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Vitamin D deficiency and Risk Factors in Patients with Crohn's Disease

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Abstract **Background:** To explore vitamin D(VD) levels in patients with Crohn's disease, and the correlation between VD levels and seasons, disease activity, lesion region, hormone therapy. To find the risk factors of VD deficiency and the role of VD in the pathogenesis and treatment of Crohn's disease. **Methods:** Between March 2018 and December 2019, 86 patients diagnosed with CD at the First Affiliated Hospital of Nanjing Medical University were identified, and 86 healthy people were selected as the control group at the same time. VD, counts of white blood cells (WBC), hemoglobin (Hb), counts of platelet(PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin (ALB) levels were recorded at the same time of colonoscopy. Logistic regression analysis of the relationship between disease activity, lesion region, hormone therapy and vitamin D deficiency in patients with Crohn's disease, and analyze possible risk factors. **Results:** The levels of VD in patients with CD was significantly lower than that in the healthy controls (35.10 nmol/L vs 67.60 nmol/L), the difference was statistically significant (Z= -10.527, P<0.001). The summer autumn group was significantly higher than the winter spring group (z = -2.215, P = 0. 027). Patients with ileum lesions have a higher proportion of vitamin D deficiency than patients with non-ileum lesions. vitamin D deficiency rate of patients in activity stage is higher than that of patients in remission stage. With the increase of the degree of inflammation, the level of vitamin D decreased. Logistic regression analysis shows that platelet count > 250 × 10^9 /L, CRP ≥ 8 mg / L, ALB < 30 g/L and hormone therapy were risk factors for vitamin D deficiency(P<0.05). **Conclusions:** Patients with CD have low levels of VD, which is related to seasons. platelet count > 250 × 109 /L, CRP ≥ 8 mg / L, ALB < 30 g/L, and hormone therapy were risk factors for V D deficiency in patient with CD.

Keywords: *Vitamin D deficiency, risk factors, Crohn's disease*

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1. Introduction

Crohn's disease(CD) is a chronic non-specific inflammatory bowel disease with complex etiology and unclear pathogenesis which characterized by manifestations like diarrhea, abdominal distension, pain, and weight loss [1,2,3,4]. Its lesions involving the ileum, colon, and perianal area. A recent systematic review showed rising trends in the incidence and prevalence of IBD worldwide [5]. It seriously threatens human health and brings heavy economic burden to the society. Although the mechanism of CD is still not fully understood, it is believed that CD is closely related to the dysfunction of the immune system including innate and adaptive immune responses.

Vitamin D is a fat-soluble vitamin absorbed from dietaryor cutaneous routes with multiple functions. It is an important immune regulator [6,7,8,9]. Data from a prospective cohort study including 72,719 women in the Nurses' Health Study showed that higher predictive levels of 25(OH)D3 significantly reduce the risk of CD [10]. A low vitamin D status has been proposed as a potential risk factor for the development of IBD based on different lines of evidence [11]. In experimental animal models, vitamin D or VDR deficient mice develop more pronounced intestinal inflammation, whereas supplementation of $1,25(OH)_2D$ suppresses colitis [12,13,14].

The importance of vitamin D in CD has gained attention recently. Here, We retrospectively analyzed the levels of VD in 86 CD patients. To investigate the correlation between VD levels and seasons, disease activity, location, hormone therapy. Discover the risk factors of VD deficiency and explore the role of vitamin D in the pathogenesis and treatment of Crohn's disease.

2. Materials and Methods

2.1. Patients

Between March 2018 and December 2019, patients diagnosed with CD at the First Affiliated Hospital of Nanjing Medical University were identified. The diagnosis

of CD was based on clinical manifestations, abdominal imaging, and intestinal pathology. A total of 86 patients with definite diagnosis, and 86 healthy people were selected as the control group at the same time. This study has been approved by our ethics committee. The data of these patients were extracted retrospectively from their medical records.

The exclusion criteria include those without vitamin D test records and incomplete clinical data. Other exclusion criteria: (1) history of glucocorticoid use in the past year. (2) in order to exclude the influence of geographical latitude and living habits on vitamin D and exclude the non Nanjing born and long-term resident population. (3) patients with any current treatment of vitamin D. (4) patients with pregnancy. (5) patients with bone disease, chronic kidney disease, liver disease, hyperthyroidism and other diseases that affect vitamin D absorption and metabolism, and those who take anticonvulsant drugs, antifungal drugs and other drugs that affect vitamin D absorption.

2.2. Description of Variables

For these patients, data including gender, age, smoking history, drinking history, weight change, symptoms, disease behavior, location, disease activity, hormone treatment. Additionally, Vitamin D(VD), counts of white blood cells (WBC), hemoglobin (Hb), counts of platelet(PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin (ALB) levels were recorded at the same time of colonoscopy.

To assess disease activity, we also recorded the score of simplified Crohn's Disease Activity Index (CDAI), As for disease activity, simplified CDAI < 3.3 denoted clinical remission, simplified CDAI < 11 denoted low activity, simplified CDAI < 26 denoted moderate activity, simplified CDAI ≥ 26 denoted high activity [15].

The simplified CDEIS method was used as the gold standard to evaluate the severity of inflammatory lesions in the intestinal wall [16]. The criteria are as follows: 1) Mild inflammation: local or diffuse erythema, increased friability, no epithelial damage, 2) Moderate inflammation: presence of aphthous or superficial ulcerations, 3) Severe inflammation: large ulcer or multiple ulcers, with intestinal stenosis, fistula, and or spontaneous. (Intestinal stenosis was defined as the intestinal lumen narrower than the adjacent lumen through endoscope could not be passed).

According to the 2011 American endocrine Association's clinical practice guidelines for vitamin D deficiency [17], Serum Vitamin D ≤ 50 nmol / L was defined as vitamin D deficiency, 50-75 nmol / L was defined as vitamin D insufficiency, Vitamin D ≥ 75 nmol / L was defined as vitamin D sufficiency. Screening risk factors for vitamin D deficiency, see in Table 1.

2.3. Statistical Analysis

The IBM SPSS 20.0 software was used for the statistical analysis of data. Discrete data were reported as frequency and percentage, using a chi-square test or Fisher's exact test for comparison. The continuous variables which were non-normally distributed expressed as the median and range, using Mann-Whitney test or Kruskal-Wallis test for comparison as appropriate. The risk factors of vitamin D deficiency were analyzed by Logistic regression analysis. The difference was statistically significant ($P < 0.05$).

Table 1. Assignment of risk factors for vitamin D deficiency

Variable	Assignment
Sex	
Female	0
Male	1
Course of disease(year)	
<1	0
1-5	1
>5	2
CD location	
L1	0
L2	1
L3	2
Intestinal stenosis	
No	0
Yes	1
Perianal lesions (fistula, ulcer, abscess)	
No	0
Yes	1
Disease activity	
Remission stage	0
Mild activity	1
Moderate activity	2
Leukocyte count(×109/L)	
≤9.5	0
>9.5	1
Hemoglobin (g / L)	
>110	0
90-110	1
60-89	2
Platelet count (× 109 / L)	
≤250	0
>250	1
C-reactive protein (mg / L)	
<8	0
≥8	1
Erythrocyte sedimentation rate (mm / 1H)	
<20	0
≥20	1
Serum albumin (g / L)	
>35	0
30-35	1
<30	2
Hormone therapy	
No	0
Yes	1

3. Result

3.1. Demographics and Clinical Characteristics

In total, 86 participants with incident CD (median age 30.0 years, 54 males, 32 females,) were identified in department of gastroenterology of the First Affiliated Hospital of Nanjing Medical University from March 2018

to December 2019, and 86 healthy individuals(median age 33.0 years, 49 males, 37 females,) were collected as control during the same period. The main characteristics of the study population are summarized in Table 2. There was no statistical difference in gender and age between the two groups. The levels of vitamin D in patients with Crohn's disease was significantly lower than that in the healthy controls (35.10 nmol/L vs 67.60 nmol/L), the difference was statistically significant (Z= -10.527, P<0.001).

Table 2. Baseline characteristics of CD patients

	Overall cohort (n=86)
Sex (M/F)	54/32
Age (years), mean (range)	32.1(14-63)
Smoking history,N(%)	
Smoking	78(91)
No smoking	8(9)
Drinking history, N(%)	
Drinking	84(98)
No drinking	2(2)
Weight change,N(%)	
No significant weight change	60(70)
Weight loss	26(30)
Symptoms,N(%)	
Diarrhea only	19(22)
Bellyache only	15(17)
Diarrhea and Bellyache	29(34)
No diarrhea and bellyache	23(27)
Disease behavior, N (%)	
B1	49(57)
B2	37(43)
B3	0(0)
CD location, N (%)	
L1	39(45)
L2	13(15)
L3	34(40)
Disease activity,N (%)	
Remission stage	62(72)
Mild activity	18(21)
Moderate activity	6(7)
Hormone therapy,N (%)	
Yes	43(50)
No	43(50)

3.2. Seasons and vitamin D levels in patients with Crohn's disease

According to the time of vitamin D test, the patients were divided into two groups: winter spring group (November 1 to April 30) and summer autumn group (May 1 to October 31). The vitamin D levels were 28.7 (13.2-59.4) nmol /L and 37.4 (8.4-37.4) nmol/L, respectively. The summer autumn group was significantly higher than the winter spring group (z = -2.215, P = 0. 027).

3.3. Lesion Region, Disease Activity and Vitamin D Levels in Patients with Crohn's Disease

A total of 86 CD patients, 91% of CD patients suffered from vitamin D deficiency, 8% of CD patients suffered from vitamin D insufficiency. 92% of CD patients with ileum lesion suffered from vitamin D deficiency and 8% suffered from vitamin D insufficiency. 85% of CD patients with colonic lesion suffered from vitamin D deficiency and 15% suffered from vitamin D insufficiency. 91% of CD patients with ileocolonic lesions suffered from vitamin D deficiency and 6% suffered from vitamin D insufficiency.

89% of CD patients in remission stage suffered from vitamin D deficiency and 10% suffered from vitamin D insufficiency, 90% of CD patients in mild activity stage suffered from vitamin D deficiency and 10% suffered from vitamin D insufficiency, 100% of CD patients in moderate activity stage suffered from vitamin D deficiency .

3.4. Levels of Vitamin D with Degrees of Inflammation in CD Cohort

According to the simplified CDEIS method, the degree of inflammation in the intestine was evaluated. The degree of intestinal inflammation is divided into mild inflammation, moderate inflammation and severe inflammation. With the increase of the degree of inflammation, the level of vitamin D decreased. Vitamin D levels in patients with moderate inflammation were lower than the patients with mild inflammation(45.6 nmol/L vs 35.7 nmol/L), Vitamin D levels in patients with severe inflammation were significantly lower than the patients with moderate inflammation(35.7 nmol/L vs 29.4 nmol/L) (Z= -2.086, P=0.037), Vitamin D levels in patients with severe inflammation were significantly lower than the patients with mild inflammation(45.6 nmol/L vs 29.4 nmol/L) (Z= -3.174, P=0.002), see in Figure 1.

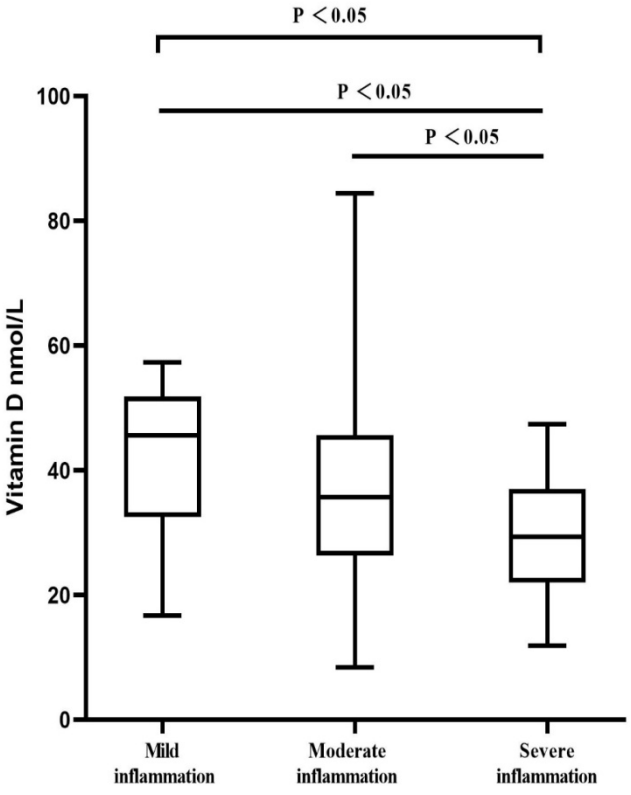

Figure 1. Levels of vitamin D with degrees of inflammation in CD cohort

Table 3. Single factor Logistic regression analysis of the risk of vitamin D deficiency in patients with Crohn's disease

Variable	Regression coefficient β	Standard error	Wald χ2	P	OR	95%CI
Sex	-1.553	1.198	1.679	0.195	0.212	0.020-2.217
Course of disease(year)	3.079	1.892	2.650	0.104	21.736	0.0533-885.657
CD location						
L1	-1.967	1.271	2.397	0.122	0.140	0.120-1.687
L2	-1.25	2.441	0.262	0.609	0.286	0.020-34.279
Intestinal stenosis	-0.591	1.561	0.143	0.705	0.554	0.026-11.806
Perianal lesions (fistula, ulcer, abscess)	1.114	1.555	0.514	0.474	3.038	0.145-64.185
Disease activity	-1.239	1.115	1.234	0.267	0.290	0.033-2.577
Leukocyte count > 9.5 ×109/L	-0.304	1.522	0.038	0.845	0.738	0.035-15.451
Hemoglobin < 90 g / L	1.848	1.579	1.370	0.242	6.349	0.287-140.214
Platelet count > 250 × 109 / L	3.415	1.330	6.590	0.010	30.419	0.492-72.737
C-reactive protein ≥8 mg / L	2.776	1.180	5.535	0.019	16.049	0.734-56.146
Erythrocyte sedimentation rate ≥20 mm / 1H	-0.389	1.229	0.100	0.752	0.687	0.061-7.539
Serum albumin < 30 g / L	3.311	1.268	6.824	0.009	27.398	2.286-128.387
Hormone therapy	1.96	0.984	3.966	0.046	7.101	1.032-48.889

Table 4. Multiple factor Logistic regression analysis of the risk of vitamin D deficiency in patients with Crohn's disease

Variable	Regression coefficient β	Standard error	Wald χ2	P	OR	95%CI
Platelet count > 250 × 109 / L	1.776	0.805	4.871	0.027	5.904	1.220-28.574
C-reactive protein ≥8 mg / L	2.081	0.828	6.320	0.012	8.010	1.582-40.566
Serum albumin < 30 g / L	1.785	1.272	5.982	0.016	5.982	0.492-72.738
Hormone therapy	1.662	0.798	4.341	0.037	0.190	0.040-0.906

3.5. Risk Factors of Vitamin D deficiency in Crohn's Disease Patients

Single factor Logistic regression analysis showed that: High risk of vitamin D deficiency in patients with platelet count > 250 × 10^9 / L, C-reactive protein≥8 mg/L, Serum albumin < 30 g / L, hormone therapy(P<0.05). There was no significant difference in sex, course of disease, CD location, intestinal stenosis, perianal lesions, disease activity, leukocyte count >9.5 ×10^9/L, hemoglobin < 90 g/L, and erythrocyte sedimentation rate ≥20 mm/1H (P > 0.05), see in Table 3. Multi factor Logistic regression was used to analyze the variables with statistical significance (platelet count > 250 × 10^9 / L, C-reactive protein≥8 mg/L, Serum albumin < 30 g / L, Hormone therapy) in single factor analysis, It was found that platelet count > 250 × 10^9 /L, C-reactive protein ≥ 8 mg / L, serum albumin < 30 g/L, and hormone therapy were risk factors for vitamin D deficiency(P<0.05), see in Table 4.

4. Discussion

In our study, vitamin D level of Crohn's disease patients is significantly lower than that of healthy people. The results are consistent with those of Ham NS, et al [18]. In a cohort study of Chinese adults with IBD, Tan et al. found that the level of 25(OH)D in IBD patients was significantly lower than that in healthy controls [19]. The causes of vitamin D deficiency in IBD patients may be: (1) Active diseases increase patients' indoor activities and reduce their exposure to sunlight; (2) Intestinal symptoms limit vitamin D intake through diet; (3) Intestinal diseases cause vitamin D malabsorption; (4) Diarrhea can increase vitamin D excretion.

Vitamin D plays an important role in maintaining healthy bone development and stable calcium and phosphorus metabolism [20,21,22,23]. Vitamin D deficiency can reduce ionized calcium in serum, lead to increased secondary parathyroid hormone secretion, enhance osteoclast function and increase bone resorption, thus leading to bone mass reduction and osteoporosis. Vitamin D deficiency is related to season and geographical location [24,25,26]. In this study, the level of Vitamin D in patients in winter and spring was significantly lower than that in summer and autumn, further confirming this point. The reason is that in winter or at higher latitudes, the human body is exposed to less sunlight, thus reducing vitamin D synthesis. Vitamin D is mainly absorbed in jejunum and ileum of human body. This study found that patients with ileum lesions have a higher proportion of vitamin D deficiency than patients with non-ileum lesions. It is confirmed that malabsorption caused by ileum lesions is one of the main causes of vitamin D deficiency. At the same time, the data of this study show that the vitamin D deficiency rate of patients in activity stage is higher than that of patients in remission stage. In the active phase, intestinal mucosal damage affects vitamin D absorption, so patients in active phase should pay attention to vitamin D supplementation to prevent osteoporosis caused by vitamin D deficiency.

Univariate and multivariate analysis showed that CRP ≥ 8 mg/L was one of the risk factors for vitamin D deficiency in Crohn's disease patients .CRP is an important indicator of infection, suggesting that infection may be one of the causes of vitamin D deficiency in Crohn's disease patients. In addition, platelet count >250× 10^9/L, Seroum albumen < 30 g/L, hormonotherapy are all risk factors for vitamin D deficiency in Crohn's disease patients. The results of this study suggest that, if the patient's platelet count continues to be greater than 250 × 10^9 / L, and serum albumin continues to be less than 30 g / L in the diagnosis and treatment of patients with

Crohn's disease, Indicate that patients are at the risk of vitamin D deficiency, and vitamin D should be supplemented in time. Hormonal therapy is one of the main schemes of induced remission therapy for Crohn's disease at present, and hormone therapy is one of the risk factors for vitamin D deficiency. Therefore, in hormone therapy, the dosage of hormone should be reduced in time on the premise of ensuring the therapeutic effect, and attention should be paid to monitoring changes in vitamin D level and supplement vitamin D in time, so as to reduce the occurrence of osteoporosis and even fracture. In the 2011 American Society of Endocrine Clinical Practice Guidelines for the Treatment of Vitamin D Deficiency [17], experts recommend that obese, malabsorption syndrome, and those taking drugs that affect vitamin D metabolism use large doses of vitamin D (2-3 times the dose, at least 6000-10000 IU/d) to treat vitamin D deficiency, so that the blood 25(OH)D level is higher than 30 ng/ml and the maintenance treatment volume is 3000-6000 IU/d. At present, there is no definite guideline or consensus on whether or not patients with Crohn's disease need vitamin D supplementation and the specific dosage. Therefore, a large sample, multi-center prospective study is needed to determine the therapeutic effect of vitamin D and the optimal dose of vitamin D supplementation, so as to formulate a vitamin D supplementation plan for Crohn's patients in line with China's national conditions.

5. Conclusions

To sum up, this study suggests that Crohn's disease patients have decreased vitamin D levels. Vitamin D level is related to seasons, lesion region and disease activity. Hormone therapy is a risk factor for vitamin D deficiency. The possibility of osteoporosis and fracture should be closely monitored when patients with Crohn's disease receive hormone therapy. The therapeutic effect of vitamin D on Crohn's disease and the specific dosage still need to be further studied.

Authors' Contributions

Wei-Juan Song study, survey designs, data collection, Rui-Xia Yang study and survey designs, data analysis, and writing up the first draft of the paper, All authors contributed to the draft and have seen and approved the final version of the report.

Conflicts of Interest

All the authors declared no conflicts of interest.

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