REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Vitamin D and inflammatory bowel disease: what do we know so far?

Authors:
Antonio María Caballero Mateos, Raúl Vicente Olmedo-Martín, Amparo Roa-Colomo, María del Mar Díaz Alcázar, Manuel Valenzuela Barranco

DOI: 10.17235/reed.2020.7061/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Caballero Mateos Antonio María, Olmedo-Martín Raúl Vicente, Roa-Colomo Amparo, Díaz Alcázar María del Mar, Valenzuela Barranco Manuel. Vitamin D and inflammatory bowel disease: what do we know so far?. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.7061/2020.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

REV 7061 inglés

Vitamin D and inflammatory bowel disease: what do we know so far?

Antonio M. Caballero Mateos, Raúl Vicente Olmedo Martín, Amparo Roa Colomo, María del Mar Díaz Alcázar and Manuel Valenzuela Barranco

Department of Digestive Diseases. [1]Hospital Universitario Virgen de las Nieves. Granada, Spain. [2]Hospital Regional de Málaga. Málaga, Spain. [3]Hospital Clínico San Cecilio. Granada, Spain. [4]Universidad de Granada. Granada, Spain

Received: 28/03/2020

Accepted: 01/4/2020

Correspondence: Antonio M. Caballero Mateos. Hospital Clínico San Cecilio. Av. del Conocimiento, s/n. 18016 Granada, Spain

e-mail: ogy1492@hotmail.com

ABSTRACT

In the last years,several studies have focused on the involement of vitamin D in different physiological and pathological processes. One of the most interesting actions occurs in the Inflammatory bowel disease, where a higher prevalence of vitamin D deficiency has been observed. This study aimed to review the literature in order to explain its relationship with the disease, the risk factors, measuring the importance of sun exposure, describing how treatments are affected or observing the effect of vitamin supplementation in this type of patients.

Keywords: Inflammatory bowel disease. Vitamin D. Crohn's disease. Ulcerative colitis.

INTRODUCTION

The alteration of the intestinal barrier, predisposing genetic factors, luminal antigens of the digestive tract, environmental factors and an exaggerated immune response

play a fundamental role in the pathogenesis of inflammatory bowel disease (IBD). The role of vitamin D in gut homeostasis and how low levels could take part in different immune-mediated diseases has been demonstrated in the last years.

Vitamin D and calcium malabsorption (both secondary to the inflammatory activity of the gut mucosa or intestinal resection) and a hypercatabolic state provoke a greater prevalence of vitamin D deficiency in IBD as well as osteopenia and osteoporosis. Tobacco, low physical activity and low sunlight exposure are other factors related to vitamin D deficiency in IBD patients.

A recent meta-analysis showed greater prevalence of vitamin D deficiency in patients with Crohn's disease (CD) and ulcerative colitis (UC), as well as a greater risk of incidence than in controls (1). Furthermore, this deficiency has been related to higher inflammatory activity and lower quality of life. Knowing this, multiple experimental and interventional studies have been performed with the goal of analyzing the role of the treatment with vitamin D supplements. However, the results were discordant.

THE PHYSIOLOGY OF VITAMIN D

Ninety per cent of vitamin D is synthetized endogenously in a process where solar radiation is needed, and the remaining 10 % comes from the diet. There are two main forms of vitamin D, D2 (ergocalciferol) and D3 (cholecalciferol). The synthesis of D3 starts in the skin from 7-dehidrocolesterol (7-DHC), which is transformed into cholecalciferol through photolysis, mediated by ultraviolet radiation. Cholecalciferol is later hydrolyzed into calcidiol 25(OH)D, which is the main metabolite and the one used to measure vitamin D levels of the individual. The activation occurs in the kidney, where a second hydrolysis is produced, transforming cholecalciferol into 1,25(OH2)D or calcitriol. Vitamin D2 comes only from the diet (fungus and yeast) and the activation pathway is very similar to D3's. All these processes are regulated by the parathormone (PTH) and by calcium and phosphorus levels.

Vitamin D is responsible for the regulation of calcium and phosphorus, by acting on intestinal absorption, renal excretion and mobilization of calcium from bone. This can be performed by direct action in different tissues or through the vitamin D receptor (VDR). The bond between vitamin D and VDR, and later with the retinoid-X receptor, is

responsible for promoting genetic transcription.

Vitamin D anti-inflammatory action has been demonstrated in the digestive tract, as well as its role in the permeability of the intestinal barrier, the modification of the intestinal microbiome and the regulation of autophagy through different pathways. The vitamin-VDR complex stimulates the expression of occludin and other proteins in the intercellular spaces, aiding the gut barrier integrity. Thus, the intestinal barrier can filter potentially harmful substances such as bacterial lipopolysaccharides. These changes in the barrier affect the gut microbiota, promoting a reduction in the decrease bacterial strains responsible for a stronger immune response. VDR expression is induced by T cells and 25-hydroxilase (key enzyme in the process of activating the vitamin D) expressed in B cells, macrophages and dendritic cells, and it is sometimes induced by interferon and Toll-like receptors (TLR).

The modulating role of vitamin D in immune cells is via different pathways:

- It stimulates the synthesis of anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β.
- It decreases the synthesis of IL- 12, and consequently of TNFα.
- It inhibits the differentiation and maturation of dendritic cells and T lymphocytes.
- It promotes the differentiation of T1 Th1 and Th17 lymphocyte strains into Th2 and regulatory T cells.
- It promotes apoptosis of the Th1 activated cells and the resulting decrease of proinflammatory cytokines such as ICAM 1, interferon or TNF-α in patients with CD (2).
- Depending on the target cell, vitamin D regulates the expression and response of the TLR. TLR are microbial peptides receptors that induce immune responses against them. In monocytes, it avoids the normal response of the production of TNF-α to stimuli from lipopolysaccharide or lipoteichoic acid via the suppression of the TLR2 and TLR4 expression (10). On the other hand, vitamin D induces the expression of TLR2 in macrophages, and the synthesis of antimicrobial peptides such as CYP27B1 and defensin 2, through the NOD 2 and the CAMP pathways (3). Greater levels of CAMP have been observed in CD

patients treated with vitamin D supplements compared to patients treated with placebo (4).

VITAMIN D AND INFLAMMATORY BOWEL DISEASE

Relation and prevalence

The most used cut-off defines 25(OH)D deficiency as < 20 ng/ml, however, not all the medical societies agree. The cut-off is established as 20 ng/ml, from the endocrine point of view and in order to accomplish the vitamin D functions in the bone. Nevertheless, it is considered that the cut-off must be raised to 30 ng/dl in order to reach its immunomodulator effect.

There are several prevalence studies of vitamin D deficiency and its relation to different parameters related to the disease (Table 1). Different meta-analyses carried out so far estimate a prevalence between 38.1-57.7 % in CD and 31.6 % in UC (5). A decrease of 3.99 ng/dl in the levels of 25(OH) have also been observed compared with healthy controls. The estimated risk of vitamin D deficiency in IBD patients was higher than in controls (OR 1.64).

These results coincide with those obtained by Gubatan et al. in a recent meta-analysis of over 27 observational studies and 8,326 IBD patients (6). Patients with vitamin D deficiency showed a greater risk of clinical active disease (OR 1.53), in both CD (OR 1.66) and UC (OR 1.47). They also have a greater risk of mucosal inflammation in CD (OR 1.39) and UC, although it did not reach statistical significance (OR 1.18). There were no differences using various endoscopic scales, fecal calprotectin (FC) or different vitamin D cut-offs (20 or 30 ng/ml). Furthermore, they showed a greater risk of clinical relapse in both pathologies (OR 1.35), which was higher in CD than in UC (OR 1.35 *vs* 1.20) and also a poorer quality of life (OR 1.29).

The most used clinical scales were Crohn's Disease Activity Index (CDAI) in CD and Simple Clinical Colitis Activity Index/Partial Mayo score (SCCAI) in UC. Other studies have used biological parameters such as C reactive protein (CRP) and FC. Studies could not clearly relate CRP with vitamin D levels, showing discordant results. This might be explained by the selection of outpatients with a better clinical state. The increase in CRP in IBD is considered as a low sensitivity marker. FC is well correlated with clinical

and endoscopic parameters, as well as histologic findings. In this case, studies have shown an inverse correlation between vitamin D levels and FC, even using different vitamin D cut-off levels. Some studies have shown a correlation between vitamin D concentration and different endoscopic indexes, where the endoscopic activity was higher in patients with vitamin D deficiency, in both CD and UC (27).

Risk factors

Several risk factors have been described for presenting vitamin D deficiency in IBD patients. The most frequently identified are tobacco, a history of intestinal surgical resection, female sex, obesity and pregnancy. Other risk factors have been proposed such as solar exposure, vitamin D intake, the season where the measure was taken, an ileal affection or fistulizing disease.

IBD and solar exposure

Various studies have shown how the risk of IBD incidence increases at higher latitudes, even in the same country. Patients under treatment with thiopurines or some kind of biologics tend to reduce their sun exposure and the use of sun protection in order to minimize the risk of skin cancer.

Fatigue and quality of life

Gubatan et al. described in their meta-analysis how vitamin D deficiency was related to a higher risk of quality of life deterioration (OR 1.29). In fact, an improvement has been demonstrated when vitamin D levels are restored above 30 ng/ml.

Vitamin D and treatments in IBD

Systemic steroids produce a decrease in calcium absorption, as well as an increase in its renal excretion, secondary to bone resorption and calcium mobilization. On the other hand, steroids induce the transcription of 24-hydroxilase, the hormone responsible for the catabolism of the vitamin.

Direct effects of thiopurines in vitamin D metabolism have not been proven. Cholestyramine, a drug often used in IBD patients, might decrease the absorption of

vitamin D and other fat-soluble vitamins. Recent studies of the relationship between anti-TNFα treatments and vitamin D have not shown a direct effect on the metabolism of vitamin D. However, it has been proposed that levels of vitamin D might be relevant in the response to anti-TNFα agents and the duration of their effects. Santos-Antunes et al. (28) described how low levels of vitamin D were associated with an increase in the incidence of dermatologic adverse events secondary to the treatment. This was mainly observed in patients who presented antinuclear antibodies (ANA) before starting the treatment. Besides, they showed an increase of ANA during treatment and there was a correlation with the appearance of anti-drug antibodies. Consequently, there was a decrease of anti-TNFα activity. Other studies observed that patients with adequate pretreatment levels of vitamin D showed a better clinical response, with a higher probability of remission and a longer treatment length (29). Therefore, studies recommend the measurement and correction of vitamin D levels before starting anti-TNFα treatment.

Vitamin D supplementation in patients with IBD

So far, there have been multiple experimental studies with different designs, but their results are not entirely consistent (Table 2).

Most of the studies do not include a high number of patients, except for the study from Tan, with 154 patients. All achieved a significant increase in vitamin D levels. The dosage varied from oral intake of 1,200 UI daily to a single intramuscular 300,000 UI dose of vitamin D3. Nevertheless, the results in relation to clinical aspects or inflammatory parameters were disappointing. Only two obtained a decrease in the CDAI clinical scale and none in different activity scales in UC.

A recent meta-analysis performed by Li et al. (39) included these studies and some others performed in pediatric patients. This study concluded that levels of vitamin D increased significantly in patients treated mainly with high doses, even in those patients with a deficiency. Treatments would have a low risk of adverse events. Patients treated with vitamin D showed a statically significant lower relapse rate, compared to those treated with placebo. No relationship was observed between the supplements and IBD biomarkers. The authors concluded that IBD patients should be

treated with vitamin D supplements in order to correct its frequent deficiency and diminish the risk of clinical relapse.

CONCLUSIONS

Vitamin D is a fundamental element for the homeostasis of different systems. One of its main functions is the regulation of the calcium metabolism in the gut and bone. Its role in the regulation of the innate and adaptive immunity has been observed in the last years, with an apparent inhibitory effect. Thus, it has an important role in immune disorders and in the gut barrier, as in IBD.

There are multiple retrospective and observational studies relating vitamin D deficiency with active IBD and its complications, such as the need for surgery, hospitalization or malignancy. Vitamin levels could be used as a biomarker of the disease due to the relationship between the deficiency and the inflammatory state. A recent study proposed the measurement of vitamin D levels for monitoring patients under treatment with infliximab due to its strong correlation, along with the drug levels (40). A prospective study has recently shown that patients with CD had normal vitamin D levels before presenting the disease. Years later, once diagnosed and treated, they presented vitamin deficiency. This suggests that this deficiency is a consequence of the disease and not a cause of it (41).

National institutes in the United States recommend a daily intake of 600-4,000 UI of vitamin D. However, the upper threshold does not apply to patients with a deficiency, as frequently occurs in IBD patients. Interventional studies emphasize the importance of treatments with vitamin D supplements in order to restore vitamin levels and decrease the risk of clinical relapse. The dosage or administration route has not yet been established in these cases.

Although it is clear that efforts have been made in the last years to better understand the role of vitamin D and demonstrate its relationship with IBD, many questions remain open:

- What is the best cut-off to define deficiency? Which is the minimum concentration to ensure its effect on immunity? What about IBD?

- How does solar exposure affect the disease? What is the best way to measure it? Could it be considered as a fundamental tool in IBD therapy?
- Is there actually a causal relationship between the deficiency and the appearance of IBD or its complications?
- What kind of IBD patients would benefit most from vitamin supplements? What kind of patients present a higher risk of deficiency? Would a screening test be necessary in every IBD patient?
- What is the best route of vitamin D administration? What is the best dosage?

New studies with a higher statistical power are needed to answer all these questions and many others. They will help to better understand the role of vitamin D in this type of disease and find the best way to prevent its deficiency.

REFERENCES

1. Del Pinto R, Pietropaoli D, Chandar AK, et al. Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. Inflamm Bowel Dis 2015;21:2708-17. DOI: 10.1097/MIB.0000000000000546

2. Reich KM, Fedorak RN, Madsen K, et al. Vitamin D improves inflammatory bowel disease outcomes: basic science and clinical review. World J Gastroenterol 2014;20:4934-47. DOI: 10.3748/wjg.v20.i17.4934

3. Wang TT, Dabbas B, Laperriere D, et al. Direct and indirect induction by 1.25-dihydroxivitamin D3 of the NOD2/CARD15-defensin β2 innate immune pathway defective in Crohn disease. J Biol Chem 2010;285:2227-31. DOI: 10.1074/jbc.C109.071225

4. Raftery T, Martineau AR, Greiller CL, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: results from a randomised doubleblind placebo-controlled study. United European Gastroenterol J 2015;3(3):294-302. DOI: 10.1177/2050640615572176

5. Sadeghian M, Saneei P, Siassi F, et al. Vitamin D status in relation to Crohn's disease: meta-analysis of observational studies. Nutrition 2016;32:505-14. DOI: 10.1016/j.nut.2015.11.008

6. Gubatan J, Chou ND, Nielsen OH, et al. Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease. Aliment Pharmacol Ther 2019;50(11-12):1146-58. DOI: 10.1111/apt.15506

7. Hassan V, Hassan S, Seyed-Javad P, et al. Association between serum 25 (OH) vitamin D concentrations and inflammatory bowel diseases (IBDs) activity. Med J Malaysia 2013;68:34-8. PMID: 23466764

8. Jørgensen SP, Hvas CL, Agnholt J, et al. Active Crohn's disease is associated with low vitamin D levels. J Crohns Colitis 2013;7:e407-13. DOI: 10.1016/j.crohns.2013.01.012

9. Hlavaty T, Krajcovicova A, Koller T, et al. Higher vitamin D serum concentration increases health related quality of life in patients with inflammatory bowel diseases. World J Gastroenterol 2014;20(42):15787-96. DOI: 10.3748/wjg.v20.i42.15787

10. Zator ZA, Cantu SM, Konijeti GG, et al. Pretreatment 25-hydroxyvitamin D levels and durability of anti-tumor necrosis factor-α therapy in inflammatory bowel diseases. J Parenter Enteral Nutr 2014;38:385-91. DOI: 10.1177/0148607113504002

11. Raftery T, Merrick M, Healy M, et al. Vitamin D status is associated with intestinal inflammation as measured by fecal calprotectin in Crohn's disease in clinical remission. Dig Dis Sci 2015;60:2427-35. DOI: 10.1007/s10620-015-3620-1

12. Raffner Basson A, Swart R, Jordaan E, et al. Vitamin D deficiency increases the risk for moderate to severe disease activity in Crohn's disease patients in South Africa, measured by the Harvey Bradshaw Index. J Am Coll Nutr 2016;35:163-74. DOI: 10.1080/07315724.2015.1039665

13. Frigstad SO, Høivik M, Jahnsen J, et al. Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population. Scand J Gastroenterol 2017;52:100-6. DOI: 10.1080/00365521.2016.1233577

14. Meckel K, Li YC, Lim J, et al. Serum 25-hydroxyvitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. Am J Clin Nutr 2016;104:113-20. DOI: 10.3945/ajcn.115.123786

15. Kabbani TA, Koutroubakis IE, Schoen RE, et al. Association of vitamin D level with clinical status in inflammatory bowel disease: a 5-year longitudinal study. Am J

Gastroenterol 2016;111:712-9. DOI: 10.1038/ajg.2016.53

16. Ghaly S, Murray K, Baird A, et al. High vitamin D-binding protein concentration, low albumin, and mode of remission predict relapse in Crohn's disease. Inflamm Bowel Dis 2016;22:2456-64. DOI: 10.1097/MIB.0000000000000894

17. Ye L, Lin Z, Liu J, et al. Vitamin D deficiency is associated with endoscopic severity in patients with Crohn's disease. Gastroenterol Res Pract 2017;1-5. DOI: 10.1155/2017/4869718

18. Winter RW, Collins E, Cao B, et al. Higher 25-hydroxyvitamin D levels are associated with greater odds of remission with anti-tumour necrosis factor-α medications among patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2017;45:653-9. DOI: 10.1111/apt.13936

19. Schäffler H, Schmidt M, Huth A, et al. Clinical factors are associated with vitamin D levels in IBD patients - A retrospective analysis. J Dig Dis 2017;19:24-32. DOI: 10.1111/1751-2980.12565

20. Gubatan J, Mitsuhashi S, Zenlea T, et al. Low serum vitamin D during remission increases risk of clinical relapse in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2016;15:240-6. DOI: 10.1016/j.cgh.2016.05.035

21. Alrefai D, Jones J, El-Matary W, et al. The association of vitamin D status with disease activity in a cohort of Crohn's disease patients in Canada. Nutrients 2017;9:1112. DOI: 10.3390/nu9101112

22. Olmedo Martín RV, González Molero I, Olveira Fuster G, et al. Deficiencia de vitamina D en pacientes ambulatorios con enfermedad inflamatoria intestinal: prevalencia y asociación con la actividad clínica-biológica. Rev Esp Enferm Dig 2019;111(1):46-54. DOI: 10.17235/reed.2018.5714/2018

23. Bours P, Wielders J, Vermeijden JR, et al. Seasonal variation of serum 25-hydroxyvitamin D levels in adult patients with inflammatory bowel disease. Osteoporos Int 2011;22:2857-67. DOI: 10.1007/s00198-010-1484-y

24. Scolaro BL, Barretta C, Matos CH, et al. Deficiency of vitamin D and its relation with clinical and laboratory activity of inflammatory bowel diseases. J Coloproctol 2018;38:99-104. DOI: 10.1016/j.jcol.2017.11.005

25. Hausmann J, Kubesch A, Amiri M, et al. Vitamin D deficiency is associated with increased disease activity in patients with inflammatory bowel disease. J Clin Med 2019;8:1319. DOI: 10.3390/jcm8091319

26. López-Muñoz P, Beltrán B, Sáez-González E, et al. Influence of vitamin D deficiency on inflammatory markers and clinical disease activity in IBD patients. Nutrients 2019;11:1059. DOI: 10.3390/nu11051059

27. Meckel K, Li YC, Kocherginsky M, et al. Serum 25-hydroxivitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. Am J Clin Nutr 2016;104(1):113-20. DOI: 10.3945/ajcn.115.123786

28. Santos-Antunes J, Nunes AC, Lopes S, et al. The relevance of vitamin D and antinuclear antibodies in patients with inflammatory bowel disease under anti-TNF treatment: a prospective study. Inflamm Bowel Dis 2016;2(5):1101-6. DOI: 10.1097/MIB.0000000000000697

29. Winter RW, Collins E, Cao B, et al. Higher 25-hydroxivitamin D levels are associated with greater odds of remission with anti-tumour necrosis factor-α medications among patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2017;45(5):653-9. DOI: 10.1111/apt.13936

30. Jørgensen SP, Agnholt J, Glerup H, et al. Clinical trial: vitamin D3 treatment in Crohn's disease - A randomized double-blind placebo controlled study. Aliment Pharmacol Therap 2010;32:377-83. DOI: 10.1111/j.1365-2036.2010.04355.x

31. Yang L, Weaver V, Smith JP, et al. Therapeutic effect of vitamin D supplementation in a pilot study of Crohn's patients. Clin Transl Gastroenterol 2013;4:e33. DOI: 10.1038/ctg.2013.1

32. Dadaei T, Safapoor MH, Asadzadeh Aghdaei H, et al. Effect of vitamin D3 supplementation on TNF-α serum level and disease activity index in Iranian IBD patients. Gastroenterol Hepatol Bed Bench 2015;8(1):49-55.

33. Sharifi A, Hosseinzadeh-Attar MJ, Vahedi H, et al. A randomized controlled trial on the effect of vitamin D3 on inflammation and cathelicidin gene expression in ulcerative colitis patients. Saudi J Gastroenterol 2016;22:316-23. DOI: 10.4103/1319-3767.187606

34. Garg M, Hendy P, Ding JN, et al. The effect of vitamin D on intestinal inflammation in patients with ulcerative colitis. J Crohns Colitis 2018;12(8):963-72. DOI: 10.1093/ecco-jcc/jjy052

35. Mathur J, Naing S, Mils P, et al. A randomized clinical trial of vitamin D3 (cholecalciferol) in ulcerative colitis patients with hypovitaminosis D3. Peer J 2017;5:e3654. DOI: 10.7717/peerj.3654

36. Narula N, Cooray M, Anglin R. Impact of high-dose vitamin D3 supplementation in patients with Crohn's disease in remission: a pilot randomized double-blind controlled study. Dig Dis Sci 2017;62:448-55. DOI: 10.1007/s10620-016-4396-7

37. Tan B, Li P, Lv H, et al. Treatment of vitamin D deficiency in Chinese inflammatory bowel disease patients: a prospective, randomized, open-label pilot study. J Dig Dis 2018;19(4):215-24. DOI: 10.1111/1751-2980.1259

38. Jun JC, Yoon H, Choi YJ, et al. The effect of vitamin D administration on inflammatory markers in patients with inflammatory bowel disease. Intest Res 2019;17(2):210-7. DOI: 10.5217/ir.2018.00081

39. Li J, Chen N, Wang D, et al. Efficacy of vitamin D in treatment of inflammatory bowel disease. Medicine 2018;97:e12662. DOI: 10.1097/MD.0000000000012662

40. Mechie NC, Mavropoulou E, Ellenrieder V, et al. Distinct association of serum vitamin D concentration with disease activity and trough levels of infliximab and adalimumab during inflammatory bowel disease treatment. Digestion 2019;1-10. E-pub ahead of print. DOI: 10.1159/000502515

41. Limketkai BN, Singla MB, Rodríguez B, et al. Levels of vitamin D are low after Crohn's disease is established but not before. Clin Gastroenterol Hepatol 2019;18(8):1769-76. DOI: 10.1016/j.cgh.2019.09.034

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Table 1. Studies of prevalence of vitamin D deficiency in IBD patients and its relationship with different aspects of the disease

Author	*Year*	*Country*	*Design*	*Vitamin D deficiency cut-off (ng/ml)*	*Number of patients*	*Results*
Hassan (7)	2012	Iran	Retrospective observational	10	60 (26 CD/34 UC)	No association with IBD activity
Jorgensen (8)	2013	Denmark	Cross-sectional	20	182 CD	Inverse relationship with CDAI and CRP
Hlavaty (9)	2014	Slovakia	Cross-sectional	20	220 (141 CD/79 UC)	Correlation with the quality of life
Zator (10)	2014	United States	Retrospective observational	30	101 (74 CD/27 UC)	Association with a worse response to anti-TNFα
Raftery (11)	2015	Ireland	Cross-sectional	20	119 CD	No association with CDAI nor CRP Association with FC in patients with clinical remission
Raffner-Basson (12)	2015	South Africa	Retrospective observational	20	186 CD	Higher risk of clinical activity
Frigstad (13)	2016	Norway	Prospective observational	20	408 (230 CD/178 UC)	Increased risk of activity and association with high levels of FC
Meckel (14)	2016	United States	Cross-sectional	20	230 UC	Increased risk of endoscopic activity
Kabbani (15)	2016	United States	Prospective observational	20	965 (598 CD/367 UC)	Increased risk of clinical activity, surgery, resource consumption and

						worsening of quality of life
Ghaly (16)	2016	Australia	Prospective observational	20	309 CD	Increased risk of clinical relapse
Ye (17)	2017	China	Cross-sectional	20	131 CD	Increased risk of clinical and endoscopic activity
Winter (18)	2017	United States	Retrospective observational	20	173 (116 CD/57 UC)	Increased risk of relapse in patients treated with anti-TNFα (OR 2.64)
Schaffler (19)	2017	Germany	Retrospective observational	20	208 (123 CD/85 UC)	Increased risk of activity
Gubatan (20)	2017	United States	Prospective observational	35	70 CU	Increased risk of clinical activity, hospitalization and treatment intensification
Alferai (21)	2017	Canada	Prospective observational	12	201 CD	Increased risk of clinical activity
Olmedo (22)	2017	Spain	Cross-sectional	20	224 (150 CD/74 UC)	Increased risk of clinical activity and FC in patients with CD
Bours (23)	2018	Netherlands	Retrospective observational	20	216 (131 CD/185 UC)	Increased risk of clinical activity
Scolaro (24)	2018	Brazil	Retrospective observational	20	60 (34 CD/26 UC)	Increased risk of clinical activity and inflammation of the mucosa
Hausmann	2019	Germany	Retrospective	30	470 (272 CD/198	Increased risk of

(25)			observational		UC)	clinical activity and inflammatory parameters
López-Muñoz (26)	2019	Spain	Retrospective observational	30	84	Increased risk of clinical activity, relapses and the need for treatment intensification

CD: Crohn's disease; UC: ulcerative colitis; CRP: C reactive protein; CDAI: Crohn's Disease Activity Index; IBD: inflammatory bowel disease; FC: fecal calprotectin; OR: odds ratio.

Table 2. Experimental studies with vitamin D supplements in patients with IBD

Author (year)	*Number of patients*	*Treatment*	*Dose (IU)*	*Duration (months)*	*Control*	*Average increase of Vit D (Ng/Ml)*	*Results*
Jorgensen (2010) (30)	108 CD	VitD3 oral/24 h	1,200	3	Placebo	10.8	No reduction of relapses
Yang (2013) (31)	18 CD	VitD3 oral/24 h	5,000	6	-	28	Decrease of CRP and CDAI
Raftery (2015) (11)	27 CD	VitD3 oral/24 h	2,000	3	Placebo	9.2	Decrease of CRP, no changes in FC
Dadaei (2015) (32)	108 (16 CD/92 UC)	VitD3 oral/7 days	50,000	3	No VitD	52.4	No changes in anti-TNFα levels
Sharifi (2016) (33)	90 UC	One single dose VitD3 im	300,000	3	Placebo	7.5	Reduction of CRP
Garg (2017) (34)	10 (5 CD/5 UC)	VitD3 oral with a dose adjustment /4 weeks	10,000	3	-	20.8	Reduction of CDAI, no changes in CF
Mathur (2017) (35)	18 UC	VitD3 oral/24 h	4,000	3	2,000 UI VitD3	16.8	Reduction of PCR, not in Partial Mayo Scale
Narula (2017) (36)	34 CD	VitD3 oral/24 h	10,000	12	1,000 UI VitD3	34.8	No decrease of relapses
Tan (2018) (37)	145 (71 CD/74 UC)	VitD3 oral/3 months	150,000	12	Placebo	EC: 12.4 CU: 17.4	No clinical changes nor CRP or FC
Jun (2018) (38)	70 (29	VitD3	1,000	6	-	CD: 22.6	No decrease of CRP

	CD/41 UC)	oral/24 h				CU: 24.2	

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; CRP: C reactive protein; CDAI: Crohn's Disease Activity Index; FC: fecal calprotectin.