., 2020) and may also be a factor for IBS as well.

Vitamin D and the Microbiome

Research on the mechanisms by which vitamin D influences the microbiome in a variety of conditions is growing. A recent systematic review found 22 of the 24 studies that reported an association between vitamin D and the gut microbiome (Waterhouse et al., 2019). The findings indicated primarily indirect mechanisms because bacteria do not express the vitamin D receptor. In contrast, immunocytes such as macrophages, B and T lymphocytes, neutrophils, and dendritic cells do express vitamin D receptors that enable the actions of vitamin D (Di Rosa, Malaguarnera, Nicoletti, & Malaguarnera, 2011). Vitamin D has been shown to stimulate macrophages to produce antimicrobial peptides, such as defensin and cathelicidin, which results

in killing of some specific bacteria, allowing greater opportunity for the growth of protective microbial species (Tabatabaeizadeh, Tafazoli, Ferns, Avan, & Ghayour-Mobarhan, 2018).

Vitamin D decreases inflammatory activity against certain bacteria by regulating cell-mediated immune responses through inhibition of T-cell proliferation and inducing a shift from inflammatory Th1 cytokines to anti-inflammatory Th2 cytokines. In addition, vitamin D plays a role in maintaining the mucosal barrier function by upregulating the expression of proteins that support tight junctions and suppress epithelial cell apoptosis (i.e., programmed cell death) (Aranow, 2011; Waterhouse et al., 2019).

Studies assessing the effect of vitamin D on specific microbiota are still relatively few and provide disparate results. A systematic review of studies that included healthy individuals, as well as studies of mice and humans with a variety of conditions (multiple sclerosis, cystic fibrosis, ulcerative colitis, Crohn disease, prediabetes), found that variability in the study design, mice and humans populations studied, measure of vitamin D intake/status, methods used to measure the microbiome, and data analysis, all led to challenges in synthesizing the results and drawing conclusions about the different abundances of taxa and microbial diversity (Waterhouse et al., 2019). Still, in both mouse and human studies, associations were found between increased serum levels of vitamin D and β diversity. In contrast, there did not seem to be a consistent association between vitamin D and α diversity.

Most of the human studies conducted to date have had considerable limitations including observational studies with confounding risks and randomized trials with small samples (≤25) (Waterhouse et al., 2019). A more recent study by Singh Rawat, Alwakeel, Sharif, and Al Khodor (2020) examined the microbiomes of 80 females aged 17–28 years who were vitamin D deficient (96% were ≤20 ng/ml) or insufficient (4% were between 20 and 30 ng/ml) and treated with 12 weeks of vitamin D supplementation. Postsupplementation, they had a higher bacteroidetes/firmicutes ratio (Singh et al., 2020), which has been previously associated with gut health in other studies (Yang et al., 2015).

Verrucomicrobia and actinobacteria phyla also increased in abundance with vitamin D supplementation. Another smaller study of healthy individuals aged 18–40 years found that those in the third highest tertile of vitamin D (26.5 ± 9.6 ng/ml) had more abundant *Prevotella* and less abundant *Haemophilus* and *Veillonella* (part of the firmicutes phyla) than those in the lowest (21.5 ± 9.0 ng/ml) and middle tertiles (23.5 ± 10.0 ng/ml) (Luthold, Fernandes, Franco-de-Moraes, Folchetti, & Ferreira, 2017). When comparing patients who received 16 weeks of vitamin D supplementation with a placebo group, there was higher abundance of *Lachnospira* genus and lower abundance of *Blautia* genus (Bashir et al., 2016; Charoenngam, Shirvani, Kalajian, Song, & Holick, 2020; Naderpoor et al., 2019).

Despite substantial heterogeneity, evidence has been found to support the hypothesis that vitamin D influences the composition of the gut microbiome. Nevertheless, until larger population–based studies are completed, full understanding of the extent to which vitamin D modulates the microbiome will be limited.

Vitamin D, the Microbiome, and IBS

Studies examining the microbiome in individuals with IBS have also identified disparate results, which may reflect the study design or the variety of IBS subtypes (e.g., constipation or diarrhea prone). Compared with healthy controls, individuals with IBS whose gut microbiome was examined at the bacterial phyla level have been shown to have lower quantities of bifidobacteria and lactobacilli (Chong et al., 2019; Kerckhoffs et al., 2009).

Increased pain, urgency, looser stools, and worse quality of life have been associated with lower microbial diversity among individuals with IBS (Carroll, Ringel-Kulka, Siddle, & Ringel, 2012; Giamarellos-Bourboulis et al., 2015; Hollister et al., 2020; Jeffery et al., 2012). At the family level, rikenellaceae, christensenellaceae, dehalobabacteriaceae, oscillospiraceae, mogibacteriaceae, ruminococcacea, sutterellaceae, desulfoyibrionaceae, and erysipelotrichaceae abundances have been associated with lower extraintestinal pain and at the phyla level, higher firmicutes to bacteroidetes ratio has been positively associated with loose stools (Hollister et al., 2020). More research is needed to fully understand changes in the microbiome associated with IBS.

The potential role of vitamin D in modulating the gut microbiome to influence symptoms among individuals with IBS is promising but remains to be elucidated. A recent systematic review of RCTs examining the health effects of vitamin D and probiotics on multiple conditions found that cosupplementation (i.e., vitamin D with probiotics) yielded greater health benefits than vitamin D alone or placebo (Abboud et al., 2020). Beneficial effects included improved disease severity, mental health, metabolic parameters, inflammation, and dyslipidemia.

Interestingly, the only study that did not report a significant difference in symptoms between the treatment arms (vitamin D alone and vitamin D with probiotics) and placebo was in IBS but the investigators determined that sun exposure may have been a confounder (Tazzyman et al., 2015). The study examined the effect of vitamin D and probiotic supplementation

on vitamin D status and IBS symptoms and found that all the groups experienced increased vitamin D levels, including the placebo group. Of participants receiving vitamin D supplementation, the percentage of participants who reached sufficient levels (>20 ng/ml) increased significantly—the vitamin D alone group increased from 25.0% to 92.3%, and the vitamin D with probiotic group increased from 22.2% to 87.5%. Unexpectantly, so did the placebo group, which increased from 18% to 60% (Tazzyman et al., 2015). The data showed a general improvement in symptom score within all the groups and differences did not reach the level of significance. Ultimately, the investigators discovered that the increase of vitamin D across all groups was likely due to the season change and subsequent confounder of sun exposure. Placebo effect may also need to be considered as a factor.

The potential role of gut microbiome in modulating vitamin D is not clear. At this time there appears to be no evidence that the gut microbiome plays a direct role in metabolism of vitamin D (unlike some other vitamins), but the microbiota may affect the serum concentrations of vitamin D or its mechanisms of action by enhancing the expression and activity of the vitamin D receptor (Jones, Martoni, & Prakash, 2013; Wu et al., 2010) as demonstrated in an RCT examining the effects of probiotic supplementation (Jones et al., 2013). To date, the effect of vitamin D status on microbiota composition in individuals with IBS has not been thoroughly examined. This bidirectional relationship could support the use of vitamin D with probiotics to modulate the microbiome and improve symptoms in IBS but requires further investigation before a clear recommendation can be made.

Implications for Practice

There are indications that vitamin D is important for gut health, yet uncertainties remain around the exact cause and effect in IBS. Nonetheless, because studies have identified higher rates of vitamin D deficiency/insufficiency in individuals with IBS, it is important to consider the potential impact on this population's overall health. Interestingly, individuals with IBS also have a substantially increased risk of osteoporosis (Wongtrakul, Charoenngam, & Ungprasert, 2020), so vitamin D is not just potentially important for their gut health but is also important for their bone health. Hence, early intervention to prevent the development of osteoporosis including adequate intake of vitamin D and calcium, weight-bearing exercise, and possibly early screening for osteoporosis may also be beneficial to patients with IBS.

For these reasons, nurses can help educate patients about the importance of vitamin D for individuals with IBS. Vitamin D deficiency is a major health problem that is highly prevalent throughout the world, including countries in both the northern and southern latitudes, affecting almost 50% of the population across all ethnicities and age groups (Nair & Maseeh, 2012; Ramasamy, 2020). Deficient and insufficient vitamin D in the general population are mostly attributed to lifestyle and comorbidities leading to decreased sun exposure, and insufficient dietary intake but may be due to decreased endogenous synthesis, increased hepatic catabolism secondary to medications, and in some cases, end organ resistance (Sizar, Khare, Goyal, Bansal, & Givler, 2020). Sun exposure is often affected by an individual's outdoor activities, sunscreen use, skin pigmentation, and clothing. Latitude and seasonal changes also have a significant impact on the amount of opportunity an individual may have for vitamin D synthesis from the sun. Individuals with IBS who are vitamin D deficient/insufficient may be experiencing one or more of these causes with the most common causes likely being a combination of lifestyle choices (limited sunlight) and restrictive diets that limited dairy, as well as other micronutrients.

Although there is a high prevalence of vitamin D deficiency in individuals with IBS, not all are deficient or insufficient. Therefore, testing an individual's serum vitamin D level is recommended before considering supplementation as a therapeutic modality. Baseline 25(OH)D, BMI, type of vitamin taken (D_2 or D_3), comorbidities, medications, and genetics all affect a person's response to supplementation, so obtaining a baseline measurement and testing again after starting supplementation is appropriate. The best assessment of vitamin D status is to measure the serum 25(OH)D. The recommendations for vitamin D serum levels are based on musculoskeletal health outcomes and vary depending on the guideline utilized (Table 3).

As previously noted, dietary sources of vitamin D are limited but worth encouraging (Table 1). Another vitamin D source important to discuss with patients is sunlight, which must be utilized with caution (ultraviolet light). During sun exposure, ultraviolet B transforms 7-dehydrocholesterol to pre–vitamin D_3 (Ramasamy, 2020). Webb et al. (2018a, 2018b) suggested 9 minutes of daily sun exposure for Caucasians and 25 minutes for individuals with darker skin at the latitude of the United Kingdom in March through September. Whereas others indicated that in the summertime, Caucasians living in 42° latitude (e.g., Washington State and Minnesota) could expose their arms and legs to sunlight for 5–15 minutes between 10 A.M. and 3 P.M., 2–3 times per week to adequately prevent vitamin D deficiency in March through October (Holick et al., 2011). Nevertheless, skin pigmentation, sunscreen, time of day, season, and latitude can all affect vitamin D synthesis, and the literature is

TABLE 3. Recommended Vitamin D Serum Levels (Ramasamy, 2020)

Vitamin D	ESPG	IOM	SACN	EFSA
Deficiency	<50 nmol/L (<20 ng/ml)	Severe <12.5 nmol/L (<5 ng/ml) Moderate <12.5–29 nmol/L (<5–11.6 ng/ml) Mild 30–49 nmol/L (<12–19.6 ng/ml)	<25 nmol/L (<10 ng/ml)	
Insufficiency	52.5–72.5 nmol/L (<21–29 ng/ml)			
Sufficient	75–250 nmol/L (30–100 ng/ml)	≥50 nmol/L (≥20 ng/ml)		≥50 nmol/L (≥20 ng/ml)

Note. EFSA = European Food Safety Authority; ESPG = Endocrine Society Practice Guidelines; IOM = Institute of Medicine; SACN = Scientific Advisory Committee on Nutrition.

not consistent in recommendations for sun exposure (Ramasamy, 2020).

Furthermore, the increased risk for skin cancer from ultraviolet radiation must be considered. Proper use of sunscreen and good sun protection practices designed to prevent skin cancer can lead to decreases in vitamin D synthesis. Therefore, oral supplementation may be a safer way of increasing vitamin D levels. Supplementation, if needed, is best utilizing vitamin D_3 (not D_2).

The recommendations for daily allowances of vitamin D from a combination of food and supplements are currently based on musculoskeletal health outcomes and have not been established specifically for gastrointestinal conditions. They also vary depending on the guideline utilized (Table 4). Currently, there are no specific recommendations for individuals with IBS, but it would be reasonable to monitor your patients' vitamin D serum level to determine whether their supplementation is adequate to achieve sufficiency of vitamin D over time.

Future Directions

Because of the role of vitamin D in many of the processes associated with IBS, we suggest that its deficiency may negatively impact the ability of some IBS interventions (e.g., probiotics, antibiotics, and fecal microbiota transfer) to successfully modulate the microbiome enough to have a long-term effect on IBS. There is a lack of well-designed clinical trials examining the effect of vitamin D status on gut microbiota and symptoms in individuals with IBS. If vitamin D status in individuals with IBS does in fact impact the microbiome and long-term benefits of treatments such as probiotics and fecal microbiota transfer, then further research examining vitamin D status and microbiome composition may help in the development of more effective treatment protocols. Nurses have a great opportunity to develop and participate in well-designed therapeutic studies to explore whether enhanced vitamin D status will support a healthy microbiome in individuals with IBS and ultimately help treat the condition more effectively.

Conclusion

Irritable bowel syndrome is a highly prevalent disorder of the gut-brain interaction characterized by chronic, recurring abdominal pain and altered bowel habits that pose a great burden on individuals and the healthcare system. Its underlying pathophysiology is still

TABLE 4. Vitamin D3 Dietary Intake Recommended in Various Guidelines (Ramasamy, 2020)

ESPG Age (Dose/Day)	IOM Age (Dose/Day)	SACN Age (Dose/Day)	EFSA Age (Dose/Day)
0–1 year (400–1,000 IU)	0–1 year (400 IU)	0–1 year (340–400 IU)	7–11 months (400 IU)
2–8 years (600–1,000 IU)	1–70 years (400–600 IU)	>1 year (400 IU)	1 to >18 years (400–600 IU)
9–18 years (600–1,000 IU)			
19–70 years (1,500–2,000 IU)	Pregnancy and lactation (400–600 IU)	Pregnancy and lactation (400 IU)	Pregnancy and lactation (600 IU)

Note. EFSA = European Food Safety Authority; ESPG = Endocrine Society Practice Guidelines; IOM = Institute of Medicine; SACN = Scientific Advisory Committee on Nutrition.

uncertain, but research indicates that IBS, at least in part, is related to microbiome disturbances. Studies have shown that the gut microbiota of individuals with IBS differs from healthy controls and may have less biodiversity. Probiotics, antibiotics, and fecal microbiota transfer can manipulate the host microbiome and may lead to gut health benefits for individuals with IBS. However, IBS-specific microbiota patterns have not yet been identified. In addition, the benefits of treatments aimed at modulating the microbiome do not consistently persist over time.

Vitamin D status has been identified as an important factor in gut homeostasis through regulatory mechanisms, immune modulation, epithelial barrier function, and influence on gut microbiota. For this reason, it may have a role in the success and longevity of microbiome-modulating treatments, and therefore cosupplementation of vitamin D with other treatments, such as probiotics, may be of value, but uncertainties remain and deserve further research. In the meantime, nurses can support patient awareness of the studies indicating that vitamin D deficiency is common in IBS and that individuals with IBS are at an increased risk for osteoporosis. Therefore, vitamin D testing and treatment of any identified vitamin D deficiency/insufficiency are reasonable steps for them to consider for optimizing their health. ✪

REFERENCES

Abbasnezhad, A., Amani, R., Hajiani, E., Alavinejad, P., Cheraghian, B., & Ghadiri, A. (2016). Effect of vitamin D on gastrointestinal symptoms and health-related quality of life in irritable bowel syndrome patients: A randomized double-blind clinical trial. *Neurogastroenterology and Motility*, *28*(10), 1533–1544. doi:10.1111/nmo.12851

Abbasnezhad, A., Amani, R., Hasanvand, A., Yousefi Rad, E., Alipour, M., Saboori, S., & Choghakhori, R. (2019). Association of serum vitamin D concentration with clinical symptoms and quality of life in patients with irritable bowel syndrome. *Journal of the American College of Nutrition*, *38*(4), 327–333. doi:10.1080/07315724.2018.1510349

Abboud, M., Rizk, R., AlAnouti, F., Papandreou, D., Haidar, S., & Mahboub, N. (2020). The health effects of vitamin D and probiotic co-supplementation: A systematic review of randomized controlled trials. *Nutrients*, *13*(1), 111. doi:10.3390/nu13010111

Aranow, C. (2011). Vitamin D and the immune system. *Journal of Investigative Medicine*, *59*(6), 881–886. doi:10.2310/JIM.0b013e31821b8755

Bakke, D., Chatterjee, I., Agrawal, A., Dai, Y., & Sun, J. (2018). Regulation of microbiota by vitamin d receptor: A nuclear weapon in metabolic diseases. *Nucl Receptor Research*, *5*, 101377. doi:10.11131/2018/101377

Bashir, M., Prietl, B., Tauschmann, M., Mautner, S. I., Kump, P. K., Treiber, G., … Pieber, T. R. (2016). Effects of high doses of vitamin D3 on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract. *European Journal of Nutrition*, *55*(4), 1479–1489. doi:10.1007/s00394-015-0966-2

Battistini, C., Ballan, R., Herkenhoff, M. E., Saad, S. M. I., & Sun, J. (2020). Vitamin D modulates intestinal microbiota in inflammatory bowel diseases. *International Journal of Molecular Sciences*, *22*(1), 362. doi:10.3390/ijms22010362

Bikle, D. D. (2007). Vitamin D insufficiency/deficiency in gastrointestinal disorders. *Journal of Bone and Mineral Research*, *22*(Suppl. 2), V50–V54. doi:10.1359/jbmr.07s208

Canavan, C., West, J., & Card, T. (2014). Review article: The economic impact of the irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics*, *40*(9), 1023–1034. doi:10.1111/apt.12938

Cantorna, M. T., Rogers, C. J., & Arora, J. (2019). Aligning the paradoxical role of vitamin D in gastrointestinal immunity. *Trends in Endocrinology and Metabolism*, *30*(7), 459–466. doi:10.1016/j.tem.2019.04.005

Carroll, I. M., Ringel-Kulka, T., Siddle, J. P., & Ringel, Y. (2012). Alterations in composition and diversity of the intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. *Neurogastroenterology and Motility*, *24*(6), 521–530, e248. doi:10.1111/j.1365-2982.2012.01891.x

Charoenngam, N., Shirvani, A., Kalajian, T. A., Song, A., & Holick, M. F. (2020). The effect of various doses of oral vitamin D(3) supplementation on gut microbiota in healthy adults: A randomized, double-blinded, dose-response Study. *Anticancer Research*, *40*(1), 551–556. doi:10.21873/anticanres.13984

Chong, P. P., Chin, V. K., Looi, C. Y., Wong, W. F., Madhavan, P., & Yong, V. C. (2019). The microbiome and irritable bowel syndrome—a review on the pathophysiology, current research and future therapy. *Frontiers in Microbiology*, *10*, 1136. doi:10.3389/fmicb.2019.01136

Del Pinto, R., Pietropaoli, D., Chandar, A. K., Ferri, C., & Cominelli, F. (2015). Association between inflammatory bowel disease and vitamin D deficiency: A systematic review and meta-analysis. *Inflammatory Bowel Diseases*, *21*(11), 2708–2717. doi:10.1097/mib.0000000000000546

Di Rosa, M., Malaguarnera, M., Nicoletti, F., & Malaguarnera, L. (2011). Vitamin D3: A helpful immuno-modulator. *Immunology*, *134*(2), 123–139. doi:10.1111/j.1365-2567.2011.03482.x

Dimitrov, V., & White, J. H. (2016). Species-specific regulation of innate immunity by vitamin D signaling. *Journal of Steroid Biochemistry and Molecular Biology*, *164*, 246–253. doi:10.1016/j.jsbmb.2015.09.016

Distrutti, E., Monaldi, L., Ricci, P., & Fiorucci, S. (2016). Gut microbiota role in irritable bowel syndrome: New therapeutic strategies. *World Journal of Gastroenterology*, *22*(7), 2219–2241. doi:10.3748/wjg.v22.i7.2219

Drossman, D. A. (2016). Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology*, *150*, 1262–1279. doi:10.1053/j.gastro.2016.02.032

Drossman, D. A. (2017). Improving the treatment of irritable bowel syndrome with the Rome IV multidimensional clinical profile. *Gastroenterol Hepatol (N Y)*, *13*(11), 694–696.

El Amrousy, D., Hassan, S., El Ashry, H., Yousef, M., & Hodeib, H. (2018). Vitamin D supplementation in adolescents with irritable bowel syndrome: Is it useful? A randomized controlled trial. *Saudi Journal of Gastroenterology*, *24*(2), 109–114. doi:10.4103/sjg.SJG_438_17

Fakhoury, H. M. A., Kvietys, P. R., AlKattan, W., Anouti, F. A., Elahi, M. A., Karras, S. N., & Grant, W. B. (2020). Vitamin D and intestinal homeostasis: Barrier, microbiota, and immune modulation. *Journal of Steroid Biochemistry and Molecular Biology*, *200*, 105663. doi:10.1016/j.jsbmb.2020.105663

Ghaly, S., Hart, P. H., & Lawrance, I. C. (2019). Inflammatory bowel diseases: interrelationships between dietary vitamin D, exposure to UV radiation and the fecal microbiome. *Expert Review of Gastroenterology & Hepatology*, *13*(11), 1039–1048. doi:10.1080/17474124.2019.1685874

Giamarellos-Bourboulis, E., Tang, J., Pyleris, E., Pistiki, A., Barbatzas, C., Brown, J., … Pimentel, M. (2015). Molecular assessment of differences in the duodenal microbiome in subjects with irritable bowel syndrome. *Scandinavian Journal of Gastroenterology*, *50*(9), 1076–1087. doi:10.3109/00365521.2015.1027261

Gubatan, J., Chou, N. D., Nielsen, O. H., & Moss, A. C. (2019). Systematic review with meta-analysis: Association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics*, *50*(11–12), 1146–1158. doi:10.1111/apt.15506

Harris, L. A., & Baffy, N. (2017). Modulation of the gut microbiota: A focus on treatments for irritable bowel syndrome. *Postgraduate Medicine*, *129*(8), 872–888. doi:10.1080/00325481.2017.1383819

He, L., Liu, T., Shi, Y., Tian, F., Hu, H., Deb, D. K., … Li, Y. C. (2018). Gut epithelial vitamin D receptor regulates microbiota-dependent mucosal inflammation by suppressing intestinal epithelial cell apoptosis. *Endocrinology*, *159*(2), 967–979. doi:10.1210/en.2017-00748

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., … Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, *96*(7), 1911–1930. doi:10.1210/jc.2011-0385

Hollister, E. B., Cain, K. C., Shulman, R. J., Jarrett, M. E., Burr, R. L., Ko, C., … Heitkemper, M. M. (2020). Relationships of microbiome markers with extraintestinal, psychological distress and gastrointestinal symptoms, and quality of life in women with irritable bowel syndrome. *Journal of Clinical Gastroenterology*, *54*(2), 175–183. doi:10.1097/mcg.0000000000001107

Holtmann, G., Shah, A., & Morrison, M. (2017). Pathophysiology of functional gastrointestinal disorders: A holistic overview. *Digestive Diseases*, *35*(Suppl. 1), 5–13. doi:10.1159/000485409

Jalili, M., Hekmatdoost, A., Vahedi, H., Poustchi, H., Khademi, B., Saadi, M., … Janani, L. (2016). Co-administration of soy isoflavones and vitamin D in management of irritable bowel disease. *PLoS One*, *11*(8), e0158545. doi:10.1371/journal.pone.0158545

Jeffery, I. B., O'Toole, P. W., Öhman, L., Claesson, M. J., Deane, J., Quigley, E. M., & Simrén, M. (2012). An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*, *61*(7), 997–1006. doi:10.1136/gutjnl-2011-301501

Jones, M. L., Martoni, C. J., & Prakash, S. (2013). Oral supplementation with probiotic L. reuteri NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: A post hoc analysis of a randomized controlled trial. *Journal of Clinical Endocrinology & Metabolism*, *98*(7), 2944–2951. doi:10.1210/jc.2012-4262

Kerckhoffs, A. P., Samsom, M., van der Rest, M. E., de Vogel, J., Knol, J., Ben-Amor, K., & Akkermans, L. M. (2009). Lower Bifidobacteria counts in both duodenal mucosa-associated and fecal microbiota in irritable bowel syndrome patients. *World Journal of Gastroenterology*, *15*(23), 2887–2892. doi:10.3748/wjg.15.2887

Khalighi Sikaroudi, M., Mokhtare, M., Shidfar, F., Janani, L., Faghihi Kashani, A., Masoodi, M., … Shidfar, S. (2020). Effects of vitamin D3 supplementation on clinical symptoms, quality of life, serum serotonin (5-hydroxytryptamine), 5-hydroxyindole acetic acid, and ratio of 5-HIAA/5-HT in patients with diarrhea-predominant irritable bowel syndrome: A randomized clinical trial. *EXCLI Journal*, *19*, 652–667. doi:10.17179/excli2020-2247

Khayyat, Y., & Attar, S. (2015). Vitamin D deficiency in patients with irritable bowel syndrome: Does it exist? *Oman Medical Journal*, *30*(2), 115–118. doi:10.5001/omj.2015.25

Klem, F., Wadhwa, A., Prokop, L. J., Sundt, W. J., Farrugia, G., Camilleri, M., … Grover, M. (2017). Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: A systematic review and meta-analysis. *Gastroenterology*, *152*(5), 1042–1054. e1041. doi:10.1053/j.gastro.2016.12.039

Kojecký, V., Matouš, J., Zádorová, Z., Gřiva, M., Kianička, B., & Uher, M. (2019). Vitamin D supplementation dose needs to be higher in patients with inflammatory bowel disease: Interventional study. *Vnitrni Lekarstvi*, *65*(7–8), 470–474.

Kong, J., Zhang, Z., Musch, M. W., Ning, G., Sun, J., Hart, J., … Li, Y. C. (2008). Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *American Journal of Physiology Gastrointestinal and Liver Physiology*, *294*(1), G208–G216. doi:10.1152/ajpgi.00398.2007

LeBlanc, J. G., Milani, C., de Giori, G. S., Sesma, F., van Sinderen, D., & Ventura, M. (2013). Bacteria as vitamin suppliers to their host: A gut microbiota perspective. *Current Opinion in Biotechnology*, *24*(2), 160–168. doi:10.1016/j.copbio.2012.08.005

Li, J., Chen, N., Wang, D., Zhang, J., & Gong, X. (2018). Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. *Medicine*, *97*(46), e12662. doi:10.1097/md.0000000000012662

Li, Y. C., Chen, Y., & Du, J. (2015). Critical roles of intestinal epithelial vitamin D receptor signaling in controlling gut mucosal inflammation. *Journal of Steroid Biochemistry and Molecular Biology*, *148*, 179–183. doi:10.1016/j.jsbmb.2015.01.011

Lim, H. S., Kim, S. K., & Hong, S. J. (2018). Food elimination diet and nutritional deficiency in patients with inflammatory bowel disease. *Clinical Nutrition Research*, *7*(1), 48–55. doi:10.7762/cnr.2018.7.1.48

Lovell, R. M., & Ford, A. C. (2012). Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clinical Gastroenterology and Hepatology*, *10*(7), 712–721. e714. doi:10.1016/j.cgh.2012.02.029

Luthold, R. V., Fernandes, G. R., Franco-de-Moraes, A. C., Folchetti, L. G., & Ferreira, S. R. (2017). Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals. *Metabolism*, *69*, 76–86. doi:10.1016/j.metabol.2017.01.007

Maguire, L. H., Song, M., Strate, L. E., Giovannucci, E. L., & Chan, A. T. (2013). Higher serum levels of vitamin D are associated with a reduced risk of diverticulitis. *Clinical Gastroenterology and Hepatology*, *11*(12), 1631–1635. doi:10.1016/j.cgh.2013.07.035

Myint, A., Sauk, J. S., & Limketkai, B. N. (2020). The role of vitamin D in inflammatory bowel disease: A guide for clinical

practice. *Expert Review of Gastroenterology & Hepatology*, *14*(7), 539–552. doi:10.1080/17474124.2020.1775580

Naderpoor, N., Mousa, A., Fernanda Gomez Arango, L., Barrett, H. L., Dekker Nitert, M., & de Courten, B. (2019). Effect of Vitamin D supplementation on faecal microbiota: A randomised clinical trial. *Nutrients*, *11*(12), 2888. doi:10.3390/nu11122888

Nair, R., & Maseeh, A. (2012). Vitamin D: The "sunshine" vitamin. *Journal of Pharmacology & Pharmacotherapeutics*, *3*(2), 118–126. doi:10.4103/0976-500x.95506

Nwosu, B. U., Maranda, L., & Candela, N. (2017). Vitamin D status in pediatric irritable bowel syndrome. *PLoS One*, *12*(2), e0172183. doi:10.1371/journal.pone.0172183

Protiva, P., Pendyala, S., Nelson, C., Augenlicht, L. H., Lipkin, M., & Holt, P. R. (2016). Calcium and 1,25-dihydroxyvitamin D3 modulate genes of immune and inflammatory pathways in the human colon: A human crossover trial. *American Journal of Clinical Nutrition*, *103*(5), 1224–1231. doi:10.3945/ajcn.114.105304

Ramasamy, I. (2020). Vitamin D metabolism and guidelines for vitamin D supplementation. *Clinical of Biochemistry Reviews*, *41*(3), 103–126. doi:10.33176/aacb-20-00006

Santos-Antunes, J., Nunes, A. C., Lopes, S., & Macedo, G. (2016). The relevance of vitamin D and antinuclear antibodies in patients with inflammatory bowel disease under anti-TNF treatment: A prospective study. *Inflammatory Bowel Diseases*, *22*(5), 1101–1106. doi:10.1097/mib.0000000000000697

Shang, M., & Sun, J. (2017). Vitamin D/VDR, probiotics, and gastrointestinal diseases. *Current Medicinal Chemistry*, *24*(9), 876–887. doi:10.2174/0929867323666161202150008

Singh, P., Rawat, A., Alwakeel, M., Sharif, E., & Al Khodor, S. (2020). The potential role of vitamin D supplementation as a gut microbiota modifier in healthy individuals. *Scientific Reports*, *10*(1), 21641. doi:10.1038/s41598-020-77806-4

Sizar, O., Khare, S., Goyal, A., Bansal, P., & Givler, A. (2020). Vitamin D deficiency. In *StatPearls*. Treasure Island, FL: StatPearls Publishing.

Sun, J. (2018). Dietary vitamin D, vitamin D receptor, and microbiome. *Current Opinion in Clinical Nutrition and Metabolic Care*, *21*(6), 471–474. doi:10.1097/mco.0000000000000516

Tabatabaeizadeh, S. A., Tafazoli, N., Ferns, G. A., Avan, A., & Ghayour-Mobarhan, M. (2018). Vitamin D, the gut microbiome and inflammatory bowel disease. *Journal of Research in Medical Sciences*, *23*, 75. doi:10.4103/jrms.JRMS_606_17

Tan, B., Li, P., Lv, H., Yang, H., Li, Y., Li, J., … Qian, J. M. (2018). Treatment of vitamin D deficiency in Chinese inflammatory bowel disease patients: A prospective, randomized, open-label, pilot study. *Journal of Digestive Diseases*, *19*(4), 215–224. doi:10.1111/1751-2980.12590

Tana, C., Umesaki, Y., Imaoka, A., Handa, T., Kanazawa, M., & Fukudo, S. (2010). Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. *Neurogastroenterology & Motility*, *22*(5), 512–519, e114–e515. doi:10.1111/j.1365-2982.2009.01427.x

Tazzyman, S., Richards, N., Trueman, A. R., Evans, A. L., Grant, V. A., Garaiova, I., … Corfe, B. M. (2015). Vitamin D associates with improved quality of life in participants with irritable bowel syndrome: Outcomes from a pilot trial. *BMJ Open Gastroenterology*, *2*(1), e000052. doi:10.1136/bmjgast-2015-000052

USDA. (2020). *Food sources of vitamin D. Dietary Guidelines for Americans*. Retrieved February 24, 2021, from https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials/food-sources-select-nutrients/food-sources

Waterhouse, M., Hope, B., Krause, L., Morrison, M., Protani, M. M., Zakrzewski, M., & Neale, R. E. (2019). Vitamin D and the gut microbiome: A systematic review of in vivo studies. *European Journal of Nutrition*, *58*(7), 2895–2910. doi:10.1007/s00394-018-1842-7

Webb, A. R., Kazantzidis, A., Kift, R. C., Farrar, M. D., Wilkinson, J., & Rhodes, L. E. (2018a). Colour counts: Sunlight and skin type as drivers of vitamin D deficiency at UK latitudes. *Nutrients*, *10*(4), 457. doi:10.3390/nu10040457

Webb, A. R., Kazantzidis, A., Kift, R. C., Farrar, M. D., Wilkinson, J., & Rhodes, L. E. (2018b). Meeting vitamin D requirements in White Caucasians at UK latitudes: Providing a choice. *Nutrients*, *10*(4), 497. doi:10.3390/nu10040497

Winter, R. W., Collins, E., Cao, B., Carrellas, M., Crowell, A. M., & Korzenik, J. R. (2017). Higher 25-hydroxyvitamin D levels are associated with greater odds of remission with anti-tumour necrosis factor-α medications among patients with inflammatory bowel diseases. *Alimentary Pharmacology and Therapeutics*, *45*(5), 653–659. doi:10.1111/apt.13936

Wongtrakul, W., Charoenngam, N., & Ungprasert, P. (2020). The association between irritable bowel syndrome and osteoporosis: A systematic review and meta-analysis. *Osteoporosis International*, *31*(6), 1049–1057. doi:10.1007/s00198-020-05318-y

Wu, S., Liao, A. P., Xia, Y., Li, Y. C., Li, J. D., Sartor, R. B., & Sun, J. (2010). Vitamin D receptor negatively regulates bacterial-stimulated NF-kappaB activity in intestine. *American Journal of Pathology*, *177*(2), 686–697. doi:10.2353/ajpath.2010.090998

Yamamoto, E. A., & Jørgensen, T. N. (2019). Relationships between vitamin D, gut microbiome, and systemic autoimmunity. *Frontiers in Immunology*, *10*, 3141. doi:10.3389/fimmu.2019.03141

Yang, T., Santisteban, M. M., Rodriguez, V., Li, E., Ahmari, N., Carvajal, J. M., … Mohamadzadeh, M. (2015). Gut dysbiosis is linked to hypertension. *Hypertension*, *65*(6), 1331–1340. doi:10.1161/hypertensionaha.115.05315

Yuk, J. M., Shin, D. M., Lee, H. M., Yang, C. S., Jin, H. S., Kim, K. K., … Jo, E. K. (2009). Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. *Cell Host & Microbe*, *6*(3), 231–243. doi:10.1016/j.chom.2009.08.004

Zator, Z. A., Cantu, S. M., Konijeti, G. G., Nguyen, D. D., Sauk, J., Yajnik, V., & Ananthakrishnan, A. N. (2014). Pretreatment 25-hydroxyvitamin D levels and durability of anti-tumor necrosis factor-α therapy in inflammatory bowel diseases. *JPEN Journal of Parenteral and Enteral Nutrition*, *38*(3), 385–391. doi:10.1177/0148607113504002

The test for this nursing continuing professional development activity can be taken at www.NursingCenter.com/CE/gastro