The Role of Vitamin D in the Pathogenesis and Management of Inflammatory Bowel Disease

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ABSTRACT

Vitamin D is widely recognized for its role in maintaining bone metabolism and health. However, recent studies indicated that vitamin D also played important role in regulating the immune system. Patients with inflammatory bowel disease (IBD) are commonly found to be vitamin D deficient; whether it serves as risk factor of IBD or as the consequence of disease activity is still debatable. Growing evidences showed that vitamin D supplementation in IBD patients with the target to achieve normal or optimal serum level might suppress the inflammatory process, reduce disease severity, maintain remission status, and improve quality of life.

Keywords: *inflammatory bowel disease, vitamin D, immunity*

ABSTRAK

Vitamin D telah lama dikenal dalam mengatur metabolisme dan kesehatan tulang. Akan tetapi, beberapa studi terakhir menunjukkan bahwa vitamin D juga memegang peranan penting dalam pengaturan sistem imun. Pasien dengan inflammatory bowel disease (IBD) sering ditemukan mengalami defisiensi vitamin D, akan tetapi hingga saat ini masih menjadi perdebatan apakah defisiensi vitamin D merupakan faktor resiko ataupun konsekuensi dari aktivitas penyakit IBD. Bukti terbaru menunjukkan bahwa pemberian suplementasi vitamin D pada pasien dengan IBD dengan target kadar serum normal atau optimal, dapat menekan proses inflamasi, menurunkan keparahan penyakit, mempertahankan status remisi, dan meningkatkan kualitas hidup.

Kata kunci: *inflammatory bowel disease, vitamin D, imunitas*

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the digestive tract IBD consist of two forms, which are ulcerative colitis (UC) and Crohn's disease (CD).[1] Prevalence data of IBD in Indonesia was mainly derived from hospital based endoscopy unit. The IBD prevalence in Indonesia ranged from 1.16% to 26.5%; while UC was 5.4-26.5% and CD was reported to be between 1-10.2%.[2] The pathogenesis of IBD is considered as multifactorial, which consists of interactions of genetic, immunity, environmental, and gut microbial factors.[1] Chronic inflammation of the intestinal due to IBD will lead to malabsorption of the nutrients which frequently present as unintentional weight loss and also another serious long term complication, which is colorectal cancer.[3] The mainstay treatment of IBD consist of anti-inflammatory drugs, such as: mesalamine, budenoside,

and newer biologic agents to maintain remission; also, in selected cases surgery may be required.[4]

Vitamin D is a lipid soluble vitamin with long standing history playing important role for bone metabolism and density.[5] Daily requirements of vitamin D intake are mainly derived from diet and photosynthesis which occurs in the skin.[6] Nowadays, vitamin D is recognized for its significant role in regulating immune function, inflammatory response, and possibly in some pathogenesis of autoimmune diseases.[7] Immune regulating effect of vitamin D is achieved by modulating the innate and adaptive immune system.[6]

Vitamin D deficiency is common in IBD patients. Theoretically, vitamin D deficiency may occur in IBD patients who undergo gut resection or as the consequence of malabsorption due to gut inflammation.[8] However, growing evidences indicate vitamin D deficiency may also serve as important environmental risk factor for IBD pathogenesis.[8] Recent studies showed that vitamin D supplementation until achieving normal or optimal level in IBD patients may alter the clinical course of the disease, and proposed to be considered as adjunctive therapy in management of IBD.[9] Therefore, in this review we examined the role of vitamin D and IBD based on latest evidences.

VITAMIN D SYNTHESIS AND METABOLISM

Vitamin D (calciferol) has two major forms based on their side chain structures, which are: vitamin D2 (ergocaliciferol) and vitamin D3 (cholecalciferol).[10] Vitamin D2 is mainly derived from diet containing plant sterol ergosterol or other fortified food. While, vitamin D3 has two sources which are from diet of animal source foods and synthesis of 7-dehydrocholesterol in the skin by ultraviolet (UV) radiation.[11] The recommended dietary allowances (RDAs) of vitamin D issue by United State Institute of Medicine (IOM) for people aged 1-70 years are 600 IU (15 mcg), and 800 IU (20 mcg) for people aged >70 years.[10] The main source of vitamin D for daily body requirement is from cutaneous photosynthesis; therefore, inadequate exposure to sunlight are linked with vitamin D deficiency.[6]

Vitamin D derived from diet and photosynthesis need to undergo several steps of metabolism and two enzymatic hydroxylations processes to be converted to 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) which is the biological active vitamin D form and commonly called as calcitriol. First, vitamin D will be transported in the blood by vitamin D binding protein (DBP) and hydroxylated in the liver by cythochrome P450 vitamin D 25 –hydroxylase (CYP2R1, CYP2D11, CYP2D25) to become 25-hydroxyvitamin D ($25(OH)D_3$). Second hydroxylation will occur in the kidneys by 25(OH)D-1-OHase (CYP27B1) resulting in calcitriol.[10-12] (Figure 1) Calcitriol ($1,25(OH)_2D$) acts as a ligand which binds to vitamin D receptor (VDR) and regulates the transcription and expression of targeted vitamin D genes.[13] Previously discovered targeted genes of VDR were mainly resolved around bone and calcium haemostatic metabolisms; recently VDR was also found to be an exerting target to other cells which regulates innate and adaptive immune system.[14] VDR can be found in skin, colon, intestinal enterocytes, pancreatic islets, renal distal tubules, hair follicles, and cells of the immune system.[15,16]

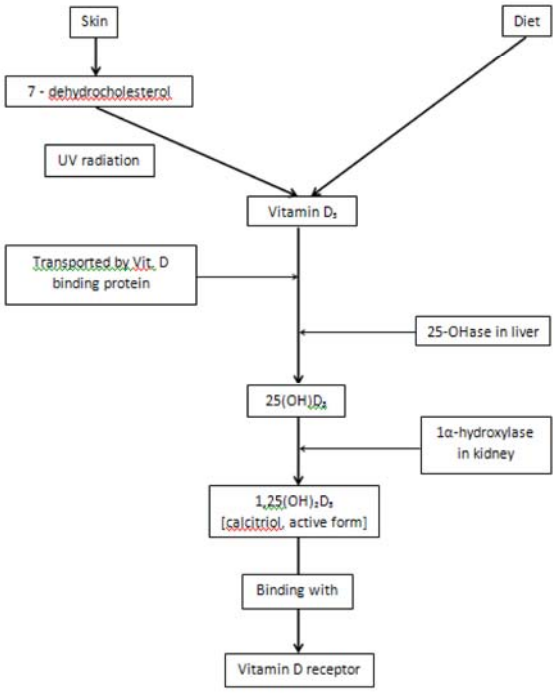

Figure 1. Vitamin D metabolism pathway

ROLE OF VITAMIN D IN IMMUNITY

One of the beneficial effects of vitamin D supplementation is immune system enhancement. Studies showed that vitamin D deficiency increased the risk of acquired autoimmune disease, tuberculosis, severe infections and mortality in critically ill patients.[17-19] Immunomodulator effect of vitamin D is linked to the finding of VDR expressed by many immune cells, such as T & B cell lymphocytes, monocytes, and antigen-presenting-cells; therefore it can be concluded that vitamin D may modulate innate and adaptive immune system.[7]

Vitamin D enhances the innate immune system through pathogen sensing mechanism by monocyte CYP27B1 (a vitamin D-activating enzyme), increase monocyte proliferation, and antimicrobial protein (cathelicidin), IL-1, and IL-10 production. After pathogens are phagocytosed, CYP27B1 and VDR inside the monocyte will be activated, resulting in the utilization of 25(OH)D in the blood and alteration to 1,25 $(OH)_2D$ locally (intracrine process).[20-22] Calcitriol will bind to endogenous monocyte VDR and induce the production of cathelicidin which in turn augment the eradication of pathogens inside the monocyte.[20] The immunomodulatory effect of vitamin D toward dendritic cell are related with the immune tolerance and suppression mechanism which interplay with adaptive immune system. Therefore, it is hypothesized that it may help in autoimmune disease.[21,22] The binding of 1,25 $(OH)_2D$ with dendritic cell VDR induce suppression of the dendritic cell maturation, antigen presentation, IL-12 production, and increase production of IL-10. IL-12 suppression will lead to decreased production of T helper 1 T-cells and increased production of Thelper 2. Meanwhile IL-10 is regarded as immunosuppressive cytokines.[22]

Vitamin D may exert immunosuppressive or tolerogenic effect in adaptive immune system by inhibiting through inhibition of T cell proliferation, B cell differentiation and immunoglobulin secretion, Th17 suppression, and enhancing T regulatory (Treg) production.[7,23] Suppression of T cell will inhibit pro-inflammatory cytokine production. Treg regulates excessive inflammation process which may help in autoimmune disease.[20] Th17 produced IL-17, which in many autoimmune diseases, such as IBD, systemic lupus erythematous and others are found to be elevated.[24]

VITAMIN D DEFICIENCY STATUS: RISK FACTORS AND MODULATING FACTORS OF DISEASE ACTIVITY IN IBD PATIENTS

Many studies found that patients with IBD had low level of Vitamin D; therefore, Vitamin D status was considered linked as one of the environmental risk factors for IBD.[25] However, there were some points which need to considered from the result of those studies: (1) Whether Vitamin D deficiency preceded the occurrence of IBD or Vitamin D deficiency was the implication of clinical course of IBD; (2) Use of different cut off levels of 2,5(OH)D to determine the adequacy level of vitamin D status; (3) Varied measurement of 2,5(OH)D level between studies which might be affected by duration of sun exposures (winter or summer) and geographical location.[10,26,27,28]

There are two guidelines which are used to define the cut-off level for the vitamin D adequacy status. The first one is the guideline by IOM in 2011, defining vitamin D deficiency as 2,5(OH)D level < 30 nmol/L (12 ng/mL), inadequate vitamin D as 30-50 nmol/L(12-20 ng/mL), and sufficient as 2,5(OH)D level above 50 nmol/L (20 ng/mL).[10] Another guideline published by the Endocrine Society in 2011 defines vitamin D deficiency as 2,5(OH)D level below 50 nmol/L (20 ng/mL) and vitamin D insufficiency as 52.5-72.5 nmol/L (21-29 ng/mL).[27]

Studies found that the prevalence of vitamin D deficiency in IBD patients ranged from 8% up to 95%.[8] Recent observational multi-centre study in Norway found 49% of total patients had 2,5(OH)D level below 50 nmol/L. Vitamin D deficiency was more common in CD compared to ulcerative colitis (UC) patients (53% vs. 44%). This study also attained that vitamin D deficiency was related with severity of IBD, which was described as higher relapse rate and higher inflammatory level.[29] A cross sectional study by Raftery et al showed that vitamin D level were inversely correlated with faecal calprotectin level, which was regarded as a marker of intestinal inflammation in IBD.[30] Torki et al found that up to 39% of IBD patients in Iran were having 2,5(OH)D level < 50 nmol/L; also, low vitamin D level was independently associated with status of disease activity.[31] Retrospective cohort study by Ulitsky et al which included 504 IBD patients (403 CD and 101 UC) and had more than 10 years mean disease duration, showed that 49.8% of the patients were vitamin D deficient and 10.9% had severe vitamin D deficiency. This study also reported that vitamin D was associated with lower quality of life and increased disease activity in CD.[32] A cohort study consisted of 220 IBD patients found that higher vitamin D level (50-59 ng/ml) were associated with better quality of life (assessed with short IBD questionnaire).[33] Recently published study revealed that normal vitamin D level status in IBD patients managed with anti-TNFα medications had more than two times higher odds of remission compared to low level vitamin D IBD patients.[34] Prospective study by Gubatan et al exhibited that among 70 patients with UC, lower vitamin D level was found in relapse group (29.5 ng/mL vs. 50.3 ng/mL, $p = 0.001$). Serum vitamin D level of 35 ng/ml or less had predictive role for increased risk of clinical relapse with sensitivity of 70% and specificity of

74%.[35] A five year longitudinal study consisting of 965 IBD patients (61.9% CD and 38.1% UC) found that almost 30% of the patients were having low level of vitamin D. After 5 years of observation, IBD patients with low level vitamin D were found to have higher morbidity, number of hospitalization and surgery, need of steroids, higher disease activity score, and lower quality of life.[36] A retrospective multi-centre study in USA concluded that IBD patients with vitamin D level < 20 ng/ml were twice more prone to acquire *Clostridium difficille* infection.[37] Two meta-analyses published in 2015, found that IBD patients had lower vitamin D serum level.[38,39] Meta-analysis by Lu et al concluded that there were more patients with active CD had low vitamin D level.[39] McCarthy et al found that there was vitamin D level variation among CD patients related with season; in winter, vitamin D level tend to be lower.[28]

While data show the prevalence of vitamin D deficiency in IBD patients, it is difficult to determine whether vitamin D deficiency was risk factor of developing IBD or was the consequence of IBD; as most of the studies measured the vitamin D level on established IBD patients. Several causes of low vitamin D level in IBD patients are decreased sunlight exposure, decreased oral intake of vitamin D, and also reduced ability to absorb vitamin D.[32] Farraye et al showed that there was 30% reduction of vitamin D2 absorption capability in CD patients.[40] Furthermore, ileum terminale resection performed in IBD patients might further impair the absorption of vitamin D.[32]

PATHOGENESIS OF IBD IN RELATION TO GENETIC AND VDR GENES POLYMORPHISM

The pathogenesis of IBD remains elusive. Current theory highlights the interaction between environment, genetic predisposition, immune system, and mucosal ecology.[41] Nucleotide-binding oligomerization domain 2 (NOD2) gene mutation was found to be responsible in the pathogenesis of CD. NOD2 acts in the regulation of mucosal intestinal barrier by recognition of peptidoglycan produced by bacteria, induction of protective inflammatory response, production of antimicrobial peptide defensin beta2 (DEFB2/HBD2), and autophagy. However, the mutation of NOD2 gene will lead to loss of peptidoglycan sensing and lack of protective inflammatory response, which in turn will result in dysbiosis, barrier dysfunction, and chronic inflammation.[41,42] Recent study found that NOD2 was among the targeted gene of 1,25 $(OH)_2D$ signaling; stimulation of NOD2 by 1,25 $(OH)_2D$ will lead to enhanced autophagy.[43] Vitamin D deficiency may impair the stimulation of NOD2, which may lead to impaired mucosal barrier.[44]

VDR gene polymorphisms had been studied and implicated to increase the risk of suffering from IBD; however the studies generated mixed and inconclusive result. This study used the same location of the VDR gene with IBD-associated genes, the chromosome 12.[41] VDR gene polymorphism may affect the expression and transcription process, which may play influential role in inflammation process.[45] Some of the commonly studied VDR polymorphisms associated with IBD are TaqI, BsmI, FokI, and ApaI.[41,46]

VITAMIN D SUPPLEMENTATION AS ADJUNCTIVE THERAPY IN IBD

Based on the physiology of vitamin D immunomodulatory effects described above, several studies had been conducted to assess the benefit of vitamin D supplementation in IBD management. In vitro study showed that the inflamed and non-inflamed colon of the UC patients that were cultured with 1,25(OH)2D3 had decreased claudin-1, claudin-2 protein level, IL-13 and IL-6, and increased claudin-4 and claudin-7; therefore, it could be concluded that vitamin D might modulate the cytokine inflammation synthesis and regulate the tight junction protein expression.[47] Elimrani et al found that vitamin D supplemented mice had lower colitis activity index, histological inflammation score, weight loss, and IL-6 level and higher survival rates compared to vitamin D deficient mice.[48] Vitamin D may inhibit the excessive apoptosis of intestinal epithelial cells due to chronic inflammation in IBD patients. Mice with 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced-colitis treated with paricalcitol were having lower expression of caspase-3 and p53 upregulated modulator of apoptosis (PUMA), but not the p53 expression; which was regarded as the important protein in inducing apoptosis pathway.[49] Study in chronic colitis mice showed that vitamin D supplementation might induce VDR resulting in the inhibition of TGF-β1/Smad3 pathway in colonic subepithelial myofibroblasts (SEMF) which in turn prevent intestinal fibrosis.[50]

A double-blind randomized controlled trial conducted by Sharifi et al investigated the effect of high dosage (300,000 IU) of vitamin D3 supplementation administered once through intramuscular injection on systemic inflammation marker of IBD (erythrocyte

sedimentation rates [ESR] and C-reactive protein [CRP] level) and cathelicidin (LL37) gene expression among 90 UC patients on remission. Expression of LL37 gene will lead to increased production of human cationin antimicrobial protein 18 (hCAP18). Baseline of vitamin D levels between the intervention and placebo group were not significantly different. After intervention, ESR and Hs-CRP level were decreased

Table 1. Human studies regarding vitamin D supplementation in inflammatory bowel disease (IBD) patients.

Study	Study design	Sample	Intervention	Result
Miheller et al, 2009	Prospective cohort study	37 inactive CD patients	Group A: treated with 1,25 (OH)2D [active form of vit D] Group B: treated with plain vitamin D For 6 weeks, 3 and 12 months	Significant decrease of CDAI and CRP level in Group A at the 6 weeks.
Jørgensen et al, 2010	Randomized double blind placebo-controlled trial	94 CD patients	Group A: treated with oral 1200 IU vitamin D3 daily (46 patients) Group B: given placebo (48 patients) Intervention period: 12 months	Significant increase of serum 25OHD level seen after 3 months supplementation in Group A and lower relapse rate in Group A compared to Group B (13% vs. 29%; P=0.06)
Yang et al, 2013	Open-labeled prospective clinical study	18 mild-moderate CD patients	1,000 IU Vitamin D3 were given daily for two weeks, and then the dose was escalated to achieve 40 ng/ml 25 (OH)D3 serum concentration or maximum 5,000 IU daily. Intervention period: 24 weeks	Two weeks of 1,000 IU vitamin D3 daily was not adequate to raise the vitamin D serum level. 78% of patients need 5,000 IU daily to achieve the target vitamin D level. Reduced CDAI score (p<0.0001) and increased QoL (p=0.0004) were found after 24 weeks vit D supplementation; however, no significant changes were found in cytokines level.
Ananthakrishnan et al, 2013	Retrospective Cohort	3217 IBD patients (55% CD)	None	Serum level of 25 (OH)D <20 ng/ml was associated with increased risk of surgery (OR:1.76; 95% CI, 1.24-2.51) and IBD related hospitalization (OR 2.07; 95% CI, 1.59-2.68) compared to patients with >30 ng/ml 25 (OH)D. Normalization of 25 (OH)D level decreased the risk of surgery (OR 0.56; 95% CI: 0.32-0.98)
Raftery et al, 2015	Double-blind randomized placebo-controlled study	27 CD patients in remission	Group A: 13 patients supplemented with 2,000 IU vitamin D3 Group B: 14 patients given placebo Intervention period: 3 months	Patients with serum level of 25 (OH)D ≥75 nmol/L were found to have higher QoL (p=0.037), higher LL-37 concentrations (p<0.001), lower CRP (p=0.019), and lower insignificant CDAI scores (p=0.082).
Dadaei et al, 2015	RCT, analysis with intention to treat	108 IBD patients with Serum 25OHD <30 ng/ml	Group A: 53 patients were treated with 50,000 IU vitamin D3 Group B: 55 patients served as control Intervention period: 12 weeks	Insignificant decrease of TNF-α were found in Group A (p=0.07, CI 95%:-0.45 to 8.14) TNF-α level were significantly correlated with clinical disease activity index before and after intervention.
Sharifi et al, 2016	RCT, analysis with intention to treat	90 UC patients on remission	Group A: 46 patients were treated with 300,000 IU intramuscular vitamin D once. Group B: 44 patients given placebo	Significant decrease of Hs-CRP level (p = 0.023), ESR level (p < 0.001), and higher cathellicidin level which reflected by hCAP18 gene expression (p < 0.001) in group treated with vitamin D.
Kabbani et al, 2016	Five year longitudinal study	965 IBD patients (61.9% CD & 52.3% female)	Taken from longitudinal IBD natural history registry. Routine testing of serum vitamin D level were done. Vitamin D supplementation was given to patients with status of deficiency or insufficiency. The protocol: 50,000 IU vitamin D weekly or biweekly for at least 12 weeks.	Low vitamin D level was associated with more treatment, hospital admissions, and surgery (p<0.05); also higher pain, disease activity scores, and lower QoL (P,0.05). Patients with vitamin D supplementation were associated with reduced utilization of healthcare.
Narula et al, 2017	Randomized double blind placebo-controlled trial	34 CD patients in remission	Group A: 18 patients received 10,000 IU vitamin D3 daily, Group B: 16 patients received 1000 IU vitamin D3 daily Intervention period: 12 months	Intention to treat analysis result: no significant different in term of clinical relapse rate between Group A and B (33.3%vs. 68.8%, p=0.0844) Per-protocol analysis: Clinical relapse rate were lower in high dose vitamin D supplemented group compared to low dose group (0% vs. 37.5%; p=0.049)

significantly and there was significant increase of LL37 gene expression among UC patients in vitamin D supplemented group.[51] This finding was also supported by the study conducted by Raftery et al, that among CD patients in remission who were supplemented with vitamin D 2000 IU/day for 3 months were associated with increased LL37 concentration and maintenance of intestinal permeability. Among those UC patients, those with 25(OH)D level ≥ 75nmol/L were associated with reduced CRP level, higher quality of life and LL37 concentration.[52] Jorgensen et al found insignificant lower relapse rate among vitamin D (1200 IU) supplemented CD patients after three months of intervention compared to placebo group (13% vs. 29 %, p = 0.06).[53] A small cohort study consisting of 18 CD patients with mild-moderate degree (150-400 Crohn's disease activity index [CDAI]) were supplemented with oral vitamin D3 1000 IU daily and were up titrated until they achieved 25(OH)D3 serum level of 40 ng/ml or maximum dose of 5000 IU daily. The result was vitamin D supplementation significantly reduced CDAI index and improved the quality of life.[54] Anathakrishnan et al who conducted retrospective analysis consisting of 3,217 IBD American patients (55% were CD), found that normalization of serum vitamin D level would lower half of the risk for surgery among CD patients.[55] Mihaller compared the effectivity of the active form of vitamin D (1,25(OH)2D) with plain form of vitamin D (25 (OH)D) supplementation in CD patients. After 6 weeks of supplementation, there were significant reduction of CDAI, CRP, and bone turnover in active vitamin D form group.[56] Recently published study in 2017 reported that high dose vitamin D3 supplementation (10,000 IU) daily was associated with significant improvement of 25 (OH) D level; however, the rates of clinical relapse were similar to the group who were supplemented with low dose vitamin D3 (1000 IU) daily (68.8% vs. 33.3%, p = 0.084).[57] Treatment of low vitamin D level before initiating anti-TNF medication are needed, because there is significant association with positivity for antinuclear antibodies (ANA) which is linked to higher failure rates and adverse event of anti-TNF therapy.[58] The target of vitamin D level which exert optimal imummodulatory effect that may benefit IBD patients, has not been formally established. A literature review by Raftery et al suggested that achieving serum level vitamin D of ≥75 nmol/L might be needed to benefit CD patients.[59] Human studies regarding the use of vitamin D supplementation for IBD management are summarized in Table 1.

CONCLUSION

Currently the role of vitamin in IBD pathogenesis and management has been recognized, especially due to the nature of immunomodulatory effect of vitamin D. Most studies found higher prevalence of low vitamin D level in IBD patients; however it remained difficult to determine whether vitamin D deficiency is the risk factor of developing IBD or the consequence of IBD activity course. Recent human studies indicate that vitamin D supplementation especially in vitamin D deficiency IBD patient may benefit in term of alleviating disease activity, maintaining clinical remission, and improving quality of life. Therefore, we suggest vitamin D level assessment in IBD patients. Local data regarding the prevalence of vitamin D deficiency, benefit of vitamin D supplementation, and optimum vitamin D level among Indonesian IBD patients are needed to make specific recommendation.

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