

# The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome

Sukran Tastan Sakarya · Yesim Akyol ·  
Abdulkerim Bedir · Ferhan Canturk

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**Abstract** We proposed to assess serum antioxidant vitamins and magnesium (Mg) levels in patients with fibromyalgia (FM) in comparison to healthy controls. Additionally, the association between the serum antioxidant vitamins, magnesium levels, and clinical parameters in FM patients was also investigated. Forty female patients, aged between 30 and 50 years, were diagnosed with FM according to ACR-1990 criteria, and 40 healthy controls were included in the present study. Socio-demographic characteristics of participants, accompanying symptoms, and number of tender points (TP) of the patients were recorded. The intensity of pain was measured using the visual analogue scale (VAS). The functional status and depression levels were evaluated with Fibromyalgia Impact Questionnaire (FIQ) and Beck Depression Inventory (BDI), respectively. Serum vitamins A, C, and E and Mg levels were measured. There were no significant differences in the levels of vitamins A, C, and E and Mg between control subjects and patients with fibromyalgia ( $p>0.05$ ). In addition, no statistically significant correlations were found between mean levels of serum vitamins A, C, and E, and Mg and number of TP, scores of VAS, FIQ, and BDI in patients with FM ( $p>0.05$ ). According to the results of this study, it was asserted that other complex mechanism may play an important role in the pathophysiology of FM without plasma antioxidant vitamins and Mg levels.

**Keywords** Antioxidant vitamins · Fibromyalgia · Magnesium · Oxidative stress

## Introduction

Reactive oxygen species (ROS) are highly reactive chemical species with an unpaired electron and formed by catalyzing transition metals like iron, copper, or manganese [1]. ROS are formed in oxidative processes that normally occur at relatively low levels in all cells and tissues. Under normal conditions, the concentrations of ROS are kept under strict control by the activity of a complex defense system including enzymes and non-enzymatic species. In contrast, high doses and/or inadequate removal ROS results in oxidative stress, which may cause severe metabolic malfunctions and damage to biological macromolecules [2, 3]. In recent years, a great number of studies have investigated the possible role of oxidative stress in the etiopathogenesis of various rheumatological disease including rheumatoid arthritis, ankylosing spondylitis, and chronic fatigue syndrome [4–6].

Fibromyalgia (FM) is rheumatic disorder characterized by musculoskeletal pain, stiffness, and tenderness of specific anatomic sites [7]. The etiology of FM is still unknown and also it is associated with many factors and predictors [8, 9]. Oxidative stress and/or an imbalance of trace element status may play an important role in the pathophysiology of FM [10–13].

Vitamins A, E, and C are known to be a powerful non-enzymatic antioxidant [14, 15]. Vitamins A and E are essential fat-soluble vitamins. They are the major chain-breaking antioxidants in body tissues and are considered the first line defense against lipid peroxidation, protecting cell

S. T. Sakarya · Y. Akyol (✉) · F. Canturk  
Department of Physical Medicine and Rehabilitation,  
Medical Faculty, Ondokuz Mayıs University,  
Samsun, Turkey  
e-mail: yesimakyl@yahoo.com

A. Bedir  
Department of Biochemistry, Medical Faculty,  
Ondokuz Mayıs University,  
Samsun, Turkey

membranes at an early stage through free radical-quenching activity [16–18]. Vitamin C is the major water-soluble vitamin. It, as well as being a free radical scavenger, also transforms vitamin E to its active form [19]. Magnesium (Mg) is a trace element, which plays a considerable role in ATP synthesis, and it is important for adequate muscle metabolism [20]. In recent years, serum Mg levels have been researched to reveal etiopathogenesis of patients with FM [21, 22].

In literature, there have been few studies that investigate the role of antioxidant vitamins and Mg in the etiopathogenesis of FM, and their results are contradictory [21–24]. We proposed to assess serum antioxidant vitamins and Mg levels in patients with FM in comparison to healthy controls. The association between the serum antioxidant vitamins, Mg levels, and clinical parameters in FM patients was also investigated.

## Materials and methods

Forty ( $n=40$ ) premenopausal women who met the 1990 American College of Rheumatology (ACR) criteria for the diagnosis of FM [25] were enrolled in the study. Forty ( $n=40$ ) age, sex, geographic location matched demographically similar healthy premenopausal women were selected as controls. Informed consent was obtained from all subjects, and the study protocol was approved by the local ethics committee. Routine blood tests, sedimentation rate, liver and kidney blood tests, thyroid hormone concentration, and sex hormone profiles of the patients and controls were evaluated. The criteria for exclusion were severe chronic diseases (e.g., chronic renal/liver failure, hepatitis), other rheumatic diseases, severe neuropsychiatric, endocrinologic disorders (e.g., diabetes mellitus, hypo, or hyperthyroidism), painful or disabling medical conditions, neuropathic pain disease, and undesired habits (e.g., smoking, alcohol, etc.). Neither patients nor controls were using any medicine that effects the serum antioxidant vitamins and Mg levels and statin. None of the patients was under the treatment of antidepressants and analgesics and were only included if they had stopped using them at least 4 weeks before study.

The demographic features [age, height, body weight, body mass index (BMI), duration of disease] and accompanying symptoms [fatigue, headache, dyspnea, pollakiuria, morning stiffness (generalized stiffness of the muscles and joints after waking up in the morning especially in the hands, arms, legs, and feet lasting for 45 min or longer), sleep disorders, anxiety, dysmenorrhea, Raynaud's-like symptoms, and irritable bowel syndrome] of the patients were documented. The patients were examined in terms of widespread chronic pain, number of tender points (TP), functional capacity, and depression

level. Severity of pain was evaluated using 10 cm visual analogue scale (VAS). Higher scores of VAS indicate more severe symptoms [26]. TP defined by ACR were determined by applying a 4-kg pressure with the thumb on specific body points and the number of TP recorded. Tender point examination was carried out by the exertion of a uniform amount of manual finger pressure, until fingernail bed blanches. Functional capacity in daily living activities was evaluated by Turkish version of fibromyalgia impact questionnaire (FIQ) [27]. Depression rate was assessed by Beck Depression Inventory (BDI). The test consists of 21 questions scaled in a Likert format. The higher score shows increased depression of subjects [28]. The score over 17 was accepted to be a sign of depression.

For laboratory investigations, venous blood was taken from the cubital vein into plain and anticoagulation tubes containing sodium EDTA and protected against light, after an overnight fast and with all morning medication omitted. After serum and plasma samples were separated by centrifugation at  $1,500\times g$  for 10 min at  $+4^{\circ}\text{C}$ , the serum samples were used for immediate Mg analysis, while the plasma samples were stored in a freezer ( $-70^{\circ}\text{C}$ ) until the time of vitamin assay analysis. Mg levels were measured with colorimetric method (Magon/Xylidyl blue) by Roche Modular equipment. Plasma vitamins A, E, and C levels were measured with High Performance Liquid Chromatography (HPLC) system (Agilent Technologies, Waldbronn, Germany) using the commercial kits (Chromsystems Instruments and Chemicals GmbH, München, Germany).

## Statistical analyses

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) software, version 11.0 for Windows, was used for all statistical analyses. Normality analyses were made with the Kolmogorov–Smirnov test. Data showing a normal distribution were expressed with mean value  $\pm$  standard deviation. To test for statistical differences between two groups, Student's *t* tests were used. For correlation between results, the Pearson's correlation coefficient was performed. The sociodemographical characteristics of the groups were evaluated by chi-square test. *p* values less than 0.05 were considered statistically significant.

## Results

Demographic and clinical characteristics of patients with FM and controls are shown in Table 1. Demographic characteristics were statistically similar in groups ( $p>0.05$ ). TP number, VAS (pain) score, BDI score, and FIQ score were significantly ( $p<0.001$ ) higher in patients with FM than controls. The most frequently encountered symptoms

**Table 1** Demographic, clinical characteristics, laboratory measurements, and signs and symptoms of patients with fibromyalgia and control

Characteristics	Fibromyalgia (n=40) mean±SD	Control (n=40) mean±SD	p value	Frequency (n, %)
<b>Demographic characteristics</b>				
Age (years)	33.61±7.55	31.67±7.03	0.134	
Height (cm)	161.9±5.30	163.2±6.09	0.398	
Body weight (kg)	61.4±4.91	60.6±6.06	0.554	
BMI (kg/m <sup>2</sup> )	23.42±1.58	22.79±1.59	0.076	
<b>Clinical characteristics</b>				
Tender point number	13.95±1.75	1.68±1.82	0.001	
Duration of disease (years)	4.25±3.11	–	–	
VAS pain score (cm)	8.00±1.48	0.35±0.77	0.001	
FIQ score	61.32±9.23	4.94±4.11	0.001	
BDI score	11.23±4.87	2.10±2.48	0.001	
<b>Laboratory measurements</b>				
FT4 (ng/mL)	0.99±0.14	1.08±0.16	0.078	
FT3 (pg/mL)	2.65±0.44	2.83±0.36	0.063	
TSH (μIU/mL)	1.62±0.98	1.66±0.94	0.826	
FSH (mIU/ml)	8.14±9.52	9.44±18.99	0.711	
LH (m IU/mL)	5.63±4.23	6.27±6.65	0.620	
E2 (pg/mL)	78.55±53.69	103.23±84.13	0.108	
Vitamin A (mmol/L)	1.46±0.47	1.25±0.26	0.119	
Vitamin C (mmol/L)	3.69±2.20	3.70±2.33	0.974	
Vitamin E (mmol/L)	24.39±5.25	21.98±5.48	0.072	
Magnesium (mmol/L)	0.87±0.07	0.87±0.08	0.977	
<b>Signs and symptoms</b>				
Fatigue				40 (100)
Anxiety				38 (95)
Sleep disorders				37 (92.5)
Headache				37 (92.5)
Morning stiffness				33 (82.5)
Irritable bowel syndrome				27 (67.5)
Dyspnea				24 (60)
Dysmenorrhea				21 (52.5)
Pollakiuria				13 (32.5)
Raynaud's-like symptoms				8 (20)

p value is significant when <0.05

BMI body mass index, FIQ Fibromyalgia Impact Questionnaire, FSH follicle-stimulating hormone, VAS visual analogue scale, BDI Beck Depression Inventory, LH Luteinising hormone, TSH thyroid-stimulating hormone, ST3 free thyroxine, ST4 free triiodothyronine, E2 estradiol, mean ± SD mean±standard deviation

accompanying patients with FM were fatigue (100%) and anxiety (95%), as shown in Table 1.

The mean concentrations of thyroid hormones (thyroid-stimulating hormone—TSH, free triiodothyronine—FT3, free thyroxine—FT4), sex hormones (follicle-stimulating hormone—FSH, Luteinising hormone—LH, estradiol—E2), vitamins A, C, and E and Mg in plasma of patients with FM and controls are shown in Table 1. There were no significant differences between groups according to TSH, FT3, FT4, FSH, LH, and E2 (p>0.05). The mean values of vitamins A, C, and E in patients and controls were 1.46 and 1.25, 3.69, and 3.70, 24.39, and 21.98 mmol/L, respectively. Patients and controls both had a mean Mg level of 0,87 mmol/L. There were no significant differences in the levels of vitamins A, C, and E and Mg between control subjects and

patients with FM (p>0.05). In addition, no statistically significant correlations were found between mean levels of serum vitamins A, C, and E and Mg and number of TP, scores of VAS (pain), FIQ, and BDI in patients with FM (p>0.05; Table 2).

**Discussion**

The etiology and pathogenesis of FM are not clearly understood. Recent studies have demonstrated that oxidative stress and serum trace elements may have a role in the pathophysiology of FM [10, 11]. For the purpose to support the etiopathogenesis of FM, we assessed serum antioxidant vitamins, Mg trace element levels in patients with FM in

**Table 2** Correlation between serum antioxidant vitamins, magnesium levels and clinical findings in patients with fibromyalgia

	Vitamin A	Vitamin C	Vitamin E	Magnesium
Tender point number				
<i>r</i>	-0.110	-0.170	-0.150	0.121
<i>p</i>	0.499	0.294	0.357	0.457
VAS pain score (cm)				
<i>r</i>	-0.195	0.081	-0.311	0.165
<i>p</i>	0.228	0.621	0.051	0.309
FIQ score				
<i>r</i>	-0.083	-0.115	-0.171	0.014
<i>p</i>	0.611	0.481	0.291	0.934
BDI score				
<i>r</i>	0.177	-0.098	-0.246	-0.032
<i>p</i>	0.276	0.548	0.126	0.844

*p* value is significant when <0.05

VAS Visual Analogue Scale, FIQ Fibromyalgia Impact Questionnaire, *r* Pearson's correlation coefficient, BDI Beck Depression Inventory

comparison to healthy controls. Additionally, the association between the serum antioxidant vitamins, Mg levels, and clinical parameters in FM patients was also investigated. As a result, there were no significant differences in the levels of vitamins A, C, and E and Mg between control subjects and patients with FM. In addition, no correlations were found between levels of serum vitamins A, C, and E and Mg and number of TP, severity of pain, functional capacity, and depression in patients with FM.

The increase in toxic ROS and decrease in antioxidant defense mechanism are defined as oxidative stress and contribute to local tissue injury, organ dysfunction, and many disorders including inflammation, carcinogenesis, atherosclerosis, and neurodegenerative diseases [3]. The role of free radical-mediated oxidative damage was investigated in the etiopathogenesis of FM. Fassbenger and Wegner [29] reported that muscle tender points in FM result from local hypoxia. Lund et al. [30] indicated abnormal oxygen pressure at the muscle surface above trigger points. Another study showed microcirculatory disturbances in tender points [31]. These studies lead to the importance on oxidative stress as a basic pathologic process in FM.

In literature, there are studies on enzymatic antioxidant capacity of plasma (superoxide dismutase, catalase, glutathione peroxidase, adenosine deaminase) in patients with FM [10, 32, 33]. These study findings may support the hypothesis of FM as an oxidative disorder. Vitamins A, E, and C are known to be a powerful non-enzymatic antioxidant [14, 15]. To our knowledge, there are two studies on vitamins A and E concentrations and one publication on vitamin C concentration in blood of patients with FM [23, 24]. Eisinger et al. [24] measured plasma vitamins A and E concentrations in 28

patients with FM and 20 age-matched controls, and they found that there were no statistically significant changes in any of the vitamin concentrations in the patients. In contrast, Akkus et al. [23] showed that vitamins A and E levels in 30 female patients with FM were lower than in 30 age- and sex-matched controls and plasma vitamin C concentrations of patients did not change. They reported that plasma vitamins A and E concentrations in the patients may be used as a result of their role action on radical inhibition. In the present study, there were no significant differences in the levels of plasma vitamins A, C, and E between control subjects and patients with fibromyalgia. The study population of the study of Akkus et al. is similar to that of our study, but their results had considerable difference. They used spectrophotometric analysis, but we analyzed our data with HPLC. Since we did not use the same method, the results cannot be comparable. There are little and paradoxical data, so more clinical trials are needed to explore the issue.

The role of Mg deficiency in patients with FM is controversial. Similar to the current study in past years, Prescott et al. [34] and Rosborg et al. [22] reported that serum Mg level of patients with FM were normal. In contrast, Sendur et al. [21] reported that Mg levels in plasma of patients with FM were lower than control. In another study by Eisinger et al. [12], the erythrocyte Mg level was slightly lower in patients with FM. Abraham and Flechas [13] also found that Mg deficiency plays a possible role in mechanism of pain in FM. They thought this was related to the role of Mg in the production of ATP. The present investigation gave no support for the hypothesis that Mg deficiency in plasma plays a significant role in the development of FM.

Pain is a major symptom of FM. The number of TP is also important [7]. Depression is usually accompanying with FM [35]. We thought that levels of antioxidant vitamin and Mg might affect these symptoms. We investigated this issue but found no correlation between severity of pain, functional capacity, number of TP, levels of depression, and antioxidant vitamin and Mg levels. In literature, we encountered no study investigating the correlation between antioxidant vitamins and clinical parameters. The association between serum Mg level and clinical parameters was investigated only by Sendur et al. [21]. They found no statistically significant association between Mg levels and clinical parameters (pain, number of TP, functional capacity, disease duration, morning stiffness).

The major limitation of the current study is the limited number of patients who were all women. Future studies should include larger populations and both sexes. Previous studies of FS patients in our country had similar results of age and duration of disease as in the current study [10, 21, 23].

According to the results of this study, it was asserted that other complex mechanism may play an important role in

the pathophysiology of FM without plasma antioxidant vitamins and Mg levels. These findings justify further researches to explore the effect of antioxidant vitamins and Mg trace element in FM.

**Disclosures** None

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