Vitamins in Inflammatory Bowel Disease

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The pathogenesis of inflammatory bowel disease (IBD) highlights the role of mucosal immunology and changes in the gut microbiome triggered by genetic and environmental factors including diet regiments, as suggested by many nutritional studies. Along with medications usually used for IBD treatment, therapeutic strategies also include the supplementation of micronutrients such as vitamin D, folic acid, iron, and zinc.

IBD genetics vitamin D B9

1. Introduction

The pathogenesis of inflammatory bowel disease (IBD) highlights the role of mucosal immunology and changes in the gut microbiome triggered by genetic and environmental factors including diet regiments, as suggested by many nutritional studies [1][2][3][4]. Oxidative damage that occurs in CD and UC is a result of an altered balance between free radical production with antioxidant depletion and micronutrients, leading to antioxidant repletion [1][2][3][4]. The presence or absence of anti-inflammatory agents such as antioxidants obtained through dietary intake or supplementation can impact the course of IBD. The intestinal tissue damage and altered gut microbiota caused by oxidative stress are significantly impacted by the presence of tissue repair mediators. Modulating the intestinal microbiota remains an attractive therapeutic potential for IBD [1][2][3][4]. Changes in dietary habits were also found to be strongly associated with a determined increased risk of autoimmune disease in a pediatric population [5][6]. So far, dietary constituents have been considered precipitants or promoters of complex interactions in IBD pathology, while nutritional deficiency with imbalances of specific micronutrients has been associated with the course of the disease [1][2]. Nevertheless, the role of modifiable environmental and behavioral factors such as diet remains poorly understood.

The majority of IBD patients show an interest in the active management of their disease, especially through dietary modifications [7]. Specifically, long-term dieting has shown the most significant effect in shaping the intestinal microbiome [8]. Therapeutic strategies in IBD, along with medications, encompass nutritional interventions including not only the elimination of potential food triggers but also the improvement of the nutritional status of patients [1][2][9]. The supplementation of micronutrients and macronutrients is important in everyday clinical practice in reducing the primary or secondary symptoms of disease [2]. Nevertheless, overuse or treatment with doses far exceeding the recommended daily allowances can be harmful and lead to adverse effects on the course of IBD. Especially during the coronavirus (COVID-19) pandemic, the frequent use of over-the-counter supplements among IBD patients has contributed to inadequate and uncontrolled strategies in therapy management.

2. Role of Vitamins in Inflammatory Bowel Disease

2.1. Vitamin D

According to numerous investigations, the deficiency of vitamin D has been highlighted as a key factor in the pathogenesis of IBD (**Table 1**) [10][11]. Vitamin D is a liposoluble vitamin, and its hormonal form of 1,25-dihydroxy vitamin D3 [1,25(OH)2D3], also called calcitriol, is important for various pathways of the immune system mediated via nuclear vitamin D receptor (VDR) in immune cells such as T and B lymphocytes, monocytes and macrophages. Vitamin D has a role in immune cell differentiation, the modulation of the gut microbiota, gene transcription, and barrier integrity [11]. A reduction in the serum levels of vitamin D is associated with an increased risk for infection (**Table 1**) [10][11]. The role of vitamin D includes the support of intestinal epithelial junctions and the upregulation of junction proteins including claudins, ZO-1, and occludins. The disruption of the mucosal barrier was noted in an IBD investigation in polarized epithelial Caco-2bbe cells grown in a medium with or without vitamin D and challenged with adherent invasive *E. coli* strain (AIEC). The investigation showed that Caco-2bbe cells incubated with 1,25(OH)2D3 were protected against AIEC-induced disruption. Additionally, vitamin D-deficient mice with DSS-induced colitis showed significant increases in the quantities of *Bacteroidetes* and were more susceptible to AIEC colonization. According to previous studies, vitamin D contributes to the homeostasis of the intestinal barrier function and protection against adherent invasive *E. coli* [12]. Additionally, it has been suggested that patients with IBD are at an increased risk of *Clostridium difficile* infection. Vitamin D has a prophylactic role against infection, influencing the production of antimicrobial compounds such as cathelicidins and modulating the microbiome [13]. VDR regulates the biological action of 1,25(OH)2D3 and has a role in the genetic, immune, environmental and microbial aspects of IBD. Dionne at al. study indicated that 1,25(OH)2D3 in CD patients significantly decreases the proinflammatory activity of M1-type macrophage but does not provide a reduction in the anti-inflammatory actions of M2-type macrophages. The level of anti-inflammatory cytokine IL-10 was not affected in the investigation [14]. The deficiency of vitamin D is also correlated with disease activity in IBD patients, so administration targeting a concentration of 30 ng/mL could potentially reduce disease activity [11]. Even though reports have shown lower vitamin D levels in IBD patients compared with the healthy population, it is not clear yet if the vitamin D deficiency is a consequence of the disease itself or if it has a role in disease pathogenesis. A study that followed subjects in two time points before (up to 8 years) and one time point after IBD diagnosis showed that the vitamin D level was not altered in IBD patients prior to disease onset compared with matched controls, but it was reduced after the disease was established [15].

Table 1. Frequent deficiencies of micronutrients in IBD.

Micronutrient	Signs of Deficiencies	Risk Factor for Deficiencies in IBD	Laboratory Values of Deficiencies	References
Vitamin D	Hypocalcemia, osteomalacia, osteoporosis.	Ileal localization of CD; resection of ileum > 20 cm; significant gastric resection; SIBO; diet.	25(OH)D < 20 ng/mL.	[11][15]

Micronutrient	Signs of Deficiencies	Risk Factor for Deficiencies in IBD	Laboratory Values of Deficiencies	References
Folate (B9)	Megaloblastic, macrocytic anemia; diarrhea; nervous instability; dementia.	Restrictive diet in IBD; GI resections; therapy of Sulfasalazine and methotrexate; SIBO.	Low serum levels of folate; elevated MCV and homocysteine.	[16][17][18]
Vitamin B12	Megaloblastic, macrocytic anemia; tiredness. mouth ulcers; muscle weakness; disturbed vision; psychological problems.	More frequent in CD than in UC patients; ileal resection > 30 cm; gastric resection; SIBO.	Low serum levels of vitamin B12.	[11][19]
Vitamin A	Dry eye and skin; night blindness; infertility; delayed growth; throat and chest infections; poor wound healing; acne.	CD patient with repeated small bowel resections.	Low serum levels of vitamin A	[20][21][22]
Iron	Microcytic, hypochromic anemia; tachycardia; fatigue; sleepiness; headache; anorexia; nausea; pallor.	GI bleeding, more frequent in UC, achlorhydria, SIBO.	Low serum levels of iron, serum ferritin < 100 ng/mL, transferrin saturation < 20%, elevated transferrin receptor levels.	[10][23]
Zinc	Altered growth, hypogonadism, impaired night vision, anorexia, diarrhea alterations in taste and smell, alopecia, impaired wound healing.	CD fistulizing disease, PPI/H2 blockers, protein deficiency, malabsorptive disorders, diarrhea, restrictive diet.	Low plasma/serum zinc	[24][25]

SIBO—small intestinal bacterial overgrowth (SIBO); GI—gastrointestinal.

lating the release of antimicrobial peptides in the gut interaction pathways. Furthermore, beneficial microbial metabolites, including butyrate, stimulate VDR signaling [11]. Ananthakrishnan et al. showed that one third of IBD patients included in their study had a vitamin D deficiency and that its decreased levels correlated with colon cancer incidence in patients with IBD [26]. For the most common confounders of vitamin D deficiency have been indicated low intensity of sunlight and dis-ease duration and activity [26]. Further studies determined that 30 ng/mL of serum circulated vitamin D form, 25(OH)D3, can inhibit the secretion of proin-flammatory cytokines (IL-6 and TNF-α) induced by lipopolysaccharide (LPS) of the bacterial wall [27][28].

2.2. Vitamin D-Related Genetics

It has been demonstrated in numerous candidate gene approach and genome-wide association studies (GWAS) that vitamin D status is partly determined by genetic factors. Several genes and genetic variants located in or near those genes, such as *DHCR7*, *GC*, *CYP2R1*, *CYP24A1* and *VDR*, have been recognized as significant modulators of vitamin D level and bioavailability [29]. Indicated genes encode proteins/enzymes involved in vitamin D transport and metabolism, namely, *DHCR7* encodes enzymes expressed in the skin that are involved in cholecalciferol synthesis, *GC* encodes a vitamin D-binding protein that has a role in vitamin D precursor transport, *CYP2R1* is a 25-hydroxylase involved in vitamin D precursor activation, and a *CYP24A1* encodes 24-hydroxylase that

participates in the inactivation of vitamin D metabolites. Variants of *DHCR7* (rs12785878), *GC* (rs4588; rs7041), *CYP2R1* (rs10741657, rs1993116, and rs10766197) and *CYP24A1* (rs6013897) genes have been found to be associated with the serum level of 25-OHD [30][31], a form in which vitamin D is abundantly present in the circulation. The *VDR* gene encodes the vitamin D receptor, a transcription factor that regulates the expression of numerous genes after binding to the active form of vitamin D. Variants in this gene have been linked with the disease phenotype rather than with the level of the vitamin D.

It was demonstrated by Chip-seq that VDR-binding sites were significantly enriched near autoimmune-associated genes identified in GWAS, including the *PTPN2* gene linked to Crohn's disease [32]. Research on different experimental models of the inflamed gut showed that intestinal epithelial VDR regulates the IBD-associated autophagy gene *ATG16L1* and lysozyme expression, as well as gut microbial assemblage—all important for maintaining the intestinal homeostasis [33]. Numerous studies have evaluated the association between IBD occurrence and genetic variants in the *VDR* gene since this gene maps to the region on chromosome 12 shown to be linked to IBD. The results regarding the association between *VDR* and IBD have been inconsistent, probably due to underpowered studies, different prevalences of vitamin D deficiency, and genetic diversity between different ethnic groups [15][34][35][36][37][38][39][40].

The FokI variant (rs2228570), which introduces an alternative translation start site, and three silent genetic variants of BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236) in the *VDR* gene appear to be sporadically associated with IBD in diverse populations (**Table 2**). The association between the TaqI "t" (nucleotide C) allele and CD occurrence has been demonstrated in Caucasian populations [15][34][35][36]. Although the TaqI variant is a synonymous, "silent" variant located in the exon 9 of the *VDR* gene, it was shown that homozygous "tt" (genotype CC) carriers had significantly lower levels of the VDR protein in the PBMC of CD patients. The study also demonstrated that lower VDR levels were not associated with the changes in the mRNA expression nor with the production of the truncated protein [41]. In addition, CD carriers of the "tt" genotype exhibited a significantly higher risk (OR = 3.6) of having a B3-penetrating phenotype [41]. Regarding other variants, the results are not uniform; the FokI "f" (nucleotide T) variant was associated with CD in Iranian population [39] and with UC in Asian populations [36][40]; the presence of the BsmI "B" allele (nucleotide T) has been linked with an increased susceptibility to UC in Israeli Ashkenazi [37] and Han Chinese patients [38]; a meta-study indicated that carriers of the ApaI "AA" genotype (TT genotype) had an increased risk for CD regardless of population stratification [36]. Overall, these results highlight the importance of examining population genetics in assessing disease burden or defining strategies for precision medicine/nutrition.

Table 2. Genetic variants that are associated with micronutrient levels and are potentially relevant to IBD pathogenesis, comorbidities or treatment.

Micronutrient	Genetic Variant Common Name	Variant ID	Nucleotide Change	Effect Allele	Functionality of the Effect Allele	Association of Effect Allele with IBD	Studied Population(s)	References
Vitamin D	*VDR* FokI	rs2228570	T>G	T	Associated with higher transcriptional activity of VDR	Associated with CD and UC occurrence	Iranian, Asian	[36][39][40]
	VDR BsmI	rs1544410	G>T	T	Unclear	Increased susceptibility to UC	Israeli Ashkenazi, Han Chinese	[37][38]
	VDR ApaI	rs7975232	G>T	T	Unclear	Increased risk to CD	European, Asian	[36]
	VDR TaqI	rs731236	T>C	C	Associated with lower transcriptional activity of VDR	Associated with CD occurrence; increased risk for penetrating phenotype	Caucasian	[15][34][35][38][41]
Folate (B9)	*MTHFR* 677	rs1801133	C>T	T	Reduction in MTHFR enzyme activity that provides a bioactive form of vitamin B9	Possible elevated risk for IBD in carriers of TT genotype	Meta-analysis	[42][43]
	MTHFR 1298	rs1801131	A>C	C	Reduction in MTHFR enzyme activity that provides a bioactive form of vitamin B9	Greater risk of UC and IBD; more likely to experience side effects of methotrexate compared with patients with the wild-type genotype	Meta-analysis	[44][45]
Vitamin B12	*FUT2* W143X	rs601338	G>A	A	Associated with the ABO non-secretory phenotype and higher levels of B12	Susceptibility locus for CD	Caucasian	[46][47]
	FUT2 I129F	rs1047781	A>T	T	Associated with reduced ABO secretor	Association with CD	Asians	[48]

Micronutrient	Genetic Variant Common Name	Variant ID	Nucleotide Change	Effect Allele	Functionality of the Effect Allele	Association of Effect Allele with IBD	Studied Population(s)	References
					phenotype and higher B12 levels			
Vitamin A	*PNPLA3* I148M	rs738409	C>G	G	Associated with vitamin A levels and chronic liver diseases (NAFLD)	IBD carriers of the 148M allele have a higher risk of hepatic steatosis and higher biomarkers of liver damage	Two Italian cohorts	[49]
	CYP26B1 L264S	rs2241057	T>C	T	Linked to reduced vitamin A catabolism compared with the minor C allele	Higher frequency of TT carriers in CD compared with healthy controls	Swedish	[50]
Iron	*TMPRSS* 6736V	rs855791	T>C	C	Associated with lower iron levels	Not found to be associated with IBD in one Mendelian randomization study; potential contribution in predicting response to oral iron supplementation in celiac disease patients affected by iron deficiency anemia	European	[51][52]
	HFE C282Y	rs1800562	G>A	A	Associated with increased iron levels and severe form of hereditary haemochromatosis in European populations	Not found to be associated with IBD in one Mendelian randomization study; associated with iron deficiency anemia in celiac disease patients	European	[54][55] [30][31]
Zinc	*SLC39A8* A391T	rs13107325	G>A	A	Located in zinc transporter gene;	Associated with CD, disease location/behavior,	Netherlands	[53]

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the TaqI variant were associated with a better response to vitamin D supplementation [56].

2.3. Folate and Vitamin B12

Folate (vitamin B9) is a one-carbon moiety donor cofactor involved in nucleotide synthesis and methylation metabolic pathways. Due to an impaired methylation cycle, folate deficiency causes the accumulation of homocysteine, a metabolite associated with oxidative stress and inflammation (**Table 1**). Folate deficiency and elevated homocysteine levels are related to various pathological conditions such as anemia, low bone mineral density, thromboembolic events and birth defects [16].

Micronutrient	Genetic Variant Common Name	Variant ID	Nucleotide Change	Effect Allele	Functionality of the Effect Allele [58]	Association of Effect Allele with IBD [59]	Studied Population(s)	References
					might alter zinc metabolism	shifts in the composition of gut microbiota in both CD and healthy subjects		[60][61] [62]

on [17][57] e [17][18]. l cancer sk of IBD reduce complications of IBD [59][62].

Among IBD patients, around 20% have reduced folate levels and around 30% have increased homocysteine levels, which is much more common than in healthy people [17][63][64][65]. Bermejo et al. reported a higher prevalence of folate deficiency among CD patients (22%) compared with UC patients (4.3%), as well as an association with disease severity but not ileal resection (**Table 1**) [42]. Folate deficiency may be due to a reduced folate intake caused by the avoidance of folate-rich food, active inflammation that causes higher folate utilization, and the reduced absorption of folate due to intestinal damage, small bowel resection, or certain medications often prescribed to IBD patients (such as methotrexate and sulfasalazine) [66]. A recent meta-analysis showed that IBD patients consume an inadequate amount of cereals, legumes, fruit, vegetables, and dairy, which causes a lower intake of energy, calcium, fiber, and folate [67]. Vitamin B9 metabolites are absorbed in the proximal parts of the small bowel, so small bowel resection and severe intestinal inflammation related to IBD (which causes structural alterations of the bowel) reduce folate absorption [16]. To avoid folate deficiency, regular folate level monitoring and supplementation are recommended in IBD patients with a high risk of folate deficiency [68].

Vitamin B12 (cobalamin) and folic acid have significant roles in erythropoiesis and are often associated with anemia in patients with IBD [2][66]. Cobalamin and folate are crucial for nucleic acid synthesis and the process of erythropoiesis [2]. In the course of differentiation, erythroblasts need vitamin B12 and folic acid for proliferation, while their deficiency leads to macrocytosis, the apoptosis of erythroblasts, and anemia [2][66]. According to a previous investigation, the prevalence of vitamin B12 deficiency ranges between 6 and 38% [11][69]. Dietary vitamin B12 binds an intrinsic factor synthesized by the parietal cells in the duodenum for its further absorption in the terminal ileum. Hence, vitamin B12 deficiency is much more frequent in CD than in UC patients [19]. According to Battat et al., the crucial risk factor for vitamin B12 deficiency is an ileal resection of more than 30 cm [69]. Nevertheless, CD with ileal localization is not a risk factor for cobalamin deficiency [69]. A previous investigation determined that UC patients have a vitamin B12 deficiency similar to that of the general population [10]. However, UC patients with ileo-anal J-pouch could have vitamin B12 deficiency due to small bacterial overgrowth [11].

The recent guideline recommendations of the European Crohn's and Colitis Organization (ECCO) endorsed checking folate and vitamin B12 levels at a minimum of once per year or when macrocytosis is present, especially in IBD patients not receiving thiopurines [70]. Even though folate deficiency and elevated homocysteine levels have been linked to IBD-associated colon cancer, preclinical studies with folic acid supplementation contradict previous published data [2][71].

2.4. Folate-Related Genetics

Besides the adequate intake and absorption of vitamin B9, optimal levels of folate bioactive forms and homocysteine are maintained by folate cycle enzymes and transporters. The activity of those proteins show marked inter-individual differences that depend on genetics. One of the key polymorphic enzymes of the folate cycle is methylenetetrahydrofolate reductase (MTHFR), which provides methyltetrahidrofolate, a bioactive form of vitamin B9 involved in re-methylation pathways. There are two common missense variants of the *MTHFR* gene that cause the reduced activity of the enzyme: c.677C>T (p.Ala222Val) and c.1298A>C (p.Glu429Ala), which have been extensively studied in IBD and other diseases.

Variant c.677T (rs1801133) causes a 70% reduction in enzyme activity [72]. Each copy of the low-activity T allele causes a greater reduction in folate and a higher level of homocysteine [73][74]. Initial reports found an elevated risk of IBD in carriers of the TT genotype, but the majority of subsequent studies, including high-quality studies, did not corroborate this finding [44][67]; however, further research is needed.

Variant c.1298A>C (rs1801131) causes a 40% reduction in enzyme activity [43], and it is less studied than the c.677C>T variant. The lower-activity c.677T and c.1298C variants very rarely lie on the same chromosome. However, in compound heterozygotes of the c.677C>T and c.1298A>C variants, higher homocysteine levels are expected [74]. Interestingly, a recent meta-analysis associated the presence of the lower-activity C allele of the c.1298A>C variant with a greater risk of UC and IBD [44] (**Table 2**). The same meta-analysis did not show compelling evidence that the c.677C>T variant is associated with IBD development.

Methotrexate is one of the immune-modulating drugs often prescribed to IBD patients. By inhibiting some of the key involved enzymes, methotrexate disrupts the folate cycle. This results in immune-modulating effects, including higher rates of the apoptosis of the immune cells and elevated levels of adenosine, a natural anti-inflammatory agent [75]. In addition to its therapeutic effects, methotrexate could also exert toxic effects, most notably on GIT, liver and bone marrow [76]. These side effects might be more common in patients with *MTHFR* variants [45][77], though more research is needed, especially studies involving IBD patients. Variants in other pharmacogenes, such as those involved in folate and methotrexate transport (most notably *SLCO1B1* and *SLC19A1*), might also play a role in response to methotrexate therapy in pediatric IBD patients and rheumatoid arthritis patients [78][79]. Methotrexate side effects can be mitigated by folate supplementation, so identifying patients at risk, such as those who carry unfavorable genetic variants, could be of great benefit.

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