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The Relationship between Vitamin D Deficiency and Increased Oxidative Stress in Patients with Colon Cancer

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ABSTRACT

Background & Objective: Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. Oxidative stress is one of the involved factors in CRC onset and progression. Recent examinations have revealed antioxidant characteristics of vitamin D. Given the vital role of this vitamin in balancing free radicals and antioxidant capacity, in this study we intended to review the association between vitamin D deficiency and oxidative stress in CRC patients.

Materials & Methods: In the present case-control study, 30 CRC patients and 32 healthy individuals were entered, based on the defined inclusion and exclusion criteria. Peripheral blood was taken from the subjects. Thiobarbituric acid reactive substance (TBARS) values, total antioxidant capacity, and serum vitamin D were measured. Data were interpreted using SPSS 18 software; t-test and the Mann Whitney test were applied.

Results: The outcomes explained that TBARS values were significantly greater in patients group ($P < 0.005$), but no meaningful difference was monitored in the total antioxidant capacity. 21 (70%) patients and 14 (44%) control subjects had inadequate vitamin D. There was a significant association between serum vitamin D in both groups ($P < 0.005$). A notable negative relationship was found between vitamin D values and oxidative stress indicator ($p=0.05$, $r = -0.249$).

Conclusion: insufficient vitamin D can lead to an increase in oxidative stress, which is directly associated with CRC. Serum vitamin D levels were also inadequate in high percentage of cancer patients. Given the predominance of vitamin D insufficiency in the population, more extensive studies are required to prove the impact of deficiency on disease pathogenesis.

Keywords: Colorectal cancer, Vitamin D, Oxidative stress

Introduction

Colorectal cancer (CRC) remains one of the major health problems and the third most frequent malignancy globally, with approximately 1.8 million unique cases and 880,000 deaths per year (1). The CRC incidence may be attributed to various modifiable and non-modifiable risk factors. There is growing support for the oxidative stress role in CRC initiation and progression (2). Reactive oxygen species (ROS) have a physiological role at low levels, but become destructive and toxic to cells at elevated levels. Previous studies showed that oxidative stress leads to lipid, proteins, and DNA oxidation in vivo (3, 4).

Nevertheless, the elevated lipid peroxidation products and oxidized DNA base (8OHdG–8-hydroxy-2′-deoxyguanosine) levels are detected in tumor and clinical samples of CRC patients (5, 6). Several investigations have reported the antioxidant feature of vitamin D in different cells, including colon cells in men (7). Prospective literature and experimental studies strongly support a theory, which high serum concentration of vitamin D has protective effects against CRC progression (8). Numerous studies described the binding of active form of vitamin D (1,25 (OH)2 Vit D3) to the vitamin D receptor (VDR), which protects cells by inhibiting peroxidation on membrane lipids, stabilizing chromosomal structure, inducing

apoptosis in most cancer cells, and preventing DNA double-strand breaks (9). There are several techniques for evaluating lipid peroxidation and antioxidant potential in biological samples. The ferric reducing/antioxidant power (FRAP) assay is a relatively easy, fast, and low-cost direct technique for evaluating the total antioxidant activity in the tissue and biological samples (10, 11).

On the other hand, the thiobarbituric acid reactive substances (TBARS) assay has become one of the most extensively used assays to determine lipid oxidation in several types of biological samples. Despite the numerous methodology described in the different papers, all TBARS assays share standard features (12). In the current case-control research, the serum levels of vitamin D and oxidative stress content were examined in CRC patients and healthy persons. Later, the potential connection between these factors and the risk occurrence of CRC were examined.

Materials and Methods

Subject recruitment

CRC patients (n= 30) were selected from Shahid Rajai Hospital, Babolsar University of Medical Sciences, Babolsar, Iran. The Committee of the Clinical Research Ethical in Babolsar University of Medical Sciences, Iran approved the current examination (Ethical code: IR.MUBABOL.HRI.REC.1399.030). All participants in this inquiry received sufficient information about the examination; they signed an informed consent. The examination was administered within February 2019-May 2020. Patients were entered the study based on pathological, preclinical, and confirmed colonoscopy data; all patients were at the stage 1. Also, patients with autoimmune and blood disorders were excluded. Individ-uals, who participated in the screening program of colon cancer, and their colonoscopy results were negative were also selected as control: their blood specimen was also collected (n = 32).

Sample preparation

Early-morning blood samples (5 mL) were received from the subjects' peripheral vein after 12 h fasting. Later the clot development, the serum was separated via centrifugation at 3000 rpm for 15 min at room temperature. The serum was carried within micro tubes and saved at −70 °C to evaluate the biochemical factors.

Measurement of 25-(OH) D3 concentrations

25-(OH) D3 levels measurement in the samples was accomplished employing ELISA-kit assay (Elisa kit of 25-(OH) D3, Pasrsazmoon, Iran) and Luminex-100 apparatus (Luminex, Bio-Rad). The range of 100-30 nm/ml was considered as average value, ≥ 30 ng/ ml as sufficient, and < 30 as insufficient.

The dimension of antioxidant content

TBARS and FRAP assays were conducted to determine oxidative stress content in the current study. Measuring the totals of TBARS amounts, specifically malondialdehyde (MDA) as a lipid peroxidation marker, is mostly performed using the spectrophotometric method. For preparing the TCATBA-HCl reagent, 15 g of trichloroacetic acid and 375 g of TBA were dissolved in 100 mL of 0.25 N HCl. Then, 1 ml of serum sample was added to 2 ml of TCA-TBA-HCL reagent in the test tube and mixed vigorously. The solution was heated in a boiling water bath for 15 min. After chilling, a centrifuge was performed for 10 minutes, and the clear supernatant was used to measure.

The absorbance of the samples was read at 532 nm. The standard curve was then drawn using the absorbance of the standard samples; the TBARS levels of the samples were found based on the standard curve. Besides, the FRAP assay protocol applied. Shortly, Ferric to ferrous ion reduction at low pH due to antioxidants' presence produces a blue-colored Ferrous tripyridyltriazine complex with a maximum absorption of 532 nm; it constitutes the basis of the FRAP assay. The absorbance changes were investigated between the test and standard specimens at the cited wavelength, and the results were reported in micromole/liter.

Statistical analysis

Statistics interpretation was proceeded applying SPSS (version 18). Kolmogorov-Smirnov test was applied to evaluate the normality of the quantitative variables. Quantitative and qualitative variables were displayed as mean ± SD, respectively. Chi-Square and independent sample t-test were utilized for data analysis.

Results

Patients and samples

The blood samples of 30 CRC patients and 30 healthy persons were collected. The patient group participants' mean age was 53.65 ± 13.8 years old; it was 48.02 ± 8.37 years old in the control group (Table 1). About 65% of participants in each group were male, and 35% of them were female. Pathologically, all new CRC patients were at the stage III. There was no statically notable variation in gender, age, hypertension, body mass index (BMI), diabetes mellitus, and smoking between the two groups.

Table 1. Demographical and clinical characterizations of all participants

	N	Age (Year)	BMI (Kg/m^2)	Familial history	Smoking
Cancer	30	58.00± 9.11	24.21± 3.11	3/30 (10%)	8/30(27%)
Control	30	59.85±10.69	24.61± 3.21	0/30 (0 %)	11/30(%36)
P-value	-	0.58	0.28	0.33	0.14

Table 1. Quantitative and qualitative variables were presented as mean ± standard deviation (SD), respectively. A sample t-test was used for data analysis. *P<0.05 vs. healthy controls. Abbreviation: BMI: body mass index.

Assessment of antioxidant content

TBARS values as lipid peroxidation markers in patients' serum were significantly higher in patients group (P <0.000). However, the amount of FRAP as an indicator of serum antioxidant potential in these two groups did not alter significantly (p> 0.05) (Table 2).

Table2. Mean ±SD of Vitamin D, TBARS and, FRAP in colon cancer and control groups

	CRC (30)	Control (30)	
Variable	mean±Sd	mean±Sd	P-value
(OH) Vitamin.D	19.45±10.72	35.15±16.65	0.000
TBARS	0.35±0.09	0.25±0.03	0.000
FRAP	0.72±0.22	0.76±0.2	0.46

Table 2. Quantitative variables were provided as mean ± standard deviation (SD). A sample t-test was applied for analysis. *P<0.001 vs. healthy controls. Abbreviation: CRC: colorectal cancer; TBARS: thiobarbituric acid reactive substances; FRAP: ferric reducing/antioxidant power.

Evaluation of 25-(OH) D3 concentrations

The serum concentrations of 25-(OH) D3 in the CRC patients were evaluated and matched to controls. Vitamin D levels in patients with CRC were significantly different compared to controls (P < 0.000) (Table 3). According to the results reported in Table 2, 70% of CRC patients and 44% of the control group were categorized in vitamin D insufficient group.

Table 3. Distribution and frequency of individuals with insufficient and sufficient Vitamin D in the patient and control group.

	CRC (30)		Control (30)	
(OH) Vitamin.D	mean±Sd	N	mean±Sd	N
ng/ml 30 <(OH) Vitamin.D	13.98±7.79	21(70%)	21.42±3.98	14 (44%)
(OH) Vitamin D≥ ng/ml 30	32.2±1.89	9 (30%)	45.83±14.75	18 (56%)

Table 3. Quantitative variables were provided as mean ± standard deviation (SD). Abbreviation: CRC: colorectal cancer.

In Table 4, a significant negative correlation was found between TBARS and Vitamin D (p=0.05, r = -0.249). No significant correlation was observed between FRAP, Vitamin D and TBARS.

Table 4. Correlations between parameters in the studied population.

		FRAP	TBARS	(OH) Vitamin D
FRAP	Pearson Correlation	1	0.114	-0.061
	p-value	-	0.379	0.638
TBARS	Pearson Correlation	0.114	1	-0.249
	p-value	0.379	-	0.05
(OH) Vitamin D	Pearson Correlation	-0.061	-0.249	1
	p-value	0.638	0.05	-

Table 4. The Chi-Square test was utilized for data analysis. *P<0.05 as significant statistical significance. Abbreviation: TBARS: thiobarbituric acid reactive substances; FRAP: ferric reducing/antioxidant power.

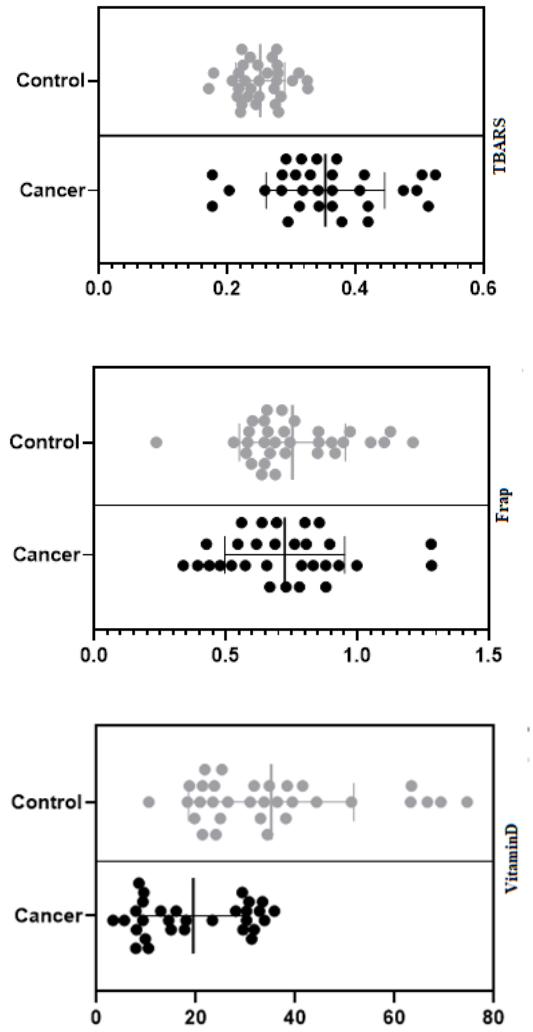

Figure 1. Comparison of TBARS, FRAP, and Vitamin D assay between the control and patient groups. Abbreviation: TBARS: thiobarbituric acid reactive substances; FRAP: ferric reducing/antioxidant power

Discussion

In the current case-control investigation, the finding showed that TBARS values were significantly greater in CRC patients, but no significant difference was found in the total antioxidant capacity. There was a significant association between serum status of vitamin D in both groups (P <0.005). The serum level of 25-(OH) D3 in the CRC patients was less than controls.

CRC is a heterogeneous disease, which is characterized by specific morphological and molecular alterations. Epidemiological studies have indicated a strong direct association between oxidative stress and CRC development risk (13, 14). It has been proven, that free radicals are raised via exposure to toxins, smoking, stress, and inflammation caused by metabolic sicknesses, diet, and lifestyle factors (15). When free radicals are generated in the excessive amounts under pathological conditions, they may react with DNA, lipids, and proteins, and may modulate gene expression and intracellular signaling pathways. It is widely established that oxidative stress is associated with cellular membrane degeneration and DNA damage due to lipid peroxidation (13).

The previous work by Skrzydlewska et al. revealed plasma and tissue MDA concentrations, as a final product of lipid peroxidation, were increased in CRC patients (16). It has been confirmed that MDA is a mutagen and reacts with deoxyguanosine (dG) to create a significant DNA adduct. 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) is an oxidative stress biomarker, and its level is higher in leukocytes and CRC patients urine. Researchers have also proved induced mismatched pairing due to8-oxodG, which results in C (cytosine) to A (adenine) and/or G (guanine) to T (thymine) switching (13). Accumulating evidence has shown that the major intracellular DNA damages caused by free radicals are single and double-strand DNA breaks, genomic instability, and genetic alteration, which are more relevant in CRC (17, 18). The common genetic mutations in CRC include Kirsten rat sarcoma viral oncogene homolog (KRAS), p53, adenomatous polyposis coli (APC), and V-Raf murine sarcoma viral oncogene homolog B (BRAF) (19). CRC carcinogenesis is based on the accumulation of RAS mutations, as an oncogene and tumor suppressor genes of APC and TP53 (20). Bartsch and his coworkers observed a direct association between oxidative stress, DNA damage, and increased p53 and APC mutation frequency in CRC (21).

So, oxidative modifications could contribute to CRC pathogenesis by gene mutations and redox related signaling pathways. Thus endogenous and dietary antioxidants can prevent CRC progression by eliminating free radicals (22). In 2020, a systematic review in the children and adolescents in china reported a relationship between vitamin D status and biomarkers of oxidative stress and inflammation, such as interleukin-6 (IL-6), MDA, superoxide dismutase (SOD), and CRP (23, 24). There are several lines of evidence that vitamin D may act as an antioxidant and a reducing agent against DNA damage in the colon cells (22, 25). The available observational evidence suggested a strong link between vitamin D deficiency and CRC (26).

Melissa Y. Wei et al. reported, that the excessive vitamin D level is related to a low risk of colorectal adenoma (27, 28). Vitamin D might decrease CRC risk via several mechanisms. The active form of vitamin D binds to the VDR, and regulates the expression of more than 200 genes associated with cell growth, immune response, cellular differentiation, and DNA repair system (29). These findings are consistent with this hypothesis, that high intakes of vitamin D3 may decrease oxidative DNA damage and oxidative stress

in the colon and also reduce the risk of colorectal neoplasms. An animal study reported that the levels of 8-OHdG, an oxidative damage marker, elevated in the colon cell of VDR-/- mice; but, it decreased in the colon cells of VDR+/- mice with the partial function of Vit D **(30)**.

This study investigated oxidative status by FRAP and TBARS assay, and vitamin D status by ELISA in the serum of CRC patients and healthy individuals. Our results from the TBARS assay revealed that serum levels of oxidants in patients with CRC were significantly higher than healthy subjects; on the other hand, obtained data from FRAP assay were not statistically significant in both groups. All new cases with CRC were at the stage III, and vitamin D concentration in CRC patients was significantly lower than healthy individuals. Like the current finding, a recent case-control study by Wolpin et al. demonstrated, that relatively low levels of circulating vitamin D enhanced the risk of colorectal adenomas. A higher level of this factor may be related to improved survival after CRC diagnosis **(31, 32)**. In another study, Savoie et al. did not find any significant relationship between vitamin D levels and CRC diagnosis **(33)**.

Moreover, correlation was found between the CRC stage and serum vitamin D concentration; patients with lower concentration of vitamin D had a worse prognosis **(34)**. Vitamin D can control colon cells' proliferation and differentiation through binding to the VDR **(35)**. In the early stages of CRC, the VDR expression is upregulated, but it is downregulated at advanced stages and CRC metastases **(36)**. Larriba et al. reported that two transcription factors (SNAIL1 and SNAIL2) are induced during epithelial-to-mesenchymal transition (EMT); they significantly repress the VDR gene expression during CRC progression and metastasis **(37)**.

Conclusion

In summary, this case-control study strongly supports an association between CRC carcinogenesis with vitamin D deficiency and oxidative stress. These results suggest oxidative stress in CRC patients due to vitamin D deficiency. Thus, based on the present and previous data, daily intake of vitamin D will help to reduce the risk of CRC. This study is limited by the small sample size and lack of specific data of patients; therefore, further considerations should continue with greater sample size and multicenter studies to validate these data's values. Due to vitamin D role in cellular functions range, it is recommended to study other adverse effects of vitamin D deficiency in CRC patients.

Ethical standards statement:

The Ethics Committee of Babol University of Medical Sciences approved this study (IR.MUBA-BOL.HRI.REC.1399.030).

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Conflict of Interest

The authors stated no conflict of interest.

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