Original Article

Evaluation of Serum Vitamin D Level in Patients with Inflammatory Bowel Disease in Duhok Governorate

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Abstract

Background: Vitamin D deficiency is a common problem in patients with inflammatory bowel diseases (IBDs). **Objectives:** The aim of the current study was to measure serum Vitamin D concentrations (25 (OH) D) in patients with IBD and examine its relation to the severity of disease. **Materials and Methods:** This was a prospective cross-sectional study of adult patients diagnosed with IBD including ulcerative colitis and Crohn's disease compared to sex-matched controls from an outpatient clinic in a public hospital in Iraq between February 2018 and May 2018. The Vitamin D deficiency levels were assessed as below 20 ng/ml as deficient, between 20 and 30 ng/ml as insufficient, and >30 ng/ml as sufficient level. **Results:** Serum Vitamin D levels were measured in 145 patients including 68 patients (median age: 30.5 ± 17.25) and 77 healthy controls (median age: 52.00 ± 12.25) ranged 18–63 years. Further, the median length of disease progression was 3.0 years. Serum Vitamin D levels were significantly lower in patients (IBD or separately) compared to healthy controls. However, such significant difference was not found between patients with respect to Vitamin D and disease severity. In addition, it was confirmed that disease severity is related to Vitamin D deficiency in IBD patients. **Conclusions:** The current study revealed that the patients with IBD have a significantly lower level of Vitamin D compared to healthy control group. In addition, the Vitamin D deficiency is related to disease severity.

Keywords: Crohn's disease, inflammatory bowel disease, ulcerative colitis, Vitamin D

Introduction

Inflammatory bowel disease or IBD refers to Crohn's disease (CD) and ulcerative colitis (UC) depicted by chronic inflammation of the gastrointestinal tract, in which recurrent remission and exacerbation are experienced by patients.[1] The precise etiology of pathophysiology of IBD is not fully realized, but it appears that a complex interplay factors are responsible for this issue including immune system dysregulation, gut microbiota, environmental, and hereditary risk factors.[2] In addition, some other factors have been proposed to have the roles in IBD pathophysiology. It has been mentioned that maybe Vitamin D deficiency is involved in disease pathogenesis, severity, and possibly treatment.

Vitamin D, a fat-soluble vitamin, regulate metabolism of bone, phosphorus, and calcium by its active form, calcitriol (1, 25-dihydroxyvitamin D 3). Apart from its regulation role, Vitamin D has a role in function of immune system, which its deficiency has been shown to be an environmental risk factor for autoimmune diseases such as CD and UC.[3] The investigations conducted in the world have reported repeatedly low levels of serum 25-hydroxyvitamin D in patients with IBDs and an association between disease activity and Vitamin D status. The low serum levels of Vitamin D have been documented in many immune-related diseases accenting the role of immunoregulation.[4]

In patients with IBD, Vitamin D deficiency is a common fact reaching up to 65% in patients with CD.[5] The current study aimed to measure serum vitamin D concentration (25 (OH) D) in patients with IBD and its relation to the severity of disease in Duhok Governorate. It was expected that the patients with CD or UC have a significantly lower serum Vitamin D compared to healthy controls.

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Materials and Methods

Study design and recruitment

A cross-sectional study of 68 consecutive individuals with a confirmed diagnosis of IBD (24 male, 44 female) and 77 sex-matched healthy adult controls aged 18 years and older (41 male, 36 female) were prospectively recruited from February 2018 through May 2018. The individuals were recruited from patients attended the outpatient setting of internal medicine Department, Azadi Teaching Hospital in Duhok city/Iraqi Kurdistan. Their sex-matched healthy controls were selected among patients' companions of the same department of the hospital. About 35.3% male patients and 53.2% male controls were included in this study.

Ethical considerations

The study was approved by Local Health Ethics Committee in Duhok governorate, the written informed consent form was obtained from all patients and individuals prior recruitment to the study. In addition, the required information was given to the study subjects. The guarantee was given for confidentiality of their personal information.

Diagnostic and measurement criteria

The diagnoses of CD or UC were established according to clinical examination, endoscopic, histological, and radiological findings by the study author, the medical internist.[6,7] To confirm the diagnosis of CD and UC, medical investigation indices including erythrocyte sedimentation rate (ESR), serum albumin, complete blood picture (CBC), and C-reactive protein (CRP) were performed for patients in medical laboratory of the same hospital. A 5 ml volume of fasting sample was taken from all patients and individuals by an experienced phlebotomist**.** The blood samples were collected by venipuncture into a nonethylenediaminetetraacetic acid tube and were processed for serum extraction. Later, the serum was stored at −20°C for later analysis, and serum Vitamin D levels were measured by radioimmunoassay (DiaSorin Inc 25-OH D assay, Stillwater, Minnesota, USA).

The Harvey–Bradshaw Index (HBI) was used to assess disease activity for each patient. HBI scores the CD as <5 indicating remission, between 5 and 7 indicating mild disease, between 8 and 16 indicating moderate disease, and >16 as severe disease.[8] The UC activity was assessed by Disease Activity Index.[9] The index rates the disease activity as normal (0), mild (1), moderate (2), and severe (3) in scale, and maximum score is 12.

Demographics and smoking status information were recorded through the direct interview with study participants. The classification of smoking status was current smoker or never smoker. There is no consensus on cutoffs criterion for Vitamin D deficiency by the investigators. Therefore, individuals having serum Vitamin D <20 ng/ml were considered as Vitamin D deficient, those having between 21 and 30 ng/ml as Vitamin D insufficient, and >30 as sufficient level of Vitamin D.[10,11]

Those patients confirmed with tuberculosis, consuming Vitamin D or calcium supplements since the last 6 months, those with history of hepatic, renal, or thyroid issues, and also pregnant women (identified by a urine test) were excluded from the study participation.

Patients' presentations

The patients presented with the following signs and symptoms: 88.2% with diarrhea included 91.7% bloody type and 8.3% with frequency diarrhea, 14.7% had weight loss, 14.7% with iron deficiency anemia, 17.6% with abdominal pain, and 2.9% with abdominal mass; some patients presented with extraintestinal manifestations and some other presentations as well.

Statistical methods

On statistical analyses, the values are presented as mean ± standard deviation for normal data, median ± interquartile for nonnormal data, and frequency and percentage for categorical aspects of study participants including prevalence of Vitamin D deficiency in patients and controls. Mann–Whitney, independent *t*-test, Chi-square, and Fishers' exact tests were performed for statistical differences. $P < 0.05$ was considered as statistically significant difference, and data were analyzed using SPSS 23 (IBM Corp; USA).

Results

Characteristics of the study participants

The total eligible patients and healthy controls for study analysis were 71 and 77, respectively. Only three patients refused to be registered and two did not present their satisfaction to give tests as advised by the author. Therefore, 68 patients with IBD (ranged 18–58) including 52 UC and 16 CD patients and 77 sex-matched healthy controls (ranged 28–63) were recruited into the study, as shown in Table 1.

The matching was performed between patients and controls for genders. Baseline and clinical characteristics of patients and controls were shown in Table 1. The ethnicity origin of majority of patients (97.1%) and all controls were Kurdish and living in Duhok-Iraq. The patients were significantly younger (median age: 30.5 ± 17.25 years) than controls (median age: 52.00 ± 12.25 years; $P<0.001$). Genders in patients and controls as mentioned previously were matched; 35.5% of males in patients versus 53.2% of males among controls ($P = 0.111$). The study showed that a greater percentage of patients (33.3%) in comparison with 2.1% in healthy controls were current smokers ($P = 0.000$). Most of the patients had UC (76.5%) compared with only 23.5% with CD, and median duration of their diseases was 3.00 ± 2.00 years.

Prevalence of Vitamin D deficiency in inflammatory bowel disease compared with controls

The serum vitamin D of patients were measured, and it was shown that the patients had a significantly lower level than controls ($P = 0.000$). The median serum Vitamin D in patients was 9.00 ± 5.72 ng/ml. In addition, the study showed that the

Table 1: Baseline clinical and biochemical characteristics of patients and controls

Characteristics	Patients (n=68)	Controls (n=77)	P
Age (median, IQR)	30.5±17.25	52.00±12.25	0.000 (Mann-Whitney)
Gender, frequency (%)			
Male	24 (35.3)	41 (53.2)	0.111 (χ^2)
Ethnic origin (%)			
Kurdish	97.1	100	0.420 (Fishers' exact test)
Current smoker (%)			
Yes	33.3	2.1	0.000 (χ^2)
Past surgical history (%)			
Yes	6.3	-	
IBD diseases, frequency (%)			
CD	16 (23.5)	-	
UC	52 (76.5)	-	
Disease duration (years) (median, interquartile)	3.00±2.00	-	
Laboratory investigations			
CBC (SD)	9.77±1.44	-	
CRP	24.00±25.5	-	
ESR (SD)	42.59±17.20	-	
Serum albumin	3.25±0.6	-	
Serum Vitamin D	9.00±5.72	-	
Serum Vitamin D levels (%), ng/ml			
<20 (deficient)	56 (82.4)	18 (23.4)	0.000 (χ^2)
Between 21-30 (insufficient)	12 (17.6)	16 (20.8)	
>30 (sufficient)	0 (0.0)	43 (55.8)	
Severity of disease (%)			
Mild	12 (17.65)	-	
Moderate	23 (33.82)	-	
Severe	33 (48.53)	-	
Diabetes Type 2	6 (8.8)	2 (2.9)	0.304 (Fishers' exact test)

CRP: C-reactive protein, CBC: Complete blood picture, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, CD: Crohn's disease, UC: Ulcerative colitis, IBD: Inflammatory bowel diseases, IQR: Interquartile range

prevalence of serum Vitamin D deficiency in IBD patients was 82.4% and 23.4% in healthy controls. The prevalence of Vitamin D insufficiency in patients was 17.6% and 20.8% in controls. None of the patients had sufficient Vitamin D level (greater than 30 ng/ml); however, 55.3% of healthy controls were in normal Vitamin D level. The difference between prevalence rates in patients and controls was statistically significant (P = 0.000) [Table 1].

Laboratory investigations

With respect to laboratory investigations, the means of CBC and ESR were 9.77 ± 1.44 and 42.59 ± 17.20, respectively. The medians of CRP, serum albumin, and serum vitamin D were 24.00 ± 25.5, 3.25 ± 0.6, and 9.00 ± 5.72, respectively. Most of them were recognized as patients with severe status and moderate, 48.53% and 33.82%, respectively, and only a small percentage (17.65%) were in mild severity. The patients and controls were not significant difference in diabetes type 2 (P = 0.170), as shown in Table 1.

Table 2 depicts the baseline and clinical characteristics between the patients with CD and UC. According to that, it was more likely that the patients with CD underwent surgical operations for their clinical manifestations (28.6%) compared with UC patients (P = 0.042).

Factors associated with serum 25(OH) D levels in Crohn's disease and controls

The CD and UC patients were not substantially different in age (P = 0.339), gender (P = 0.881), smoking (P = 0.378), disease duration (P = 0.835), severity of disease (P = 0.479), and diabetes type 2 (P = 1.00). With respect to the main aim of the study, it was shown that UC and CD patients had no statistically difference in disease severity (P = 0.479) and Vitamin D deficiency (P = 0.297).

Prevalence of Vitamin D deficiency in ulcerative colitis and Crohn's disease patients

The prevalence rates of serum Vitamin D deficiency in UC and CD patients were so high, 76.9% and 100%, respectively. About 23.1% of UC patients had insufficient serum Vitamin D level compared with none of CD patients. The astonishing finding was that none of UC and CD patients had sufficient serum Vitamin D level in the study sample. The difference between serum Vitamin D levels among UC and CD patients was not statistically substantial (P = 0.479), as shown in Table 2 and Figure 1.

In Table 3, the difference in Vitamin D deficiency levels between UC and controls and between CD and controls were examined. The findings showed that most of the UC (P = 0.000) and CD patients (P = 0.000) have a Vitamin D deficiency compared to controls.

Further analysis was performed to find association of Vitamin D levels with disease severity in IBD and UC patients, as shown in Table 4. The analysis showed that most of the patients with <20 ng/ml serum Vitamin D had a severe status of disease and the most of the patients with Vitamin D level between 21 and 30 ng/ml have the mild disease severity. Moreover, the similar situation was found in patients with UC disease, as shown in Table 4 (the CD patients sample was no so enough to conduct this analysis). However, no patient was found with normal serum Vitamin D level. In addition, it was not shown that smoking is associated with Vitamin D deficiency in patients (P = 1.00), and disease duration was not statistically substantial among different Vitamin D levels (P = 0.053).

Discussion

The results of this study found that the serum Vitamin D deficiency in IBD, UC, and CD patients were 82.4%, 76.9, and 100%, respectively, and had a significantly lower level of

Table 2: Baseline clinical and biochemical characteristics of patients

Characteristics	UC (n=52)	CD (n=16)	P
Age (median, IQR)	31.50	27.50	0.339 (Mann-Whitney)
Gender (%)			
Male	34.6	37.5	0.881 (χ^2)
Current smoker (%)			
Yes	38.5	14.3	0.378 (Fishers' exact test)
Past surgical history (%)			
Yes	0.0	28.6	0.042 (Fishers' exact test)
Disease duration	3.0	3.0	0.835 (Mann-Whitney)
Serum Vitamin D, mean±SD	8.55	9.50	0.903 (Mann-Whitney)
Serum Vitamin D levels (%), ng/ml			
<20 (deficient)	76.9	100	0.297 (Fishers' exact test)
21-30 (insufficient)	23.1	0.0	
>30 (sufficient normal)	0.0	0.0	
Severity of disease			
Mild	24.0	0.0	0.479 (Fishers' exact test)
Moderate	32.0	37.5	
Severe	44.0	62.5	
Diabetes Type 2 (%), yes	11.5	0.0	1.00 (Fishers' exact test)

CD: Crohn's disease, UC: Ulcerative colitis, SD: Standard deviation, IQR: Interquartile range

Table 3: Serum Vitamin D levels in ulcerative colitis and Crohn's disease patients compared with healthy controls

Serum Vitamin D levels (ng/ml)	Study participants (%)			P
	Controls (n=77)	UC (n=52)	CD (n=16)	
<20	23.4	76.9	100	UC versus control (P<0.001)*
21-30	21.3	23.1	0.0	
>30	55.3	0.0	0.0	CD versus controls (P<0.001)**

*χ^2, **Fishers' exact tests were performed for statistical analysis.
CD: Crohn's disease, UC: Ulcerative colitis

Vitamin D compared with healthy controls (23.4%). However, the study did not show that Vitamin D levels between UC and CD patients were substantially different. In this study, those patients with a higher level of Vitamin D deficiency had a severe disease.

The prevalence rates of Vitamin D deficiency levels reported in this study show a deep concern to patients with IBD in this region. The results obtained from the current study carried out in Iraq may be difficult to be interpreted or establish between-country comparisons as the findings reflect the study designs, geographic regions, study participants, seasonality, and different cutoffs for Vitamin D deficiency. In line with the present study, the studies carried out in other regions reported a high prevalence of Vitamin D deficiency in IBD patients. For instance, in patients with CD, 63% has been reported by Suibhne *et al*.[12] in Dublin/Ireland and 49.8% among IBD patients reported by Ulitsky *et al*.[13]

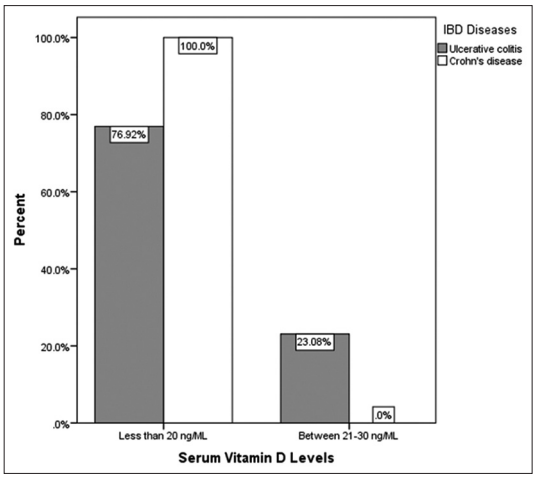

Figure 1: Prevalence of Vitamin D deficiency in ulcerative colitis and Crohn's disease patients

The findings reported in the current study are in line with several studies, but not all.[12,14] In agreement with the present study, other studies carried out in different regions supported my study finding that concentrations of serum 25-hydroyvitamin D in patients are significantly lower in CD patients than in controls in winter and summer seasons[5,15,16] in IBD patients,[17-19] in UC patients.[20,21] Moreover, insignificant difference was observed between UC and CD patients.[13,17,19]

The factors impacting Vitamin D status have been evaluated by several studies accenting low sunlight exposure as a cause for hypovitaminosis. The relationship between the gradient sunlight in different geographic latitudes, particularly in Northern latitudes and the pathophysiological mechanisms involving Vitamin D status relies on not only dietary resources but also ultraviolet (UV) irradiation and exposure.[22]

Farraye *et al*.[23] evaluated the reasons behind different Vitamin D status and absorption ability of Vitamin D_2 in comparing CD patients and healthy controls in a study. At the beginning, 42% of patients had Vitamin D deficiency (≤20 ng/ml) and 29% were insufficient (21–30 ng/ml). The authors understood that 12 h after 50,000 IU ingestion of Vitamin D_2, the levels of circulating metabolite were substantially lower in CD patients in comparison with healthy controls. This confirmed that CD patients significantly had a 30% decrease in Vitamin D_2 absorption, and Vitamin D absorption was substantially decreased compared with controls. This phenomenon has been confirmed by Vogelsang *et al*.[24] as well. They demonstrated 10% reduction in Vitamin D absorption ($25(OH)D_3$) following 4 and 8 h of orally administration of 5 μg of 25(OH)D3/kg body weight.

The current available evidence-based studies accent that Vitamin D deficiency is changeable according to study seasons as Suibhne *et al*.[12] reported that Vitamin D deficiency significantly is higher in winter than summer seasons in CD patients, 68% versus 50% (P < 0.001).[12] They found that more individuals in patients with CD and controls were Vitamin D deficient

Table 4: Association of serum Vitamin D levels in patients with disease severity

Characteristics (n=68)	Vitamin D levels			P
	<20 ng/ml	21-30 ng/ml	>30 ng/ml	
IBD patients				
Disease severity (%)				
Mild	7.4	66.7	0.0	0.005*
Moderate	37.0	16.7	0.0	
Severe	55.6	16.7	0.0	
UC patients				
Disease severity (%)				
Mild	10.5	66.7	0.0	0.036*
Moderate	36.8	16.7	0.0	
Severe	52.6	16.7	0.0	
IBD patients				
Smoking (%)				
Current smoker	33.3	33.3	0.0	1.000*
Never smoker	66.7	66.7	0.0	
Disease duration	Mean square between groups: 51.44, F: 4.11			0.053**

*Fishers' exact test, **One-way ANOVA were performed for statistical analysis. IBD: Inflammatory bowel diseases, UC: Ulcerative colitis

in winter, 68% versus 50%; $P < 0.001$ and 58% versus 46%; $P = 0.08$, respectively, and supported by Bours *et al*.[25] in Ireland and[13] in North America despite individuals have similar Vitamin D intake through food resources and supplements.[16] The highest Vitamin D status is seen in Northern European individuals around later-summer (August–September) and the lowest level around later-winter (February–March).[26] In Iraq, between July and November is considered as hot months; therefore, it appears that the highest Vitamin D status is detectable.

In fact, Joseph *et al*.[5] and de Bruyn *et al*.[4] reported a converse relationship between sun exposure and lower levels of Vitamin D in Indian and Dutch patients, respectively. In these studies, low sun exposure was defined as no sunny holidays, more sunscreen, and no solarium use.

It appears that Vitamin D deficiency is the result of the disease rather than cause of the IBD as it has not been documented that Vitamin D-containing supplements able to raise it to sufficient 25(OH)D levels, particularly in winter season. Suibhne *et al*.[12] reported that the patients who consumed a Vitamin D supplement in winter had a higher mean serum levels of 25(OH)D (48.89 ± 4.52 nmol/L) in comparison with those did not take the vitamin supplements (39.11 ± 4.19 nmol/L; $P = 0.08$, mean ± standard error); however, its mean level was below the sufficient cutoff (50 nmol/L) confirming vitamin supplements is unable to prevent deficiency.

As aforementioned, developing Vitamin D deficiency has been reported to be owing to a number of risk factors including latitude and sunlight exposure.[16] The amount of ultraviolet B radiation is insufficient in winter in northern latitude countries like Europe[27] and Canada[28] in winter to stimulate the skin to produce Vitamin D. Accordingly, the reliance on intake through dietary resources is raised during winter months to save sufficient Vitamin D status.

The link between sun exposure and development risk of CD or UC has been examined by Nerich *et al*.[29] High exposure to sunlight has been shown to be related to substantial reduction risk in CD development, but not UC. The results of the same group after 4 years showed the similar findings, increased risk of CD development with a reduction in sunlight exposure in France; however, Vitamin D intake was not shown to be linked with a decreased risk in CD or UC.[30]

Lacking sunlight or low exposure to sunlight is considered as predictor of Vitamin D status. In addition, disease-related characteristics including smoking and longer disease duration are conversely associated with Vitamin D levels.[12] However, I did not find that Vitamin D levels among smoker and nonsmoker patients is different and no substantial difference was found across different Vitamin D levels.

People living in regions with less sunlight have lower circulating 25-hyroxyvitamin D levels and higher prevalence rates of IBD.[31] However, the population living in sunny regions are nor exempt from this issue[32] due to public habits, skin pigmentation, low Vitamin D dietary intake, and indoor lifestyles as supported by Joseph *et al*.[5] that disease severity and sunlight exposure quantum were related factors with Vitamin D level in serum.

In the current study, the IBD patients had a significant difference in age and sex. However, since the age and gender have not been shown to be associated with Vitamin D deficiency,[12] I did not anticipate any bias in this regard.

In agreement with the current study, Joseph *et al*.[5] confirmed that disease severity is a factor enabling to affect the serum Vitamin D level.

Since dietary intake and sunlight exposure are two important factors of Vitamin D status, it is required to raise awareness on

Vitamin D status, screening programs, and sufficient vitamin supplements in the IBD management attending outpatient settings.

Strengths and limitations

As mentioned previously, dietary intake and sunlight exposure lifestyles of the participated individuals as important factors of Vitamin D have not been considered in the current study. In addition, the inherent limitation of the cross-sectional studies is evident with respect to reverse causality and causal inference about the impact of race and Vitamin D status. Moreover, the current study was conducted in a single public tertiary setting in Iraq. Hence, I am not certain whether the current findings can be generalizable to entire country, or other regions in different countries with various geographical latitudes and lifestyles. This issue has not been examined in this region yet, therefore, it has a significance to the health system. In addition, the patients who were included in this study were recruited from one of the busiest tertiary settings in Duhok governorate reflecting the situation of the patients in this region. The patients were recruited from the same geographic location and in this same year and month with similar weather that approves uniform exposure to solar exposure.

Conclusions

The study showed that the Vitamin D deficiency is so high in IBD patients including CD and UC in the sample size. Therefore, it shows a considerable concern to patients with IBD as those with a higher level of Vitamin D deficiency had more severe disease compared with patients with insufficient Vitamin D in this region.

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Conflicts of interest

There are no conflicts of interest.

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