10.18606/2318-1419/amazonia.sci.health.v12n1p232-247

ARTIGO DE REVISÃO

<< Recebido em: 02/11/2023 Aceito em: 27/01/2024. >>

Effects of vitamin d deficiency on inflammatory markers in Inflammatory Bowel Diseases: a systematic review of observational studies

Efeitos da deficiência de vitamina D sobre marcadores inflamatórios em Doenças Inflamatórias Intestinais: uma revisão sistemática de estudos observacionais

Mayara Storel Beserra de Moura[1], Gleyson Moura dos Santos[2], Paulo Víctor de Lima Sousa[3], Vitória Ribeiro Mendes[4], Regina Márcia Soares Cavalcante[5], José Miguel Luz Parente[6], Cecilia Maria Resende Gonçalves de Carvalho[7], Karoline de Macêdo Gonçalves Frota[8], Nadir do Nascimento Nogueira[9].

ABSTRACT

Objectives: In this review, we systematically evaluated the effects of vitamin D deficiency on inflammatory markers in Inflammatory Bowel Diseases (IBD). Research Methods & Procedures: We conducted a systematic review of observational studies in the PubMed, Scopus, Science Direct, and Web of Science databases. The selection of papers and evaluation of their methodological quality were carried out by two independent reviewers and disagreements were resolved by a third reviewer. Data Analysis: Ten papers were included, out of which only three found no association between vitamin D and inflammatory markers. The cut-off points for vitamin D deficiency ranged from <20 to ≤35 ng/mL. Conclusions: Vitamin D deficiency is associated with an increase in inflammatory markers in patients with IBD, demonstrating the importance of this micronutrient in modulating the inflammatory response.

Keywords: Crohn disease. Inflammation. Inflammatory bowel disease. Ulcerative colitis. Vitamin D Deficiency.

RESUMO

Objetivos: Nesta revisão, avaliamos sistematicamente os efeitos da deficiência de vitamina D nos marcadores inflamatórios nas Doenças Inflamatórias Intestinais (DII). Métodos e procedimentos de pesquisa: Realizamos uma revisão sistemática de estudos observacionais nas bases de dados PubMed, Scopus, Science Direct e Web of Science. A seleção dos artigos e a avaliação da qualidade metodológica foram realizadas por dois revisores independentes e as divergências foram resolvidas por um terceiro revisor. Análise dos dados: Foram incluídos dez artigos, dos quais apenas três não encontraram associação entre vitamina D e marcadores inflamatórios. Os pontos de corte para deficiência de vitamina D variaram de <20 a ≤35 ng/mL. Conclusões: A deficiência de vitamina D está associada ao aumento de marcadores inflamatórios em pacientes com DII, demonstrando a importância deste micronutriente na modulação da resposta inflamatória.

Palavras-chave: Colite Ulcerativa. Deficiência de Vitamina D. Doença de Crohn. Doenças Inflamatórias Intestinais. Inflamação.

[1]PhD student in the Postgraduate Program in Food and Nutrition, Federal University of Piauí, Teresina - PI, Brazil. Email: mayarastorel@hotmail.com. ORCID: https://orcid.org/0000-0003-2012-1291.

[2]PhD from the Postgraduate Program in Food and Nutrition, Federal University of Piauí, Teresina - PI, Brazil. Email: g_leyson_moura@hotmail.com. ORCID: https://orcid.org/0000-0003-0904-1995.

[3]PhD from the Postgraduate Program in Food and Nutrition, Federal University of Piauí, Teresina - PI, Brazil. Email: paulovictor.lima@hotmail.com. ORCID: https://orcid.org/0000-0003-1486-0661.

[4]Master's student in Sciences and Health at the Federal University of Piauí, Teresina-PI, Brazil. Email: vikmendes@hotmail.com. ORCID: https://orcid.org/0000-0001-9389-0425.

[5]PhD from the Postgraduate Program in Food and Nutrition, Federal University of Piauí, Teresina - PI, Brazil. Email: reginalunna@hotmail.com. ORCID: https://orcid.org/0000-0002-0500-9990.

[6]PhD in Medical Sciences from the State University of Campinas, Campinas – SP, Brazil. Email: jparente@ufpi.edu.br. ORCID: https://orcid.org/0000-0003-4563-2784.

[7]Post-doctorate in Nutrition and Public Health from the Faculty of Public Health of the University of São Paulo. SP, Brazil. Email: ceciliacvalho@ufpi.edu.br. ORCID: https://orcid.org/0000-0002-8707-1447.

1. INTRODUCTION

Inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory conditions of unknown etiology. However, scientific evidence points to the probable involvement of an exacerbated mucosal immune response to components of the intestinal microbiota in genetically predisposed individuals.[1,2,3,4] In a recent survey comprising the years from 1990 to 2017, it was observed that the number of people with IBD increased from 3.7 million to 6.8 million, which represents an increase of 85.1% in the global prevalence of IBD.[5]

These diseases still have no cure and have periods of remission and relapse, with the latter being characterized by an exacerbated mucosal immune response and chronic inflammation[6,2,7] resulting from the imbalance between cytokines with pro-inflammatory activity, regulatory T cells in the blood, and the inflamed intestinal mucosa.[8,9]

Micronutrient deficiencies are frequently observed in patients with IBD. In particular, vitamin D (VitD) deficiency has been verified in clinical, endoscopic, and histological disease recurrence.[10,11] This vitamin is directly related with the regulation of the immune system[12], reducing the proliferation of Th1 effector T lymphocytes and Th2 differentiation, as well as inhibiting dendritic cell differentiation, which are protective mechanisms against IBD.[13,14] Thus, low VitD concentrations are directly associated with increased disease activity, mucosal inflammation, clinical recurrence, and low quality of life.[15] These parameters can be improved by adjusting the status of this micronutrient through VitD supplementation regardless of dose, according to a meta-analysis.[16]

Considering the high prevalence of IBD, as well as the effect of VitD on the inflammatory condition in IBD, the aim of this study was to evaluate the effects of VitD deficiency on inflammatory markers in IBD through a systematic review of observational studies.

2. REVIEW METHODOLOGY

2.1 Eligibility Criteria

This is a systematic review of observational studies of the scientific literature. The PECO strategy (Table 1) was used in the elaboration of the guiding question of this review: does VitD deficiency modulate inflammatory markers in IBD?

The review included observational studies (cross-sectional and cohort studies). No restrictions in terms of year of publication, type of inflammatory markers that were related to the effects of VitD in adult patients with IBD, and gender were performed. Pilot studies, papers that did not offer access to the full content, reviews, animal studies, studies with children, clinical trials, and studies with other diseases were excluded.

Table 1. PECO criteria for inclusion of studies.

Abbreviation	Definitions	Ask components
P	Participants/Population	Patients with DII
E	Exposure	VitD deficiency
C	Comparison	No exposure to VitD deficiency
O	Outcome	Increase in inflammatory markers

Source: Own preparation, 2023.

2.2 Information Sources

The systematic literature search was conducted in the electronic databases Pubmed, Scopus, Science Direct, and Web of Science. The review protocol was registered with PROSPERO (Ref: CRD42022310842).

2.3 Search Strategy

In the search, strategy was used keywords combined using boolean operators (AND and OR), related to "inflammatory bowel disease", "Crohn disease", "ulcerative colitis", "vitamin D", cholecalciferol e "inflammatory markers", adapted appropriately for each database. No limits were applied to the language, and foreign documents were translated.

PUBMED: ((((("inflammatory bowel disease"[All Fields] OR "Crohn disease"[All Fields]) OR "Crohn disease"[MeSH Terms]) OR "ulcerative colitis"[All Fields]) AND ((("vitamin D"[All Fields] OR "vitamin D"[MeSH Terms]) OR ("cholecalciferol"[MeSH Terms] OR "cholecalciferol"[All Fields])) OR "cholecalciferol"[MeSH Terms])) AND "inflammatory markers"[All Fields].

SCOPUS: (TITLE-ABS-KEY ("inflammatory bowel disease" OR "Crohn's disease" OR "ulcerative colitis") AND TITLE-ABS-KEY ("vitamin D" OR “cholecalciferol) AND TITLE-ABS-KEY

("inflammatory markers") AND NOT TITLE-ABS-KEY ("review" [publication AND type])) AND (LIMIT-TO (DOCTYPE, "ar")) AND (EXCLUDE (EXACTKEYWORD, "Animals")).

SCIENCE DIRECT: (TITLE-ABS-KEY ("Inflammatory bowel disease" OR "Crohn disease" OR "ulcerative colites") AND TITLE-ABS-KEY ("vitamin D" OR cholecalciferol) AND TITLE-ABS-KEY ("inflammatory markers").

WEB OF SCIENCE: ((((((((((((((((((TI=("inflammatory bowel disease")) OR AB=("inflammatory bowel disease")) OR KP=("inflammatory bowel disease")) OR TI=("Crohn disease")) OR AB=("Crohn disease")) OR KP=("Crohn disease")) OR TI=("ulcerative colitis")) OR AB=("ulcerative colitis")) OR KP=("ulcerative colitis")) AND TI=("vitamin D")) OR AB=("vitamin D")) OR KP=("vitamin D")) OR TI=(cholecalciferol)) OR AB=(cholecalciferol)) OR KP=(cholecalciferol)) AND TI=("inflammatory markers")) OR AB=("inflammatory markers")) OR KP=("inflammatory markers"))) NOT ALL=(review)) NOT ALL=(Animals).

2.4 Selection Process

The selection of papers was carried out by two independent reviewers (GMDS and MSBM), who identified eligible papers by reading the title and excluding those considered irrelevant, performing the same procedure when reading the abstract and the full text. Disagreement between researchers was resolved by a third reviewer (PVLS). Subsequently, to maximize the results, a manual search was performed to verify if the references cited in the retrieved studies would also fit the eligibility criteria. The last search was updated in August 2023.

2.5 Risk For Bias Assessment

The Newcastle-Ottawa[17] scale was used for cohort studies, whereas the Joanna Briggs Institute's (2014)[18] Critical Appraisal Tools were used for cross-sectional studies. In each protocol, the percentage of "yes" answers for each study was calculated and the risk of bias was classified as high (≤ 49%), moderate (between 50 and 69%), and low (≥ 70%).[18] The risk of bias was assessed by two independent reviewers (MSBM and PVLS). The results were compared and differences were resolved with the participation of a third reviewer (GMDS). PRISMA recommendations were adopted in this review[19] and the summary of results was organized based on the following relevant information obtained from the eligible papers: authors' names, year of

publication, location, type of study, duration, sample size, gender, age, inflammatory markers, VitD cut-off points, and key outcomes.

3. RESULTS

A total of 2,685 papers were identified in the selected databases. As shown in Figure 1, after excluding irrelevant papers, 198 remained for the stage of reading titles and abstracts. Of these, only ten papers were identified as eligible for this systematic review.

From the evaluation of the eligible studies (Table 2), it was observed that these were carried out in 1,435 adults with IBD, 495 with CD, and 940 with UC, being 672 men and 763 women, with mean age ranging from 35.7 to 48.6 years, of different ethnicities, followed-up for a period from six months to three years, in nine countries (Brazil, Netherlands, United States of America, Canada, Switzerland, Iran, Spain, Poland, and Germany), and published from 2011 to 2021. Out of the selected papers 50% are cohort studies and 50% cross-sectional studies.

As shown in Table 2, the authors considered the cut-off point from ≤20 ng/mL to ≤35 ng/mL as VitD deficiency, and related it to the following inflammatory markers: red cell distribution width (RDW), erythrocyte sedimentation rate (ESR), fibrinogen (FBG), mean platelet volume (MPV), leukocytes, platelet count, fecal calprotectin (FC), C-reactive protein (CRP), albumin, and cytokines IL-4, IL-10, IL-6, IL-8, IL-17A, and TNF-α. Only three studies found no association between VitD and inflammatory markers.

3.1 Vitamin D and Hematological Markers

Out of the total number of papers, seven[20-26] related VitD with hematological markers. Bours et al.[20] demonstrated that participants in the lowest quartile (<16.8 ng/mL) of the VitD classification had a greater increase in RDW and ESR, with RDW being more expressive in patients with CD. Concomitantly, increased disease activity was observed. Scolaro et al.[23] also found that patients with VitD deficiency showed a positive association with ESR rates. However, other authors have not observed a significant association of VitD with FBG[24], MPV[26], leukocytes[21,25,26] and platelet count[26].

3.2 Vitamin D and Fecal Calprotectin

Out the four papers that investigated the relationship between VitD and FC concentrations, only two[21,24] identified a significant association between these parameters. Caviezel et al.[21] demonstrated an inverse correlation between FC and VitD in patients with CD, a result not observed in UC. In CD patients, this correlation was identified only in those with acute inflammation, characterized by FC >100 µg/g, with a significant impact on 25(OH) D concentrations.

In the study by López - Muñoz et al.[24], there was an inverse correlation between VitD and FC for patients with CD and UC. In addition, significant differences were observed for FC when comparing the VitD groups with severe (<15 ng/mL) and moderate (>15-30 ng mL) deficiency and sufficiency (>30 ng mL), with FC values of 345 µg/g, 46 µg/g, and 30 µg/g, respectively, thus demonstrating that FC values change as a function of VitD concentrations. In addition, it was also possible to observe that the group with severe deficiency was the one with the highest probability of having relapses and undergoing clinical consultations and hospitalizations.

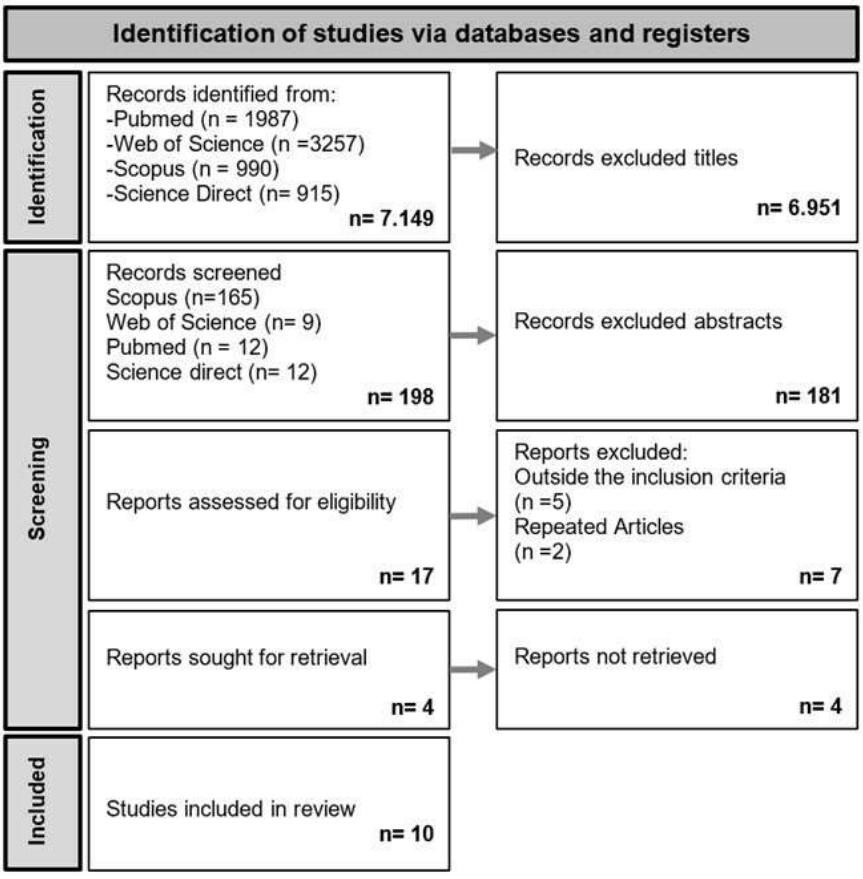

Figure 1. PRISMA flowchart of study selection.
Source: Own preparation, according to findings, 2023

Table 2. Characteristics of observational studies are included in this review.

Author, year, country	Type of study	Duration	Participants (n)	Type of DII (Mean Age (y))	Inflammatory markers	Cut-off point for VitD deficiency	Outcomes of interest
Bours et al., 2011, Netherlands[20]	Cohort studies	6 mo	(316): 136 M/180W	UC (48.5)	RDW, ESR, CRP	<20 ng/mL	Lowest quartile of VitD (<16.8 ng/mL): ↑RDW, ↑ESR, = CRP
Meckel et al., 2016, USA[27]	Cross-sectional studies	N/A	(230): 123 M/107W	UC (45.8)	TNF-α, IL-8	<20 ng/mL	Inverse association: TNF-α, IL-8
Alrefai et al., 2017, Canada[28]	Cohort studies	3 y	(201): 118M/83W	CD (41.5)	CRP	≤20 ng/mL.	↓VitD: ↑ CRP
Caviezel et al., 2018, Switzerland[21]	Cross-sectional studies	N/A	(156) CD: 51 M/48 W UC: 26 M/31 W	DC (41,2) UC (41.5)	CRP, FC, Leukocytes	<20 ng/mL	Inverse correlation (DC): FC, CRP, FC >100 µg/g: ↓VitD
Guabatan et al., 2018, USA[29]	Cohort studies	12 mo	(70): 25 M/45W	UC (48.6)	IL-4, IL-10 IL-6, IL-8, IL-17A, TNF-α, IFN-γ	≤35 ng/mL	Positive correlation: IL-10, (IL-4+IL-10/IL-17A+TNF-α) and (IL-4+IL-10/IL-6+TNF-α).
'Sharifi et al., 2018, Itan[22]	Cross-sectional studies	N/A	(90): 51 M/39 W	UC (36.0)	ESR, CRP	<30 ng/mL	= ESR, = CRP
Scolaro et al., 2018, Brazil[23]	Cross-sectional studies	N/A	(60): CD:34 UC:26	CD/ UC Not described	FC, CRP, ESR	<30 ng/mL	↓VitD: ↑ESR, = CRP, =FC
López-Muñoz et al., 2019, Spain[24]	Cohort studies	3 y	(85): 46 M/39 W UC:25 CD: 60	CD/ UC (43.7)	CRP, FC, FBG	<30 ng/mL.	Inverse correlation: FC (DC/RCU); CRP (RCU), =FBG
Aksan et al., 2020, Germany[25]	Cross-sectional studies	N/A	(188): 88 M/100 W CD: 84 UC: 104	CD/ UC (45.5)	Albumin, Leukocytes, CRP, FC	<20 ng/mL	=Albumin, = Leukocytes, = CRP, =FC
Zielińska et al., 2021, Poland[26]	Cohort studies	Not described	(39): 22M/17W CD:17 UC: 22	CD/ UC (35.74) GC: (38.73)	Leukocytes, PLT, VPM, CRP	<25 ng/mL	= Leukocytes, = PLT, =VPM, = CRP

Legend: VitD: vitamin D; CD: Crohn's disease; UC: ulcerative colitis; CG: group control; ESR: erythrocyte sedimentation rate; FBG: fibrinogen; FC: fecal calprotectin; IFN-γ: Interferon-gamma IL: interleukin; CRP: C-reactive protein; RDW: red blood cell distribution width; TNF-α: tumor necrosis factor α; MPV: mean platelet volume; PLT: blood platelets; M: men; W: woman; N/A: not applicable; = No significant association, ↑: increase; ↓: reduction; USA: *United States* of America. Source: Own preparation, according to findings, 202

3.3 Vitamin D and Acute-Phase Proteins

Out of the ten papers included, eight analyzed acute-phase proteins: CRP[23] and CRP and albumin.[20-22,24-26,28] Alrefai et al.[30] observed that patients with CD and VitD deficiency had high CRP. Similarly, Calviezel et al.[21] found that CRP showed an inverse correlation with VitD concentrations in these patients, which is a result that was not observed for the UC group. However, no significant differences were observed between VitD and CRP when these patients were classified as inflamed (CRP >5 mg/L) and non-inflamed (CRP ≤5 mg/L). On the contrary, López-Muñoz et al.[24] observed a strong correlation between CRP and VitD exclusively in patients with UC.

Supporting the results of the aforementioned studies, Alrefai et al.[28] also observed in patients with CD and VitD insufficiency (≤30 ng/mL) that the chance of having the active disease was 3.4-fold greater than in the reference group (VitD deficiency ≤ 20 ng/mL). On the other hand, other studies did not observe significant differences between CRP and VitD.[20,22,25,26] As for the relationship between VitD and albumin, only one study that did not observe a significant different was identified.[25]

3.4 Vitamin D and Cytokines

Regarding cytokines, two studies evaluated the relationship between these proteins and VitD. Meckel et al.[27] demonstrated an inverse and significant association between the serum concentrations of VitD, TNF-α, and IL-8, as people with high VitD concentrations (>20ng/mL) showed 1.8 and 6-fold decrease in the expression of TNF-α and IL-8, respectively. Guabatan et al.[29] found a positive correlation between VitD and IL-10 concentrations and the anti-inflammatory profile (IL-4+IL-10). They also found that higher VitD concentrations were correlated with increasing levels of anti-inflammatory and pro-inflammatory cytokines (IL-4+IL-10/IL-17A+TNF-α and IL-4+IL-10/IL-6+TNF-α). Thus, the results indicate that higher concentrations of VitD are associated with the phenotype of anti-inflammatory cytokines.

3.5 Risk of Bias Assessment

Regarding the quality of the eligible cohort studies (Table 3), four had a low risk of bias, characterizing excellent methodological quality in the evaluated domains. Only one paper had a high risk of bias. Regarding cross-sectional studies (Table 4), only one paper had a high risk of bias. The others showed good methodological quality.

Table 3. Evaluation of risk for bias for observational (Cohort) studies using the Newcastle-Ottawa Tool[17].

ITEM	E1	E2	E3	E4	E5
SELECTION					
Representativeness of the exposed cohort	1	1	1	1	0
Selection of the non-exposed cohort	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1
Demonstration that outcome of interest was not present at start of study	1	1	1	0	0
COMPARABILITY					
Comparability of cohorts on the basis of the design or analysis	2	2	2	1	1
OUTCOME					
Assessment of outcome	1	1	1	1	1
Was follow-up long enough for outcomes to occur	1	1	1	1	0
Adequacy of follow-up of cohorts	1	1	1	1	0
TOTAL	9/9	9/9	9/9	7/9	4/9
%	100	100	100	77.77	44.4
CLASSIFICATION	LR	LR	LR	LR	HR

Legends: E: study; E1: Bours et al.[20]; E2: Alrefai et al.[28]; E3: Guabatan et al.[29]; E4: López-Muñoz et al.[24]; E5: Zielińska et al.[26]; LR: low risk; HR: high risk. Source: Own preparation, according to findings, 2023.

Table 4. Evaluation of risk for bias for observational (cross-sectional) studies using the Joanna Briggs Institute Prevalence Critical Appraisal Tool[18].

ITEM	E6	E7	E8	E9	E10
Were the criteria for inclusion in the sample clearly defined?	1	1	1	1	1
Were the study subjects and the setting described in detail?	1	1	1	1	1
Was the exposure measured in a valid and reliable way?	1	1	1	0	1
Were objective, standard criteria used for measurement of the condition?	1	1	1	0	1
We're confounding factors identified?	1	1	0	0	0
Were strategies to deal with confounding factors stated?	1	1	0	0	0
Were the outcomes measured in a valid and reliable way?	1	1	1	0	1
Was appropriate statistical analysis used?	1	1	1	1	1
TOTAL	8/8	8/8	6/8	3/8	6/8
%	100	100	75	37.5	75
CLASSIFICATION	LR	LR	LR	HR	LR

Legends: E: study; E6: Meckel et al.[27]; E7: Caviezel et al.,[21]; E8: Sharifi et al.,[22]; E9: Scolaro et al.[23]; E10: Aksan et al.,[25]; LR: low risk; HR: high risk. Source: Own preparation, according to findings, 2023.

4. DISCUSSION

This systematic review was carried out to investigate the relationship between VitD deficiency and inflammatory markers in patients with IBD. Studies have shown that VitD deficiency is frequent among patients with IBD when compared to the general population and the deficiency of this vitamin is considered an environmental factor in the pathogenesis of these diseases,[30,31] playing a significant role in the inflammatory response of these patients.[32,13]

Low VitD concentrations in patients with IBD result in the need for more medications (such as steroids) and immunobiological treatment, besides causing an increased risk of clinical relapse and an increased number of emergency room visits and hospital admissions, indicating a more severe disease.[33] From this perspective, studies have shown that the normalization of VitD concentrations is associated with a reduction in disease activity, surgeries, and inflammatory markers in patients with IBD.[34,35]

Although there is no consensus regarding the cut-off points for classifying VitD deficiency status, the most used ones are those established by the guidelines of the Institute of Medicine (IOM) and the Endocrine Society, which characterize the deficiency of this vitamin by values of < 20 ng / ml and < 30 ng / ml, respectively.[36,37] The studies included in this review adopted four cut-off points for the classification of VitD deficiency, making it difficult to interpret and compare the results.

Among the markers evaluated, higher concentrations of RDW were related to the lowest quartile of VitD concentration in patients with UC.[20] Although RDW is traditionally used for the diagnosis of anemia, it can also be a marker of systemic and chronic inflammation.[38] VitD deficiency can cause changes in this marker[39], being associated with the increase of other inflammatory proteins, such as ESR and IL-6, when at high concentrations.[40,41]

Regarding the ESR, an increase in this marker was also observed in patients with UC in the lowest quartile of VitD concentration.[20] Similar results were found in other studies, in which vitamin supplementation reduced ESR rates in patients with IBD when compared to the placebo group.[42,43] On the other hand, a meta-analysis showed that the concentrations of this marker did not decrease after treatment with VitD compared to the placebo group.[44] These data demonstrate the need for further studies to establish a possible relationship between ESR and VitD in the inflammatory condition of patients with IBD.

The association between the parameters VitD and FC observed in this review[21,24], several studies show that FC is widely used for the detection and control of IBD activity. In patients with VitD deficiency this protein tends to be found at high concentrations, thus showing an association between low concentrations of this micronutrient and increased disease activity.[23,45-47]

Although the results of the relationship between VitD and FC concentrations are promising, this hypothesis needs to be explored in intervention studies that examine the effects of VitD supplementation on local inflammation, as well as on endoscopic and histological parameters in active disease.[46]

The association between VitD concentrations and CRP is still conflicting. However, a recent meta-analysis found a significant inverse relationship between oral VitD supplementation and CRP in patients with IBD.[48] This result was also found in an intervention study carried out in children by El Amrousy et al.[43] It is important to highlight that supplementation with high doses of VitD can be recommended an adjunctive therapy for IBD, emphasizing that individualization must be respected, as well as regular follow-up to monitor adverse reactions, especially in children.[44]

The recommendation of VitD supplementation in IBD is still questionable particularly due to problems of malabsorption, requiring high doses to reach adequate concentrations. However, this strategy can be effective to improve the inflammatory condition due to the relationship of this vitamin with inflammatory markers (such as CRP and ESR) and the suppression of the Th1-type response, resulting in an improvement in the clinical activity of the disease.[32] On the other hand, the effectiveness of VitD supplementation depends on the initial concentration of the vitamin, the administered dose, and the intervention time.[49]

It is important to highlight that VitD is produced mainly in the deep layers of the epidermis after exposure to sunlight (UVB) or obtained through dietary intake. Thus, several factors contribute to the deficiency, such as malabsorption, reduced food consumption, the season of the year, physical activity, and insufficient exposure to sunlight or intestinal inflammation.[50,51] Thus, it is necessary to take into account these factors for the establishment of the deficiency of this vitamin.

Some limitations can be cited regarding the eligible studies: different cut-off points adopted for VitD; different follow-up times for patients; heterogeneity and reduced number of VitD-related inflammatory biomarkers; different study locations, which may interfere with their endogenous synthesis; sample heterogeneity; and size of the investigated population.

5. CONCLUSIONS

VitD deficiency in IBD patients is associated with increased concentrations of pro-inflammatory markers, demonstrating the relevant role played by this vitamin in the modulation of the immune response. Taking into account the various factors involved in VitD deficiency and the complex pathophysiology of IBD, as well as the heterogeneity of the protocols adopted by the studies (which make a more detailed analysis of the results difficult), new clinical and longitudinal studies with standardized evaluation methods and

VitD markers should be performed in the different degrees of clinical activity of IBD for a better understanding of the relationship between this vitamin and the inflammatory response in IBD.

AUTHOR CONTRIBUTIONS

Conceptualization: MSBM, GMS, PVLM, VRM, CMRGC, KMGF, JMLP and NNN. Methodology: MSBM, GMS, PVLM and NNN. Investigation: MSBM, GMS and PVLM. Writing: MSBM, GMS, PVLM and NNN. Review & Editing: VRM, CMRGC, KMGF, JMLP and NNN.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Sokol H, Mahlaoui N, Aguilar C, Bach P, Join-Lambert O, Garraffo A et al. Intestinal dysbiosis in inflammatory bowel disease associated with primary immunodeficiency. J Allergy Clin Immunol. 2019; 143(2):775-778. https://doi.org/10.1016/j.jaci.2018.09.021.

2. Ungaro F, Tacconi C, Massimino L, Corsetto PA, Correale C, Fonteyne P et al. MFSD2A Promotes Endothelial Generation of Inflammation-Resolving Lipid Mediators and Reduces Colitis in Mice. Gastroenterology. 2017; 153(5):1363-1377. https://doi.org/10.1053/j.gastro.2017.07.048.

3. Weng YJ, Gan HY, Li X, Huang Y, Li ZC, Deng HM et al. Correlation of diet, microbiota and metabolite networks in inflammatory bowel disease. J Dig Dis. 2019; 20(9):447-459. https://doi.org/10.1111/1751-2980.12795.

4. Sartor RB, Wu GD. Roles for Intestinal Bacteria, Viruses, and Fungi in Pathogenesis of Inflammatory Bowel Diseases and Therapeutic Approaches. Gastroenterology. 2017; 152(2):327-339. https://doi.org/10.1053/j.gastro.2016.10.012.

5. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020; 5: 17–30. https://doi.org/10.1016/S2468-1253(19)30333-4.

6. Mirsepasi-Lauridsen HC, Vrankx K, Engberg J, Friis-Møller A, Brynskov J, Nordgaard-Lassen I et al. Disease-Specific Enteric Microbiome Dysbiosis in Inflammatory Bowel Disease. Front Med (Lausanne). 2018; 5:304. https://doi.org/10.3389/fmed.2018.00304.

7. Weingarden AR, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. Gut Microbes. 2017; 8(3):238-252. https://doi.org/10.1080/19490976.2017.1290757.

8. Bamias G, Arseneau KO, Cominelli F. Cytokines and mucosal immunity. Curr Opin Gastroenterol. 2014; 30(6):547-52. https://doi.org/10.1097/MOG.0000000000000118.

9. Wang B, Yao M, Lv L, Ling Z, Li L. The Human Microbiota in Health and Disease, Engineering. 2017; 3(1): 71-82. https://doi.org/10.1016/J.ENG.2017.01.008.

10. MacMaster MJ, Damianopoulou S, Thomson C, Talwar D, Stefanowicz F, Catchpole A et al. A prospective analysis of micronutrient status in quiescent inflammatory bowel disease. Clin Nutr. 2021; 40(1):327-331. https://doi.org/10.1016/j.clnu.2020.05.010.

11. Valvano M, Magistroni M, Mancusi A, D'Ascenzo D, Longo S, Stefanelli G et al. The Usefulness of Serum Vitamin D Levels in the Assessment of IBD Activity and Response to Biologics. Nutrients. 2021; 13(2):323. https://doi.org/10.3390/nu13020323.

12. Bouillon R, Antonio L. Nutritional rickets: Historic overview and plan for worldwide eradication. J Steroid Biochem Mol Biol. 2020; 198:105563. https://doi.org/10.1016/j.jsbmb.2019.105563.

13. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. Nutrients. 2015; 7(4):3011-21. https://doi.org/10.3390/nu7043011.

14. Zammit SC, Ellul P, Girardin G, Valpiani D, Nielsen KR, Olsen J et al. Vitamin D deficiency in a European inflammatory bowel disease inception cohort: an Epi-IBD study. Eur J Gastroenterol Hepatol. 2018; 30(11):1297-1303. https://doi.org/10.1097/MEG.0000000000001238

15. Gubatan J, Chou ND, Nielsen OH, Moss AC. 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):1146-1158. https://doi.org/10.1111/apt.15506

16. Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. Medicine (Baltimore). 2018; 97(46):e12662. http://doi.org/10.1097/MD.0000000000012662

17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

18. Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. https://doi.org/10.46658/JBIMES-20-01

19. Galvão TF, Pansani TSA, Harrad D. Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA. Epidemiol Serv Saúde. 2015; 24(2):335–42. https://doi.org/10.5123/S1679-49742015000200017

20. Bours PH, Wielders JP, Vermeijden JR, Wiel AV. Seasonal variation of serum 25-hydroxyvitamin D levels in adult patients with inflammatory bowel disease. Osteoporos Int. 2011;22(11):2857-67. https://doi.org/10.1007/s00198-010-1484-y

21. Caviezel D, Maissen S, Hendrik Niess J, Kiss C, Hruz P. High Prevalence of Vitamin D Deficiency among Patients with Inflammatory Bowel Disease. Inflamm Intest Dis. 2018; 2(4):200–210. https://doi.org/10.1159/000489010

22. Sharifi A, Nedjat S, Vahedi H, Veghari G, Hosseinzadeh-Attar MJ. Vitamin D status and its relation to inflammatory markers in patients with mild to moderate ulcerative colitis. Middle East J Dig Dis. 2018; 10(2):84-89. https://doi.org/10.15171/mejdd.2018.95

23. Scolaro BL, Barretta C, Matos CH, Malluta EF, Almeida IBT, Braggio LD et al. Deficiency of vitamin D and its relation with clinical and laboratory activity of inflammatory bowel diseases. J Coloproctol (Rio J). 2018; 38(2):99–104. https://doi.org/10.1016/j.jcol.2017.11.005

24. López-Muñoz P, Beltrán B, Sáez-González E, Alba A, Nos P, Iborra M. Influence of vitamin d deficiency on inflammatory markers and clinical disease activity in IBD patients. Nutrients. 2019; 11(5):1059. https://doi.org/10.3390/nu11051059

25. Aksan A, Tugal D, Hein N, Boettger K, Caicedo-Zea Y, Diehl I et al. Measuring vitamin d status in chronic inflammatory disorders: how does chronic inflammation affect the reliability of vitamin d metabolites in patients with IBD? J Clin Med. 2020; 9(2):547. https://doi.org/10.3390/jcm9020547.

26. Zielińska A, Sobolewska-Włodarczyk A, Wiśniewska-Jarosińska M, Gąsiorowska A, Fichna J, Sałaga M. The 25(OH)D3, but Not 1,25(OH)2D3 levels are elevated in IBD patients regardless of vitamin d supplementation and do not associate with pain severity or frequency. Pharmaceuticals (Basel). 2021; 14(3):284. https://doi.org/10.3390/ph14030284.

27. Meckel K, Li YC, Lim J, Kocherginsky M, Weber C, Almoghrabi A et al. Serum 25-hydroxyvitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. Am J Clin Nutr. 2016; 104(1):113-20. https://doi.org/10.3945/ajcn.115.123786

28. Alrefai D, Jones J, El-Matary W, Whiting SJ, Aljebreen A, Mirhosseini N et al. The Association of vitamin d status with disease activity in a cohort of crohn's disease patients in Canada. Nutrients. 2017; 9(10):1112. https://doi.org/10.3390/nu9101112

29. Gubatan J, Mitsuhashi S, Longhi MS, Zenlea T, Rosenberg L, Robson S et al. Higher serum vitamin D levels are associated with protective serum cytokine profiles in patients with ulcerative colitis. Cytokine. 2018; 103:38-45. https://doi.org/10.1016/j.cyto.2017.12.023

30. Sadeghian M, Saneei P, Siassi F, Esmaillzadeh A. Vitamin D status in relation to Crohn's disease: Meta-analysis of observational studies. Nutrition. 2016; 32(5):505-14. https://doi.org/10.1016/j.nut.2015.11.008.

31. Torella MC, Rausch A, Lasa J, Zubiaurre I. Vitamin d deficiency among inflammatorybowel disease patients in argentina: a cross-sectional study. Arq Gastroenterol. 2018; 55(3):216-220. https://doi.org/10.1590/S0004-2803.201800000-57.

32. Battistini C, Ballan R, Herkenhoff ME, Saad SMI, Sun J. Vitamin D modulates intestinal microbiota in inflammatory bowel diseases. Int J Mol Sci. 2020; 22(1):362. https://doi.org/10.3390/ijms22010362

33. Gubatan J, Mitsuhashi S, Zenlea T, Rosenberg L, Robson S, Moss AC. Low serum vitamin d during remission increases risk of clinical relapse in patients with Ulcerative Colitis. Clin Gastroenterol Hepatol. 2017; 15(2):240-246. https://doi.org/10.1016/j.cgh.2016.05.035.

34. Bendix M, Dige A, Jørgensen SP, Dahlerup JF, Bibby BM, Deleuran B et al. Seven weeks of high-dose vitamin d treatment reduces the need for infliximab dose-escalation and decreases inflammatory markers in Crohn's Disease during one-year follow-up. Nutrients. 2021; 13(4):1083. https://doi.org/10.3390/nu13041083.

35. Guzman-Prado Y, Samson O, Segal JP, Limdi JK, Hayee B. Vitamin d therapy in adults with Inflammatory Bowel Disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2020; 26(12):1819-1830. https://doi.org/10.1093/ibd/izaa087.

36. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US); 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56070/(https://doi.org/10.17226/13050)

37. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96(7):1911-30. https://doi.org/10.1210/jc.2011-0385.

38. Hunziker S, Celi LA, Lee J, Howell MD. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. Crit Care. 2012; 16(R89). https://doi.org/10.1186/cc11351

39. Sim JJ, Lac PT, Liu IL, Meguerditchian SO, Kumar VA, Kujubu DA et al. Vitamin D deficiency and anemia: a cross-sectional study. Ann Hematol. 2010; 89(5):447-52. https://doi.org/10.1007/s00277-009-0850-3.

40. Clarke K, Sagunarthy R, Kansal S. RDW as an additional marker in inflammatory bowel disease/undifferentiated colitis. Dig Dis Sci. 2008; 53(9):2521-3. https://doi.org/10.1007/s10620-007-0176-8.

41. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009; 133(4):628-32. https://doi.org/10.5858/133.4.628.

42. Deng S, He Y, Nian X, Sun E, Li L. Relationship between Vitamin D levels and pain and disease activity in patients with newly diagnosed axial spondyloarthritis. Int J Nurs Sci. 2019; 7(1):54-59. https://doi.org/10.1016/j.ijnss.2019.12.005.

43. El Amrousy D, El Ashry H, Hodeib H, Hassan S. Vitamin D in children with Inflammatory Bowel Disease: a randomized controlled clinical trial. J Clin Gastroenterol. 2021; 55(9):815-820. https://doi.org/10.1097/MCG.0000000000001443.

44. Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of Vitamin D in treatment of inflammatory bowel disease: a meta-analysis. Medicine (Baltimore). 2018; 97(46):e12662. https://doi.org/10.1097/MD.0000000000012662.

45. Ko KH, Kim YS, Lee BK, Choi JH, Woo YM, Kim JY et al. Vitamin D deficiency is associated with disease activity in patients with Crohn's disease. Intest Res. 2019; 17(1):70-77. https://doi.org/10.5217/ir.2018.00022.

46. Raftery T, Merrick M, Healy M, Mahmud N, O'Morain C, Smith S 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(8):2427-35. https://doi.org/10.1007/s10620-015-3620-1.

47. Garg M, Rosella O, Lubel JS, Gibson PR. Association of circulating vitamin D concentrations with intestinal but not systemic inflammation in inflammatory bowel disease. Inflamm Bowel Dis. 2013; 19(12):2634-43. https://doi.org/10.1097/01.MIB.0000436957.77533.b2.

48. Guo Y, Zhang T, Wang Y, Liu R, Chang M, Wang X. Effects of oral vitamin D supplementation on inflammatory bowel disease: a systematic review and meta-analysis. Food & Function. 2021; 12(17): 7588–7606. https://doi.org/10.1039/d1fo00613d.

49. Carvalho CMG, Ribeiro SM. Aging, low-grade systemic inflammation and vitamin D: a mini-review. Eur J Clin Nutr. 2017; 71(4):434-440. https://doi.org/10.1038/ejcn.2016.177.

50. Bendik I, Friedel A, Roos FF, Weber P, Eggersdorfer M. Vitamin D: a critical and essential micronutrient for human health. Front Physiol. 2014; 5:248. https://doi.org/10.3389/fphys.2014.00248.

51. Narula N, Marshall JK. Management of inflammatory bowel disease with vitamin D: beyond bone health. J Crohns Colitis. 2012; 6(4):397-404. https://doi.org/10.1016/j.crohns.2011.10.015.