Effects of vitamin D supplementation on depression in patients with colorectal cancer

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Keywords: Vitamin, Depression, Colorectal cancer

Posted Date: February 6th, 2020

DOI: <https://doi.org/10.21203/rs.2.22782/v1>

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Abstract

Background: The relation and possible mechanism of vitamin D supplementation on depression in colorectal cancer (CRC) patients was not clearly ; **Objective:** This study investigates the effect of vitamin D supplementation on depression in colorectal cancer (CRC) patients. **Methods :** We recruited 168 CRC patients and 168 healthy control subjects into this study. 17-item Hamilton Depression Rating Scale (HDRS-17) was used to assess depression. **Results:** We found that 25-hydroxyvitamin D (25(OH)D) concentrations were independently associated with depression among CRC patients. For the 45 depressed patients receiving vitamin D3 supplementation, depression scores decreased markedly with 25(OH)D concentrations increasing to normal. **Conclusion:** Therefore, we advise monitoring this indicator in CRC patients and supplementing with vitamin D 3 when their 25(OH)D concentrations are low.

Background

Depression is an extremely frequent complication among survivors of colorectal cancer (CRC), with prevalence ranging from 24–57%. [1, 2] Depressive complication has been related to reduced quality of life [3] and increased mortality. [4]

The profuseness of vitamin D receptors and vitamin D activating enzyme 1 α -hydroxylase in the center nervous system suggests involvement of vitamin D in certain psychological processes. [5] Low concentrations of vitamin D have been associated with depression in both clinical and healthy populations. [6, 7] Moreover, recent prospective studies and clinical randomized controlled trials (RCT) have demonstrated positive effects of vitamin D supplementation on depression. [8, 9]

Vitamin D deficiency is extremely frequent complication among CRC patients. [10] Low concentrations of vitamin D have been related to increased mortality among survivors of CRC. [11] Moreover, recent studies have demonstrated a positive effect of vitamin D supplementation on prognosis of CRC survivors. [12]. Base on both the involvement of vitamin D in depression in non-CRC individuals and high prevalence of vitamin D deficiency in CRC patients, whether vitamin D supplementation exerts positive effects on depression in CRC patients was examined.

Method

Study population and design

We prospectively recruited 168 outpatients with CRC in the clinics of two facilities in Zhejiang QuHua Hospital and First Affiliated Hospital of Jiaxing University to participate in this study during the period from May 1, 2016, and October 10, 2018. Eligibility criteria were: (1) Chinese ethnicity; (2) aged 18 years or older; (3) having a diagnosis of CRC in their medical record; (4) having willingness to give written informed consent. Exclusion criteria were: (1) patients with cognitive dysfunction; (2) patients with hypercalcaemia, alone or together with hyperparathyroidism; (3) patients with a history of mental or

psychological disease. Meantime, 168 age- and sex-matched healthy volunteers, without pre-existing vitamin D3 supplementation, were consecutively recruited from a health survey. Qualified patients were included into the cross-sectional study to evaluate the correlation between vitamin D concentrations and depression. Patients without sufficient 25-hydroxyvitamin D (25(OH)D) (≤ 75 nmol/L) received vitamin D3 supplementation (cholecalciferol) 2000 IU/d for six months. According to whether there existed depression, we stratified patients into subgroups further. Regular follow-up visits were carried out after 3 months (T1) and 6 months (T2). Written informed consents were obtained from all participating subjects. The study was approved by the Ethics Committee of Zhejiang QuHua Hospital and all methods were conducted in compliance with our local guidelines and clinical regulations.

Clinical assessment

Depressive symptoms were screened using the 17-item Hamilton Depression Rating Scale (HDRS-17).[13] Patients with a HDRS-17 score of ≥ 7 were given the Chinese version of Structured Clinical Interview for Depression (SCID) and Statistical Manual of Mental Disorders, 4th edition, to make a proper diagnosis. Pain intensity was assessed using a numerical rating scale from 10 to 0, with 10 for “extremely painful” and 0 indicating “no pain”. Social support was examined by two items as follows: (1) When suffering from worries, would you like to pour them to somebody (using a numerical rating scale from 1 to 4: 1 never; 2 only pouring my worries to my spouse or parents; 3 when my friends and relatives asking me, I will pour my worries to them; 4 pouring my worries to others on my own initiative)? (2) When suffering from difficulties, would you like to ask help from others (using a numerical rating scale from 1 to 4: 1 never; 2 occasionally; 3 sometimes; 4 always)? Social support of patients was evaluated by the total scores from 2 to 8, with high score indicating good social status. Serum 25(OH)D, an optimal indicator of vitamin D metabolic condition, was measured using the competitive protein-binding assay with the intra-assay coefficients of variation of 7–10%.

Outcome measure

The primary outcome evaluated absolute changes in HDRS-17 scores after 3 and 6 months of vitamin D treatment. For the HDRS-17, the widely-accepted definitions of response (at least a 50% reduction from baseline in the total score) were adopted in this study.[14]

Statistical analysis

Categorical variables were compared using Pearson χ^2 test. Fisher’s exact test was performed instead if any of expected counts were < 5 . Student’s t test was performed for normally distributed variables, while Mann–Whitney U test used was for parametric variables. Serum concentrations of 25(OH)D were divided into four quartiles (≤ 30.0 , 30.1–43.0, 43.1–55.0 and ≥ 55.1 nmol/L), because the raw vitamin D data were skewed. Conditional logistic regression including those factors with $p < 0.10$ in the univariate analysis was used to examine which variables were independently associated with depressive disorders. Linear mixed models were used to analyze the repeated measurements with missing values. The results were expressed as adjusted odds ratios (OR) with the corresponding 95% confidence intervals (CI). All

statistical calculations were performed using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA). Concentration of statistical significance was defined as $p < 0.05$.

Results

A total of 168 patients were enrolled in the present study. A total of 53 patients (31.5%, 36 men, 17 women) were diagnosed with depression. CRC patients showed markedly lower serum concentrations of 25-hydroxyvitamin D (25(OH)D) as compared to normal controls (45.12 ± 15.45 vs. 63.14 ± 16.46 nmol/L, $p < 0.001$). No correlation was found between 25(OH)D and age and gender in patients with CRC. Patients with depression had poorer financial situation, less social support and more pain. Significant differences were found between patients with depression and those without depression in 25(OH)D concentration quartiles of CRC patients ($p < 0.001$). The proportion of patients in the lowest quartile (≤ 30.0 nmol/L) was significantly higher in the depression group ($p < 0.001$), while the proportion of patients in higher quartiles (43.1–55.0 and ≥ 55.1 nmol/L) was markedly lower in the depression group ($p < 0.001$ and $p = 0.011$, respectively) (Table 1).

Table 1
Demographic and clinical characteristics of the samples under study

Variables	Depressed (n = 53)	Not depressed (n = 115)	P value
Sex			0.088
Male	36(67.9)	92(80.0)	
Female	17(32.1)	23(20.0)	
Age			0.398
≤ 50 year	18(43.0)	37(32.2)	
50–60 years	24(45.3)	43(37.4)	
≥ 60 years	11(20.8)	35(30.4)	
Education			0.443
≤ 6 years	35(66.0)	73(63.5)	
> 6 years	18(34.0)	42(36.5)	
Financial situation			0.013
Poor	34(62.4)	50(43.5)	
Satisfactory	19(35.8)	65(56.5)	
Marital status			0.743
Married	49(92.5)	108(93.9)	
Not married	4(7.5)	7(6.1)	
Number of children			0.993
0	8(15.1)	15(13.0)	
1	14(26.4)	32(27.8)	
> 1	31(58.5)	68(59.1)	
Living situation			0.342
With spouse and children	41(77.4)	96(83.5)	
Other living situation	12(22.6)	19(16.5)	
Social support			< 0.001
< 4			
4–6			
Note: Values are shown as number (percentage); CRC, colorectal cancer; 25(OH)D, 25-hydroxyvitamin D.			

Variables	Depressed (n = 53)	Not depressed (n = 115)	P value
	30(56.6)	24(20.9)	< 0.001
	13(24.5)	70(60.9)	< 0.001
> 6	10(18.9)	21(18.3)	0.925
Cancer stage			0.332
Duke's A or B	25(46.3)	44(38.3)	
Duke's C or D	29(53.7)	71(61.7)	
Duration of CRC			0.447
< 1 year	20(37.7)	35(30.4)	
1–2 years	23(43.4)	62(53.9)	
> 3 years	10(18.9)	18(15.7)	
Cancer treatments			
Surgery, yes	50(94.3)	104(91.7)	0.552
Chemotherapy, yes	44(83.0)	91(79.1)	0.556
Radiation, yes	10(18.9)	24(20.9)	0.764
Other, yes	2(3.8)	3(2.6)	0.651
Pain			< 0.001
No	19(38.5)	82(71.3)	
Yes	34(64.2)	33(28.7)	
25(OH)D			< 0.001
Quartile 1	26(49.1)	13(11.3)	< 0.001
Quartile 2	19(35.8)	28(24.3)	0.123
Quartile 3	4(7.5)	46(40.0)	< 0.001
Quartile 4	4(7.5)	28(26.1)	0.011
Note: Values are shown as number (percentage); CRC, colorectal cancer; 25(OH)D, 25-hydroxyvitamin D.			

In logistic regression analysis, serum 25(OH)D concentrations (≤ 30.0 and ≥ 43.1 nmol/L) were independently associated with the presence of depression among CRC patients (OR, 8.840; 95% CI, 2.462–31.734, $p = 0.001$ and OR, 0.031; 95% CI, 0.008–0.124, $p < 0.001$, respectively). Additionally, less

social support and pain were markedly associated with the presence of depression among CRC patients (OR, 4.351; 95% CI, 1.324–14.303, $p = 0.015$; OR, 6.358; 95% CI, 1.607–25.156, $p = 0.008$, respectively).

We excluded 38 patients for not meeting the predetermined supplementation criteria ($n = 19$) or because they declined our invitation ($n = 19$). Consequently, 130 (45 with and 85 without depression), began to take 2000 IU vitamin D3 per day for six months. Of these patients, the baseline characteristics were similar to those of the entire cohort. We observed reductions in HDRS-17 scores in depressed patients after 3 (9 vs. 12, $p < 0.001$) and 6 months (8 vs. 12, $p < 0.001$). There was no change being observed in non-depressed patients (Fig. 1). The treatment response was consistent with the restoration of vitamin D concentrations, which increased to normal after 3 and 6 months in patients with (75.13 and 75.47 nmol/L, respectively) and without depression (76.71 and 77.07 nmol/L, respectively) (all $p < 0.001$). Specifically, we observed significant improvements (at least a 50% reduction from baseline in the total HDRS scores) in the majority of depressed patients after both 3 and 6 months.

Discussion

To our knowledge, this is the first report investigating the possible effects of vitamin D supplementation on depression in CRC patients. Our results suggest that serum concentrations of vitamin D were significantly associated with the presence of depression among CRC patients and vitamin D supplementation can improve depression in most CRC patients, which might have significant implications in providing novel proposal for the prevention and treatment of depressive complication in CRC patients.

We observed that serum concentrations of vitamin D were independently related to the presence of depression in CRC patients. Moreover, we found that the correction of vitamin D inadequacy exerts positive effects on depression in CRC patients. Caroline[9] found vitamin D supplementation significantly ameliorated depressive symptoms in women with chronic liver disease. Meanwhile, one randomized controlled trial showed vitamin D therapy was effective in decreasing perinatal depression concentrations.[8]

The exact role of vitamin D in the pathophysiology of depression remains unknown. A possible explanation is the neuroprotective role for vitamin D via its effects on inflammatory response. A growing body of evidences has supported an important role of cytokines in the pathophysiology of depression.[15, 16] CRC patients have increased serum concentrations of the cytokines mentioned above.[17] Vitamin D plays a key role in modulating the secretion of cytokines.[18] Vitamin D may modulate the association of depression and inflammation via its role in the immune system.[19, 20]

There are several limitations in this study. First, the effect of other potential factors on serum vitamin D concentrations, such as lifestyle changes, dietary intake, and seasonal variation, was not considered in this study. Second, the present study was not an RCT, a design we avoided owing to ethical concerns, as we were unwilling to withhold treatment for vitamin D inadequacy. Finally, the fluctuating characteristic of vitamin D makes it preferable to complete all measurements on the same day.

Conclusion

The results demonstrate depression was independently correlated with vitamin D concentrations in CRC patients. A therapeutic vitamin D supplementation may be recommended in CRC patients with low concentrations of vitamin D. Larger RCTs should be encouraged to confirm this study.

Declarations

Acknowledgements

The study investigators would like to acknowledge Han Bin for his contribution to the development of the study protocol.

Author Contributions

Study concept and design, D.-J.W and C.-W.Y. Acquisition of data, C.-Y.S., W.-W.F. and X.-C. H.-Z.L. Analysis and interpretation of data, D.-J.W. C.-W.Y. and W.-W.F. All authors read and approved the final manuscript.

Competing Interests

All authors declare that they have no competing interests.

Ethics Approval And Consent To Participate

The research was reviewed and approved by ZheJiang QuHua Hospital and the First Affiliated Hospital of Jiaxing University Ethics committee. Written informed consent was obtained from all participants.

Availability Of Data And Materials

The authors claim that consent has been received for each patient enrolled, and that in this article patients' personal data do not appear.

Competing Interests

There is no conflict of interest in this study, including financial, personal or any other potential conflict.

Funding

This work was funded by a grant from the QuZhou Municipal Sci-Tech Bureau Program (2019106) and Clinical Research Project in Medical Committee of Zhejiang Province (No. 2013ZYC-A89), the Key Discipline of Jiaxing Oncology Medicine Construction Project [No.2019-zc-11]. The authors express their gratitude to all subjects who participated in the current study.

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Figures

Figure 1

Changes in depression during the study