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Correlations of inflammatory cytokines in the intestinal mucosa, serum inflammation, oxidative stresses and immune changes with vitamin deficiency in ulcerative colitis patients

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory disease. Studies in China and foreign countries have shown that vitamins have anti-inflammation and immunoregulation functions in patients with UC, but the specific mechanism is not yet clear. In this study, the levels of inflammatory cytokines in the intestinal mucosa, serum inflammatory indexes, oxidative stress indexes and immune-related indexes were detected, and their correlations with vitamin deficiency and clinical significance were discussed. Enzyme-linked immunosorbent assay (ELISA) was adopted to detect the serum level of 25-hydroxyvitamin D_3, immunohistochemistry was applied to examine the expression of inflammatory cytokines in the intestinal mucosa, serum inflammatory indexes, oxidative stress indexes and immune-related indexes were measured, and their correlations were analyzed. Inflammatory and oxidative stress indexes in the UC group were notably higher than in the control group. The Vitamin deficiency group had more inflammatory cytokines than the normal vitamin group. Oxidative stress indexes such as superoxide dismutase (SOD) and malondialdehyde (MDA) in the vitamin deficiency group were significantly different from those in the normal vitamin group, but no difference was found in myeloperoxidase (MPO). Immune-related indexes, complement 3 (C3) and interferon-gamma (IFN-γ), in the normal vitamin group were higher than those in the vitamin deficiency group. Besides, interleukin-4 (IL-4) (r=-0.37, p=0.04) and IL-1β (r=-0.31, p=0.04) had significant correlations with vitamins. Vitamins in patients with UC have significant correlations with inflammatory responses in vivo, which can be used to predict inflammatory responses in vivo and have strong clinical significance. Vitamins are also related to oxidative stresses to some extent but have little effect on immune-related indexes.

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Introduction

Ulcerative colitis (UC) is a disease with obvious gastrointestinal and systemic symptoms. The disease is closely associated with immune responses and is accompanied by changes in a variety of inflammatory indexes (1, 2). UC often occurs in the rectum and sigmoid colon and can also invade the whole colon with the development of the disease. The pathogenesis of UC varies with different individual genes or external influences (3). In recent years, the incidence rate of UC has been increasing in the world, and UC cases in China are also on the rise. UC patients are mainly aged 15-35 years old, and men and women have approximately the same incidence rate of UC. The symptoms of UC primarily include abdominal pain, diarrhea and obvious systemic symptoms. In addition, UC has a relatively long course and is easy to recur, thus substantially influencing people's normal life.

According to a great many scientific researches in China and foreign countries, vitamins, especially vitamin D (4-6), are of great significance in the progression of UC (7, 8). Vitamin D protects the intestinal mucosa and barrier during the pathogenesis of UC, and it can regulate intestinal microorganisms, improve the intestinal microenvironment of UC patients, and suppress the development of UC (9). Meanwhile, vitamin D can reduce oxidative stress responses (10). Most importantly, vitamin D is able to regulate the local and whole immune system of the intestinal tract in UC patients as well as the expression of related cytokines, reduce the release of inflammatory cytokines, impede intestinal immune responses and relieve symptoms (11, 12). Vitamin D deficiency may aggravate intestinal and systemic inflammatory responses and oxidative stresses in UC patients so that the immune system cannot be regulated, thus aggravating UC.

In this study, the levels of inflammatory cytokines in the intestinal mucosa, serum inflammatory indexes, oxidative stress indexes and immune-related indexes in UC

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patients and non-UC healthy controls were tested, and the correlations of these indexes with vitamin deficiency and clinical significance were analyzed. The research results are as follows.

Materials and Methods

General data and grouping

UC patients (n=120) and healthy people (n=120) receiving physical examinations in Chongqing first people's hospital were included in the UC group and control group, respectively. According to the serum level of 25-hydroxyvitamin D_3 in peripheral venous blood, the UC group was further divided into the normal vitamin group (serum 25-hydroxyvitamin D_3>30 ng/mL) and vitamin deficiency group (serum 25-hydroxyvitamin D_3 ≤30 ng/mL).

Statistical analysis revealed that there were no statistical differences in general data between the UC group and the control group (p>0.05), so this study was worthy of investigation. In the UC group, there were 67 males and 53 females aged 18-58 years old, with an average age of (28.19±2.17) years old. In the control group, there were 63 males and 57 females aged 20-60 years old, with an average age of (31.91±4.15) years old. All subjects in the UC group and control group signed the informed consent of the related department. This study was approved by the Ethics Committee of Chongqing first people's hospital and met the related regulations.

Related standards

Inclusion criteria for patients in the UC group: 1) patients meeting the diagnostic criteria for UC formulated by the Digestive Disease Branch of the Chinese Medical Association, 2) patients who underwent colonoscopy, and 3) patients who agreed to participate in this study. Exclusion criteria: 1) patients complicated with other serious physical diseases, 2) pregnant or lactating patients, 3) malignant tumor patients, or 4) patients with serious mental disorders.

Diagnostic criteria: 1) Clinical manifestations include recurrent abdominal pain and diarrhea accompanied by acute exacerbation and systemic symptoms, 2) endoscopic examination shows the diffuse distribution of lesions, accompanied by hemorrhage, edema, suppuration, erosion and ulcer in some parts as well as narrowing of the colon capsule and polyp formation.

Research methods and related indexes

Enzyme-linked immunosorbent assay (ELISA) was adopted to detect vitamin D levels in patients in the UC group and control group. Specifically, the plasma of patients in the UC group and control group was examined using a full-automatic immunity analyzer in the Clinical Laboratory. Normal vitamin group: vitamin D level ≥30 ng/mL, and vitamin deficiency group: vitamin D level <30 ng/mL.

Determination of inflammatory cytokines in the intestinal mucosa: All subjects needed to undergo enteroscopy, normal intestinal mucosa tissues and pathological intestinal mucosa tissues were taken out, respectively, using endoscopy, and mucosal inflammatory cytokines were detected by immunohistochemistry using kits. The tissues were treated with 4% paraformaldehyde (pH=7.3) for more than 2 days, then treated with gradient ethanol for dehydration and xylene and embedded with melted paraffin. After the tissues were cut into sections (5 mm), they were dewaxed and hydrated. Then reagent A, reagent B, primary antibodies, reagent C and reagent D were added dropwise to the glass slides according to the standard using the immunohistochemical kit (MXB biotechnologies). Finally, DAB was added for color development, and the expression levels of mucosa-associated inflammatory cytokines [interleukin-4 (IL-4), IL-6, IL-5, monocyte chemotactic protein 1 (MCP-1), IL-15, and IL-22] were observed after the glass slides were sealed.

Detection of serum inflammatory indexes, oxidative stress indexes and immune-related indexes: 3-5 mL of peripheral venous blood was collected from patients in the UC group and control group, blood cells were removed, and the processed samples were sent to the Clinical Laboratory for detection. Subsequently, serum inflammatory indexes [tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, IL-2 and C-reactive protein (CRP)], oxidative stress indexes [superoxide dismutase (SOD), myeloperoxidase (MPO) and malondialdehyde (MDA)] and immune-related indexes [complement 3 (C3), C4, interferon-gamma (IFN-γ), immunoglobulin G (IgG) and IgA]. All examinations were completed within 2 hours.

Statistical methods

SPSS 22.0 was adopted for statistical analysis. Measurement data were tested by the independent samples t-test. Pearson method was applied for correlation analysis, and p<0.05 suggested that the difference was statistically significant.

Results

Vitamin level in UC patients

The serum levels of vitamin D in UC patients in the normal vitamin group and vitamin deficiency group are shown in Figure 1, which revealed that the difference between the two groups was significant (p<0.05).

Inflammatory cytokines in the intestinal mucosa

The levels of inflammatory cytokines in the intestinal mucosa in the UC group and control group are shown in Table 1. According to the figure, the levels of IL-4, IL-6, IL-5, IL-15 and IL-22 in the UC group were evidently

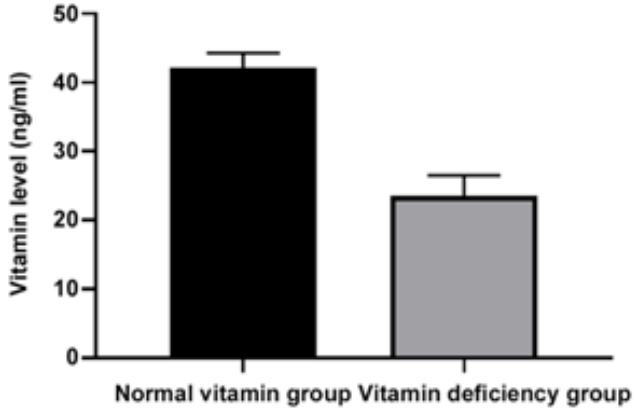

Figure 1. Vitamin level in UC patients in normal vitamin group and vitamin deficiency group.

Table 1. Comparisons of inflammatory cytokines in the intestinal mucosa between UC group and control group ($\bar{x}$±s).

Group	n	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-5 (pg/mL)	MCP-1 (pg/mL)	IL-15 (pg/mL)	IL-22 (pg/mL)
Control group	120	48.87±3.21	10.24±0.39	22.45±2.43	52.83±3.12	87.32±4.56	75.02±4.39
UC group	120	71.33C5.43	43.32±2.65	30.56±1.23	62.26±1.42	134.35±8.32	142.98±6.21
t		39.00	135.30	32.62	30.13	54.30	97.89
p		0.000	0.000	0.000	0.000	0.000	0.000

Table 2. Comparisons of inflammatory cytokines in the intestinal mucosa of UC patients between normal vitamin group and vitamin deficiency group ($\bar{x}$±s).

Group	n	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-5 (pg/mL)	MCP-1 (pg/mL)	IL-15 (pg/mL)	IL-22 (pg/mL)
Normal vitamin group	48	62.33±3.92	39.59±3.52	18.25±2.11	60.33±2.18	78.23±3.21	122.48±7.54
Vitamin deficiency group	72	80.45±2.43	62.43±2.19	52.12±6.43	64.40±2.41	169.43±6.32	156.37±3.65
t		28.57	40.08	41.47	9.60	104.00	28.96
p		0.000	0.000	0.000	0.000	0.000	0.000

Table 3. Comparisons of serum inflammation indexes between UC group and control group ($\bar{x}$±s).

Group	n	TNF-α (μg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)	IL-2 (ng/L)	CRP (mg/L)
Control group	120	102.34±4.52	3.26±0.23	7.30±1.01	3.22±0.98	0.76±0.12
UC group	120	356.82±10.39	34.95±1.46	42.81±2.12	23.61±2.11	2.21±0.31
t		247.50	234.90	165.50	96.01	47.78
p		0.000	0.000	0.000	0.000	0.000

Table 4. Comparisons of serum inflammatory indexes in UC patients between normal vitamin group and vitamin deficiency group (*x*±s).

Group	n	TNF-α (μg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)	IL-2 (ng/L)	CRP (mg/L)
Normal vitamin group	48	466.46±9.34	32.74±2.14	34.66±7.31	20.78±1.18	2.03±0.14
Vitamin deficiency group	72	307.38±12.37	33.72±1.38	48.19±3.38	30.21±2.31	2.41±0.17
t		80.12	2.99	12.00	29.37	13.35
p		0.000	0.004	0.000	0.000	0.000

higher than those in the control group (p<0.05). The levels of inflammatory cytokines in the intestinal mucosa in the normal vitamin group and vitamin deficiency group are displayed in Table 2. It was found that the vitamin deficiency group had notably higher levels of IL-4, IL-6, IL-5, MCP-1, IL-15 and IL-22 than the normal vitamin group (p<0.05).

Serum inflammation indexes

The levels of serum inflammatory indexes in the UC group and control group are shown in Table 3, which revealed that the levels of TNF-α, IL-1β, IL-6, IL-2 and CRP in the UC group were higher than those in the control group. Table 4 displays the levels of serum inflammatory indexes in the normal vitamin group and vitamin deficiency group. It was found that the vitamin deficiency group had markedly higher levels of IL-1β, IL-6, IL-2 and CRP than the normal vitamin group (p<0.05).

Oxidative stress indexes

The levels of oxidative stress indexes in the UC group and control group are shown in Table 5. It can be seen that the oxidative stress indexes in the UC group were prominently higher than those in the control group (p<0.05). The levels of oxidative stress indexes in the normal vi-

Table 5. Correlation analysis of vitamins and indexes in UC patients.

	r	*p*
IL-4	-0.37	0.04
IL-6	-0.21	0.28
IL-5	-0.11	0.03
MCP-1	-0.26	0.19
IL-15	-0.29	0.44
IL-22	-0.22	0.06
TNF-α	0.35	0.46
IL-1β	-0.31	0.04
IL-6	-0.25	0.5
IL-2	-0.37	0.15
CRP	-0.36	0.38
SOD	-0.34	0.09
MPO	-0.28	0.02
MDA	-0.26	0.05
C3	0.12	0.54
C4	-0.11	0.35
IFN-γ	0.24	0.13
IgG	0.08	0.36
IgA	0.09	0.78

Table 6. Comparisons of oxidative stress indexes between UC group and control group ($\bar{x}$±s).

Group	n	SOD (U/mL)	MPO (mg/L)	MDA (nmol/mL)
Control group	120	90.34±3.21	0.58±0.21	1.34±0.28
UC group	120	60.81±5.39	1.44±0.51	3.28±0.61
t		51.56	17.08	31.66
p		0.000	0.000	0.000

Table 7. Comparisons of oxidative stress indexes in UC patients between normal vitamin group and vitamin deficiency group ($\bar{x}$±s).

Group	n	SOD (U/mL)	MPO (mg/L)	MDA (nmol/mL)
Normal vitamin group	48	59.96±6.84	1.42±0.15	2.16±0.18
Vitamin deficiency group	72	62.32±4.11	1.45±0.21	3.45±0.43
t		2.14	0.91	22.65
p		0.035	0.364	0.000

Table 8. Comparisons of immune-related indexes between UC group and control group ($\bar{x}$±s).

Group	n	C3 (g/L)	C4 (g/L)	IFN-γ (μg/L)	IgG (g/L)	IgA (g/L)
Control group	120	1.22±0.28	0.21±0.08	1.81±0.17	8.21±1.21	2.21±0.88
UC group	120	5.26±1.31	0.89±0.14	10.78±1.21	8.38±0.98	2.41±1.05
t		33.04	46.20	80.42	1.20	1.60
p		0.000	0.000	0.000	0.233	0.111

Table 9. Comparisons of immune-related indexes in UC patients between normal vitamin group and vitamin deficiency group ($\bar{x}$±s).

Group	n	C3 (g/L)	C4 (g/L)	IFN-γ (μg/L)	IgG (g/L)	IgA (g/L)
Normal vitamin group	48	7.21±0.14	0.90±0.10	14.31±2.13	8.37±1.01	2.37±0.97
Vitamin deficiency group	72	4.33±1.41	0.88±0.08	9.41±1.26	8.42±0.77	2.43±1.19
t		17.20	1.16	14.35	0.29	0.30
p		0.000	0.249	0.000	0.770	0.762

tamin group and vitamin deficiency group are shown in Table 6. SOD and MDA levels in the vitamin deficiency group were significantly higher than those in the normal vitamin group (p<0.05), while the change in the MPO level was of no significance.

Immune-related indexes

Table 7 reveals the levels of immune-related indexes in the UC group and control group. The levels of C3, C4 and IFN-γ in the UC group were shown to be obviously higher than those in the control group (p<0.05), while the changes in the levels of IgG and IgA were of no significance. The levels of immune-related indexes in the normal vitamin group and vitamin deficiency group are shown in Table 8. It was discovered that the levels of C3 and IFN-γ in the vitamin deficiency group were lower than those in the normal vitamin group (p<0.05).

Correlation analysis of various indexes with vitamins in UC patients

The correlations of each index with vitamins in UC patients were analyzed (Table 9). Indexes remarkably related to vitamins included IL-4 (r=-0.37, p=0.04), IL-5 (r=-0.11, p=0.03), IL-1β (r=-0.31, p=0.04) and MPO (r=-0.28, p=0.02).

Discussion

UC affects the life of patients in the long term and is hard to be cured, which is characterized by hemorrhage and necrosis, accompanied by severe systemic responses, increased body temperature and obvious abdominal symptoms. The pathogenesis of UC may be associated with individual genetic differences and host reactions caused by substances in vitro, but the exact pathogenesis remains unknown (13). In the development process, however, UC leads to changes in the immune system, influences local inflammatory responses in the affected intestinal tract, and aggravates local conditions and systemic immune responses. Therefore, the immune system occupies a significant position in UC (14, 15). The intensity of inflammatory responses directly affects the progression of UC and the prognosis of patients (16). Hence, it is of great significance to explore the factors affecting inflammation and immune responses in UC patients for the treatment of UC and the improvement of patients' prognosis.

Vitamins play a crucial role in maintaining the steady state of the human body. Vitamin D regulates the metabolism of calcium and phosphorus in the normal human body, making the levels of the two elements tend to be balanced. Meanwhile, it has been reported that vitamin D has anti-infection and immunoregulation functions in a variety of diseases and reduces excessive inflammatory responses in patients, and immune dysfunction is just the most significant characteristic of UC patients. In addition, vitamin D may play an anti-inflammatory role in UC patients and prevent its development (17). Therefore, investigating the effect of vitamin D on the immune system and its specific mechanism in regulating inflammatory responses in UC patients is necessary.

In this study, it was found that vitamin D deficiency not only promoted the release of local inflammatory cytokines

(IL-4, IL-5, MCP-1, IL-15 and IL-22) in intestinal mucosa tissues, aggravated UC in patients and expanded the lesion site, but also elevated the levels of serum inflammatory indexes (IL-1β, IL-6, IL-2 and CRP) and sharpened systemic immune responses. IL-2, generally a substance that promotes inflammatory responses, has a strong biological effect. It can promote the release of other related cytokines in UC patients, thus further enhancing systemic immune responses and aggravating UC (18). IL-22, also a cytokine promoting inflammatory responses, is able to stimulate the production of acute-phase reaction proteins. IL-5 is capable of accelerating related immune cells to release inflammatory substances such as histamine and leukotriene, thereby worsening the condition of UC patients (19). This study, therefore, manifested that vitamin D deficiency in UC patients could result in the release of a large number of inflammatory substances locally and systemically, so as to accelerate the progression of UC and make it difficult to be controlled.

In addition to inflammatory responses, vitamin D was also discovered to affect oxidative stress indexes in UC patients. SOD and MPO can help eliminate oxygen free radicals in the normal human body or patients and reduce tissue and cell damage. MDA can reflect the antioxidant capacity in the body and is a common index for evaluating oxidative stress in the body (20-21). According to this study, vitamin D deficiency in UC patients obviously increased the levels of SOD and MDA but had little effect on MPO. The reason may be that vitamin D can only affect oxidation reactions in vivo through SOD and MDA, but cannot affect MPO. The specific mechanism needs to be further studied. Besides, it was indicated that although C3, C4 and IFN-γ in UC patients were evidently higher than those in the control group ($p<0.05$), the reduction of vitamin D had no effect on them and even significantly reduced the levels of C3 and IFN-γ, which may be due to the release of related anti-inflammatory cytokines caused by vitamin D, leading to the relative reduction of some pro-inflammatory cytokines.

Ultimately, this study manifested that vitamin D in UC patients was closely associated with IL-4 (r=-0.37, p=0.04), IL-5 (r=-0.11, p=0.03), IL-1β (r=-0.31, p=0.04) and MPO (r=-0.28, p=0.02), which verified that vitamin deficiency will raise the levels of inflammatory cytokines in the intestinal mucosa and peripheral blood, thus increasing inflammatory responses and enhancing oxidative stresses in vivo to some extent.

According to the results of this study, vitamin D in UC patients had significant correlations with inflammatory cytokines in the intestinal mucosa, serum inflammatory indexes and immune response indexes. The level of vitamin D in UC patients can be detected to predict inflammatory indexes and immune responses in patients and timely measures can be taken to interfere with the development of UC. Meanwhile, vitamin D can be supplemented for vitamin D deficiency to reduce inflammatory responses and oxidative stresses in vivo, which has strong clinical significance.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
YT wrote the manuscript. YT and LP collected and analyzed general data of patients. LW and LY performed ELISA. YZ and YL were responsible for detection of serum inflammatory indexes. XL and FL helped with statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the ethics committee of Chongqing first people's hospital and written informed consents were signed by the patients and/or guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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