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ORIGINAL ARTICLE

Relationship between diet, oxidative stress, and inflammation in ankylosing spondylitis

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ABSTRACT

Objectives: This study aims to investigate the relationship between disease activity, dietary phytochemical index (DPI), and serum total oxidant status (TOS) and total antioxidant status (TAS) in patients with ankylosing spondylitis (AS).

Patients and methods: Between August 2020 and January 2021, a total of 37 patients (23 males, 14 females; mean age: 39.3±9.4 years; range, 21 to 61 years) with AS and 36 age-, sex-, and body mass index-matched healthy individuals (24 males, 12 females; mean age: 37.9±8.9 years; range, 20 to 60 years) were included. Serum TAS (μmoLTroloxEq/L) and TOS (μmoL H2O2Eq/L) measurements were performed and the oxidative stress index (OSI) was calculated. Dietary evaluation was made from a one-day dietary record and DPI was calculated.

Results: Serum TAS level in AS patients was significantly lower than the healthy group (p=0.003). Serum TOS level was similar in both groups. The OSI of patients was significantly higher than the controls (p=0.035). The mean DPI, polyunsaturated fatty acid, n-3 fatty acid, and vitamin C intake of patients were significantly lower than controls (p=0.042, p=0.033, and p=0.022, respectively). A moderate positive correlation was found between the TAS level and DPI of the control group (r=0.352, p=0.035). According to medications, no significant difference was seen between the groups in terms of patients' characteristics, DPI, and laboratory tests and there was no correlation between DPI, TAS, TOS, and OSI.

Conclusion: Lower DPI and lower n-3 fatty acid and vitamin C intake in patient group demonstrated that patients with AS should pay more attention to their diet to increase serum antioxidant status.

Keywords: Ankylosing spondylitis, antioxidant capacity, dietary phytochemical index, oxidant capacity.

Ankylosing spondylitis (AS) is an inflammatory condition which is the prototype of seronegative spondyloarthropathies. It mainly affects the axial skeleton, but may also cause peripheral large joint arthritis. Due to enthesitis, bony ankylosis of the spine may occur. Ankylosing spondylitis may involve extra-articular tissues such as uveitis, bowel disease, heart, lung, skin, bone and kidney involvement. The pain and fatigue have adverse effect on patients leading to functional impairments.[1,2]

In the pathogenesis of AS, interactions between genetic factors, gut microbiota, mechanical effects on the spine and peripheral joints, innate immunity, oxidative stress, lifestyle, and environmental issues are thought to be responsible.[3-5] In addition to these factors, diet is

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currently being investigated in AS pathogenesis and progression. Dietary patterns have been reported as confounding factors in disease etiologies such as rheumatoid arthritis and cardiovascular diseases.[6,7] According to previous study results, diets rich in phytochemicals, fiber, and antioxidant provide chronic disease risk reduction.[8] Additionally, phytochemicals which are abundantly found in plant foods, act as antioxidant, balance the inflammation, and protect against the development of insulin resistance, glucose abnormalities, and lipid disorders.[8] These data have led investigators to evaluate the importance of diet in other inflammatory pathologies such as AS.

The association between AS symptoms and the oxidant-antioxidant status has also become an area of interest. It is known that oxidative mechanisms play a substantial role in initiation and perpetuation of pathogenetic pathways in rheumatological diseases.[9,10] Therefore, in the last decade, oxidative stress has been reported as a probable factor in AS pathogenesis.[5] In normal circumstances, there is a balance between oxidant radicals and the antioxidant capacity of organisms. This balance is maintained by numerous defense systems in the organism. The enzymatic (glutathione peroxidase, superoxide dismutase, catalase, glautathione-S-transferase, glutathione reductase) and the non-enzymatic (vitamin A, vitamin C, glutathione) components play an important role in this system.[11] An increase in oxidant molecules or a decrease in antioxidant molecules (such as low dietary intake of antioxidant foods) would disrupt this balance toward oxidative stress.[12] Under this abnormal condition, increased stress biomarkers may harm nucleic materials, carbohydrates, proteins and, consequently, intensify existing oxidative stress.[11] It is also assumed that already activated inflammatory cells (macrophages or T cells) may contribute to cytokine production and synovitis.[13]

Phytochemicals are known as plant-derived bioactive substances including phenolic parts (e.g., phenolic acids, flavonoids, lignans, tyrosol esters), organosulphur compounds, and isoprenoids.[14,15] Phytochemicals are found in vegetables, fruits, whole grains, legumes and nuts and in other plant-based foods. They modify and reduce oxidative stress and inflammation and, thus, protect organisms.[16-18] As a result of these health-protecting effects, the measurement of phytochemical intake has become an area of research. To examine the combined effects of foods instead of examining a unique nutrient or food group, it is recommended to study the effect of whole diet and obtain an objective perspective about nutrition-disease link.[19,20] In the light of this information, the Dietary Phytochemical index (DPI) is designed to figure out the phytochemical content of all foods in diet. It is a ratio score obtained by dividing the energy provided by foods high in phytochemicals by the total energy consumed from all foods.[21] A higher index value represents optimal dietary intake, while a lower value indicates lower phytochemical compound intake. It has previously been shown that low intake of phytochemically-rich foods may cause an increased risk of inflammatory joint disease, and polyphenolic extracts of extra-virgin olive oil have been reported to be protective against rheumatoid arthritis-associated inflammation.[22-24] In addition, together with genetic and other lifestyle factors, the Mediterranean diet, which is high in fruits and vegetables, may lower the arthritis risk.[25]

To the best of our knowledge, there is no study showing the association between DPI and AS. In the light of these data, we aimed to investigate the relationship between DPI, disease activity, and serum total oxidant status (TOS) and total antioxidant status (TAS) in patients with AS.

PATIENTS AND METHODS

Study design and study population

This cross-sectional study was conducted at Ankara City Hospital, Physical Therapy and Rehabilitation Hospital, between August 2020 and January 2021. A total of 37 patients with AS (23 males, 14 females; mean age: 39.3±9.4 years; range, 21 to 61 years) with a disease history of at least one year who met the non-radiographic axial spondyloarthritis (nr-AxSpA) and AS criteria and the 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria[26] were included. A control group consisted of 36 age-, sex- and body mass index (BMI)-matched

healthy individuals (24 males, 12 females; mean age: 37.9±8.9 years; range, 20 to 60 years). Exclusion criteria were as follows: alcohol use, smoking, pregnancy or lactating, nutritional supplement use, age ≤18 years and ≥65 years, any additional disease that may affect oxidative status such as diabetes, hyperthyroidism, respiratory diseases, malignancy, and cardiac, hematological, metabolic or other diseases. The disease activity of patients was evaluated with the Ankylosing Spondylitis Disease Activity Score (ASDAS).[27] Four disease activity levels are defined according to the ASDAS: inactive (ASDAS <1.3), moderate (≥1.3 to <2.1), high (≥2.1 to ≤3.5), and very high (>3.5).[28,29] Demographic characteristics and a detailed medical history of the patients were recorded. The patients were grouped according to medications (no medication, non-steroidal anti-inflammatory drug [NSAID], biological agent) and compared in terms of demographic, clinical, and biochemical parameters.

A written informed consent was obtained from each participant. The study protocol was approved by the Ankara City Hospital Ethics Committee (2020/E1-20-938). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT04772976).

Anthropometric measurements

Anthropometric characteristics such as body weight, height, and hip and waist circumferences were recorded. The BMI was calculated as dividing body weight (kg) by height $(m)^2$. Circumference of the waist was evaluated at 2-cm distal from the umbilicus, and circumference of the hip was measured at the widest perimeter.

Laboratory tests

Blood samples were collected at 08:00-09:00 AM after 8-h fasting. Complete blood count, fasting blood glucose, triglyceride, high- and low-density lipoprotein, total cholesterol, and C-reactive protein (CRP) levels were measured. For serum TOS (μmoL H2O2Eq/L) and TAS (μmoLTroloxEq/L) measurements, blood samples were centrifuged at 3,600 rpm/min for 10 min and the serum was separated to the Eppendorf™ tubes (Eppendorf AG, Hamburg, Germany). The TAS and TOS analyses were made using the method designed by Erel.[30,31] The oxidative stress index (OSI) level was determined using the following formula: OSI=TOS/TAS×10.

Dietary evaluation

A one-day dietary record was taken from all participants by a trained dietitian. Portion sizes and volumes were estimated with a picture book of portion sizes including 120 photographs of different foods, each with three to five different portion sizes.[32] The BeBiS version 7.2 software (Bebispro for Windows, Stuttgart, Germany; Turkish Version, 2010) was used to calculate the daily intake of macronutrients, micronutrients, and energy.[33] The DPI was calculated from the dietary records using the method described by McCarty et al.[21] (DPI=daily energy received from phytochemical-rich foods (kJ)/daily total energy intake (kJ)×100). Fruits and vegetables, whole grains, legumes, oil seeds, olive, olive oil and soy products were included in the category of foods rich in phytochemicals, while potato was not considered a vegetable due to the high starch content. Foods rich in phytochemical content such as 100% natural vegetable and fruit juices and tomato sauce were included in the vegetable and fruit groups. Foods low in phytochemicals such as animal products, white rice, white flour, potato products, and added refined oils and sugars were not included in the DPI calculation.

Statistical analysis

Study power analysis and sample size calculation were performed using the G*Power version 3.1.9.7 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).[34] The fixed effects, special, main effects and interactions and type of power analysis were used as *post-hoc* test to calculate the power based on alpha (α), sample size (n), and effect size (d). With a sample size of 37 patients and 36 healthy individuals and $\alpha=0.05$, the power of the current study was calculated as 0.93.

Statistical analysis was performed using the IBM SPSS for Mac version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (min-max) values, while categorical variables were presented in

Table 1. Demographic and clinical characteristics of study population

Characteristics	Patient group (n=37) n	%	Mean±SD	Healthy group (n=36) n	%	Mean±SD	*p*
Age (year)			39.3±9.4			37.9±8.9	0.368
Sex							0.688
Female	14	37.8		12	33.3		
Male	23	62.2		24	66.7		
Education							**0.004**
Primary School	15	40.5		4	11.1		
Secondary-High School	12	32.5		10	27.8		
University or Higher	10	27.0		22	61.1		
Disease interval (year)			8.8±7.6			NA	
ASDAS-CRP			2.7±0.8			NA	
BMI (kg/m^2)			25.8±5.0			25.1±3.4	0.877
Waist circumference (cm)			91.7±12.4			91.8±11.9	0.391
Hip circumference (cm)			104.8±11.3			104.0±7.3	0.699
Waist/hip ratio			0.9±0.1			0.9±0.1	0.553
C-reactive protein (mg/dL, 0-5)			9.7±11.9				
TAS (µmolTroloxEq/L)			1.8±0.2			2.0±0.3	**0.003**
TOS (µmol H_2O_2Eq/L)			3.6±1.2			3.2±0.7	0.566
OSI			0.2±0.1			0.2±0.0	**0.035**

SD: Standard deviation; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C reactive protein; BMI: Body mass index; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index.

Table 2. Dietary phytochemical index, daily energy and nutrients intake of study population

Parameters	Patient group Mean±SD	Healthy group Mean±SD	*p*
Dietary phytochemical index	18.7±9.8	24.7±11.6	**0.022**
Total energy intake (kcal)	2,258.8±594.9	2,219.2±517.2	0.757
Carbohydrates (g/day)	265.9±74.7	243.9±74.8	0.275
Protein (g/day)	74.8±31.9	76.9±20.7	0.399
Fat (g/day)	96.2±30.1	101.1±25.2	0.440
MUFA (g/day)	32.7±12.4	33.4±10.0	0.651
PUFA (g/day)	26.8±14.1	33.8±15.5	**0.042**
n-3 fatty acid	1.2±0.4	2.1±1.6	**0.042**
n-6 fatty acid	25.5±14.0	31.7±14.8	0.058
SFA (g/day)	30.6±12.6	27.3±7.8	0.414
Cholesterol (mg/day)	226.0±161.6	235.3±130.4	0.463
Fiber (g/day)	21.9±6.5	25.0±8.3	0.105
Vitamin A (mcg/day)	349.2±202.6	287.3±121.8	0.421
Vitamin C (mg/day)	79.3±45.9	128.7±93.5	**0.033**
Vitamin E (mg/day)	28.4±15.7	29.0±13.1	0.716

SD: Standard deviation; MUFA: Monounsaturated fatty acid; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid.

Table 3. Correlation between DPI, TAS, TOS, OSI, ASDAS, CRP, and VAS

			DPI	TAS	TOS	OSI	ASDAS	CRP	VAS
Patient group	DPI	r	1.000	0.111	0.135	0.163	0.227	0.167	0.105
		p	-	0.515	0.425	0.334	0.177	0.323	0.538
	TAS	r	0.111	1.000	0.139	-0.203	**-0.332**	-0.192	-0.324
		p	0.515	-	0.416	0.228	**0.045**	0.254	0.050
	TOS	r	0.135	0.139	1.000	**0.911**	0.092	0.223	0.124
		p	0.425	0.416	-	**<0.001**	0.589	0.184	0.464
	OSI	r	0.163	-0.203	**0.911**	1.000	0.194	0.313	0.182
		p	0.334	0.228	**<0.001**	-	0.249	0.059	0.281
	ASDAS	r	0.227	**-0.332**	0.092	0.194	1.000	**0.661**	**0.766**
		p	0.177	**0.045**	0.589	0.249	-	**<0.001**	**<0.001**
	CRP	r	0.167	-0.192	0.223	0.313	**0.661**	1.000	0.191
		p	0.323	0.254	0.184	0.059	**<0.001**	-	0.259
	VAS	r	0.105	-0.324	0.124	0.182	**0.766**	0.191	1.000
		p	0.538	0.050	0.464	0.281	**<0.001**	0.259	-
Healthy group	DPI	r	1.000	**0.352**	0.119	-0.183	NA	NA	NA
		p	-	**0.035**	0.489	0.285	NA	NA	NA
	TAS	r	**0.352**	1.000	**0.510**	**-0.348**	NA	NA	NA
		p	**0.035**	-	**0.001**	**0.037**	NA	NA	NA
	TOS	r	0.119	**0.510**	1.000	**0.596**	NA	NA	NA
		p	0.489	**0.001**	-	**<0.001**	NA	NA	NA
	OSI	r	-0.183	**-0.348**	**0.596**	1.000	NA	NA	NA
		p	0.285	**0.037**	**<0.001**	-	NA	NA	NA

DPI: Dietary phytochemical index; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C reactive protein; VAS: Visual Analog Scale; SD: Standard deviation; NA: Not applicable.

number and percentage. Conformity of data to normal distribution was assessed using the Kolmogorov-Smirnov test. Inter-group comparisons were made using the chi-square test, Student t-test, or the Mann-Whitney U test. A *p* value of <0.05 was considered statistically significant.

RESULTS

The main characteristics of the patient and control groups are shown in Table 1. No significant difference was observed between the patient and control groups in terms of age and sex. However, the education status of the control group was higher than the patient group (p=0.004). According to the mean ASDAS-CRP level of the patients, disease activity was high. The TAS level of the patients was significantly lower than the healthy controls (p=0.003). The TOS level was similar in both groups. The OSI of the patients was significantly higher than the control group (p=0.035).

The DPI, and daily energy and nutrient intake of the patients and control groups are shown in Table 2. The mean DPI, polyunsaturated fatty acid (PUFA), and vitamin C intake of the patients were significantly lower than the healthy controls (p=0.042, p=0.033 and

Table 4. Characteristics of patients according to medication groups

Characteristics	No medication (n=10)			NSAID (n=15)			Biologic agent (n=12)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			37.7±5.6			40.3±10.1			39.6±11.3	0.576
Sex										0.268
Female	3	30.0		8	53.3		3	25.0		
Male	7	70.0		7	46.7		9	75.0		
Disease interval (year)			5.8±6.0			7.5±5.2			12.8±10.0	0.130
BMI (kg/m^2)			25.4±2.2			25.1±5.3			27.1±6.2	0.721
Waist circumference (cm)			89.2±4.5			89.0±11.5			97.2±16.4	0.492
Hip circumference (cm)			104.0±4.0			102.4±9.4			108.5±16.3	0.389
Waist/hip ratio			0.8±0.06			0.8±0.1			0.9±0.04	0.228
ASDAS-CRP			2.5±0.7			3.0±0.7			2.3±0.8	0.148
VAS (mm)			6.2±2.2			6.8±2.3			4.1±1.8	0.110
C-reactive protein (mg/dL, 0-5)			5.8±5.8			10.0±10.4			12.4±16.6	0.190
TAS (µmolTroloxEq/L)			1.8±0.2			1.7±0.2			1.7±0.1	0.415
TOS (µmol H2O2Eq/L)			3.1±0.9			3.8±1.4			3.6±1.1	0.448
OSI			0.2±0.0			0.2±0.1			0.20±0.06	0.144
DPI			20.3±14.5			20.4±6.8			15.0±7.9	0.241

SD: Standard deviation; NSAID: Non-steroidal anti-inflammatory drug; BMI: Body mass index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C reactive protein; VAS: Visual Analog Scale; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; DPI: Dietary phytochemical index.

Table 5. Correlation of TAS, TOS and OSI with DPI in the patient group

Parameters	No medication (n=10)		NSAID (n=15)		Biologic agent (n=12)	
	r	p	r	p	r	p
TAS	-0.061	0.868	0.287	0.299	0.284	0.372
TOS	0.018	0.960	0.155	0.580	0.168	0.601
OSI	0.049	0.894	0.150	0.593	0.224	0.484

TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; DPI: Dietary phytochemical index.

p=0.022, respectively).

The correlation between DPI, TAS, TOS, and OSI are shown in Table 3. A moderate positive correlation was found between the TAS level and DPI of the control group (r=0.352, p=0.035). However, no correlation was found between the DPI and the other parameters.

The characteristics of patients according to medications are summarized in Table 4. There was no significant difference between the groups. Correlations between the DPI, TAS, TOS, and OSI in the medication groups are shown in Table 5. We found no significant correlation between the DPI, TAS, TOS, and OSI.

DISCUSSION

The main results of the current study have shown that TAS level in AS patients was significantly lower than healthy individuals. Serum TOS level was similar in both groups, while the OSI of the patients was significantly higher than the controls. The mean DPI of patients was significantly lower than the controls. A moderate positive correlation was found between the TAS and DPI in the control group.

Markers of oxidative stress and antioxidative status have been previously studied in rheumatic diseases. Although several biomarkers have been used for this assessment in different studies, patients with AS have mostly shown decreased antioxidant status and increased oxidant status than healthy individuals.[35] In a study using the same automated measurement as in the current study, significant differences were determined in TAS, TOS, and OSI between patients with AS and a healthy group.[36] In another study, nitric oxide, an indicator of oxidant status, was similar in both groups.[37] In the current study, the TAS level of AS patients was significantly lower and the OSI level was significantly higher than those of the healthy control subjects. The TOS level was similar in both groups. The discrepancy between studies may be due to complex interactions between oxidative and anti-oxidative molecules, although it has also been reported that anti-tumor necrosis factor (TNF) agents inhibit production of reactive oxygen species (ROS) and neutrophil chemotaxis.[38]

As in the current study, most researchers have hypothesized that disease activity may influence oxidative biomarker concentrations. In a study in which the patients were classified into active (the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4) and inactive (BASDAI <4) groups, the overall oxidative biomarker level was found to be higher in active patients.[35] Some researchers did not classify patients according to disease activity and analyzed for correlation between clinical and laboratory parameters. Solmaz et al.[5] reported a significant correlation between disease activity scores, TOS, and TAS, whereas other studies did not report any correlation. Ozgocmen et al.[37] compared 30 patients with AS and 16 healthy individuals and found no significant correlation between oxidant/antioxidant parameters and CRP, erythrocyte sedimentation rate, and BASDAI.[37] In the current study, a significant moderate negative correlation was observed between the ASDAS and TAS level; however, no correlation was found between the ASDAS, TOS, and OSI.

Diets including vegetables and fruits, whole grain, plant-based foods, nuts and legumes contain high phytochemicals, fiber and antioxidants.[39] Phytochemical rich foods are known to be protective against cardiovascular and metabolic diseases, high blood pressure, and hypertriglyceridemia.[40-42] These protective effects are considered to lower oxidative stress and inflammation.[18] Previous reports investigated the DPI-disease risk and an inverse relationship between DPI and obesity, oxidative stress, hypercholesterolemia, insulin resistance, prediabetes and hypertension was reported.[14] In addition, a decrease in oxidative stress together with high DPI was also found by Vincent et al.[24] In the current study, a moderate positive correlation was observed between DPI and TAS in the control group, while there was no significant correlation between DPI and oxidative biomarkers in the patient group. Disease-related effects and/or dietary factors on oxidative biomarkers may have caused the absence of such a correlation in the patient group.

There is overwhelming evidence of the relationship between diet and inflammatory diseases. In a study by Sundström et al.,[43] energy intake of patients with AS was significantly higher than that of the control group and there was no significant difference in protein, carbohydrate, and fat intake. In the current study, the mean energy intake of patients was higher than that of the control group; however, the difference was not statistically significant. The PUFA, n-3 fatty acid, and vitamin C intake was significantly lower in the patient group than in the control group. The PUFAs are known to have beneficial effects on health. However, n-6 and n-3 components of PUFA have opposing actions. The n-6 fatty acids enhance inflammation, while n-3 fatty acids have anti-inflammatory effects.[44] Similarly, vitamin C has both immune-modulatory and antioxidant effects.[45] Considering the effects of PUFA, n-3 fatty acid, and vitamin C on inflammation and oxidative processes, significantly lower intake of these nutrients may have contributed to the lower TAS in the patient group.[44-46] Other nutrient intake levels were similar in both groups. In AS, dietary interventions have also been previously investigated. Appelboom and Durez[46] investigated the effect of dairy product exclusion on AS symptoms and reported that approximately half of patients reported good improvement and continued this diet in mid-long term. In another study, a low starch, high protein, vegetable and fruit diet was applied, and erythrocyte sedimentation rate was seen to be decreased.[47] In a previous report by Montonen et al.,[48] high

whole-grain bread consumption was related with both higher circulating levels of anti-oxidant molecules and anti-inflammatory state. These results give hope to both health professionals and patients that beneficial effects can be provided by nutrients. Therefore, decreasing disease activity and minimizing oxidative process may be good reasons to consume phytochemical rich foods.

Tumor necrosis factor has substantial effects on cytokine production. Therefore, anti-TNF agents are expected to diminish inflammation and pain in rheumatic diseases.[49] There are also several studies in the literature indicating the link between anti-TNF agents and ROS production.[38,50] A previous study reported that patients using anti-TNF treatments had the highest TAS and lowest TOS, compared to the NSAID group and control group.[51] In the current study, the patients were divided into subgroups; however, no significant difference was found between the anti-TNF, NSAID or no medication groups in respect of TAS, TOS, or OSI.

Relatively small sample size and heterogeneity in medical treatments are the main limitations of this study.

In conclusion, the results of this study indicated that TAS values were lower and OSI scores were higher in patients with AS compared to the healthy individuals. Although a positive correlation was present between DPI and TAS in the control group, there was no correlation between DPI and oxidative biomarkers in the AS group. In addition, NSAID or anti-TNF treatments were not associated with TAS, TOS, and DPI. A high disease activity and, thus, generalized inflammation in the AS group despite medical treatments may have affected the oxidative biomarkers. Lower DPI and lower n-3 fatty acid and vitamin C intake in patient group demonstrated that patients with AS should pay more attention to their diet to increase serum antioxidant status. Nevertheless, further large-scale, prospective studies are needed to draw a firm conclusion.

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