Original Article

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Evaluation of the Relationship Between Quality of Life, Serum 25 (OH) Vitamin D Levels, and Anxiety and Depression in Patients with Irritable Bowel Syndrome: A Case-Control Study

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Abstract

Aim: Recent data have highlighted the association between serum vitamin D deficiency and gastrointestinal system diseases and the effect of vitamin D on intestinal functions. Our study assesses the relationship between IBS disease and quality of life, depression, anxiety, and serum vitamin D levels.

Methods: The study was conducted between January 1st, 2020, and April 30th, 2020. The study data were collected from patient files and the hospital's digital file system. A total of 142 patients with IBS and 142 patients from non-IBS control groups were enrolled in this study. ROMA IV criteria were used to diagnose IBS. Accordingly, the SF-36 quality of life scale score, serum vitamin D levels, the Hamilton depression rating scale (HDRS), the Beck anxiety inventory (BAI), and the participants' scores were evaluated.

Results: The univariate analysis showed that marital status, body mass index, smoking status, glomerular filtration rate, serum albumin, alanine aminotransferase and aspartate aminotransferase levels were not associated with disease risk. A higher level of education, a low serum vitamin D level, a decrease in physical component scale and mental component scale scores, and increasing BAI and HDRS scores increased the disease risk ($p=0.003$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.008$, $p<0.001$ and $p<0.001$ respectively).

Conclusion: We propose that a high education level, low serum vitamin D, and an increase in BAI and HDRS scores may be independent risk factors for IBS.

Keywords: Vitamin D, irritable bowel syndrome, quality of life, anxiety, depression

Introduction

Irritable bowel syndrome (IBS) is a chronic gastrointestinal system disease that causes abdominal bloating, pain, and changes in bowel habits (1). Although its etiopathogenesis is not well known, many factors have been implicated as causative factors, including genetics, the endocrine system, emotional stress, and axial disease between the brain and the intestinal microbiota. Furthermore, the global prevalence of IBS currently stands between 10 and 20% (2,3). The associations between IBS and diseases such as chronic fatigue syndrome, depression, anxiety disorder, fibromyalgia, headache, and sexual dysfunction have also been observed (4). Furthermore, IBS also increases emotional stress with changes in bowel habits, such as chronic abdominal pain, persistent diarrhea, or constipation, resulting in a person's quality of life being negatively affected. Recurrent symptoms worsen a person's mental and social health (5,6). In IBS patients, the presence of symptoms, the frequencies and durations of these symptoms, the treatment modalities used, and IBS-related changes in diet and psychological state affect the quality of life. The presence of extra-intestinal symptoms and the severity of the symptoms also affect the quality of life of patients with IBS in a negative direction. Additionally, it was found that low educational and sociocultural levels render coping with IBS and its

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symptoms difficult, thus negatively affecting the quality of life of IBS patients (7,8).

When compared with normal individuals in the community, the psychological status and recurrent gastrointestinal symptoms of patients with IBS reduce their quality of life (9). Furthermore, patients' quality of life is also affected by the duration of the illness, the frequency of symptoms, their adaptation to the illness, and the training they receive about the illness. Moreover, factors such as receiving an IBS diagnosis, having fears and worries about the disease, lacking information on diagnosis and treatment, and being unable to cope with problems can negatively impact the patient's quality of life (10).

Gastrointestinal disease can lead to the malabsorption of certain compounds, such as vitamin D, thereby causing a deficiency in this vitamin. Globally, the prevalence of hypovitaminosis D is between 30 and 50% (11). The primary role of vitamin D is in calcium metabolism. Additionally, more than 200 genes have been implicated in the proliferation, apoptosis, and differentiation of vitamin D during the cell cycle. The vitamin D receptor can be found in the central nervous system, immune system, and intestines (12,13). The relationship between vitamin D and IBS disease is vague. Recently, high-dose vitamin D treatment has been deemed beneficial for patients with diarrhea-predominant IBS. Nonetheless, the effect of vitamin D in such instances remains unclear. It is unclear whether vitamin D helps reduce the symptoms of IBS or whether it lessens the symptoms of anxiety and depression, which are commonly observed in patients with IBS (14,15). Notably, there is a significant relationship between vitamin D deficiency and anxiety and depression, yet the effect of vitamin D deficiency on patients' quality of life remains unclear (16).

In our study, we sought to examine the complex and unclear association between IBS disease, quality of life, depression, anxiety, and vitamin D by comparing patients with IBS with healthy individuals and by evaluating potential associations in this network of relationships.

Materials and Methods

Compliance with Ethical Standards

Written informed consent was obtained from all participants, and the study protocol was approved by the University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (2020/01-07). The authors report no conflicts of interest and no grant support. This research did not receive any specific grant from funding agencies from within the public, commercial, or not-for-profit sectors.

Study Design

The study involved 242 patients with IBS who were diagnosed based on the Rome IV criteria. An additional 258 healthy, non-IBS patients also took part in the study. All participants were admitted to the internal medicine outpatient clinic between January 1, 2020, and April 30, 2020. Moreover, study participants were aged between 26 and 50 years.

Of the 242 individuals initially selected to be included in the control group, 100 were excluded from the study because of viral hepatitis, liver diseases, intestinal malabsorption, and other intestinal diseases. Of the 254 patients with IBS initially selected to be included in the patient group, 56 patients were excluded from the study due to a history of active infection and drug use, and 48 patients were excluded from the study due to meeting one or more of the criteria listed in the study exclusion criteria (Figure 1).

The Inclusion Criteria

To be diagnosed with IBS according to the ROMA IV criteria in the age range of 26-50 years.

The Exclusion Criteria

Hepatitis B and C disease, hepatosteatosis, and other liver diseases; bile duct pathologies; malabsorption (including celiac disease); diabetes mellitus; any malignancy; pregnancy; lactation; active infection; history of alcohol use; dyspepsia; peptic ulcer; inflammatory bowel disease; gastroesophageal reflux disease; individuals taking active vitamin D, vitamin C, and fish oil; individuals taking active vitamin D.

Participants and Recruitment

One hundred and forty-two IBS and 142 control groups, who were matched for age and gender, were included in the study. Thus, this served to eliminate the age and gender factors from the cases remaining after the application of the exclusion criteria. Information on the participants' marital status and education levels was also collated. For all patients with IBS, the symptoms' frequency and the duration of the illness were recorded. Following 12 h of fasting, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin tests were assessed in the participants. Moreover, the glomerular filtration rate (GFR) and the participant's body mass index (BMI) were calculated.

Vitamin D

The participants' blood samples were collected in ethylene diamine tetraacetic acid tubes. The blood was centrifuged and collected in microcentrifuge tubes. Serum 25-hydroxyvitamin D_2/D3 levels were determined using an ARCHITECT 5P02 enzyme immunoassay kit and an Abbott ARCHITECT analyzer. Vitamin D levels were measured in

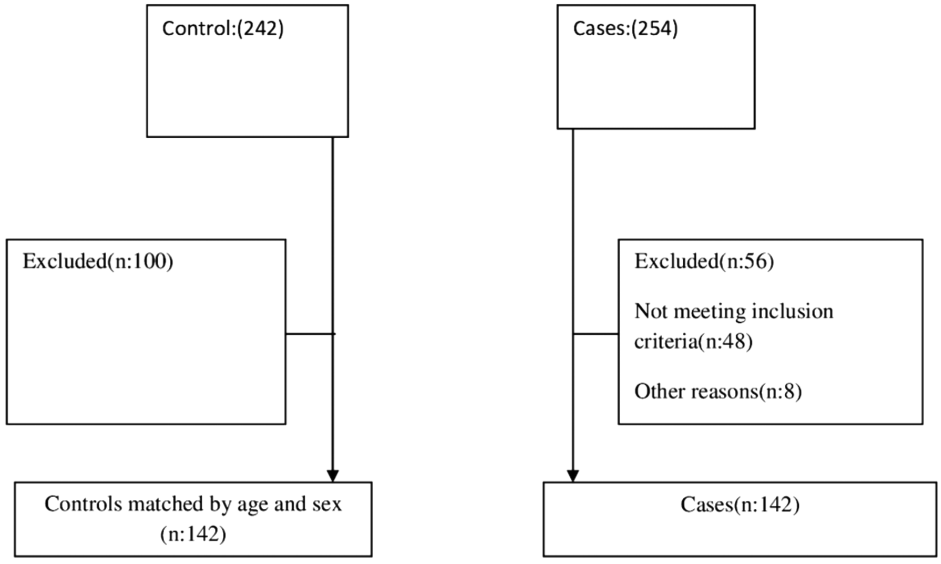

Figure 1. Flow diagram of the study

January. Participants were considered deficient if their serum 25(OH) vitamin D3 levels were less than 30 nmol/L. Serum 25(OH)D3 deficiency was determined if levels were between 30 and 50 nmol/L. Serum 25(OH)D3 vitamin levels in participants were considered adequate if they were greater than 50 nmol/l.

Participants' quality of life levels, anxiety levels, and depression levels were evaluated using the SF-36 Quality of Life Scale, the Beck anxiety inventory (BAI), and the Hamilton depression scale, respectively.

SF-36 Quality of Life Questionnaire

The SF-36 questionnaire encompasses both physical and mental health components and consists of two subscales and eight scales (17). The sections of the subscale are A. Physical health Group: 1. physical function; 2. role limitations due to physical problems; 3. pain; and 4. the general perception of health. B. Mental health Group: 5. energy/vitality, 6. social function, 7. role limitations because of emotional problems, and 8. mental health. In summary, the higher the scale score, the higher the level of quality of life.

Beck Anxiety Inventory

BAI was developed in 1961 by Beck et al. (18). It is a Likert-type self-reporting scale consisting of 21 items, where a score of 0-3 can be assigned to each item. The higher the total score, the higher the anxiety level experienced by the individual. Specifically, for this study, participants with a score of eight points and above were identified as experiencing anxiety.

Hamilton Depression Scale

Hamilton (19) developed this scale to measure depression levels. The upper limit of the scale stands at 53 points, and patients scoring less than eight points are considered normal. 8- Scores of 8-16 were accepted as mild-moderate depression and scores of 17 and above as severe depression. Once again, for this study, a score of 8 or above was considered to signify depression.

Statistical Analysis

The collated data were recorded in a spreadsheet, and statistical analyses were performed using SPSS Version 22 (IBM Corp. in Armonk, NY). The Shapiro-Wilk test was used to evaluate the distribution of the data. Descriptive data were presented as the median with an interquartile range (IQR) for non-normally distributed numerical data. Categorical data were presented using the frequency (n) and percentage (%). Pearson's chi-square test was used to compare categorical variables, and the Mann-Whitney U test was used to compare numerical variables among IBS and non-IBS groups. The disease risk was determined by univariate and multivariate binary logistic regression analyses. Demographics, clinical characteristics, health-related quality of life status, anxiety, and depression scores were included in the multivariate logistic regression model. Disease risk was assessed using odds ratios with 95% confidence intervals. A p-value where $p<0.05$ was considered statistically significant.

Results

Patients with IBS had a statistically significant higher education level, lower serum vitamin D level, and higher albumin level compared with non-IBS patients ($p<0.001$, $p<0.001$, and $p=0.012$, respectively). In contrast, all the serum albumin levels were within the reference range (3.5 to 5.5 g/dL). Of the patients with IBS, 39 reported a daily

symptom frequency, and more than 65% suffered from disease symptoms at least one day a week. Nearly one-third of patients with IBS have had the disease for one to five years (Table 1).

Table 2 lists the health-related quality of life status, anxiety, and depression scores of the patients. All subdomain, physical component scale (PCS) and mental component scale (MCS) scores were significantly higher in non-IBS patients, thus indicating that patients with IBS had a lower health-related quality of life than non-IBS patients. Furthermore, anxiety and depression scores were significantly higher in patients with IBS compared to non-IBS patients (p=0.004 and p<0.001, respectively) (Table 2).

The univariate analysis showed that marital status, BMI, smoking status, GFR, serum albumin, ALT, and AST levels were not associated with disease risk. A higher level

Table 1. Demographics and clinical characteristics

Variables	**IBS (n=142)**	**Non-IBS (n=142)**	**p-value**
Age (years), Median (IQR)	38.0 (26.0-50.0)	38.0 (26.0-50.0)	-
Female, n (%)	80 (56.3)	80 (56.3)	-
Marital status, n (%)			
Single	45 (31.7)	51 (35.9)	0.452*
Married	97 (68.3)	91 (64.1)	
Education level, n (%)			
Primary	31 (21.8)	64 (45.1)	<0.001*
Secondary	78 (54.9)	71 (50.0)	
Higher	33 (23.2)	7 (4.9)	
Current smoking status, n (%)			
Smoker	57 (40.1)	61 (43.0)	0.630*
Non-smoker	85 (59.9)	81 (57.0)	
BMI (kg/m^2), Median (IQR)	27.1 (25.1-28.2)	26.8 (25.3-27.9)	0.636**
Normal weight, n (%)	31 (21.8)	27 (19.0)	0.140*
Overweight, n (%)	92 (64.8)	105 (73.9)	
Obese, n (%)	19 (13.4)	10 (7.1)	
25(OH) vitD (nmol/L), Median (IQR)	13.0 (9.4-16.7)	16.1 (14.3-18.8)	<0.001**
Insufficiency, n (%)	6 (4.2)	9 (6.3)	0.426*
Deficiency, n (%)	136 (95.8)	133 (93.7)	
GFR (mL/min/1.73 m^2), Median (IQR)	99.7 (94.6-109.6)	101.8 (92.4-111.8)	0.454**
Albumin (g/dL), Median (IQR)	4.5 (4.3-4.6)	4.3 (4.2-4.6)	0.012**
ALT (U/L)	17.0 (13.0-27.0)	17.5 (15.0-22.0)	0.487**
AST (U/L)	18.0 (15.0-22.0)	18.0 (16.0-22.0)	0.181**
Symptom frequency, n (%)			
Everyday	39 (27.5)		
4 to 6 days per week	37 (26.1)		
2 to 3 days per week	8 (5.6)		
1 day per week	7 (4.9)		
2 to 3 days per month	17 (12.0)		
1 day per month	34 (23.9)		
Disease duration, n (%)			
1-5 years	46 (32.4)		
6-10 years	33 (23.2)		
11-15 years	24 (16.9)		
16-20 years	14 (9.9)		
More than 20 years	25 (17.6)		

Note: Mean vitamin D level of the IBS group was statistically significantly lower than that of the control group.
*Pearson chi-square test was used. **Mann-Whitney U test was used.
IBS: Irritable bowel syndrome, IQR: Interquartile range, BMI: Body mass index, GFR: Glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

of education, a low serum vitamin D level, a decrease in PCS and MCS scores, and increasing BAI and Hamilton depression rating scale (HDRS) scores increased the disease risk (p=0.003, p<0.001, p<0.001, p<0.001, p=0.008, p<0.001 and p<0.001 respectively). Additionally, two multivariate regression analysis models were also performed. In the first model, the education level, serum vitamin D level, BAI, and HDRS scores were similar, but the significance was lost between PCS, MCS, and disease risk. In the second model, all variables included in the analysis had a significant association with disease risk (Figure 2). Consequently, a higher education level, decreasing serum vitamin D levels, and increases in the BAI and HDRS scores were independent risk factors for IBS (Table 3).

Discussion

Evaluation of the quality of life scores between the IBS group and the healthy groups in this study using the SF-36 questionnaire established lower quality of life scores in the IBS group compared to the healthy group. Moreover, the difference between the results was deemed statistically significant. These findings agree with the study by Buono et al. (20), which examined 1102 patients with IBS and a healthy control group using the SF-36 quality of life questionnaire. The scores generated were also lower in patients with IBS, and the difference was found to be statistically significant. Furthermore, a study by Addante et al. (21) involving 290 patients with IBS and a healthy group also reported a lower quality of life for the IBS group compared to the control group. Thus, the findings of this study were concordant with the literature, as they established that the quality of life of the IBS group was lower in all parameters compared with the control group. Thus, we propose that the prolonged disease duration and the high frequency of symptoms in the patients with IBS contributed to reducing the patients' quality of life.

We also found a significant association between the participants' education levels and IBS disease. While the rate was higher in patients with IBS who had a primary or secondary education level, we found that the rate of IBS

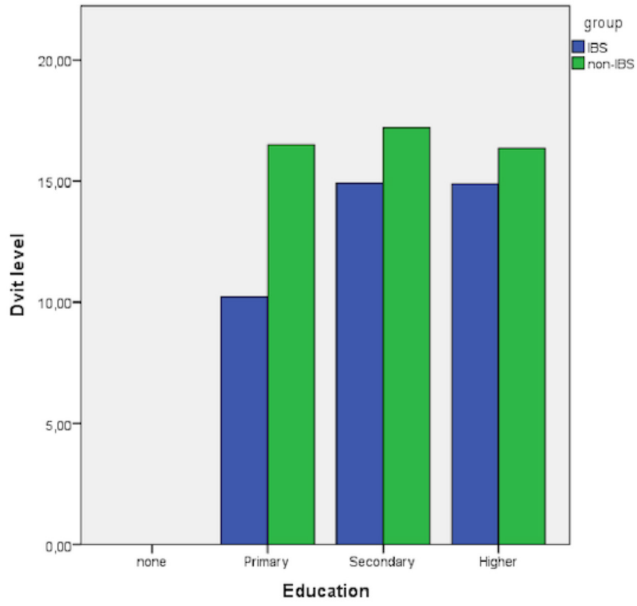

Figure 2. IBS and control group of vitamin D levels according to education in levels

IBS: Irritable bowel syndrome

Table 2. Health-related quality of life and mental health status

Variables	IBS (n=142)	Non-IBS (n=142)	p-value
SF-36, Median (IQR)			
PF	49.0 (40.0-61.0)	53.0 (45.0-66.0)	0.001*
RP	47.5 (41.0-58.0)	52.0 (45.0-62.3)	0.001*
BP	49.0 (42.0-58.3)	53.0 (47.0-65.3)	<0.001*
GH	49.0 (41.0-62.0)	54.0 (46.0-64.3)	0.008*
VT	49.0 (39.0-63.0)	53.0 (46.0-66.0)	0.007*
SF	49.0 (40.0-61.0)	53.0 (45.0-66.0)	0.001*
RE	48.5 (40.0-61.3)	52.5 (44.0-64.0)	0.011*
MH	48.0 (41.0-61.0)	52.0 (45.0-63.5)	0.005*
PCS	38.8 (35.6-42.8)	40.3 (37.5-45.1)	<0.001*
MCS	38.9 (35.6-45.3)	40.9 (37.4-47.0)	0.004*
BAI, Median (IQR)	5.0 (3.8-10.3)	4.0 (2.0-6.0)	<0.001*
HDRS, Median (IQR)	4.0 (3.0-6.0)	3.0 (3.0-5.0)	<0.001*

Note: Quality of life scale parameters were found to be statistically significantly lower in the IBS group than in the control group. On the other hand, anxiety and depression questionnaire scores were higher in the IBS group.
IBS: Irritable bowel syndrome, SF-36: 36-Item short form survey, IQR: Interquartile range, PF: Physical functioning, RP: Role limitation due to physical problems, BP: Bodily pain, GH: General perception of health, VT: Energy and vitality, SF: Social functioning, RE: Role limitation due to emotional problems, MH: Mental health, PCS: Physical component scale, MCS: Mental component scale, BAI: Beck anxiety inventory, HDRS: Hamilton depression rating scale

was lower in those with a higher education level. Thus, we conclude that education is an independent risk factor for IBS. Choghakhori et al. (22) found no difference in education levels in a study conducted between 90 patients with IBS and a control group. In a study by Chatila et al. (23) with 553 participants, no significant relationships were identified between the participants' education level and IBS, although they reported higher rates of IBS in individuals with university education. In this study, although the ratio was higher in individuals who secured education at the primary and secondary education levels, the risk of IBS was found to be statistically significant in individuals with medium and higher education levels, following a two-tailed analysis of the data. We propose that the discrepancies in the findings compared to the literature may be due to socioeconomic differences in societies.

Changes in the gut microbiota, inflammation, and the release of proinflammatory cytokines may cause changes in the gut-brain axis. Consequently, this process may negatively affect the hypothalamic-pituitary-adrenal gland axis, which contributes to stress in the body. Excessive cortisol release caused by the hypothalamus-pituitary-adrenal axis secondary to inflammation contributes to emotional stress. Excessive cortisol release has also been associated with anxiety and depression. Despite the complex relationships in the brain-gut axis, it contributes biologically, socially, and psychologically to pathophysiology (24,25). The findings of this study demonstrated higher anxiety and depression scores for patients with IBS compared to the control group. In the study by Zamani et al. (26), the rate of anxiety in patients with IBS was 39.1%, which was 3.1 times higher than that in healthy individuals. Similarly, depression was observed at a rate of 28.8%, which equates to being 3.08 times more common in patients with IBS compared to the healthy population. Despite a similar finding in this study, the data do not fully reveal whether depression causes IBS or whether IBS symptoms that worsen lead to depression. Thus, we propose that depression and anxiety disorders are independent risk factors for IBS. However, the findings are unclear, and further studies on intestinal microbiota with larger participant groups are needed.

The findings of our study indicated that patients with IBS had lower vitamin D levels compared with the control group and that 95.8% of patients with IBS had a vitamin D deficiency. These findings agree with some recent studies. Khayyat and Attar (14) concluded that 82% of patients with IBS had a vitamin D deficiency, and Abbasnezhad et al. (11) found this rate to be 85%. We attribute the higher rate noted in this study to the environmental conditions and the measurement of vitamin D levels in

Table 3. Univariate and multivariate regression analysis of the patient characteristics for disease risk

Characteristics		Univariate		Multivariate model 1		Multivariate model 2	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Marital status	Single	Ref					
	Married	1.21	0.452				
Education level	Primary	Ref		Ref		Ref	
	Secondary	2.27 (1.33-3.88)	**0.003**	3.77 (1.94-7.32)	**<0.001**	3.98 (2.07-7.63)	**0.003**
	Higher	9.73 (3.87-24.46)	**<0.001**	13.30 (4.58-38.60)	**<0.001**	14.80 (5.23-41.88)	**<0.001**
BMI		1.05 (0.98-1.13)	0.176				
Smoking status	Non-smoker	Ref					
	Smoker	0.89 (0.56-1.43)	0.630				
25(OH) Vit D level		0.90 (0.85-0.94)	**<0.001**	0.88 (0.83-0.94)	**<0.001**	0.88 (0.83-0.93)	**<0.001**
GFR		0.99 (0.97-1.02)	0.498				
Albumin		2.01 (0.87-4.67)	0.103				
ALT		1.01 (0.99-1.03)	0.321				
AST		1.01 (0.98-1.03)	0.519				
PCS		0.90 (0.85-0.95)	**<0.001**	0.91 (0.77-1.09)	0.302		
MCS		0.94 (0.90-0.98)	**0.008**	1.10 (0.97-1.25)	0.123		
BAI		1.24 (1.15-1.35)	**<0.001**	1.18 (1.05-1.33)	**0.007**	1.15 (1.05-1.27)	**<0.001**
HDRS		1.29 (1.13-1.47)	**<0.001**	1.24 (1.06-1.44)	**0.007**	1.20 (1.05-1.38)	**<0.001**

Note: The univariate analysis showed that marital status, BMI, smoking status, GFR, serum albumin, ALT, and AST levels were not associated with disease risk. A higher level of education, low serum vitamin D level, decrease in PCS and MCS scores, and increasing BAI and HDRS scores increased the disease risk.
*Pearson chi-square test was used, **Mann-Whitney U test was used.
OR: Odds ratio, CI: Confidence interval, Ref: Reference category, BMI: Body mass index, GFR: Glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PCS: Physical component scale, MCS: Mental component scale, BAI: Beck anxiety inventory, HDRS: Hamilton depression rating scale

the winter months. Vitamin D is central to the regulation of calcium and phosphorous metabolism. Furthermore, it has immune-modulatory and anti-inflammatory properties. The intestine is rich in microflora. Thus, the intestine is an important region in terms of inflammatory events that can be activated by T helper type 1 cells. One study reported that inflammation in the intestine affects vitamin D regulation (27). The 1-alpha hydroxylase enzyme found in the kidneys converts calcitriol into 1.25-dihydroxyvitamin D. This enzyme is also involved in the regulation of the epithelial barrier and inflammation. Notably, increased inflammation in the intestines can impair the functions of this enzyme, thereby impairing IBS symptoms and intestinal function (28). Currently, the findings in the literature do not clarify whether a vitamin D deficiency or insufficiency is a predisposing factor to IBS disease or whether the vitamin D level worsens the prevailing symptoms of existing IBS disease. The findings of our study did not indicate a statistically significant relationship between vitamin D deficiency or insufficiency and IBS. Nonetheless, the data did indicate that patients with low vitamin D levels had a higher risk of IBS than the normal group.

Study Limitations

The study limitations included the investigation of a single center, a small number of participants, and disregarding the patients' dietary habits. Apart from these limitations, comparing patients with IBS with a control group of matching age and gender characteristics and evaluating the quality of life along with psychological factors such as anxiety and depression can be cited among the study's strengths.

Conclusion

Our study sought to contribute to the literature on the relationship between IBS disease, psychological factors, and vitamin D, which are considered current research topics. We propose that education, anxiety, depression, and vitamin D status are all independent risk factors for IBS. However, the findings on this subject are unclear. Accordingly, we recommend that prospective studies with larger participant numbers and the examination of other factors further investigate IBS.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (2020/01-07).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.B., K.C., Design: M.B., K.C., Data Collection, or Processing: M.B., K.C., Analysis, or Interpretation: M.B., K.C., Literature Search: M.B., K.C., Writing: M.B., K.C.

Conflict of Interest: The authors report no conflicts of interest and no grant support. The authors alone are responsible for the content and writing of the paper.

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