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Could Vitamin D Affect Inflammatory Bowel Diseases Activity in Children?

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract and is divided into Crohn disease and ulcerative colitis. It occurs in genetically susceptible individuals after an exaggerated immune response to a normal stimulus such as food and intestinal flora**.** Inflammatory bowel disease is characterized by repetitive episodes of inflammation of the gastrointestinal tract caused by an abnormal immune response to gut micro flora. Inflammatory bowel disease (IBD) encompasses two types of idiopathic intestinal disease that are differentiated by their location and depth of involvement in the bowel wall. **Objectives:** To identify the association of Vitamin D level with the Inflammatory Bowel Diseases activity. **Conclusion**: This study found that 1, 25 dihydroxycholecalceferol level was lower in patients with IBD than in healthy people.and There was non statically significant correlation Between Vit D With 1,25 dihydroxycholecalceferol level in remission phase and 1,25 dihydroxycholecalceferol level in active phase.

Keywords: Vitamin D, hypovitaminosis D, inflammatory bowel diseas

INTRODUCTION:

Malnutrition is found in up to 85% of patients with IBD, in the active and remission phases. Micronutrient deficiencies are present in more than half of patients with IBD. The deficiencies are more frequent in CD than in UC and in active disease than in remission. The most common micronutrients deficiencies in IBD are vitamin B12, folate, iron, and especially vitamin D**(1).**

Vitamin D is known as the most important regulator of calcium (Ca) and phosphorus (P) metabolism related to bone health but studies suggest the new role of vitamin D in immunomodulation recently, and Vitamin D is even proposed as a treatment for autoimmune diseases such as multiple sclerosis, systemic lupus erythematous, and IBD**(2).**

Furthermore **Ananthakrishnan et al. (3)** has reported that vitamin D deficiency may play a role in the increased risk of malignancies in IBD.

However, limited studies have been conducted about the relationship between vitamin D and disease activity in IBD over a multi-year period, especially in pediatric patients so far**(4).**

Many studies have been conducted on malnutrition and micronutrient deficiencies due to the reduction of oral intake and increased gastrointestinal losses of nutrients in patients with IBD[5].

Vitamin D

Vitamin D is an essential steroid hormone with effects extending beyond its classical role in bone-mineral disease. Recently, the importance of vitamin D in the kidneys, cardiovascular disease, immune system, and cancer has been recognized[6] .

According to the 2011 report on dietary requirements for calcium and vitamin D from the Institute of Medicine (IOM), vitamin D deficiency has been defined as 25(OH)D levels < 20 ng/ml (50 nmol/l) and adequacy as levels ≥ 30 ng/ml (75 nmol/l). Serum concentrations of 25(OH) D above 50 ng/ml (125 nmol/liter) should be prevented, since risks have been identified for some outcomes[7].

Vitamin D deficiency is highly prevalent in the general population in the US and prevalence varies by geographical location, diet and co morbidities [8]. The spectrum of cardiovascular disease (CVD) in adult CKD patients includes ischemic heart disease, congestive heart failure, arrhythmias and peripheral vascular disease[9].

Vitamin D deficiency has been linked to cardiovascular mortality, both in the general population and in adult patients with CKD[10]. In adult patients with mild to moderate CKD the incidence of cardiovascular mortality is much higher than the incidence of kidney failure, making it the more important reason for increased morbidity seen in CKD[11]. It is imperative to focus on therapies that reduce the cardiovascular risk to decrease the morbidity and mortality of CKD[12].

Vitamin D Metabolism:

Vitamin D is a prohormone which plays a vital role in bone metabolism, cardiovascular disease, the immune system, and the kidneys[13].

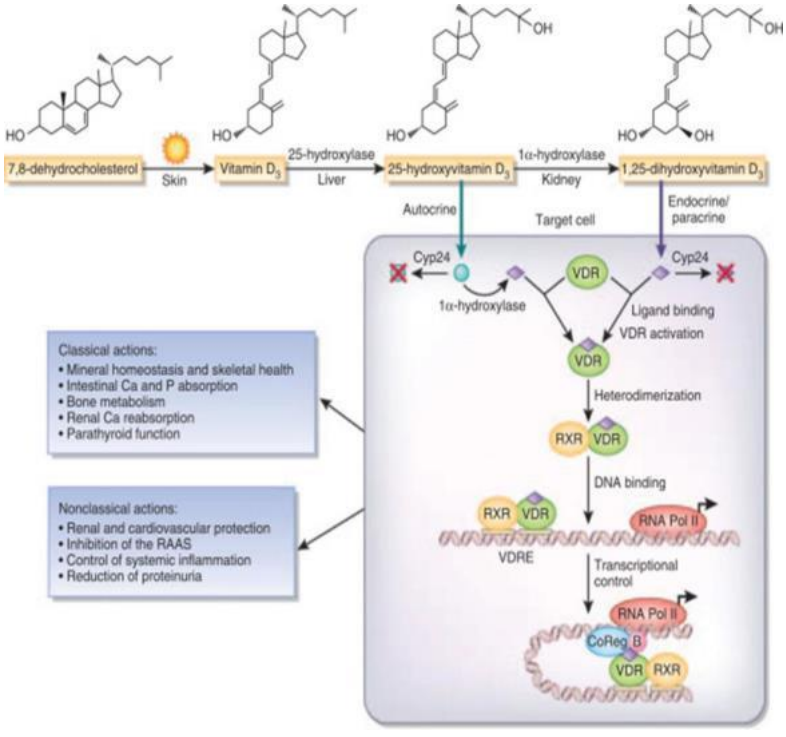


Figure (1): Mechanism of vitamin D Metabolism[13].

Vitamin D bioactivation and actions:

Classical and nonclassical vitamin D actions require vitamin D conversion to 25-hydroxyvitamin D (25(OH)D, open circle), and its bioactivation to its hormonal form 1,25-dihydroxy vitamin D (calcitriol, diamond) by renal and extra renal 1-hydroxylase and calcitriol binding to and activation of its receptor, the vitamin D receptor (VDR). Calcitriol-activated VDR binds its partner the retinoic X receptor (RXR, heterodimerization) and vitamin D-responsive elements (VDRE) in the promoter of VDR-responsive genes (DNA binding), and recruits basal transcription factors (B) and co-activator and co repressor molecules (CoReg) to induce or repress the transcription of vitamin D-responsive genes by RNA polymerase II (transcriptional regulation). The net balance between cellular uptake of calcitriol and/or 25(OH)D, the rate of 25(OH)D conversion to calcitriol versus the activity of 24-hydroxylase (cyp24), responsible for the inactivation of 25(OH)D and calcitriol (crossed blue circle and purple diamond), determines the degree of VDR activation by intracellular calcitriol. Most of these steps are impaired in kidney disease. Ca, calcium; P, phosphate; RAAS, renin-angiotensin-aldosterone system[(14)].

Mechanisms Associated with Vitamin D Status:

Vitamin D therapy decreases CAD risk due to multi-organ protective effects. There are at least several mechanisms involved in the effect of vitamin D on altered mortality[(15)].

The influence of vitamin D on mortality was suggested to be related with several mechanisms, including the down-regulation of renin-angiotensin system, protection of proper endothelial cell function, hindering vascular smooth-muscle cell proliferation, modulation of inflammatory processes, including the activation of pro-inflammatory cytokines as interleukin (IL)-8 and tumour necrosis factor (TNF)-alpha and oxidative stress, impeding anticoagulant activity, inhibition of myocardial cell hypertrophy and proliferation and finally the improvement of insulin secretion and sensitivity[(16)].

Despite the fact that the exact mechanism of CKD patient mortality has not been resolved, studies indicate that it can be associated with over vascular calcifications, left ventricle hypertrophy and in consequence left ventricle dysfunction[(15)].

Increased mortality risk in patients with low 25(OH)D levels may be the consequence of the relationship between vitamin D deficiency with cardiovascular risk factors, such as: type 2 diabetes mellitus, arterial hypertension, malnutrition, and inflammation[(17)] .

In a double-blind, randomized, placebo-controlled trial, vitamin D supressed pro-inflammatory state via the down-regulation of nuclear factor-κB activity, hampering of the production of IL-6, IL-12, interferon, and TNF while increasing that of anti-inflammatory cytokines[(18)] .

Timms et al. [(19)] suggested that vitamin D administration in case of its deficiency may inhibit several aspects of the inflammatory response to cardiovascular injury as well as slow down atherosclerotic plaque progression and limit plaque rupture. Moreover, inverse correlation has been observed between serum vitamin D levels and coronary calcification.

Vitamin D may indirectly prevent inflammation and the stimulation of endothelial progenitor cells (EPCs) and in this way it protects against the development of congestive heart failure[(20)].

The results of Multi-Ethnic Study of Atherosclerosis suggest that vitamin D deficiency is prospectively associated with elevated risk of coronary artery calcification (a measure of coronary atherosclerosis). The association of 25-hydroxyvitamin D with incident CAC was observed to be stronger among participants with lower estimated GFR[(21)].

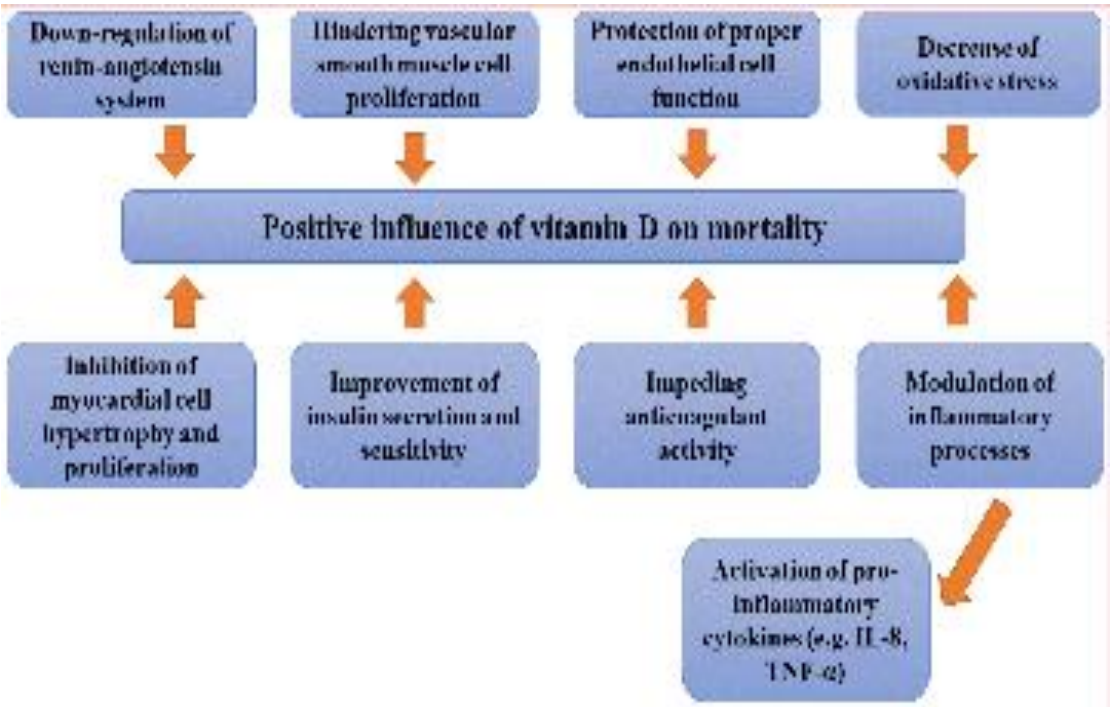


Figure (2): Mechanisms involved in the effect of vitamin D on altered mortality[15].

Prevalence of Deficiency in IBD:

Vitamin D deficiency is a public health concern with the NICE recommending oral supplementation in specific population groups including infants and children under 4 years, pregnant or breastfeeding women, people over 65 years of age and those who have low or no exposure to the sun. For example, those who cover their skin for cultural reasons, are housebound or confined indoors[22].

The population prevalence of vitamin D deficiency (serum 25-OH-D < 40 nmol/L) in some westernised countries is reported to be between 30% and 47% with the highest levels reported for those people with darkly pigmented skin. However, people with IBD are likely to be at increased risk of developing vitamin D deficiency for a number of reasons including: impaired absorption of nutrients and bile salt malabsorption, restricted dietary intake, and medical advice to avoid/protect against sunlight exposure while taking immuno-suppressive treatments such as thiopurines[23].

A number of studies have evaluated the prevalence of vitamin D deficiency and insufficiency in people with IBD[24].

Vitamin D Deficiency in IBD—Cause or Consequence:

Though vitamin D deficiency in IBD is well documented it is unclear if this is a cause or a consequence of the disease. It is notable that the highest prevalence of the disease appears in more temperate climates with lower levels of sunlight[25].

Some studies have suggested a correlation between vitamin D deficiency and increased disease activity[26,27].***)***

Low vitamin D levels associated with IBD may be due to dietary restriction or low UV light exposure, but it is also important to recognise that genetic factors also contribute to variations in circulating vitamin D[28].

Single nucleotide polymorphisms (SNP) for components of the vitamin D system have been shown to contribute to the variation of serum 25-OH-D levels in IBD patients[29].

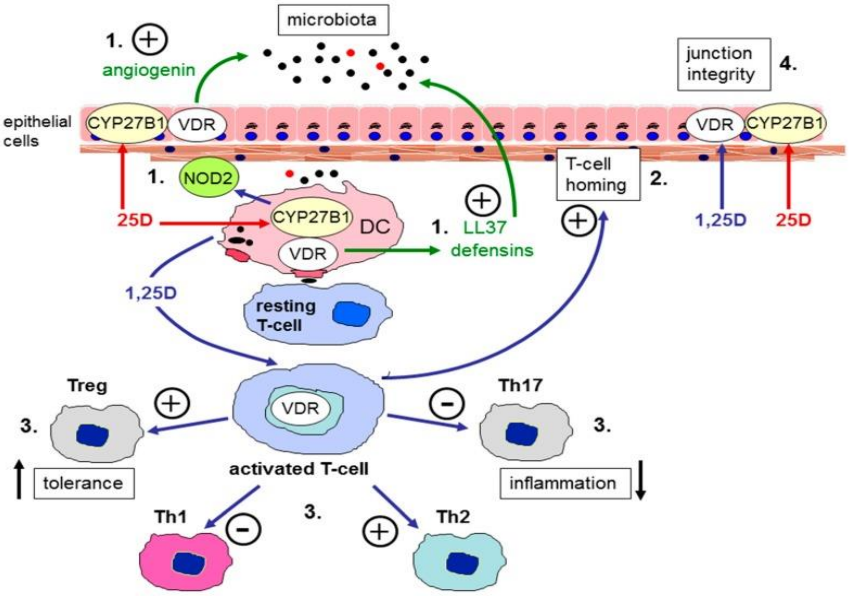
However, the contribution of SNPs to serum levels of 25-OH-D in IBD patients is very small (3%), and subsequent Mendelian randomisation analyses have not shown any link between genetic determinants of vitamin D status and risk of IBD[30].

It would seem that grounds for a causative relationship are most likely to be found in laboratory evidence of the functional effects of vitamin D, suggesting an effect of the active form of vitamin D on immune responses related to IBD[3].

Functional Effects of Vitamin D in IBD—Analysis of In Vitro and In Vivo Models:

The mechanistic basis for a role for vitamin D in IBD stems firstly from studies of immuno-modulatory properties of 1,25-(OH)2D. These include antibacterial and anti-inflammatory actions on cell from the innate and adaptive immune system that modulate the pathology of gastrointestinal dysregulation and inflammation[31,32]. Vitamin D also appears to play a pivotal role in the maintenance of gastrointestinal barrier integrity by regulating proteins associated with epithelial cell gap junctions[33].

The barrier function of vitamin D is also linked to its impact on the gastrointestinal microbiota, with serum 25-OH-D status in humans being correlated with changes in gastrointestinal bacterial genera associated with inflammatory immune responses[34]. In this way vitamin D has the potential to both prevent the onset of IBD via effects on barrier function and microbiota homeostasis, and also ameliorate disease progression through anti-inflammatory immune responses[35].



Findings from studies designed to examine the effect of bone health related therapies (including vitamin D) in paediatric IBD patients:

The cohort study of **Hradsky et al.** [36] was designed to assess the effect of vitamin D3 therapy on bone health parameters and dynamic muscle function. In total, 55 patients aged 5 - 19 years with a diagnosis of IBD were included. Patients were excluded if they had another disease with known impact on the muscle-bone unit, if they were noncompliant to treatment, if they were pregnant, if they had undergone extensive small bowel surgery, if

they were on total parenteral nutrition, or if they received growth hormone therapy. All patients received 2000 IU of vitamin D3 daily, for a median of 13.8 mo. Mean s-25OHD concentration at baseline was 58 nmol (23.2 ng/mL). This regimen resulted in 76% of the patients having s-25OHD concentration above 20 ng/mL throughout the study period. In addition, the vitamin D regimen in this cohort was associated with improvements in trabecular bone mineral density (BMD) at the tibia and muscle power. The majority of patients did not show increased PTH levels at follow-up. CRP levels were similar between baseline and follow-up visits. Similarly, PCDAI and the Paediatric Ulcerative Colitis Activity Index scores were not different between baseline and follow-up. The authors concluded that their regimen was safe.

Effects of vitamin D therapy on paediatric IBD:

The influence of vitamin D therapy on disease severity is a further potential outcome of supplementation. This is relevant as the primary effects of vitamin D in this population (on factors such as BMD, bone resorption and calcium homeostasis) are inconsistent and the significance of hypovitaminosis D in children with IBD is still unclear[(37)]**.**

In adults, more evidence of the role of vitamin D in treatment of IBD is available; small trials show promising results but remain conflicting[(38)].

Therefore, with the evidence for possible beneficial effects of vitamin D therapy on the clinical course of IBD in childhood being extremely limited, it would have been very useful if more of the included studies had reported disease severity related measures of the participants over time[(39)]**.**

Managing Vitamin D Deficiency in IBD—Sources of Vitamin D:

Sunlight Exposure:

The main source of vitamin D in humans is via synthesis in the body stimulated by sunlight exposure. The vitamin D precursor 7-dehydrocholesterol is produced by the liver and is stored in the skin. On exposure of the skin to ultraviolet B-light, this is converted to pre-vitamin D3 and enters the circulation. In the liver pre-vitamin D3 is converted to the inactive form 25(OH)D3. Renal conversion of 25(OH)D3 produces active form 1,25-(OH)2D3[(40)].

Lack of adequate exposure to sunlight is likely to lead to vitamin D deficiency with levels < 25 nmol/L[(41)].

However, it is difficult to determine what adequate exposure is. The British Dermatology Association in their 2010 consensus statement on the use of sun-exposure to prevent vitamin D deficiency noted the results of ***Rhodes et al***[(42)]*;* the time to produce vitamin D is generally short and certainly before skin begins to burn or redden. The study found that sunlight exposure for an equivalent of 13 minutes of UK summer midday sun (approximate latitude 53.4808° N, 2.2426° W), three times per week over a six-week period was sufficient to increase serum vitamin D levels above 50 nmol/L. The study was carried out in Caucasian participants with one third of their skin exposed to simulated sunlight and wearing no sunscreen.

Darker skin required a longer exposure to sunlight to produce vitamin D, so, it would not be possible to have a single recommendation for all skin types. In addition, Rhodes et al note that excessive cutaneous exposure to sunlight may in fact lead to degradation of vitamin D but they do not quantify what excessive exposure is[(42)].

A more recent global consensus statement on the treatment and prevention of rickets suggests that the use of sunlight exposure to prevent or treat vitamin D deficiency is not feasible. The authors note that there is no safe threshold of ultra violet exposure that allows for sufficient

vitamin D synthesis without increasing the risk of skin cancer[43]. This is of particular relevance to patients with IBD, where there is an increased risk of non-melanoma skin cancer in those who have received thiopurines to treat IBD[44].

Dietary Sources:

The majority of naturally occurring vitamin D in food is found in animal products and, as in humans, the quantity of vitamin D found in animal products will vary according to the vitamin D status of the animal. This will be influenced by the animal's diet, if they receive vitamin D supplementation in their feed and their exposure to sunlight[45]. In the USA the addition of vitamin D to livestock feed has been shown to improve the quality of the meat[46].

NHS , (2019) recommend the following sources of vitamin D:

- Oily fish-such as herring, mackerel, salmon and sardines.
- Liver.
- Red meat.
- Egg yolks.
- Fortified foods such as fat spreads and breakfast cereals.

Dietary Intake of Vitamin D in People with IBD:

Studies have suggested that people with IBD may restrict their diet to help manage the symptoms of their disease. This has been shown particularly in people with CD and CD-related strictures and even in remission diet may be sub-optimal. A cross sectional study was carried out with 67 CD patients in remission in Canada. Results showed that intake of vitamins C, D, niacin, thiamin, magnesium, phosphorus, potassium, and zinc were all significantly lower in CD patients compared to a control sample ($p < 0.05$) [47].

A recent UK cross sectional study of 67 patients with IBD (40 CD, 23 UC) found that 97% of patients reported food avoidance[48].

Commonly avoided foods were vegetables and wheat products. Mean vitamin D intake was 283 IU/day in the reported cohort. A further small cross-sectional study of dietary intake in 31 patients with IBD in Iceland reported that patients avoided dairy (60%) and processed meat products (55%) to manage symptoms of their IBD. Some patients reported that fish had a positive effect on their symptoms (22%)[49].

A cross-sectional study carried out in the Netherlands of 165 patients with IBD compared to healthy controls, demonstrated that patients with IBD consumed more meat and poultry with an average difference of 15.0g/day (95% CI 8.50 – 21.4); less dairy products at − 36.3 g/day (95% CI − 65.8−6.84); and slightly less fish at −1.42 g/day (95% CI − 0.94−3.79). The findings of these studies would suggest that patients with IBD are unlikely to consume adequate amounts of vitamin D rich foods to achieve the moderate recommended intake[50].

Vitamin D Supplementation:

Oral supplements containing vitamin D are widely available both over the counter and in the form of prescription only medicines. Some may be single or multi-nutrient preparations. Supplements usually contain either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3); both forms of vitamin D are metabolised by the liver to 25(OH)D. However, studies suggest that vitamin D2 appears to yield less 25-OH-D than an equal amount of vitamin D3, with vitamin D3 being more effective at raising blood levels of 25-OH-D in humans. For this reason, vitamin D3 supplementation is often recommended. The dose of vitamin D supplementation required to prevent deficiency is an issue for debate[51].

The European Food Safety Authority has set an upper tolerable limit for vitamin D supplementation of 4,000 IU daily in adults. In line with the SACN report, current NICE recommendations are 400 IU vitamin D daily[52].

Benefits of Treating Vitamin D Deficiency in IBD:

It is widely accepted that vitamin D supplementation should be provided during corticosteroid treatment in IBD for prevention of deterioration of bone health, forming standard guidance. There is increasing interest in research investigating prescribing vitamin D supplementation for modulating inflammatory biochemical processed in IBD[53]. Oral supplementation of vitamin D has been shown to be safe with only minor side-effects which on the whole are generally tolerated among children, with no difference with dosage regimes such as 2000 IU/day versus 50,000 IU/week[54].

Adult studies show similar safety profiles, with meta-analysis confirming this with the most common side-effects including thirst, nausea, dry mouth, headaches, minor gastrointestinal upset, drowsiness, and fatigue[55].

Supplementation of 40,000IU of cholecalciferol weekly successfully significantly increased vitamin D levels in patients with active UC and among subjects with inactive UC and non-UC sufferers. Moreover, there was an associated significant reduction in inflammatory markers of colitis: both C-reactive protein (CRP) and fecal calprotectin[35].

Conclusion:

There was association Between Vitamin D level with the Inflammatory Bowel Diseases activity

References:

1- Weisshof R, Chermesh I. Micronutrient deficiencies in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2015; 18(6): 576–581.

2- Mouli V, Ananthakrishnan A. Vitamin D and inflammatory bowel diseases. Aliment Pharmacol Ther. 2014;39(2):125-36.

3- Ananthakrishnan AN. Editorial: Vitamin D and IBD: Can We Get Over the "Causation" Hump? Am. J. Gastroenterol. 2016;111:720–722. doi: 10.1038/ajg.2016.47.

4- Kim S, Kang Y, Park S et al. Association of Vitamin D with Inflammatory Bowel Disease Activity in Pediatric Patients. J Korean Med Sci. 2019; 34(32): 204-12.

5- Goh J, O'Morain CA. Nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther. 2003;17(3):307–320.

6- Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol 2005; 289:F8–28 [PubMed: 15951480]

7- Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96:53–58 [PubMed: 21118827]

8- Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266–281 [PubMed: 17634462]

9- Hajhosseiny R, Khavandi K, Goldsmith DJ. Cardiovascular disease in chronic kidney disease: untying the Gordian knot. Int J Clin Pract 2013; 67:14–31 [PubMed: 22780692]

10- McCullough PA, Steigerwalt S, Tolia K, Chen SC, Li S, Norris KC, Whaley Connell A. Cardiovascular disease in chronic kidney disease: data from the Kidney Early Evaluation Program (KEEP). Curr Diab Rep 2011; 11:47–55 [PubMed: 21076895]

11- Hemmelgarn BR, Clement F, Manns BJ, Klarenbach S, James MT, Ravani P, Pannu N, Ahmed SB, MacRae J, Scott-Douglas N, Jindal K, Quinn R, Culleton BF, Wiebe N, Krause R, Thorlacius L, Tonelli M. Overview of the Alberta Kidney Disease Network. BMC Nephrol 2009; 10:30 [PubMed: 19840369]

12- Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all- cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375:2073–2081 [PubMed: 20483451]

13- Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. Kidney Int 2010; 78:140–145 [PubMed: 20182414]

14- Dusso AS, Tokumoto M. Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: a downward spiral in kidney disease. Kidney Int 2011; 79:715–729 [PubMed: 21270766]

15- Zheng Z, Shi H, Jia J, Li D, Lin S. Vitamin D supplementation and mortality risk in chronic kidney disease: A meta-analysis of 20 observational studies. BMC Nephrol. 2013, 14, 199.

16- Simpson RU, Hershey SH, Nibbelink KA. Characterization of heart size and blood pressure in the vitamin D receptor knockout mouse. J. Steroid Biochem. Mol. Biol. **2007**, 103, 521–524.

17- Pilz S, Tomaschitz A, Ritz E, Pieberm TR. Vitamin D status and arterial hypertension: A systematic review. Nat. Rev. Cardiol. **2009**, 6, 621–630. 60.

18- Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: A double-blind, randomized, placebo-controlled trial. Am. J. Clin. Nutr. 2006, 83, 754–759.

19- Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-court D, Aganna E, Price CP, Boucher BJ. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: Mechanisms for inflammatory damage in chronic disorders? QJM 2002, 95, 787–796.

20- Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Körfer R, Stehle P. Low vitamin D status: A contributing factor in the pathogenesis of congestive heart failure? J. Am. Coll. Cardiol. 2003, 41, 105–112.

21- De Boer IH, Kestenbaum B, Shoben AB, Michos ED, Sarnak MJ, Siscovick DS. 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. J. Am. Soc. Nephrol. **2009**, 20, 1805–1812.

22- National Institute for Health and Care Excellence. Vitamin D: Supplement Use in Specific Population Groups PH56. NICE; London, UK: 2017.

23- Fletcher J. Vitamin D deficiency in patients with inflammatory bowel disease. Br. J. Nurs. 2016;25:846–851. doi: 10.12968/bjon. 2016. 25.15.846.

24- Fletcher J., Swift A. Vitamin D screening in patients with inflammatory bowel disease. Gastrointest. Nurs. 2017;15:16–23. doi: 10.12968/gasn. 2017.15.9.16.

25- Raman M, Milestone AN, Walters JR, Hart AL, Ghosh S. Vitamin D and gastrointestinal diseases: Inflammatory bowel disease and colorectal cancer. Therap. Adv. Gastroenterol. 2011;4:49–62. doi: 10.1177/1756283X10377820.

26- Frigstad SO, Høivik M, Jahnsen J, Dahl SR, Cvancarova M, Grimstad T, Berset I, Huppertz-Hauss G, Hovde Ø, Torp R. Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population. Scand. J.

Gastroenterol. 2017;52:100–106. doi: 10.1080/00365521.2016. 1233577.

27- Kabbani, T. A., Koutroubakis, I. E., Schoen, R. E., Ramos-Rivers, C., Shah, N., Swoger, J., . . . Hashash, J. G. (2016). Association of vitamin D level with clinical status in inflammatory bowel disease: a 5-year longitudinal study. *Official journal of the American College of Gastroenterology| ACG, 111*(5), 712-719.

28- Wang TJ, Zhang F, Richards JB, Kestenbaum B, Van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet. 2010;376:180–188. doi: 10.1016/S0140-6736(10)60588-0.

29- Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP et al. Common genetic variants influence circulating vitamin D levels in inflammatory bowel diseases. Inflamm. Bowel Dis. 2015;21:2507–2514. doi: 10.1097/MIB.0000000000000524.

30- Lund-Nielsen J, Vedel-Krogh S, Kobylecki CJ, Brynskov J, Afzal S, Nordestgaard BG. Vitamin D and Inflammatory Bowel Disease: Mendelian Randomization Analyses in the Copenhagen Studies and UK Biobank. J. Clin. Endocrinol. Metab. 2018;103:3267–3277. doi: 10.1210/jc.2018-00250.

31- Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, Nayak A, Wesseling-Perry K, Westerman M, Hollis BW et al. Suppression of iron-regulatory hepcidin by vitamin DJ. Am. Soc. Nephrol. 2014;25:564–572. doi: 10.1681/ASN.2013 040355.

32- Cantorna MT. Vitamin D, multiple sclerosis and inflammatory bowel disease. Arch. Biochem. Biophys. 2012;523:103–106. doi: 10.1016/ j.abb.2011.11.001.

33- Zhang YG, Wu S, Lu R, Zhou D, Zhou J, Carmeliet G, Petrof E, Claud EC, Sun J. Tight junction CLDN2 gene is a direct target of the vitamin D receptor. Sci. Rep. 2015;5:10642. doi: 10.1038/srep10642.

34- Luthold RV, Fernandes GR, Franco-De-Moraes AC, Folchetti LG, Ferreira SRG. Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals. Metab. Clin. Exp. 2017; 69:76–86. doi: 10.1016/j.metabol. 2017.01.007.

35- Garg M, Rosella O, Rosella G, Wu Y, Lubel JS, Gibson PR. Evaluation of a 12-week targeted vitamin D supplementation regimen in patients with active inflammatory bowel disease. Clin Nutr (Edinburgh, Scotland). 2018;37(4):1375–82.

36- Hradsky O, Soucek O, Maratova K, Matyskova J, Copova I, Zarubova K, Bronsky J, Sumnik Z. Supplementation with 2000 IU of Cholecalciferol Is Associated with Improvement of Trabecular Bone Mineral Density and Muscle Power in Pediatric Patients with IBD. Inflamm Bowel Dis. 2017;23:514–523.

37- Pappa HM, Gordon CM, Saslowsky TM, Zholudev A, Horr B, Shih MC, Grand RJ. Vitamin D Status in Children and Young Adults With Inflammatory Bowel Disease. PEDIATRICS, 2006; 118(5), 1950–1961.

38- Nicholson I, Dalzell AM, El-Matary W. Vitamin D as a therapy for colitis: a systematic review. J Crohns Colitis. 2012;6:405–411.

39- Yin K, Agrawal DK. Vitamin D and inflammatory diseases. J Inflamm Res. 2014;7:69–87.

40- Reich KM, Fedorak RN, Madsen K, I Kroeker K. Vitamin D improves inflammatory bowel disease outcomes: Basic science and clinical review. World J. Gastroenterol. 2014;20:4934–4947. doi: 10.3748/wjg.v20.i17.4934.

41- Scientific Advisory Committee on Nutrition. SACN Vitamin D and Health Report.

Scientific Advisory Committee on Nutrition; London, UK: 2016.

42- Rhodes LE, Webb AR, Fraser HI, Kift R, Durkin MT, Allan D, O'Brien SJ, Vail A, Berry JL. Recommended Summer Sunlight Exposure Levels Can Produce Sufficient but Not the Proposed Optimal 25(OH)D Levels at UK Latitudes. J. Invest. Dermatol. 2010;130:1411–1418. doi: 10.1038/jid.2009.417.

43- Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Mäkitie O et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J. Clin. Endocrinol. Metab. 2016;101:394–415. doi: 10.1210/jc.2015-2175.

44- Magro F, Peyrin-Biroulet L, Sokol H, Aldeger X, Costa A, Higgins PD, Joyce JC, Katsanos KH, Lopez A, De Xaxars TM et al. Extra-intestinal malignancies in inflammatory bowel disease: Results of the 3rd ECCO Pathogenesis Scientific Workshop (III) J. Crohn's Colitis. 2014; 8:31–44. doi: 10.1016/j.crohns. 2013.04.006.

45- Roseland J, Phillips KM, Patterson KY, Pehrsson PR, Taylor CL. Chapter 60: Vitamin D in foods: An evolution of knowledge. In: Feldman D., editor. Vitamin D. Elsevier; New York, NY, USA: 2018. pp. 41–77.

46- Carnagey KM, Huff-Lonergan E, Trenkle A, Wertz-Lutz AE, Horst RL, Beitz DC. Use of 25-hydroxyvitamin D3 and vitamin E to improve tenderness of beef from the longissimus dorsi of heifers1,2. J. Sci. 2008;86:1649–1657. doi: 10.2527/jas.2007-0502.

47- Taylor L, Almutairdi A, Shommu N, Fedorak R, Ghosh S, Reimer RA, Panaccione R, Raman M. Cross-Sectional Analysis of Overall Dietary Intake and Mediterranean Dietary Pattern in Patients with Crohn's Disease. Nutrients. 2018; 10:1761. doi: 10.3390/nu10111761.

48- Krishnamoorthy R, Jeanes Y. PWE-115 Dietary patterns in inflammatory bowel disease-intolerances, quality of life and calcium/vitamin D intake. Gut. 2018;67:A175–A176.

49- Vidarsdottir JB, Johannsdottir SE, Thorsdottir I, Björnsson E, Ramel A. A cross-sectional study on nutrient intake and -status in inflammatory bowel disease patients. Nutr. J. 2016;15:219. doi: 10.1186/s12937-016-0178-5.

50- Opstelten JL, De Vries JH, Wools A, Siersema PD, Oldenburg B, Witteman BJ. Dietary intake of patients with inflammatory bowel disease: A comparison with individuals from a general population and associations with relapse. Clin. Nutr. 2018 doi: 10.1016/j.clnu.2018.06.983. (in press)

51- Francis R, Aspray T, Bowring C, Fraser W, Gittoes N, Javaid M, Macdonald H, Patel S, Selby P, Tanna N. National Osteoporosis Society practical clinical guideline on vitamin D and bone health. Maturitas. 2015; 80:119–121. doi: 10.1016/ j.maturitas.2014.11.018.

52- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) Scientific Opinion on the Tolerable Upper Intake Level of vitamin D. EFSA J. 2012;10:2813.

53- Hlavaty T, Krajcovicova A, Payer J. Vitamin D therapy in inflammatory bowel diseases: Who, in what form, and how much? J Crohns Colitis. 2015;9:198–209. doi: 10.1093/ecco-jcc/jju004.

54- Pappa HM, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, Quinn N, Lawton RC, Bronzwaer MES, Koenen M et al. Maintenance of Optimal Vitamin D Status in Children and Adolescents With Inflammatory Bowel Disease: A Randomized Clinical Trial Comparing Two Regimens. J. Clin. Endocrinol. Metab. 2014;99:3408–3417. doi: 10.1210/jc.2013-4218.

55- Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of

inflammatory bowel disease: A meta-analysis. Medicine. 2018; 97:e12662. doi: 10.1097/MD. 00000000000 12662.