



## Vitamin D Status and Its Relation to Inflammatory Markers in Patients with Mild to Moderate Ulcerative Colitis

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### ABSTRACT

#### BACKGROUND

Inflammatory bowel disease (IBD), Crohn's disease (CD), and Ulcerative colitis (UC) are autoimmune inflammatory diseases of the alimentary tract, which seems to be caused by the interaction of environmental and genetic factors as well as diet and nutritional factors such as vitamin D. The aim of this study was to assess the vitamin D status and its associations with erythrocyte sedimentation rate (ESR), and high-sensitivity C-reactive protein (hs-CRP) as inflammatory markers in patients with UC.

#### METHODS

In this analytical cross-sectional study 90 patients with mild to moderate UC who were resident of Tehran were assessed. 25(OH)D, parathyroid hormone (PTH), ESR and hs-CRP were measured. Dietary intake was assessed by 3-day 24h diet recall. Statistical analyses were performed using STATA (Version 12).

#### RESULTS

The average serum 25-OH-vitamin D3 was  $33.1 \pm 8.3$  ng/mL and 38.9% of the patients were vitamin D deficient or insufficient (37.3% of men and 41% of women). No significant correlation between serum 25(OH)D and hs-CRP, ESR, body mass index (BMI), and disease duration was found. There were no significant differences in serum 25(OH)D between men and women. Mean daily dietary vitamin D and calcium intakes were 189.5 Iu (95% CI: 176.0 - 203.1) and 569.5 mg (95% CI: 538.8 - 600.2) respectively.

#### CONCLUSION

In this cross-sectional study 38.9% of the patients with mild to moderate UC were vitamin D deficient or insufficient and vitamin D level was not correlated to ESR and/or hs-CRP. More studies are needed to investigate the effect of vitamin D in the pathogenesis of UC or as a part of its treatment.

#### KEYWORDS:

Vitamin D, Ulcerative Colitis, Inflammation, Inflammatory Bowel Disease

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### INTRODUCTION

Vitamin D has a known role in calcium and phosphate homeostasis. In addition, vitamin D has been linked to autoimmune diseases such as multiple sclerosis, diabetes mellitus, and inflammatory bowel disease (IBD).<sup>1</sup>

Human vitamin D sources include dermal synthesis by means of sunlight ultraviolet B radiation, or dietary intake from foods or supplements. Only



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small percentage of vitamin D intakes are being supplied from foods.<sup>2</sup> Vitamin D is metabolized in the liver to 25-hydroxy vitamin D [25(OH)D] and then is converted to 1,25-dihydroxy vitamin D by 1 $\alpha$ -hydroxylase (CYP27B1) in the kidney, which is the active form.<sup>3</sup>

Vitamin D deficiency (VDD) is defined as serum 25(OH)D levels less than 20 ng/mL (equals to 50 nmol/L).<sup>4,5</sup> Levels of 21 to 29 ng/mL indicate insufficiency, and levels of 30 to 50 ng/mL are considered as sufficient vitamin D states.<sup>6</sup> Vitamin D intoxication occurs at serum 25(OH)D levels greater than 150 ng/mL.<sup>5</sup>

IBD are autoimmune inflammatory status of the alimentary tract, mainly large and small intestine. Two main types of IBD include ulcerative colitis (UC) and Crohn's disease (CD). CD potentially affects the entire alimentary tract even the mouth, esophagus, and stomach, but UC affects colon and rectum.<sup>7,8</sup> Interaction of environmental and genetic factors seems to cause IBD.<sup>9</sup> It may also be related to diet and nutritional states. A recent meta-analysis revealed that patients with IBD had higher odds of VDD than healthy controls.<sup>10</sup> Most organs including the immune cells, and small and large intestine express vitamin D receptors (VDRs).<sup>11</sup> Mucosal VDR is lower in patients with UC compared with controls.<sup>12</sup> In addition, the intestine of VDR knock-out murine is affected by spontaneous inflammation,<sup>13</sup> which supports the hypothesis that VDD might be related to IBD.

Since there is no up-to-date study on the prevalence of VDD in Iranian patients with UC, the aim of this study was to assess the vitamin D status and its correlation with erythrocyte sedimentation rate (ESR), and high-sensitivity C-reactive protein (hs-CRP), as inflammatory markers, in patients with mild to moderate UC who were residents of Tehran.

## MATERIALS AND METHODS

In this analytical cross-sectional study all 129 Tehran (Latitude 38 N, Longitude 46 E, Elevate 1361 m) inhabitants with UC who were referred to the Digestive Disease Research Center of Shariati Hospital in Tehran and their disease status were mild to moderate based on Truelove and Witts' severity index,<sup>14</sup> and aged between 18 and 50 years and their body mass indexes (BMI) were between 18.5 and 30 Kg/m<sup>2</sup> were called to participate. Patients with current infection (WBC more than 11000 $\times$ 10<sup>9</sup>/L),

and anti-Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) therapy, those who were taking any form of vitamin D3 supplement in the 3 months preceding the study, or those who had history of hyperparathyroidism, nephrolithiasis, malignancy, or renal or hepatic failure as well as those with pregnancy and breast feeding were not included. Of the patients, 39 declined to participate (response rate = 69/8%). Finally 90 patients with UC were assessed in December 2014.

Blood sample were taken in plain tubes and the sera were separated by centrifuging at 2500 rpm for 10 min after 30 min at 37°C, and stored at -80°C. Circulating levels of 25(OH)D3 were determined using commercial ELISA kit (Calbiotech, CA, USA; Intra-assay variation < 6% and CV < 8%) according to manufacturer's instruction.

Serum hs-CRP levels were also measured using ELISA kit (Monobind, CA, USA) and PTH (parathyroid hormone) serum levels were assessed using ELISA kit (Euroimmun, Luebeck, Germany). ESRs were measured using ESR tube according to standard protocol. The demographic data were collected by personal interview using a short questionnaire specifically developed for this study.

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethic code: 9021324004-1), and written informed consent was obtained from all the participants.

Statistical analyses were performed using STATA V.<sup>12</sup> (Stata Statistical Software, College Station, TX, USA). The results are expressed as mean  $\pm$  standard deviation (SD) or number (%). Pearson correlation was applied to examine the relation between variables.

## RESULTS

In this cross-sectional study, 90 patients with mild to moderate UC (51 men and 39 women) were assessed. The mean age of the participants was 36.3  $\pm$  9.1 years. Complete clinical, and anthropometric characteristics and dietary intake are listed in table 1. Drug regimen of the patients is listed in table 2. The average serum 25-OH-vitamin D3 were 33.1  $\pm$  8.3 ng/mL (table 3). 38.9% of the patients were vitamin D deficient or insufficient (figure 1), which means that their serum 25(OH)D were below 30 ng/mL. 37.3% of men and 41% of women were vitamin D deficient or insufficient (figure 2). No significant correlations between serum 25(OH)D and

**Table 1: Basic, clinical, and dietary characteristics of the patients**

Variables	Mean	Std. Deviation	Min	Max
Age (years)	36.3	9.1	20.0	50.0
Disease duration (years)	8.3	5.6	1.0	26.0
Body mass index (kg/m <sup>2</sup> )	25.3	3.5	18.5	30.0
Systolic blood pressure (mmHg)	115.1	11.0	95	140
Diastolic blood pressure (mmHg)	76.6	10.1	60	100
Body temperature (degree Celsius)	36.3	0.4	35.2	37.0
Heart rate (beat per minute)	80.6	8.9	65	100
Hemoglobin (g/dL)	14.4	1.8	7.5	16.9
Calorie intake (Calorie)	2284.8	381.6	1451	2929
Calorie from carbohydrates (%)	49.7	5.4	31.7	59.2
Calorie from proteins (%)	18.2	2.0	14.0	22.9
Calorie from fats (%)	32.2	4.9	22.4	50.3

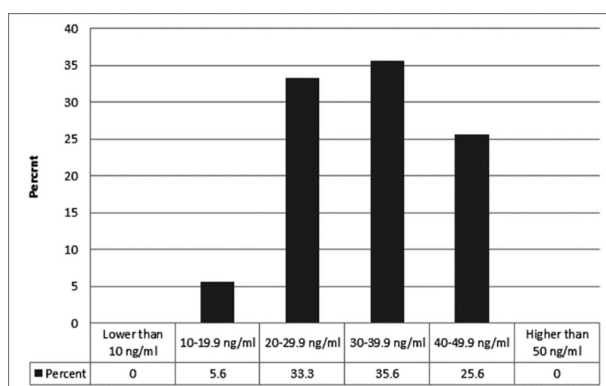
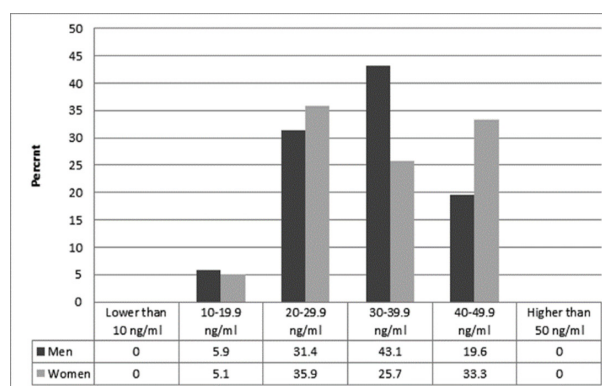
**Table 2: Drug regimen of the patients**

Drug	Number (percent)
Sulfasalazine	40 (44.4)
Mesalamine	42 (46.7)
Prednisone	6 (6.7)
Immunosuppressant drugs	17 (18.9)

**Table 3: ESR, hs-CRP and serum levels of 25(OH) vitamin D3, calcium, and parathormone of the patients**

Variables	Mean	Std. Deviation	Min	Max
Serum 25-OH-vitamin D (ng/mL)	33.1	8.3	17.1	47.5
Serum calcium (mg/dL)	9.11	.39	8.1	9.8
Serum parathormone (pg/mL)	35.4	13.2	10.2	68.5
hs-CRP (mg/L)	3.6	3.5	.0	15.3
ESR 1h (mm/h)	12.3	5.7	4	29

hs-CRP: high-sensitivity C-reactive protein  
ESR: Erythrocyte sedimentation rate

**Fig.1: Percentage of patients in each category of vitamin D status****Fig.2: Sex based percentage of patients in each category of vitamin D status**

**Table 4: Correlations between vitamin D, ESR, hs-CRP, BMI, and disease duration**

Variables		hs-CRP	ESR-1h	BMI	Disease duration
25-OH-vitamin D	R	0.069	0.16	0.15	- 0.07
	P value	0.52	0.15	0.17	0.52
hs-CRP	R		0.5	0.2	0.26
	P value		< 0.001	0.056	0.014
ESR 1h	R			-0.06	0.07
	P value			0.56	0.49

hs-CRP, ESR, BMI, and disease duration were found (table 4). Mean daily dietary vitamin D and calcium intake were 189.5 Iu (95% CI: 176.0-203.1) and 569.5 mg (95% CI: 538.8-600.2), respectively. Total calorie intake was 2284.8 (95% CI: 2204.9-2364.8), of which calorie intake from protein, fat, and carbohydrate were  $18.2 \pm 2.0$ ,  $32.2 \pm 4.9$ , and  $49.7 \pm 5.4$ , respectively.

There was no significant differences between men and women neither in serum 25(OH)D ( $32.4 \pm 8.2$  and  $34.1 \pm 8.5$  ng/mL, respectively,  $p = 0.32$ ) nor in dietary vitamin D intake ( $182.7 \pm 66.7$  and  $198.5 \pm 66.1$  ng/mL, respectively,  $p = 0.25$ ).

## DISCUSSION

The results of this cross-sectional study revealed that 38.9% of the patients with UC were vitamin D deficient or insufficient, and there was no significant correlation between serum 25(OH)D and hs-CRP, ESR, BMI, and disease duration.

Vitamin D is traditionally known for its substantial role in bone homeostasis, but recently it has been growing recognition of its immunological effects.<sup>15-17</sup> On the other hand, recent literature suggests that vitamin D levels are correlated with a wide spectrum of diseases especially autoimmune diseases such as IBD.<sup>17</sup>

The hypothesis of relation between IBD and VDD has arisen from the studies that showed those people living in southern areas have a lower risk of IBD than those living in northern parts with low sunlight exposure,<sup>18-21</sup> which is along with geographical variation in vitamin D status caused by different exposure to ultraviolet B radiation.

In a study done in 2008, Heshmat and colleagues reported that only 13% of healthy Tehran inhabitants had sufficient serum vitamin D levels.<sup>22</sup> However, compared with our study, there were differences regarding cut-off, time of the assessment, and measuring methods. But it

can be cautiously concluded that VDD in patients with UC in Tehran is not higher than healthy people. In another study only 21% of the patients with CD and 24% of the patients with UC had sufficient vitamin D levels, and vitamin D concentrations in the patients with UC were not affected by disease activity, and no correlation was seen with the inflammatory markers (CRP, fibrinogen, and ESR),<sup>23</sup> as was not seen in our study. Some other studies have reported similar 25(OH)D levels between healthy controls and patients with IBD,<sup>24,25</sup> however, others have reported lower vitamin D concentrations in IBD.<sup>26-28</sup> In the study of Souza and co-workers<sup>27</sup>, 48.5% of the 37 patients with UC were vitamin D deficient.

VDD in patients with IBD could be a result of malnutrition, inadequate dietary intake of vitamin D, lower bioavailability, or reduced outdoor physical activity, which reduces sunlight exposure.<sup>17,29</sup> It has been shown that vitamin D deficiency is common even in patients with newly diagnosed IBD, which suggests that low vitamin D may increase the incidence risk of IBD.<sup>30</sup>

In our study the correlations between serum 25(OH)D and hs-CRP, ESR, BMI, and disease duration were weak and non-significant, but an RCT recently showed that vitamin D at higher doses may have a beneficial effect on inflammation in patients with UC,<sup>31</sup> which endorses that immunological effects of vitamin D may be achieved at serum levels higher than current accepted levels for bone homeostasis.<sup>32,33</sup>

There are some limitations in our study. First of all, we had no control group to obtain odds ratio for VDD in the patients. Secondly, of the 129 eligible patients, 39 (30%) declined to participate. Thirdly, in this study only patients with mild to moderate UC with ages between 18 and 50 years and BMI between 18.5 and 30 kg/m<sup>2</sup> have been assessed.

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Authors have contributed to the study as follow:

Amrollah Sharifi: Literature search; substantial contributions to the conception and design of the study; the acquisition, analysis and interpretation of data; drafting the manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Saharnaz Nedjat: Design of the study; analysis and interpretation of data; revising manuscript critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Homayoon Vahedi: Design of the study; interpretation of the data; revising manuscript critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Gholamreza Veghari: Interpretation of data; revising manuscript critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mohammad Javad Hosseinzadeh-Attar: Design of the study; analysis and interpretation of data; revising manuscript critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## ETHICAL APPROVAL

There is nothing to be declared.

## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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