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Original Article

Assessing Effects of Serum 25-Hydroxyvitamin D Levels on Anxiety and Depression in Patients with Colorectal Adenocarcinoma

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ABSTRACT

Background and Objectives: In colorectal cancer patients experiencing depression and anxiety, vitamin D supplementation may boost mood by rectifying serum 25(OH)D levels. This study assessed the potential for vitamin D to alleviate symptoms of depression and anxiety in colorectal cancer patients with insufficient clinical evidence available.

Materials and Methods: In this study, 46 colorectal adenocarcinoma patients were included based on specific inclusion criteria. Serum 25(OH)D levels were assessed using enzyme-linked immunosorbent assay and assessed anxiety and depression using Zung's questionnaire at baseline. Based on the baseline serum 25(OH)D levels, patients were categorized into four groups of < 12 ng/ml, 12–20 ng/ml, 20–30 ng/ml and ≥ 30 ng/ml. A standard dose of vitamin D supplementation was administered based on the study protocol. After 12 w, serum 25(OH)D levels, anxiety and depression were assessed and statistical analyses were carried out.

Results: In this clinical trial, 80% of patients (median age, 56.8 y) had inadequate baseline serum 25(OH)D levels (< 30 ng/ml), with 28.3% having depressive symptoms (Zung SDS score > 50) and 37% showing anxiety symptoms (Zung SAS score ≥ 40). The average serum 25(OH)D level increased from 25.4 ng/ml before the intervention to 34.8 ng/ml post-intervention. Significant differences were reported in serum 25(OH)D levels before and after the intervention (p = 0.0001). Additionally, significant decreases were reported in the mean scores for anxiety (p = 0.021) and depression (p = 0.015) after the intervention. Changes in serum 25(OH)D levels were significant and inversely correlated with changes in depression (p = 0.0186) and anxiety (p = 0.0099) scores.

Conclusions: Vitamin D supplementation may significantly improve depression and anxiety symptoms in colorectal adenocarcinoma patients.

Keywords: 25-Hydroxyvitamin D, Colorectal cancer, Depression; Anxiety, Clinical trial

Highlights

- In general, 37% of colorectal cancer patients had anxiety scores of 50% or greater before the intervention. Significant differences were reported between the mean scores before and after the intervention.
- Moreover, 28.3% of colorectal cancer patients had depression scores greater than 50 before the intervention. Significant difference were seen between the mean scores before and after the intervention.
- Changes in serum 25(OH)D levels were significantly correlated with changes in depression and anxiety scores.
- Vitamin D supplementation decreased anxiety and depression in patients with colorectal adenocarcinoma.

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Introduction

Depressive disorder is a prevalent mental health condition, affecting an estimated 3.8% of the global population, including 5% of adults. Approximately 280 million people worldwide suffer from depression (1). Additionally, nearly 4% of the general population currently experience an anxiety disorder. In 2019, 301 million people globally had an anxiety disorder, making it the most common mental disorder (2). The incidence of depression in cancer patients is approximately 25% and may be higher in those with greater debilities (3). Furthermore, Peng et al. reviewed 15 articles published 1967–2018. They reported that patients with colorectal cancer (CRC) have a significant prevalence of depression and anxiety, which can persist even after treatment completion (4). The CRC is the second leading cause of cancer-related deaths in the United States, following lung cancer, with 149,500 new cases and 52,980 deaths reported in 2021 (5). In Iran, a greater than 50% increase in CRC cases is anticipated by 2025, potentially making it the second most common cancer in Iranian men (6). Vitamin D (VD), known for its role in calcium and phosphate homeostasis, is critical in age-related diseases, including cancers. It modulates immune function, particularly in the bowel and central nervous system (CNS) (7–11). Hypovitaminosis D (VD levels < 30 ng/ml) is highly prevalent worldwide (12, 13) and has been associated with an increased risk of major depressive disorder (MDD) and anxiety disorders (14–16, 17–20). Therefore, VD supplementation may be beneficial for the prevention and treatment of these disorders. However, genetic factors (e.g., VD receptor polymorphism and skin color), environmental factors (e.g., low sun exposure and dietary habits) and differences in supplementation regimens can affect VD bioavailability and metabolism, which may explain absence of overt psychiatric symptoms in several studies (21–23). Regarding high prevalence of depression and VD deficiency or insufficiency in CRC patients, it is hypothesized that VD supplementation can improve depression and anxiety by correcting serum 25(OH)D levels. Due to the limited number of clinical studies in this area, the present study investigated the role of VD in alleviating symptoms of depression and anxiety in CRC patients.

Materials and Methods

Aim of the study

The aim of study was to investigate effects of VD supplementation on depression and anxiety in adult colorectal adenocarcinoma patients referred to Reza Radiotherapy and Oncology Center and 22 Bahman Hospital, Mashhad, 2023.

Trial setting and design

This study was a four-arm, parallel-group, non-randomized, non-blinded, before-after phase-2 clinical trial without a control group. Based on the number of referrals to sample collection centers and patient cooperation, 46 patients were selected as the target sample size using the pilot method. All participants in this study signed information and consent forms.

Inclusion and exclusion criteria and patient's characteristics

The inclusion criteria were as follows: aged 18–70 y, ability to read and write in Persian and ability to respond to questionnaire questions. The exclusion criteria were as follows: complicated diabetes or hypertension, history of visiting a psychiatrist or psychologist in the last 6 m or taking psychotropic drugs in the last 6 m, pregnancy, breastfeeding, receiving VD or its analogs in the last 3 m and baseline serum 25(OH)D level > 100 ng/ml.

Materials

Zung self-rating depression scale (SDS) questionnaire was used to assess patients' depression levels before starting the intervention and 90 d after beginning cholecalciferol supplementation. The SDS is a 20-question self-report survey designed to assess depression levels, with responses provided on a 4-point Likert scale (24). A score of ≥ 50 indicated depression, which is further classified based on its severity. This assay was validated by Rustazadeh in 1998 and Habibpour in 2003 in high school boys and girls of Isfahan, Iran. Additionally, Alizadeh et al. reported a total reliability of 90% for this assay in their 2009 study (25).

Zung self-rating anxiety scale (SAS) questionnaire was used to assess patients' anxiety levels before starting the intervention and 90 d after beginning cholecalciferol supplementation. The SAS is a 20-question self-report survey aiming at assessment of anxiety levels, with responses rating on a 4-point Likert scale (26). The option scoring varies, with questions scoring 1–4 and others in a reverse order. The total scale scores ranged 20–80. The raw score is divided by 80 and reported as a percentage, with a percentage of ≥ 50 indicating the presence of anxiety. Intensity of anxiety is assessed based on the numerical value of the percentage. Sabet's study in 2007 verified reliability of this scale, reporting a Cronbach's alpha coefficient of 0.78. The scale formal and content validities were established (27). To assess serum 25(OH)D levels before and after the intervention, a 5-ml venous blood sample was collected from each participant and sent to the laboratory of the sampling centers using heparin-lithium tubes. The serum 25(OH)D level was assessed using enzyme-linked immunosorbent assay (ELISA), Hiperion

microplate reader (MPR4+) and 96-well kit (REF, 6724-96; LOT, H67L1A3) (Ideal Diagnostics, Iran). The VD supplementation was administered in the form of 1000-U cholecalciferol tablets from Omid Parsina Damavand Pharmaceutical, Iran (LOT, 1658029) and 50000-U cholecalciferol pearls from Zahrawi Pharmaceutical, Iran (LOT, 515).

Intervention

After collecting basic information from the patients' files or through direct questioning, patients who met the study criteria were invited to participate in the study. The study method was explained to the patients with the information that they could withdraw from the study at any time without affecting their treatment process. Informed consents were signed by all participants. No extra costs were received from the patients. Baseline anxiety and depression levels were quantitatively assessed using Zung questionnaire. The baseline serum 25(OH)D level was assessed using ELISA. Based on the baseline serum 25(OH)D levels, patients were classified into four groups of below 12 ng/ml (deficiency group (D)), ≤ 12 to 20 ng/ml (insufficiency group (I)), ≤ 20 to 30 ng/ml (borderline group (B)) and ≤ 30 ng/ml and greater (sufficient group (S)). The total necessary dose for each group within 90 d was calculated based on the established protocols and sources. Doses were administered in the form of 1000-U tablets and 50000-U pearls of cholecalciferol based on the following instructions (28, 29):

1. Deficiency group: 50,000 IU (International unit) weekly for 8 w, followed by 1,000 IU daily for the rest of 4 w (424,000 IU total within 90 d).
2. Insufficient group: 1,000 IU daily for 3 m (90,000 IU total within 90 d).
3. Borderline group: 1,000 IU daily for 2 d, then one day off (approximately 60,000 IU total within 90 d).
4. Sufficient group: 1,000 IU every other day (54,000 IU total within 90 d).

At the end of the 90-d intervention, patients recompleted the anxiety and depression questionnaires. The maximum allowable time gap between the end of the intervention, measurement of serum 25(OH)D levels and completion of the questionnaires was 4 w. First, 73 patients met the study criteria and were included in the study. However, 18 patients chose not to cooperate or did not complete the questionnaires at the end of the study and were then excluded from the study. Additionally, six patients died before the intervention began and three patients died during the intervention. Thus, 46 patients totally completed the study (Figure 1).

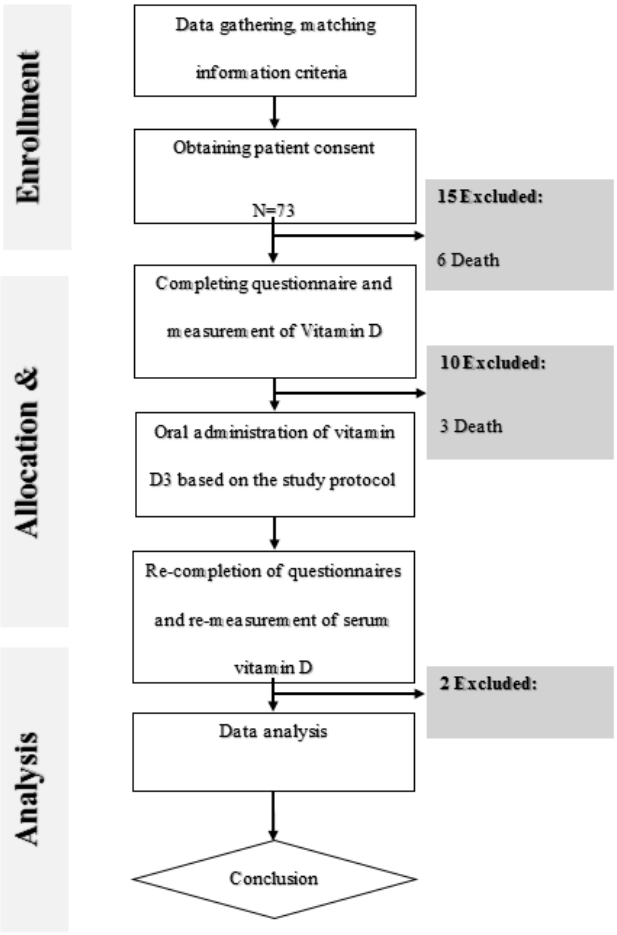

Figure 1. Flow chart diagram of this study

Statistical analysis

In this study, data description, statistical tables and indices such as the means were used. Normality of data was assessed using Shapiro-Wilk test, which verified normality of the dataset. In data analysis, parametric tests such as Student's dependent t-test were used for normally distributed data. For non-normal data, Mann-Whitney test was used. Pearson's and Spearman's correlation coefficients were used for correlation analyses, while regression and linear models were used for general analyses. Software used in this study included SPSS v.26 (IBM, USA) with a significance level set at less than 5%. Microsoft Excel v.2010 was used for data entry and creation of descriptive charts.

Results

Patient characteristics

In this study, 46 patients aged 42–69 y with a median age of 56.8 y ±8 were participated. The average time elapsed since the diagnosis of the disease at the time of entering the study was 9 m with a range of 1–36 m. Other patient characteristics are detailed in Table 1. In total, 61% of patients (n = 28) had a serum 25(OH)D level > 20 ng/ml,

while 39% (n = 18) had a level ≤ 20 ng/ml. The mean serum 25(OH)D level increased from 25.4 ng/ml before the intervention to 34.8 ng/ml after the intervention, indicating a 51.2% (9.4 ng/ml) improvement due to VD supplementation (Table 1). Results showed a significant difference in serum 25(OH)D levels in CRC patients before and after VD consumption (p = 0.0001, T-test = 10.14) (Table 2).

Table 1. Demographic and clinical characteristics of the samples in this study

Variables	Category	Frequency (%)
Gender	Male	30 (65.2%)
	Female	16 (34.8%)
Stage of cancer[1]	Stage I	3 (6.5%)
	Stage II	9 (19.6%)
	Stage III	13 (28.3%)
	Stage IV	21 (45.7%)
Pathologic grade	Well differentiated adenocarcinoma	16 (34.8%)
	Moderately differentiated adenocarcinoma	24 (52.2%)
	Poorly differentiated adenocarcinoma	6 (13%)
Ostomy bag use[2]	Yes	6 (13%)
	No	40 (87%)
Treatment Type[3]	Chemotherapy	12 (26%)
	Chemotherapy & Colon resection Surgery	8 (17%)
	Chemo radiotherapy	18 (39%)
	Chemo radiotherapy & Colon resection Surgery	8 (17%)
Intervention Group[4]	Deficiency	1 (2%)
	Insufficiency	18 (39%)
	Borderline	18 (39%)
	Sufficiency	9 (20%)
Time interval from diagnosis to entering the study[5]	≤ 1 year	35 (77%)
	> 1 year	11 (23%)

1. Based on American Joint Committee on Cancer staging system;
2. The presence of a stoma bag at the time of entering the study;
3. Including the treatments that the patient has received since the diagnosis of the disease until entering the study;
4. According to basic serum vitamin D level (below 12 ng/ml, 12 ≤to 20 ng/ml, 20≤ to30 ng/ml and 30 ng/ml≤.);
5. Including the period a patient has lived with a cancer diagnosis.

Table 2. Comparison between serum 25(OH)D levels and anxiety and depression scores of the participants before and after the intervention

Variables		Before the intervention	After the intervention	P value	T-test
serum 25(OH)D Level[1]	Minimum	6.5	18.0	0.0001	10.14
	Maximum	61.0	61.0		
	Median	23.2	32.1		
	Mean± SD	25.4±12	34.8±10.4		
Zung SAS score[2]	Minimum	25.0	26.0	0.021	2.39
	Maximum	71.0	62.0		
	Median	45.0	44.0		
	Mean± SD	45.5±11.9	41.3±9.3		
Zung SDS score[3]	Minimum	24.0	24.0	0.015	2.53
	Maximum	62.0	54.0		
	Median	42.5	38.0		
	Mean± SD	41.7±10.2	38.5±7.3		

1. Serum 25(OH)D level measured by ELIZA method;
2. Zung Self-Rating Anxiety Scale (SAS);
3. Zung Self-Rating Depression Scale (SDS).

Comparison of Zung's SAS score before and after the intervention

In this study, 37% of participants had an anxiety score of 50% or greater (21.7% had mild anxiety, 13% had moderate anxiety and 2.2% had severe anxiety). Significant differences were seen between the mean Zung's SAS scores before and after the intervention (p = 0.021) (Figure 2). The average anxiety score of patients decreased from 45.5 before the intervention to 41.3 after the intervention, indicating a 4.3% decrease (Figure 2). Moreover, VD supplementation was associated with this decrease in anxiety levels. Additionally, the percentage change in serum 25(OH)D levels included a significant inverse relationship with the percentage change in anxiety severity, meaning increases in serum 25(OH)D levels corresponded to decreases in anxiety severity (p = 0.009). Subgroup analysis in the intervention groups revealed that only serum 25(OH)D levels of 13–20 ng/ml included significant relationships between the percentage changes of serum 25(OH)D levels and percentage changes in depression scores but not in anxiety scores (p = 0.030, correlation coefficient = 0.511 for depression; p = 0.24, correlation coefficient = 0.530 for anxiety).

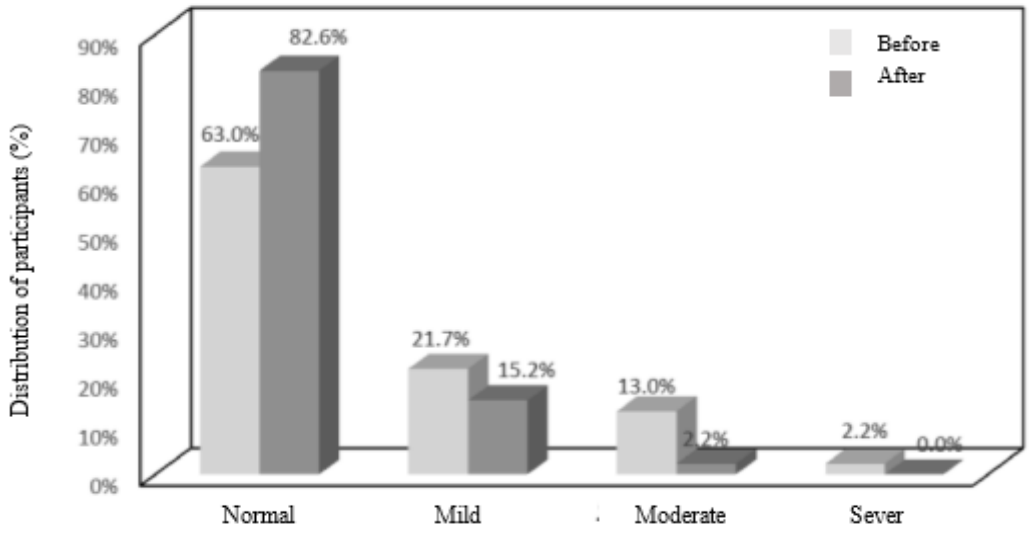

Figure 2. Distribution of anxiety in colorectal cancer patients

As the result of vitamin D intake, the number of patients with normal anxiety score increases, and therefore number of other patients with different severity decreases during 90 days.

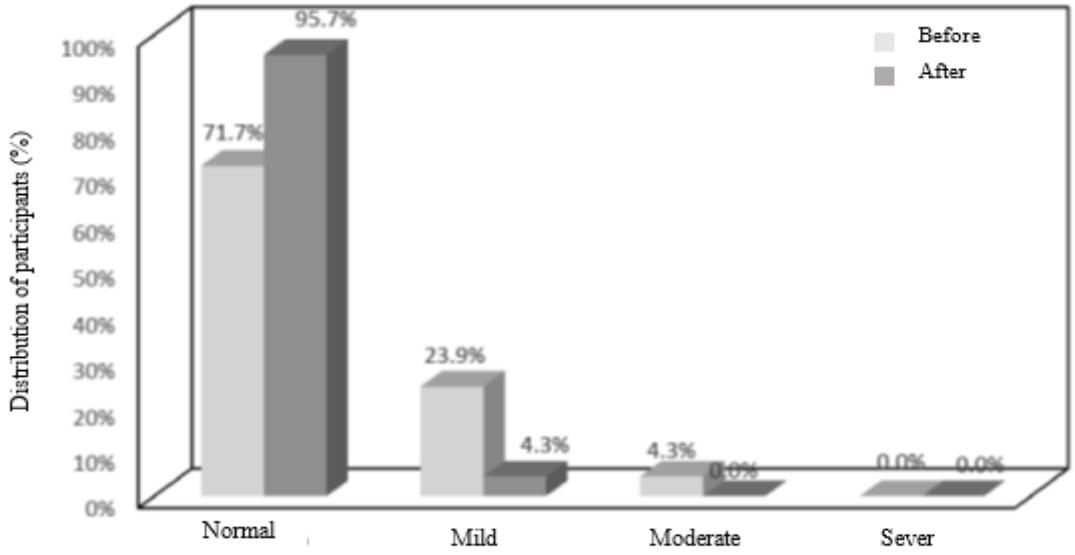

Figure 3. Distribution of depression in colorectal cancer patients

As the result of vitamin D intake, the number of patients with normal depression score increases, and therefore number of other patients with different severity decreases during 90 days.

Comparison of Zung's SDS score before and after the intervention

In this study, 28.3% of participants had a depression score greater than 50 (23.9% had mild depression and 4.3% had moderate depression). Significant differences were seen between the mean Zung's SDS scores before and after the intervention (p = 0.015). The mean depression score of patients decreased from 41.7 before the intervention to 38.5 after the intervention, indicating a 4.1% decrease (Figure 3). The VD supplementation was associated with this decrease in depression levels. Furthermore, percentage change in serum 25(OH)D levels included a significant inverse relationship with the percentage change in depression severity, meaning that increases in serum 25(OH)D levels corresponded to decreases in depression severity (p = 0.0186) (Figure 3).

Comparison of depression and anxiety scale scores between the patients with and without an ostomy bag

A comparison of depression and anxiety scale scores between the patients with an ostomy bag and those without it did not reveal any significant differences between the two groups. For depression, Mann-Whitney U test yielded a p-value of 0.706 (Mann-Whitney U = 0.375). For anxiety, the t-test resulted in a p-value of 0.675 (t-test = 0.423).

Relationships of the anxiety and depression with disease stage, grade and time elapsed since diagnosis

Pearson's and Spearman's correlation coefficients were used to investigate the relationships between the stage, grade and time elapsed since diagnosis with the Zung's SDS and SAS scores and stage, grade with serum 25(OH)D levels before and after the intervention. Results only indicated direct relationship between the stage of the disease and the baseline serum 25(OH)D level, meaning that patients in further advanced stages of the disease had higher baseline serum 25(OH)D levels (p = 0.010, correlation coefficient = 0.378).

Discussion

In this clinical trial, 90 d of supplementation with a standard dose of VD in CRC patients was associated with significant decreases in anxiety and depression scores. Relationship between depression and serum 25(OH)D has been controversial. While studies support this relationship (15, 30–32), other studies have shown no relationships (33). However, the most current study suggests a role for VD in pathogenesis of depression (34–39). For example, presence and distribution of VD receptors and 1α-hydroxylase enzyme, which catalyzes conversion of 25(OH)D to 1,25-dihydroxy vitamin D in brain areas such as the hypothalamus, frontal cortex, substantia nigra, amygdala and thalamus, support the hypothesis that VD can affect the brain (40). Additionally, presence of VD receptors in various neurons and microglial cells indicated the VD roles in immune responses within the CNS (41). Depression is strongly associated with anxiety, although studies on inflammation and anxiety symptoms are rare (42). Since altered immune responses and increased proinflammatory cytokines, including interleukin-6, might be common links between the pathogenesis of CRC (43, 44), depression (45–49) and anxiety, VD anti-inflammatory role could decrease inflammation and improve patients' psychopathology. Multiple clinical studies demonstrate that VD deficiency is associated with depression (15, 50–53). However, studies do not support these findings (54–57).

Since the cause of major depressive disorders is complex and involves psychological, biological and environmental components (58), the present study has investigated possible factors affecting anxiety and depression in CRC patients. For many cancer patients, diagnosis and treatment of cancer are highly stressful experiences that can lead to long-term negative psychological consequences, including emotional distress, depression, anxiety, sleep problem, fatigue and decreased quality of life (59–63). Additionally, cancer patients must cope with significant life changes during their treatments (64). Various levels of threat or prognostic uncertainty elicit varied responses to illness (65). Researchers have hypothesized that the search for meaning in life is more likely to occur in patients whose cancer is somewhat life-threatening (Stage II) and whose prognosis is uncertain, while this search is less observed in patients who are possibly treatable (Stage I) or generally untreatable (Stage IV) (66). Therefore, unlike studies that identify advanced stages of the cancers as a risk factor for depression and psychiatric disorders, including anxiety in CRC patients (67, 68), the present study did not show a relationship between the stage (or grade) and depression or anxiety. The effect of stage and grade, as critical components determining the prognosis of cancer, on resilience, anxiety and depression directly depends on the patient's level of knowledge and attitude about these concepts. Lack of a relationship observed in the present study might be because patients lack sufficient knowledge about these concepts or are generally unaware of their illness.

Various results of the relationships between time since diagnosis and depression and anxiety are available. For example, a study by Festerling and Lyold et al. demonstrated that a long time of treatment increases mental health disorders, especially depression, due to high mental and physical loads and the highest proportion of depressive disorder was > 5 y after diagnosis (67, 69). In Macia's study, patients showed higher resilience during treatment (70). In this study, time a patient lived with a cancer diagnosis was addressed as a potential factor affecting anxiety and depression. However, some patients experienced recurrences, metastases, or new cancer

diagnoses during the study. These varous aspects certainly affect resilience and overall mental health. Additionally, resilience in cancer outcomes is affected by pre-existing characteristics (e.g., social support) and individual adaptation mechanisms such as coping strategies, relationships with healthcare providers and psychosocial outcomes such as post-traumatic growth and quality of life (64). Therefore, the multitude of factors affecting anxiety and depression during the treatment might partially explain the current finding of unclear relationships with time of the disease diagnosis.

Cancer patients differ from individuals, who have experienced trauma as a one-time event. Due to their frequent medical visits, cancer patients live with a constant fear of relapse, hospitalization and other medical issues (71). It has been observed that cancer patients, who received chemotherapy or radiotherapy, perceive their cancers as further severe and hence demonstrate further traumatic stress symptoms (72). Several studies have shown that patients, who only did surgery, had lower depression levels, compared to those who received chemotherapy or radiotherapy (59, 72, 73). Additionally, moderate anxiety was higher in the chemotherapy group (74). However, the present study did not show a relationship between the treatment type and anxiety and depression. In this study, treatment type was referred to all treatments carried out for the patient's CRC since diagnosis. Regardless of their treatment history, most patients in sample collection centres received chemotherapy or radiotherapy at the time of entering the study. Effects of the current treatment might be more significant than those of past treatments in the occurrence of mental disorders. Additionally, cancer patients often face financial burdens linked to their care (75–78). There are evidence that financial burdens and concerns significantly affect the mental health (79–81). High costs of chemotherapy and radiotherapy contribute to the financial burden. In the present study, it was not possible to analyze factors affecting financial burden; thus, neglecting effects of this factor on psychological distress associated with treatment type. Although several studies indicate the negative effect of ostomy bags on patients' quality of life and mental health (67, 82–85), the present study did not show a relationship between ostomy bags and anxiety or depression. This might be due to the insufficient number of patients with ostomy bags in this study (only six patients).

Various factors affect serum 25(OH)D levels as well as incidence and progression of cancers (86). In this study, the relationship between serum 25(OH)D levels and cancer stage, grade and treatment type was investigated. The authors detected a direct significant relationship between the cancer stage and serum 25(OH)D level. This finding were different from the studies by Ng et al. and Bao et al., which showed that VD deficiency was higher in stage IV cancer patients (87, 88). Epidemiological studies indicate that VD deficiency increases occurrence of CRC and negatively affects survival of these patients (89). Additionally, several studies have shown that higher serum 25(OH)D levels may be linked to better survival in CRC patients (90–93). Therefore, direct relationship between cancer stage and serum 25(OH)D levels in the present study might be due to the longer survival of patients with higher VD levels, who survived longer until the later stages of the disease. These findings could be attributed to magnified random fluctuations due to the small sample size.

Calcitriol enhances differentiation of intestinal epithelia through the VD receptor, which is significantly expressed in the intestine (9, 94). Previous studies have shown that VD receptor expression increases in early stages of CRC but decreases during late cancer progression. This pattern is similar to the behavior of estrogen and progesterone receptors in breast cancer and likely contributes to the failure of treatment with VD analogs (95–97). Therefore, decreased responses of tumoral tissues to active VD, especially in high-grade tumors, might explain the present findings of no relationships between serum 25(OH)D levels and tumor grades.

In Fakih's study, likelihood of a severe deficiency in serum 25(OH)D in CRC patients with chemotherapy was four times higher than that in those without chemotherapy (98). However, the current study did not find a significant relationship between the type of treatment and serum 25(OH)D levels. Various mechanisms have been suggested to explain how treatment types affect serum 25(OH)D levels. For example, mutations in genes or enzymes responsible for the transport and metabolism of 25(OH)D can alter its levels and function (99). Genome instability and epigenetic changes induced during radiotherapy may affect serum 25(OH)D levels. It has been suggested that chemotherapy patients may not absorb dietary vitamins effectively due to subclinical mucositis. Additionally, chemotherapy can induce the metabolism of 25(OH)D into inactive compounds, such as 24 and 25-hydroxyvitamin D, by activating cytochrome P3A4 or other metabolizing enzymes (98).

Furthermore, intestinal microbiota that play a role in VD homeostasis by producing fibroblast growth factor 23 (FGF23) and increasing 25(OH)D levels can be altered during radiotherapy, chemotherapy and colon resection, potentially affecting serum 25(OH)D levels (100–104). Despite studies indicating significantly lower serum 25(OH)D levels in chemotherapy recipients, the present study did not report a significant difference in serum 25(OH)D levels between various treatment types. This discrepancy might be attributed to the fact that all patients in the present study received chemotherapy, preventing a comparison with other treatments. Since multiple

mechanisms can affect VD levels, it is challenging to assess their collective effects on serum 25(OH)D without further extensive clinical studies.

Conclusions

In conclusion, this study demonstrated that VD supplementation decreased anxiety and depression scores in patients with colorectal adenocarcinoma, with the most pronounced effects at serum 25(OH)D levels of 13–20 ng/ml. Regarding involvement of various factors in anxiety and depression of colorectal cancer patients, as well as their serum 25(OH)D levels, whether VD deficiency exacerbates depression and anxiety or not is still debatable. Therefore, further studies are needed to verify this finding.

Acknowledgement

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Trial Registration

Ethics Committee of Islamic Azad University of Mashhad, Medical Sciences Branch, approved this study (reference no. **IR.IAU.MSHD.REC.1401.107**). This study was registered with the Iranian Registry of Clinical Trials (www.irct.ir) (registration no. **IRCT20220609055113N1**).

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Consent for Publication

All authors approve this publication.

Financial disclosure

No financial competing interest to report.

Consent to participate

Signed informed consents were received from all the participants of this study.

Data Availability

Datasets used and analyzed during the current study are available from the corresponding author upon reasonable requests.

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were carried out by (RE**) and (PI**) and supervision and analysis were carried out by (VP), (AA) and (VS). Primary draft of the manuscript was written by (RE) and (VP). All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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