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Major Considerations and Outcomes of Clinical Studies on Vitamin D Deficiency in Patients with Crohn's

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Abstract

Introduction: The literature shows a bimodal incidence of Crohn's disease in relation to age, with peaks from 15-40 and from 50-80 years and more women have Crohn's disease than men. Clinical studies have shown a direct correlation of vitamin D deficiency with Crohn's disease.

Objective: Using a systematic review, the objective of this study was to identify the main correlations and outcomes of clinical studies about vitamin D in Crohn's disease.

Methods: Following the rules for systematic reviews (PRISMA), the key search terms used were Crohn's disease, vitamin D, clinical studies, immunotherapy and quality of life. After applying exclusion criteria, 117 articles were included and discussed in this study.

Conclusion: The prevalence of low serum vitamin D levels has been demonstrated in patients suffering from Crohn's disease. However, further studies that are more comprehensive are still needed, in particular investigations that aim to evaluate the effects of serum vitamin D levels on clinical treatment and the effects of vitamin D supplementation on disease activity and mucosal healing. Thus, it may be possible to optimize the treatment of Crohn's disease patients thereby improving their quality of life.

Keywords Crohn's disease; Vitamin D; Clinical trials; Immunotherapy; Quality of life

Introduction

The literature shows a bimodal incidence of Crohn's disease in relation to age; this disease mostly affects individuals between the ages of 15 and 40 and from 50 to 80 years old [1-6]. Moreover, there is a higher prevalence of women with Crohn's disease [7-9]. Clinical studies have demonstrated that the mean age of patients suffering from vitamin D deficiency is 41 years with this deficiency more frequently affecting women. Furthermore, according to De Bruyn et al. there is a direct correlation between vitamin D deficiency and Crohn's disease [9].

Crohn's disease is an inflammatory bowel disease (IBD) of uncertain etiology characterized by chronic autoimmune intestinal inflammation [10-12]. There is evidence of an important interaction between genetic and environmental factors that trigger an aberrant cellular immune response involving Th17 cells and their inflammatory cytokines [12,13]. In the context of cellular immunity, the discovery of the presence of the vitamin D receptor (VDR) in macrophages and lymphocytes has suggested a new approach to investigating autoimmune diseases [13,14].

Vitamin D appears to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages and natural killer cells (NK). In addition, there is evidence that vitamin D interferes in the in vivo and in vitro production of cytokines [14-17]. Similar epidemiological findings were reported by Ananthakrishnan et al. [18] and Azzopardi et al. [19-21]. Among the immunomodulatory effects demonstrated are decreased production of interleukin-2 (IL-2), interferon-gamma (INF-γ) and tumor necrosis factor (TNF), inhibition of IL-6 expression and inhibition of the production and secretion of autoantibodies by B-lymphocytes [19,20].

As vitamin D plays a significant role in modulating the immune system in the intestine, it is possible that its deficiency could impair the function of the intestinal barrier favoring the translocation of endotoxins such as lipopolysaccharides (LPSs) into blood circulation. LPSs are known to promote low-grade inflammation, which predisposes the patient to insulin resistance [19,21]. Numerous circulating biomarkers have been used to assess clinical inflammation and for research purposes [22,23].

Certain compositions of the intestinal microbiota have been associated with systemic inflammation and metabolic disorders. Particularly, gram-negative bacteria, which contain LPS in their outer layer, have been shown to stimulate immune response and to provoke metabolic endotoxemia, while other genera, such as bifidobacteria, reduce endotoxemia [18]. Despite being gram-negative, Akkermansia was found to improve the intestinal barrier function and to induce beneficial metabolic effects [24].

Vitamin D deficiency and the lack of VDR have been associated with intestinal dysbiosis and increased susceptibility to intestinal diseases [25-27]. Few studies have investigated whether vitamin D status contributes to disorders of the glucose metabolism by modulating the composition of the intestinal microbiota [28-30]. A better understanding of the underlying mechanisms of cardiometabolic diseases is important in respect to their impact on population mortality rates.

The Nutritionist Health Study (NutriHS) was designed to evaluate new biomarkers and predictors of Crohn's disease outcomes with this study collecting a variety of retrospective and prospective data [31]. Because of the importance of the response of the intestinal immune system to microbial stimulation and the immune modulatory role of vitamin D, it has been hypothesized that the vitamin D status is associated with the intestinal microbiota due to low-grade inflammation. In the NutriHS, the associations between vitamin D intake and 25-hydroxyvitamin D [25(OH)D] concentrations were examined in relation to fecal microbiota composition, inflammatory markers and the biochemical profile of young adults [30-32].

Therefore, using a systematic review, the present study aimed to investigate the main correlations and outcomes of clinical studies about vitamin D and Crohn's disease.

Strategy of Search and Design

Following the rules of the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses - http: // www.prisma-statement.org/), the key search terms were Crohn's disease, vitamin D, clinical studies, immunotherapy and quality of life. The literature research was conducted using the PubMed, Periodicos.com and Google Scholar online databases.

Article Eligibility

One hundred and sixty-two articles were found related to Crohn's disease and vitamin D. Initially, duplicate articles were excluded and the titles of articles were read to confirm their importance to this study. Subsequently, the abstracts were evaluated and more articles were excluded. One hundred and twenty-two articles were read with 117 that fulfilled the inclusion criteria being included and discussed in this study, according to Figure 1.

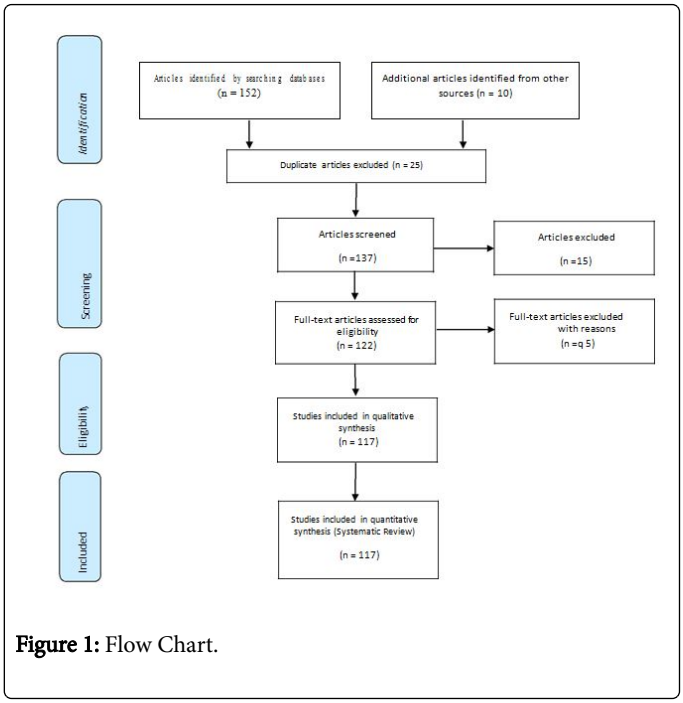

Figure 1: Flow Chart.

Literature Review and Discussion

The effect of vitamin D on the immune system translates into increased innate immunity associated with multifaceted regulation of acquired immunity [33]. A relationship between vitamin D deficiency and the prevalence of some autoimmune diseases such as Crohn's disease has been demonstrated. The literature shows a bimodal incidence of Crohn's disease in respect to age with two peaks corresponding to 15-40 years and from 50-80 years [34-37]. There is also agreement about gender involvement with a higher percentage of affected women [38,39].

The findings of the vast majority of published studies corroborated the prevalence of vitamin D deficiency in Crohn's disease; the mean serum vitamin D level among patients with Crohn's disease varied from 13.1-27 ng/mL whereas the Control Group had adequate serum vitamin D levels [40-42].

The primary source of vitamin D depends on exposure of the skin to sunlight with up to 20.0 % coming from ingestion. It is still controversial as to whether the consumption of foods containing vitamin D has a direct impact on circulating levels [43-48]. Vitamin D2 (ergocalciferol) is found in yeast, mushrooms and some vegetables and vitamin D3 (cholecalciferol), synthesized in the skin by ultraviolet radiation, is found in foods of animal origin [49].

To be biologically active, vitamin D undergoes hydroxylation in the liver mediated by 25-hydroxylase and in the kidney by 1α-hydroxylase. 1,25-dihydroxyvitamin D is recognized by its specific receptors (VDR) in different cells, primarily in the gut to increase calcium uptake and in the bone to regulate skeletal homeostasis [50,51]. Altered metabolic patterns result in metabolic disorders of calcium and phosphorus with vitamin D disorders having been implicated in some diseases [52].

Vitamin D plays important roles in innate and adaptive immune responses, in the cell cycle and in metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of

immune-mediated disorders, cancer and cardiometabolic diseases [47,49-52]. An inverse correlation between vitamin D concentrations has been described in respect to the prevalence of obesity and type 2 diabetes mellitus [53,54].

VDR play a part in the production of β cells, endothelium, cardiac myocytes and renin suggesting a role for vitamin D in immune-mediated disorders, cancer and cardiometabolic diseases [55-57]. In addition, there is evidence that vitamin D deficiency increases inflammatory cytokines and reduces insulin sensitivity with both these conditions having been described as pathophysiological links in cardiometabolic diseases [58,59]. Metabolism-induced intestinal microbiota endotoxemia has been associated with increased cardiometabolic risk [60].

Vitamin D deficiency could increase the competitive advantage of Haemophilus and Veillonella, as these pathogens are found to be relatively more abundant in subjects with low compared to high intake of vitamin D [61,62]. These gram-negative bacteria could explain the higher levels of LPS detected in people who ingest low levels of vitamin D [63-67]. On the other hand, a relatively small proportion of bacteria with beneficial effects - such as Coprococcus and Bifidobacterium - could activate intestinal immune response and induce local inflammation, requiring anti-inflammatory compensation pathways such as those dependent on 25(OH)D [68-73].

Inverse associations between inflammatory markers and 25(OH)D have been reported. These results support the role of vitamin D in maintaining the homeostasis of the immune system; some authors speculate that this occurs, in part, through interactions with the intestinal microbiota, although the study design excludes establishing cause-and-effect relationships [74].

It has been previously described that vitamin D deficient rats, exposed to a bacterial pathogen, exhibited increased endotoxin translocation and inflammatory cytokine production. There is a significant inverse correlation of 25(OH)D with E-selectin and C-reactive protein concentrations, suggesting that even among healthy individuals, the vitamin D status may cause an anti-inflammatory condition. As a matter of fact, several studies have reported that 25(OH)D plays a significant role in the immune system, as low grade inflammation is correlated with higher serum levels as well as higher consumption [75-77].

In addition, previous studies show that *Akkermansia muciniphila* is linked to effects on metabolic and inflammatory profiles [78]. Using animal models, *A. muciniphila* benefits intestinal permeability, mucosal layer thickness and the metabolism in obesity and type 2 diabetes [79].

Previously, *Haemophilus* was associated with IBD and with levels of LPS, and Veillonella with increased inflammation cytokines [80]. These gram-negative bacteria have an outer layer of LPS that is less prominent in subgroups of patients with higher intakes of 25(OH)D [81-88].

Inflammatory Bowel Disease

More recently, a prospective study evaluated serum vitamin D levels in 104 patients with Crohn's disease. Subjects with mild anal complaints, without any colorectal involvement, composed the control group. There was a high prevalence of vitamin D deficiency in patients with Crohn's disease with no evidence of deficiency among the patients in the control group [89].

Ulcerative colitis and Crohn's disease are immune-mediated diseases, the pathophysiology of which also involves the participation of Th1 cells with the production of IL-2, TNF-α and IFN-γ (2). Decreased serum levels of 25(OH)D have been described in IBD [90-92].

In a study published in the Indian Journal of Medical Research in 2009, researchers at the Christian Medical College in Vellore, India compared serum vitamin D levels in 34 patients with Crohn's disease and 34 matched controls [93]. They found that not only were patients with Crohn's disease significantly more likely to have a poor vitamin D status than healthy patients, but lower levels of vitamin D were also significantly and independently correlated with increased disease severity [93].

Another study was conducted by researchers at the McGille University Health Center by the Universite de Montreal and published in the Journal of Biological Chemistry in 2010 [94,95]. In this study, the researchers found that vitamin D acts directly on the beta-defensin-2 and NOD2 genes, both of which have been associated with Crohn's disease. Beta-defensin-2 is known to encode an antimicrobial protein, while NOD2 helps to alert cells about the presence of invading microbes. Failure of NOD2 is known to prevent the immune system from reacting adequately to intestinal infections [96,97].

A study conducted by researchers at the University of Sheffield, England and published in the BMJ Case Reports in December 2012 suggests that vitamin D supplementation may help reduce the severity of inflammatory bowel syndrome (IBS) or even completely prevent it [98,99]. The research was motivated by a case study of a woman who suffered from IBS for 25 years and who had been unable to obtain consistent relief from all traditional or alternative therapies. After hearing that some people used mega-doses of vitamin D to treat IBS, the woman started a supplementation program that restored her digestive health to virtually normal [100-102].

The mechanism by which vitamin D deficiency occurs most frequently in IBD appears to be due to a combination of effects, such as low intake, vitamin D malabsorption and decreased exposure to the sun [103-110]. In an experiment of IBD using inactivated knockout mice, vitamin D deficiency accelerated the disease with earlier onset of diarrhea and cachexia and higher mortality [111-113]. On the other hand, treatment with 1-alpha, 25-Dihydroxyvitamin D3 [1-alpha, 25(OH)(2)D3] prevented the onset of symptoms and reduced progression and severity [114-116].

A study by Jahnsen et al. [117] found vitamin D deficiency in 27.0 % of patients with Crohn's disease and 15.0 % of those with ulcerative colitis. In this context, the researchers looked at Internet forums where IBS patients discussed vitamin D supplementation. They found that among the 37 patients with IBS who reported having used the therapy, 70 percent had significant improvements in their symptoms [103].

Conclusion

A high prevalence of patients suffering from Crohn's disease has low serum vitamin D levels. However, further studies are still needed, especially in respect to evaluating serum vitamin D levels in clinical treatment and also to investigate the effects of vitamin D supplementation on disease activity and mucosal healing. Thus, it will be possible to evaluate the true effects of vitamin D supplementation in the remission of Crohn's disease and to optimize the treatment of patients and improve their quality of life.

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References

1. Rebouças PC, Netinho JG, Cunrath GS, Ronchi LS, de Melo MMC, et al. (2016) Hypovitaminosis D in patients with Crohn's disease. J coloproctol 36: 59-63.
2. Basson A (2014) Vitamin D and Crohn's disease in the adult patient: a review. JPEN J Parenter Enteral Nutr 38: 438-458.
3. Hassan V, Hassan S, Seyed-Javad P, Ahmad K, Asieh H, et al. (2013) Association between Serum 25 (OH) vitamin D concentrations and inflammatory bowel diseases (IBDs) activity. Med J Malaysia 68: 34-38.
4. Xu XR, Liu CQ, Feng BS, Liu ZJ (2014) Dysregulation of mucosal immune response in pathogenesis of inflammatory bowel disease. World J Gastroenterol 20: 3255-3264.
5. Dumitrescu G, Mihai C, Dranga M, Prelipcean CC (2014) Serum 25-hydroxyvitamin D concentrations and inflammatory bowel disease characteristics in Romania. World J Gastroenterol 20: 2392-2396.
6. Tan B, Li P, Lv H, Li Y, Wang O, et al. (2014) Vitamin D levels and bone metabolism in Chinese adult patients with inflammatory bowel disease. J Dig Dis 15: 116-123.
7. Veit LE, Maranda L, Fong J, Nwosu BU (2014) The vitamin D status in inflammatory bowel disease. PLoS ONE 9: e101583.
8. Raftery T, O'Morain CA, O'Sullivan M (2012) Vitamin D: new roles and therapeutic potential in inflammatory bowel disease. Curr Drug Metab 13: 1294-1302.
9. De Bruyn JR, Van Heeckeren R, Ponsioen CY, van den Brink GR, Löwenberg M, et al. (2014) Vitamin D deficiency in Crohn's disease and healthy controls: a prospective case–control study in the Netherlands. J Crohns Colitis 8: 1267-1273.
10. Cantorna MT, Waddell A (2014) The vitamin D receptor turns off chronically activated T cells. Ann NY Acad Sci 1317: 70-75.
11. Adorini L, Penna G (2008) Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin Pract Rheumatol 4: 404-412.
12. Cantorna MT, Zhu Y, Froicu M, Wittke A (2004) Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. Am J Clin Nutr 80: 1717S-1720S.
13. Hong Q, Xu J, Xu S, Lian L, Zhang M, et al. (2014) Association between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis. Rheumatology 53: 1994-2001.
14. Niino M, Fukazawa T, Miyazaki Y, Takahashi E, Minami N, et al. (2014) Suppression of IL-10 production by calcitriol in patients with multiple sclerosis. J Neuroimmunol 270: 86-94.
15. Turk N, Turk Z (2014) Prevalent hypovitaminosis D in Crohn's disease correlates highly with mediators of osteoimmunology. Clin Invest Med 37: E154-62.
16. Ham M, Longhi MS, Lahiff C, Cheifetz A, Robson S, et al. (2014) Vitamin D levels in adults with Crohn's disease are responsive to disease activity and treatment. Inflamm Bowel Dis 20: 856-860.
17. Jantchou P, Clavel-Chapelon F, Racine A, Kvaskoff M, Carbonnel F, et al. (2014) High residential sun exposure is associated with a low risk of incident Crohn's disease in the prospective E3N cohort. Inflamm Bowel Dis 20: 75-81.
18. Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, et al. (2013) Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis 19: 1921-1927.
19. Jørgensen SP, Hvas CL, Agnholt J, Christensen LA, Heickendorff L, et al. (2013) Active Crohn's disease is associated with low vitamin D levels. J Crohns Colitis 7: e407-13.
20. Raftery T, Merrick M, Healy M, Mahmud N, O'Morain C, et al. (2015) Vitamin D status is associated with intestinal inflammation as measured by fecal calprotectin in Crohn's disease in clinical remission. Dig Dis Sci 60: 2427-2435.
21. Azzopardi N, Ellul P (2014) Disease location and severity may predict vitamin D deficiency in Crohn's. J Crohns Colitis 8: 1336.
22. Vieth R (1999) Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 69: 842-856.
23. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, et al. (2002) Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 76: 187-192.
24. Hollis BW (2005) Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 135: 317-322.
25. Hyppönen E, Power C (2007) Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 85: 860-868.
26. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, et al. (2008) Vitamin D deficiency and risk of cardiovascular disease. Circulation 117: 503-511.
27. Salehpour A, Shidfar F, Hosseinpanah F, Vafa M, Razaghi M, et al. (2012) Vitamin D 3 and the risk of CVD in overweight and obese women: a randomized controlled trial. Br J Nutr 108: 1866-1873.
28. Hewison M (2010) Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 39: 365-379.
29. Cantorna MT (2006) Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol 92: 60-64.
30. Michos ED, Melamed ML (2008) Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care 11: 7-12.
31. Vaidya A (2013) Vitamin D and cardio-metabolic disease. Metabolism 62: 1697.
32. Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C (2011) Vitamin D and diabetes: its importance for beta cell and immune function. Mol Cell Endocrinol 347: 106-120.
33. Kim HJ, Kang CK, Park H, Lee MG (2014) Effects of vitamin D supplementation and circuit training on indices of obesity and insulin resistance in T2D and vitamin D deficient elderly women. J Exerc Nutr Biochem 18: 249.
34. Chiu KC, Chu A, Go VLW, Saad MF (2004) Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr 79: 820-825.
35. Schuch NJ, Garcia VC, Martini LA (2009) Vitamin D and endocrine diseases. Arq Bras Endocrinol Metab 53: 625-633.
36. Norman PE, Powell JT (2014) Vitamin D and cardiovascular disease. Circ Res 114: 379-393.
37. Herrmann M, Sullivan DR, Veillard A, McCorquodale T, Straub IR, et al. (2014) Serum 25-Hydroxy vitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. Diabetes Care 38: 521-528.
38. Wellen KE, Hotamisligil GS (2005) Inflammation, stress, and diabetes. J Clin Invest 115: 1111-1119.
39. Cani PD, Delzenne NM (2007) Gut microflora as a target for energy and metabolic homeostasis. Curr Opin Clin Nutr Metab Care 10: 729-734.
40. Caricilli AM, Picardi PK, de Abreu LL, Ueno M, Prada PO, et al. (2011) Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice. PLoS Biol 9: e1001212.
41. Moraes ACF, Silva IT, Almeida-Pititto B, Ferreira SRG (2014) Microbiota intestinal e risco cardiometabólico: mecanismos e modulação dietética. Arq Bras Endocrinol Metab 58: 317-327.

42. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH (1998) Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 98: 731-733.
43. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, et al. (2013) A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr 109: S1-S34.
44. Almeida-Pititto B, Ribeiro-Filho FF, Bittencourt MS, Lotufo PA, Bensenor I, et al. (2016) Usefulness of circulating E-selectin to early detection of the atherosclerotic process in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Diabetol Metab Syndr 8: 19.
45. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, et al. (2013) Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. PNAS 110: 9066-9071.
46. Kong J, Zhang Z, Musch MW, Ning G, Sun J, et al. (2008) Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am J Physiol Gastrointest Liver Physiol 294: G208-216.
47. Ooi JH, Li Y, Rogers CJ, Cantorna MT (2013) Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. J Nutr 143: 1679-1686.
48. Bashir M, Prietl B, Tauschmann M, Mautner SI, Kump PK, et al. (2015) Effects of high doses of vitamin D3 on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract. Eur J Nutr 55: 1479-1489.
49. Mai V, McCrary QM, Sinha R, Glei M (2009) Associations between dietary habits and body mass index with gut microbiota composition and fecal water genotoxicity: an observational study in African American and Caucasian American volunteers. Nutr J 8: 49.
50. Ly NP, Litonjua A, Gold DR, Celedón JC (2011) Gut microbiota, probiotics, and vitamin D: interrelated exposures influencing allergy, asthma, and obesity. J Allergy Clin Immunol 127: 1087-1094.
51. Ciubotaru I, Green SJ, Kukreja S, Barengolts E (2015) Significant differences in fecal microbiota are associated with various stages of glucose tolerance in African American male veterans. Transl Res 166: 401-411.
52. Folchetti LGD, da Silva IT, de Almeida-Pititto B, Ferreira SRG (2016) Nutritionists' Health Study cohort: a web-based approach of life events, habits and health outcomes. BMJ Open 6: e012081.
53. Guyton AC, Hall JE (2006) Textbook of medical physiology. 11th ed. Philadelphia: Saunders 2006.
54. Matsudo S, Araújo T, Marsudo V, Andrade D, Andrade E, et al. (2001) Questinário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Ver. Bras Ativ Fís Saúde 6: 5-18.
55. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, et al. (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35: 1381-1395.
56. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2011) Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96: 1911-1930.
57. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419.
58. Caporaso JG, Lauber CL, Walters W, Berg-Lyons D, Huntley J, et al. (2012) Ultra-high-throughput microbial community analysis on the Illumina HiSeq and MiSeq platforms. ISME J 6: 1621-1624.
59. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, et al. (2007) Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension 49: 1063-1069.
60. Shankar A, Sabanayagam C, Kalidindi S (2011) Serum 25-hydroxyvitamin D levels and prediabetes among subjects free of diabetes. Diabetes Care 34: 1114-1119.
61. Salehpour A, Hosseinpanah F, Shidfar F, Vafa M, Razaghi M, et al. (2012) A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. Nutr J 11: 78.
62. Ryz NR, Lochner A, Bhullar K, Ma C, Huang T, et al. (2015) Dietary vitamin D3 deficiency alters intestinal mucosal defense and increases susceptibility to Citrobacter rodentium induced colitis 2. Am J Physiol Gastrointest Liver Physiol 309: G730-42.
63. Jorde R, Sollid ST, Svartberg J, Schirmer H, Joakimsen RM, et al. (2016) Vitamin D 20 000 IU per week for five years does not prevent progression from prediabetes to diabetes. J Clin Endocrinol Metab 101: 1647-1655.
64. Mora JR, Iwata M, von Andrian UH (2008) Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol 8: 685-698.
65. Hewison M (2012) An update on vitamin D and human immunity. Clin Endocrinol (Oxf) 76: 315-325.
66. Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, et al. (2013) Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med 8: 33-40.
67. Mellenthin L, Wallaschofski H, Grotevendt A, Völzke H, Nauck M, et al. (2014) Association between serum vitamin D concentrations and inflammatory markers in the general adult population. Metab Clin Exp 63: 1056-1062.
68. Cantorna MT, McDaniel K, Bora S, Chen J, James J (2014) Vitamin D, immune regulation, the microbiota, and inflammatory bowel disease. Exp Biol Med 239: 1524-1530.
69. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, et al. (2011) Enterotypes of the human gut microbiome. Nature 473: 174-180.
70. Qin J, Li Y, Cai Z, Li S, Zhu J, et al. (2012) A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490: 55-60.
71. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, et al. (2011) Linking long-term dietary patterns with gut microbial enterotypes. Science 334: 105-108.
72. Said HS, Suda W, Nakagome S, ChinenH, Oshima K, et al. (2014) Dysbiosis of salivarymicrobiota in inflammatory bowel disease and its association with oral immunological biomarkers. DNA Res 21: 15-25.
73. Van den Bogert B, Meijerink M, Zoetendal EG, Wells JM, Kleerebezem M (2014) Immunomodulatory properties of Streptococcus and Veillonella isolates from the human small intestine microbiota. PLoS One 9: e114277.
74. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez- Humarán LG, et al. (2008) Faecalibacterium prausnitziiisan anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 105: 16731-16736.
75. Collado MC, Isolauri E, Laitinen K, Salminen S (2008) Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. Am J Clin Nutr 88: 894-899.
76. Wu X, Ma C, Han L, Nawaz M, Gao F, et al. (2010) Molecular characterisation of the faecal microbiota in patients with type II diabetes. Curr Microbiol 61: 69-78.
77. Cantarel BL, Waubant E, Chehoud C, Kuczynski J, DeSantis TZ, et al. (2015) Gut microbiota in multiple sclerosis. J Invest Med 63: 729-734.
78. Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, et al. (2012) Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol 188: 2127-2135.
79. Cantorna MT (2010) Mechanisms underlying the effect of vitamin D on the immune system. Proc Nutr Soc 69: 286-289.
80. Mangin M, Sinha R, Fincher K (2014) Inflammation and vitamin D: the infection connection. Inflamm Res 63: 803-819.
81. Assa A, Vong L, Pinnell LJ, Avitzur N, Johnson-Henry KC, et al. (2014) Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. J Infect Dis 210: 1296-1305.
82. Jones BJ, Twomey PJ (2008) Issues with vitamin D in routine clinical practice. Rheumatology 47: 1267-1268.

83. Cantorna MT (2000) Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence. Proc Soc Exp Biol Med 223: 230-233.
84. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, et al. (2006) Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 5: 114-117.
85. Lipps P (2004) Which circulating level of 25-hydroxyvitamin D is appropriate. J Steroid Biochem Mol Biol 90: 611-614.
86. Cantorna MT, Mahon B (2004) Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Bio Med (Maywood) 229: 1136-1142.
87. Lemire JM, Ince A, Takashima M (1992) 1,25-Dihydroxyvitamin D3 attenuates the expression of experimental murine lupus of MRL/I mice. Autoimmunity 12: 143-148.
88. Linker-Israeli M, Elstner E, Klinenberg JR, Wallace DJ, Koeffler HP (2001) Vitamin D(3) and its synthetic analogs inhibit the spontaneous in vitro immunoglobulin production by SLE-derived PBMC. Clin Immunol 99: 82-93.
89. Arnson Y, Amital H, Shoenfeld Y (2007) Vitamin D and autoimmunity: new etiological and therapeutic considerations. Ann Rheum Dis 66: 1137-1142.
90. Bringhurst FR, Demay MB, Kronenberg HM (2008) Hormones and Disorders of Mineral Metabolism. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR editors. Williams Textbook of Endocrinology, 11 ed. Philadelphia: Elsevier, 2008.
91. Leventis P, Patel S (2008) Clinical aspects of vitamin D in the management of rheumatoid arthritis. Rheumatology 47: 1617-1621.
92. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, et al. (2008) The complex role of vitamin D in autoimmune diseases. Scand J Immunol 68: 261-269.
93. Deluca HF, Cantorna MT (2001) Vitamin D – its role and uses in immunology. FASEB J 15: 2579-2585.
94. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C (2008) Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology 47: 920-923.
95. Nagpal S, Na S, Rathnachalam R (2005) Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 26: 662-687.
96. Bandeira F, Griz L, Dreyer P, Eufrazino C, Bandeira C, et al. (2006) Vitamin D deficiency: a global perspective. Arq Bras Endocrinol Metabol 50: 640-646.
97. Lamb EJ, Wong T, Smith DJ, Simpson DE, Coakley AJ, et al. (2002) Metabolic bone disease is present at diagnosis in patients with inflammatory bowel disease. Aliment Pharmacol Ther 16: 1985-1992.
98. Cutolo M (2009) Vitamin D and autoimmune rheumatic diseases. Rheumatology 48: 210-212.
99. Holick MF (2004) Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease and osteoporosis. Am J Clin Nutr 79: 362-371.
100. Cutolo M, Otsa K (2008) Review: vitamin D, immunity and lupus. Lupus 17: 6-10.
101. Steinman L (2007) A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell-mediated tissue damage. Nat Med 13: 139-145.
102. Yu S, Cantorna MT (2008) The vitamin D receptor is required for iNKT cell development. Proc Natl Acad Sci USA 105: 5207-5212.
103. Adorini A, Penna G (2008) Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin Pract Rheumatol 4: 404-412.
104. Harris Jr ED, Schur PH (2007) Pathogenesis of rheumatoid arthritis. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2007.
105. Manolagas SC, Werntz DA, Tsoukas CD, Provvedini DM, Vaughan JH (1986) 1,25-dihydroxyvitamin D3 receptors in lymphocytes from patients with rheumatoid arthritis. J Lab Clin Med 108: 596-600.
106. Gomez-Vaquero C, Fiter J, Enjuanes A, Nogues X, Diez-Perez A, et al. (2007) Influence of the Bsml polymorphism of the vitamin D receptor gene on rheumatoid arthritis clinical activity. J Rheumatol 34: 1823-1826.
107. Tsuji M, Fujii K, Nakano T, Nishii Y (1994) 1 a-hydroxyvitamin D3 inhibits type II collagen-induced arthritis in rats. FEBS Lett 337: 248-250.
108. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, et al. (2004) Vitamin D intake is inversely associated with rheumatoid arthritis. Arthritis Rheum 50: 72-77.
109. Costenbader KH, Feskanich D, Holmes M, Karlson EW, Benito- Garcia E (2008) Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Ann Rheum Dis 67: 530-535.
110. Nielen MMJ, Schaardenburg D, Lems WF, van de Stadt RJ, de Koning MHM, et al. (2006) Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. Arthritis Rheum 54: 3719-3724.
111. Andjelkovic Z, Vojinovic J, Pejnovic N, Popovic M, Dujic A, et al. (1999) Disease modifying and immunomodulatory effects of high dose 1a(OH) D3 in rheumatoid arthritis patients. Clin Exper Rheumatol 17: 453-456.
112. Huisman AM, White KP, Algra A, Harth M, Vieth R, et al. (2001) Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. J Rheumatol 28: 2535-2539.
113. Thudi A, Yin S, Wandstrat AE, Li QZ, Olsen NJ (2008) Vitamin D levels and disease status in Texas patients with systemic lupus erythematosus. Am J Med Sci 335: 99-104.
114. Borba VZC, Vieira JGH, Kasamatsu T, Radominski SC, Sato EI, et al. (2009) Vitamin D deficiency in patients with active systemic lupus erythematosus. Osteoporos Int 2009; 20: 427-433.
115. Carvalho JF, Blank M, Kiss E, Tarr T, Amital H, et al. (2007) Antivitamin D in SLE: preliminary results. Ann N Y Acad Sci 1109: 550-557.
116. Zold E, Szodoray P, Gaal J, Kappelmayer J, Csathy L, et al. (2008) Vitamin D deficiency in undifferentiated connective tissue disease. Arthritis Res Ther 10: R123.
117. Jahnsen J, Falch JA, Mowinckel P, Aadland E (2002) Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. Scand J Gastroenterol 37: 192-199.