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Correlation between Vitamin D Deficiency and Clinical, Endoscopic and Biological Activity in Crohn's Disease

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Abstract **Original Research Article**

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by chronic inflammation of the gastrointestinal tract extending from the mouth to the anus. Vitamin D deficiency is common in this disease. This study aims to examine the correlation between vitamin D levels and the clinical and endoscopic activity of CD. Between July 2018 and July 2023, 267 patients were followed up for CD. Of these patients, 156 benefited from a Vitamin D assay, i.e. 58.42% of patients. The mean age was 40.8 +/- 13 years. The sex ratio was F/H = 1.6 (F=96, H=60). Vitamin D deficiency was found in 93 patients (59.61%). Our analysis reveals several key findings: An association between inadequate vitamin D levels and increased severity of CD. However, the exact nature of this relationship is complex and multifactorial. Patients with CD often have problems of intestinal malabsorption due to inflammation of the intestinal mucosa, which may contribute to vitamin D deficiency. Reduced sun exposure, common in CD patients, can also contribute to vitamin D deficiency. Regular monitoring of vitamin D levels and supplementation when necessary can play a crucial role in the overall management of CD. This study highlights the importance of continuing to explore the mechanisms underlying the relationship between vitamin D and CD, with a focus on the clinical implications for better patient management. In sum, our study contributes to our understanding of the influence of vitamin D on CD, while highlighting the importance of considering this vitamin in the assessment and management of patients with this complex disease.

Keywords: Crohn's disease, vitamin D, intestinal malabsorption.

INTRODUCTION

Vitamin D deficiency is common in Crohn's disease (CD) patients and may play a role in disease activity. This vitamin is involved in the modulation of the immune response and inflammation, relevant processes in CD. However, data on the relationship between vitamin D deficiency and the clinico-endoscopic activity of CD are limited and sometimes contradictory. It is therefore necessary to clarify this association to improve the management of patients with CD [1].

METHODS

This is a retrospective descriptive and analytical study conducted over a five-year period, from July 2018 to July 2023.

All patients with Crohn's disease followed in our department and who performed a vitamin D assay were included. Patients lost to follow-up were excluded.

ESPEN recommends vitamin D testing for crohn's disease patients on corticosteroids and/or with active disease.

Vitamin D deficiency is defined as a level below 30 ng/ml, severe deficiency as a level below 10 ng/ml, and inadequate intake as between 10 and 30 ng/ml. An optimal level is considered to be above 30 ng/ml.

Demographic, clinical, biological, endoscopic, therapeutic and follow-up data on Crohn's disease associated with vitamin D deficiency were studied. Data

entry and analysis were carried out using an evaluation sheet and Excel software.

For clinical activity, we used CDAI (Crohn's Disease Activity Index) and HBI (Harvey Bradshaw Index) scores. The CDAI is interpreted as follows:

- Non-active disease: CDAI < 150
- Mild activity: 150≤CDAI<220
- Moderate activity: 220≤CDAI<450
- Severe activity: CDAI ≥ 450

The HBI is interpreted as follows:

- Non-active disease: BHI<4
- Mild disease activity: 4≤HBI≤8
- Moderate disease activity: 8<HBI≤12
- Severe disease activity: HBI >12

For biological activity, we used CRP (negative = below 6mg/l) and fecal calprotectin (negative=below 150 ug/g of stool).

For endoscopic activity, we used the CDEIS (Crohn Disease Endoscopic Index Score). Its value ranges from 0 to 44. endoscopic remission is defined by a score of 7 or less.

A descriptive analysis of the validated data was carried out, with qualitative variables expressed as numbers and percentages, and quantitative variables as mean +/- standard deviation or median with interquartile range according to variable distribution. We used the Chi-square test, the Fisher test and the one-way ANOVA test for variabel comparison. A difference was considered statistically significant if the p-value was less than 0.05. Data analysis was performed using Jamovi 2.4.11 statistical software.

RESULTS

The results of our study reveal several interesting aspects concerning the vitamin D deficiency in Crohn's disease patients, regarding its clinical and biological implications.

Of the 267 patients followed for Crohn's disease, 156 (58.42%) benefited from a vitamin D assay. The mean age of patients was 40.8 +/- 13 years, with a homogeneous distribution. The F/H ratio was 1.6, with a significant female predominance (p<0.001).

The localization of Crohn's disease was gastrointestinal in 11 patients (7%), colonic in 21 patients (16.67%), ileocolic in 60 patients (38.46%) and 6 patients (3.8%) had high-grade involvement. 30 patients had ano-perineal lesions (APL) (19.23%). The statistical difference in terms of vitamin deficiency according to CD location was non-significant p=0.564.

The phenotype was inflammatory in 33 patients (21.15%), stenosing in 40 (25.64%), fistulizing in 8 (5.13%), stenosing and fistulizing in 12 patients (7.7%). The statistical difference in terms of vitamin deficiency according to CD phenotype was non-significant p=0.187.

Patients who had undergone bowel resection (40.4% n=63) were more likely to have vitamin D deficiency (23% n=36) in comparison with patients who had not undergone bowel resection (p=0.03).

The mean vitamin D level was 21.14 ng/ml, with 59.6% of patients showing a deficiency (level < 20 ng/ml). 17.3% of patients had severe vitamin D deficiency (level < 10 ng/ml). For associated deficiencies, the phosphocalcic profile revealed hypocalcemia in 1.3% of patients. Ferritin was low in 24.4% of patients, 2 of whom had no vitamin D deficiency. Other deficiencies were also observed, such as vitamin B12 (2.6%), vitamin B9 (7.7%), and albumin (9.7%).

Vitamin D deficiency was often discovered incidentally (14.74%) or as part of the monitoring work-up. 55 of the deficient patients (35.25%) had generalized fatigue, 13 (8.3%) had diffuse bone pain, 8 (5.12%) had decreased muscle tone, and one patient had a depressive syndrome (0.64%). Bone damage was observed in some patients, notably bilateral sacroiliitis (3.8% n=6), osteoarthritis of the knees (3.8% n=6), and ankylosing spondylitis (3.2% n=5). 87.82% of patients had bone densitometry, revealing osteopenia in 35.26% and osteoporosis in 5.8%.

Regarding clinical disease activity, the median CDAI score was 120 [30; 280] and the median Harvey Bradshaw score was 3 [2; 5]. Among vitamin D-deficient patients, 18 (11.54%) had quiescent disease, 19 patients (12.18%) were in mild relapse, 41 patients (26.28%) were in moderate clinical relapse and 15 patients (9.61%) were in severe clinical relapse. This difference is statistically significant p=0.003.

In terms of the biological activity of the disease, CRP was elevated in 49 patients (31.4%), while it was negative in 41 (45.16%). 3 patients (1.92%) did not have a CRP test. There was a statistical difference in terms of vitamin D deficiency between patients with positive and negative CRP. This difference is statistically significant p<0.001. Of the deficient patients, 50 (32%) had a fecal calprotectin assay. It was negative in 8 patients (5.13%). 42 patients with a deficiency who underwent fecal calprotectin testing (27%) had an elevated level. There was a statistical difference in terms of vitamin D deficiency between patients with positive and negative fecal calprotectin. This difference is statistically significant p<0.001.

With regard to endoscopic activity, 33 (21.15%) of patients with vitamin D deficiency were in endoscopic remission. 55 patients (35.25%) had endoscopically

active disease, including 19 with severe endoscopic activity (12.2%). There was a statistical difference in terms of vitamin D deficiency between patients who were endoscopically active and those who were endoscopically quiescent. This difference was statistically significant p<0.001.

26 patients (16.67%) had strictures. There was a statistical difference in terms of vitamin D deficiency between patients with and without stricture. This difference was statistically significant, p=0.02.

All our patients received vitamin D supplementation with vitamin D3 (D cure* 25,000 IU).

Patients with a vitamin D deficiency of less than 10 ng/ml received 50,000IU per week for 8 weeks, and those with a deficiency of between 10 and 30 ng/ml received 25,000IU per week for 4 weeks. 63 patients (40.4%) underwent a control test 3 months after supplementation. 51 patients (32.7%) had a vitamin D level greater than 30 ng/ml at control. 12 patients (7.7%) were still vitamin D deficient at 3 months after supplementation, and were put on treatment a 2nd time. 4 patients (2.56%) were put on maintenance treatment with Vitamin D3 (D-cure*) 25,000 IU per month for life. These patients were also being followed in rheumatology for ankylosing spondylitis.

Among patients who did not respond to treatment, i.e. which remained deficient when tested after 3 months, the disease was in severe activity clinically in 7 patients (4.48%), and endoscopically in 8 patients (5.13%).

DISCUSSION

It is generally accepted that the best test for determining vitamin D status is to measure serum 25[OH]D [1]. The literature has shown considerable heterogeneity regarding a standard definition of vitamin D deficiency. The currently accepted definition of vitamin D deficiency is a 25[OH]D level strictly below 30 ng/dL. Insufficient intake is defined as a level between 10 and 30 ng/dL, and sufficient vitamin D as 25[OH]>30 ng/dL. Severe deficiency is defined as a level below 10 ng/ml [1].

Available reports on vitamin D status in adults with CD place the prevalence of deficiency between 22 and 70% [2]. In our study, this prevalence was 59.61%, which is a relatively high value.

Comparing vitamin D deficiency with disease activity may reflect the fact that patients seen at our tertiary referral center have more severe disease than the general Crohn's population. This hypothesis is supported by the fact that 40.4% of CD patients in our study had undergone a bowel resection, of whom 36 (23%) were vitamin D deficient; that most had been hospitalized more than once; and that almost a quarter of patients (21.5%) had been treated with biological agents.

In Morocco, the prevalence of hypovitaminosis D in the general female population ranges from 78.1% to 98.4%, when the 25OHD threshold is defined as concentrations below 20 ng/mL, and from 85.3% to 91%, when the 25OHD threshold is defined as concentrations below 30 ng/mL. For men in the general population, the rate is around 85.2% when the threshold is 30ng/mL [3]. In our study, the deficiency was more frequent in women, with a sex ratio F/H = 1.6.

Moroccan studies undertaken on the prevalence of hypovitaminosis D have highlighted rates of 76.6% in patients with various pathologies, 88.6% in patients with ankylosing spondylitis (APS), 70% in patients with rheumatoid arthritis and 75% in children with juvenile arthritis idiopathy (JIA) for a hypovitaminosis D threshold defined at 30 ng/ml [4].

Vitamin D deficiency in IBD patients has been widely reported in numerous studies. It is common for these patients to impose self-imposed dietary restrictions, generally associated with a lack of macro- and micronutrients in the diet. The influence of dietary vitamin D intake in patients with CD was not considered in our study, given its retrospective nature. One study compared patients with inactive or moderate CD with healthy controls. Inadequate dietary intake due to the exclusion of food groups such as milk, vegetables and cereals in the CD group was observed [5].

The main micronutrient deficiencies observed in IBD patients are zinc, iron, vitamin B12 and vitamin D, contributing to a critical state and influencing well-being [5]. In our study, we found a significant association with ferritin deficiency with p<0.001 and with albumin with p=0.003. Associations with calcium, vitamin B12 and B9 deficiency were not significant.

In the meta-analysis by Gubatan *et al*., the relationship between low vitamin D levels and the risks of clinically active disease, mucosal inflammation, clinical relapse and low quality of life scores in 8,316 IBD patients from observational studies was assessed. Low 25(OH)D levels were significantly associated with increased clinically active disease (p<0.00001), and clinical relapse (p=0.0004). In our study, low vitamin D levels were associated with clinically active disease severity with a significant p at 0.003. On the other hand, low vitamin D levels were associated with increased mucosal inflammation and low quality of life scores in CD patients. In fact, mucosal inflammation may lead to vitamin D malabsorption in CD, so low vitamin D levels could be considered a biomarker of inflammation in CD [6]. Accordingly, MacMaster *et al*., observed that around 30% of 93 IBD patients in remission were vitamin D deficient [7]. In our study, vitamin D deficiency was

associated with elevated endoscopic activity with a significant p<0.001.

Diagnosis is based on serum 25-OH-D levels. Biologically, hypovitaminosis D may be associated with decreased serum calcium, normal or decreased serum phosphorus, increased alkaline phosphatase, reflecting increased bone turnover, and elevated parathyroid hormone. In our study, 2 patients had low serum calcium and normal serum phosphorus. Standard radiology may show signs of bone hypertransparency, cracks perpendicular to the cortex called Looser-Milkman striae, and deformities. Severe vitamin D deficiency leads to osteomalacia. Manifestations of osteomalacia include pelvic and limb-girdle bone pain, long-bone deformity, adynamia, tetany, gait disturbances and increased fracture risk [8]. Osteoporosis may also be observed. These clinical pictures already represent an advanced stage. In our study, osteoporosis was found in 9 patients (5.8%) and osteopenia in 55 patients (35.25%), with a significant p value of less than 0.001.

Hypovitaminosis D can also give rise to psychiatric manifestations. Vitamin D receptors and enzymes involved in its metabolism have been found in various parts of the brain. Numerous studies suggest an association between hypovitaminosis D and certain psychiatric disorders: depression, cognitive deficits and schizophrenia [9]. In our study, one patient had a depressive syndrome.

Our study showed that CD in patients with vitamin D deficiency was more clinically active, with a significant p value of 0.003. Biologically, CRP was elevated in 49 patients (31.41%) (p<0.001) and fecal calprotectin in 42 patients (27%) (p<0.001). Endoscopically, the disease was active in 55 patients (35.26%), with a significant p less than 0.001. This may be explained by the fact that mucosal inflammation leads to malabsorption of vitamin D.

Lower serum 25OHD concentration may be associated with greater disease activity and slower progression in CD patients. Numerous investigations have been carried out to explore the relationships between vitamin D status, disease activity and systemic markers of inflammation, with inconsistent results [10].

Most studies have reported an inverse correlation between vitamin D status and disease activity in terms of HBI, CDAI and CRP scores [10]. A 2017 Chinese study by Lingna Ye *et al*., showed that disease severity, assessed by systematic inflammation based on CRP, albumin, and CDAI score levels was strongly and inversely correlated with 25OHD levels, in agreement with most studies.

A recent meta-analysis reported that the prevalence of vitamin D deficiency was 57.7% in patients with CD [11], which is close to the prevalence of vitamin D deficiency in our study, which was 59.61%.

The Chinese study concluded that vitamin D status may be a useful biomarker for assessing disease activity in Crohn's disease patients in clinical practice.

Supporting the results of our study, Kabbani *et al*., [12], in one of the largest prospective cohort studies, demonstrated that patients with low vitamin D levels required more hospitalizations, biological therapies, steroids, surgery and healthcare utilization.

With regard to the indications for vitamin D supplementation, the Osteoporosis Research and Information Group (GRIO) recommends treating subjects over 65 years of age without essential prior vitamin D dosage [13], particularly those with very limited autonomy. The Moroccan Society of Rheumatology (MSR), for its part, recommends treating elderly subjects (over 65), institutionalized patients and patients suffering from chronic pathologies confined to their homes at risk of vitamin D deficiency, without prior biological confirmation.

If an assay is performed, it is recommended to treat subjects with a deficiency or insufficiency confirmed by a vitamin assay according to the above-mentioned thresholds [13]. Skin synthesis is the primary natural source of vitamin D.

Currently, the MSR recommends sun exposure of the arms and legs, for 5 to 30 minutes between 10 a.m. and 3 p.m., twice a week, in spring, summer and autumn [14]. UVB exposure is a simple way of increasing 25OHD synthesis, and does not expose us to the risk of intoxication. The limitation of this recommendation is the risk of skin cancer in certain clinical situations.

The 2nd natural source is food. However, diet is not sufficient to obtain the desired optimal level of at least 30 ng/mL of 25OHD.

With regard to supplementation, experts recommend D3 rather than D2 because of its longer half-life.

The ideal frequency of administration is that which combines the best compliance with the best efficacy. The majority of authors have shown comparable efficacy between daily and punctual administration of vitamin D, provided that punctual administration is not too far apart in time (weekly or monthly). It is recommended that vitamin D be taken orally in the middle of a meal, as it is a fat-soluble vitamin. The injectable form of vitamin D is of interest only when the oral route is not possible (malabsorption syndrome or parenteral nutrition, for example). In the event of vitamin D insufficiency or deficiency, an "attack" treatment should be prescribed to bring 25OHD

levels back above the recommended target value (30 ng/mL). Maintenance therapy is then required to keep vitamin D levels within the recommended range [15].

In general, 1000 IU of vitamin D3 per day for 3 to 4 months will raise 25OHD levels by 10 ng/mL (25 nmol/L). Larger doses of vitamin D should be used in obese (2-3 times), elderly and melanodermal subjects. High doses are not recommended (300,000 to 500,000 IU). They are thought to be responsible for the degradation of 1,25(OH)2D; and to have a rapid beneficial effect on physical performance, improving mobility and thus favouring the occurrence of falls and fractures. The GRIO, ESCEO, IOF, US Endocrine Society, IOM, AGS and Institute of Medicine Dietary Reference Intakes all agree on guidelines for the treatment of hypovitaminosis D [15].

Vitamin D supplementation in IBD patients is difficult due to problems of nutrient malabsorption, and higher doses are often required to reach the recommended circulating level. Nevertheless, it appears to be a promising adjunctive therapy that can improve markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate, suppressing the Th1 immune response, while reducing the index of clinical disease activity [16, 17].

The required dosage and duration of oral vitamin D varies from patient to patient, depending on the degree of malabsorption. If calcium intake is also inadequate, calcium citrate is preferred to calcium carbonate because of its better absorption. High oral doses of calcium and vitamin D are recommended by the American Gastroenterology Association (AGA): 2 to 3 times the usual doses (1000 to 2000 IU/d of vitamin D). Patients who remain deficient or insufficient despite high doses of vitamin D should be treated with the more easily absorbed hydroxylated metabolites of vitamin D, by parenteral administration, or by exposure to UV radiation (tanning booths or sunlight) [15].

Crohn's disease is one of the situations requiring monitoring after vitamin D supplementation, according to the MSR, because of intestinal malabsorption.

The efficacy of treatment is checked by measuring [25OHD] 3 to 4 months after introduction [18]. Thereafter, an annual check-up to verify compliance may be considered.

There are no specific recommendations concerning the prevention of vitamin D deficiency in patients with Crohn's disease. Nevertheless, Myint et al. published a clinical practice guideline, as a standard of care, and recommended the administration of a maintenance dose of between 1,000 and 2,000 IU/day of cholecalciferol and its discontinuation when the disease is in remission [18].

Our study still has its limitations: the sample size is not large enough due to its retrospective nature. The controversial role of vitamin D in the assessment of disease activity and response to treatment still requires evidence from a well-designed prospective study.

CONCLUSION

This study revealed a high prevalence of vitamin D deficiency (59.61%) in patients with chronic inflammatory bowel disease (IBD). The main risk factors included female gender, intestinal resection and the presence of strictures. The symptoms associated with this deficiency underline its systemic impact, and a significant correlation was observed with clinical scores and inflammatory markers, suggesting a link with disease activity. Bone densitometry results also showed alterations in bone mineral density associated with vitamin D deficiency. Supplementation treatment generally improved vitamin status, although some patients required long-term follow-up or supplementation, particularly in cases of severe disease activity. In conclusion, this study highlights the importance of screening for and managing vitamin D deficiency in IBD patients, with significant clinical implications for the overall management of these patients.

These results underline the importance of screening and treating vitamin D deficiency in Crohn's disease patients, particularly those with gastrointestinal symptoms, bone involvement or associated deficiencies. Vitamin D supplementation appears to be beneficial for most patients, but some may require follow-up and specific treatment in the event of initial non-response.

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