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Original Article

Vitamin K levels in Fibromyalgia Syndrome Patients and Their Associations with Pain, Disease Activity, Quality of Life and Inflammatory Cytokines

Ayşe Merve Çıracıoğlu, M.D.[*,1], Onur Armağan, Prof. Dr.[†], Sema Uslu, Prof. Dr.[‡], Funda Berkan, Prof. Dr.[†], Merih Özgen, Prof. Dr.[†], Suheyla Dal Erdoğan, M.D.[†], Ertuğrul Çolak, Prof. Dr.[§]

[*] Department of Physical Medicine and Rehabilitation, Tavşanlı Doç. Dr. Mustafa Kalemli Hospital, Kütahya, Turkey
[†] Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey
[‡] Department of Biochemistry, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey
[§] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

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ABSTRACT

Background: Fibromyalgia syndrome (FMS) is a chronic pain condition that requires multidisciplinary treatment. Vitamin K is an antioxidant that plays a role in many reactions in the body, and its effectiveness in FMS has not been studied before.

Aim: We aimed to evaluate vitamin K levels in FMS patients and their relationship with pain, disease activity, quality of life, and inflammatory cytokines.

Method: Eighty-eight female patients with FMS and 87 controls were included in the study. Vitamin K and inflammatory cytokine (interleukin-6 [IL-6], IL-8, tumor necrosis factor [TNF]-alfa) serum levels were measured in both groups. Visual Analog Scale (VAS), Fibromyalgia Impact Questionnaire (FIQ), and Short Form-36 (SF-36) scales were used.

Results: No statistically significant differences in vitamin K levels between the two groups, and no relationships were found between these levels and pain, FIQ, SF-36, and inflammatory cytokines ($p > .05$). While IL-6 and TNF-alpha levels were found to be high in the FMS group compared with the control group ($p < .05$), no difference in IL-8 levels was noted ($p > .05$). In the FMS group, positive correlations were found between IL-6 and FIQ, and between TNF-alpha and physical role difficulty($p > .05$).

Conclusions: Overall, the results of this study do not provide any evidence of an association between FMS and vitamin K levels. However, high IL-6 and TNF-alpha levels suggest that low-intensity inflammation may accompany FMS and have a negative impact on physical activity. Future studies are needed to determine the relationship between vitamin K and FMS.

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition usually accompanied by somatic symptoms such as sleep disorders, gastrointestinal problems, fatigue, memory problems, and psychological comorbidities. The prevalence of FMS is ~ 2% to 8%, and the disease is more common in women (Clauw, 2014).

Recent studies on the etiology of FMS have emphasized various potential mechanisms, such as central nervous system sensitivity, sleep disturbance, affective disorder, genetic abnormalities, inflammation, neurohumoral dysfunction, and autonomic dysfunction (Clauw, 2014). The relationship between inflammation and FMS has not been fully demonstrated. Some cytokines, such as interleukin (IL)-1B, tumor necrosis factor (TNF)-alpha, interleukin IL-Ra (IL-Ra), interferon (IFN)-gamma, IL-2, IL-6, IL-8, and IL-10 are increased in the serum of patients with FMS. Studies have shown that cytokines such as IL-6, IL-8, and TNF-alpha have clinical significance in patients with FMS and are associated with central and peripheral pain (Wallace et al., 2001).

A multidisciplinary approach that includes both pharmacologic and non-pharmacologic treatments is required in the management of FMS. Antiepileptic and antidepressant derivative drugs used in treatment have multiple side effects (Choy et al., 2009). These un-

Abbreviations: FMS, Fibromyalgia Syndrome; Vit K, Vitamin K; Interleukin, IL-; QL, Quality of Life.

[1] Address correspondence to Ayşe Merve Çıracıoğlu, X.X
E-mail addresses: draysemerveaydogan@gmail.com (A.M. Çıracıoğlu), dronuarmagan@hotmail.com (O. Armağan), semaoguzuslu@gmail.com (S. Uslu), funda26izmir@gmail.com (F. Berkan), merihsarhus@hotmail.com (M. Özgen), suheyla-dal@hotmail.com (S. Dal Erdoğan), ecolak@ogu.edu.tr (E. Çolak).

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wanted side effects reduce treatment compliance and cause an increase in the use of alternative and complementary therapies by patients and clinicians. Patients with FMS often take nutritional supplements, but the effects of these supplements on symptoms are unknown (Pfalzgraf et al., 2020). Although studies are showing the effect of vitamin deficiencies on symptoms, the number of these studies is insufficient and their quality is low. These studies are based on the hypotheses that vitamins and minerals act through mechanisms that reduce oxidative stress and inflammation. In a meta-analysis conducted in 2017, there was no difference in vitamin B12, folic acid, sodium, potassium, selenium, and iodine serum blood levels in patients with FMS compared with the control group, while B1, vitamin A, vitamin E, and magnesium levels were found to be significantly lower. Low vitamin D levels are common in patients with FMS, and post-replacement pain relief and improved quality of life have been observed (Joustra et al., 2017).

Vitamin K is a generic term for compounds such as phylloquinone (PK, vitamin K1) and menaquinone series (vitamin K2), which act as cofactors in many biochemical reactions and have regulatory effects mainly on the activities of the coagulation system, cardiovascular system, musculoskeletal system, reactive oxygen production, and proinflammatory cytokines (Ozgen et al., 2019). It is known that vitamin K protects cells against oxidative damage by blocking the activation of 12-lipooxygenase in arachidonic acid metabolism (Olorunnisola et al., 2019). There are also studies showing that vitamin K supplements reduce the production of proinflammatory cytokines and that there is an association between low vitamin K serum levels and high levels of proinflammatory markers (Reddi et al., 1995; Shea et al., 2008). It has been suggested that it produces this effect by inhibiting nuclear factor kappa_B (NF-kappaB). Adequate levels of vitamin K are thought to be associated with the prevention of musculoskeletal diseases involving chronic inflammation, such as osteoarthritis, osteoporosis, and rheumatoid arthritis (Chin, 2020; Ohsaki et al., 2006; Simes et al., 2019). In a study conducted on patients with dysmenorrhea, a decrease in pain was achieved by injecting vitamin K into acupuncture points. However, the effect of these vitamins on inflammation and pain needs more in-depth research (Wang et al., 2004).

Based on the effects of vitamin K on inflammation, oxidative stress, and the musculoskeletal system, we planned our study on the hypothesis that these vitamins can modulate pain. We aimed to compare vitamin K levels between patients with FMS and the control group and to investigate the relationships between these levels and quality of life, functional status, pain, and inflammatory markers. This study is the first to examine the relationship between vitamin K levels and FMS. Such studies are needed to understand the relationship of vitamin and mineral levels to FMS and the effects of these supplements on symptoms. In addition, this study is important in terms of examining the relationship between vitamin K and pain at the level of evidence-based medicine.

Methods

Patients

This prospective observational case study was conducted at the Physical Medicine and Rehabilitation Clinics of Eskisehir Osmangazi University Medical Faculty between March 2018 and January 2020. The required sample size was determined by power analysis based on previous studies. The PASS 11 program and two t-tests tests were used for the power analysis. With a significance level of 0.05 and a power of 80%, a total of 176 (88 patients and 88 controls) were required for the study.

We included 88 female patients with FMS and 87 controls who met the inclusion criteria in our study (Fig. 1). The control group was selected from individuals who had completed their treatment for isolated musculoskeletal pain in our clinic and came to the control examination. Written and verbal consent was provided by each patient. The present study was approved by the Eskisehir Osmangazi University Clinical Research Ethics Committee under decision number 22.01.2018/8.

Procedures

All participants were examined at the initial stage, and their demographic data (age, gender, education, body mass index [BMI], and marital status) were recorded. Painful tender points were identified and recorded during the examinations in the FMS group. The FMS group completed a Visual Analog Scale (VAS) for pain level determination, the Short Form-36 (SF-36) for quality-of-life determination, and the Fibromyalgia Impact Questionnaire (FIQ) for disease activity determination. Vitamin K and proinflammatory cytokine levels in serum were measured in both groups.

FMS diagnostic criteria, first defined by the ACR in 1990, are still preferred in clinical practice. According to these criteria, it is expected that there will be tenderness on palpation in at least 11 of the 18 determined points on the body with widespread pain lasting more than 3 months (Wolfe et al., 1990).

The VAS evaluates pain levels on a 100-point scale, with 0 points indicating no pain and 100 points corresponding to the most severe pain ever experienced. The participants were asked to describe the average degree of pain that they experienced in the last week.

The FIQ evaluates disease activity in FMS. This scale consists of categories such as physical function, absenteeism, feeling unwell, difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. The first item consists of 11 questions about the physical disorder. Each item is rated on a 4-point Likert-type scale (0 = always, 3 = never). The values scored by the patient are added together and divided by the number of items scored. Since the other items (between 4 and 10) are evaluated over 10 units, the result obtained is multiplied by 3.33 and normalized. In the second item, a low number means the higher impairment (0 = 7, 7 = 0). The result obtained is normalized by multiplying by 1.43. In the third item, a high number means the higher impairment (7 = 7, 0 = 0). The result obtained is normalized by multiplying by 1.43. Items 4 to 10 are scored in increments of 10. The total score is obtained by summing all the points. Higher score corresponds to greater disability. The average score for patients with FMS is 50, while patients with severe FMS symptoms usually score 70 or higher. FIQ is a comprehensively validated fibromyalgia-specific tool that captures the overall impact of fibromyalgia symptomatology. It is available in 8 different languages and referenced in more than 100 publications (Bennett, 2005).

The SF-36 is an evaluation scale used in musculoskeletal diseases. The scale contains 36 items representing 8 domains, including Physical Function, Physical Role Difficulty, Emotional Role Difficulty, Energy/Vitality, Mental Health, Social Functioning, Pain, and General Health Perception. Each domain is scored according to the arithmetic mean of the corresponding items The score ranges from 0 (worst health status) to 100 (best health status). Studies support that SF-36 is an acceptable measure of 2 independent constructs of physical and mental health. Therefore, the use of SF-36 is recommended for chronic pain patients (LoMartire et al., 2020).

Vitamin K and inflammatory cytokines (IL-6, IL-8, TNF-alpha) were measured in blood samples collected from female patients diagnosed with FMS and healthy women on an empty stomach in the Department of Biochemistry. By the laboratory technician,

Paitent Group	Control Group
Inclusion criteria -Female patients diagnosed with FMS according to the 1990 ACR criteria	**Inclusion criteria** -Female aged 18 to 65
Exclusion criteria -Chronic heart disease -Kidney and liver disease -Rheumatological disease -Anticoagulant use -Antidepressant drug use -Long-term use of antibiotics -Steroids use -Alcohol use (more than one glass of white wine per day) -Uncontrolled diabetes and hypertension -Intestinal diseases -Vitamin supplementation	**Exclusion criteria** -FMS - Widespread musculoskeletal pain -Chronic heart disease -Kidney and liver disease -Rheumatological disease -Anticoagulant use -Antidepressant drug use -Long-term use of antibiotics -Steroids use -Alcohol use (more than one glass of white wine per day) -Uncontrolled diabetes and hypertension -Intestinal diseases -Vitamin supplementation

Figure 1. Inclusion and exclusion criteria for both groups. FMS = fibromyalgia syndrome; ACR = American College of Rheumatology.

10 cc of blood was taken from the arm vein of the participants with a 21-gauge needle and placed in the biochemistry tubes. The blood samples were collected into biochemistry tubes, which were centrifuged at 1,500 rpm for 10 minutes, and then the separated serum was placed in capped plastic tubes and stored at -80°C until analysis. Stored serum samples were thawed just prior to analysis.

Vitamins K1 and K2

Serum samples were analyzed in an ELx808 BIOTEK device using a vitamin K1 enzyme-linked immunosorbent assay kit (E1114Hu; Bioassay, China) and a vitamin K2 enzyme-linked immunosorbent assay (ELISA) kit (E2176Hu; Bioassay, China). Bioassay-derived K1 and K2 ELISAs are solid-phase enzyme-dependent immunosorbent assays performed on a microtiter plate. The optical density (OD) of almost every well was determined using a microplate reader set to 450 nm. Vitamin K1 and K2 concentrations in serum samples are expressed in ng/mL compared with the OD of the standard curve. CV(Clauw) = SD/mean x 100, Intra-assay: CV<8%, Inter-assay: CV<10%.

IL-6, IL-8, and TNF-alpha

Serum samples were analyzed on an ELx808 BIOTEK device using an IL-6 ELISA kit (KAP1261; DIASOURCE, China), IL-8 ELISA kit (KAP1301; DIASOURCE, China), and TNF-alpha ELISA kit (KAP1751; DIASOURCE, China). DIASOURCE-induced IL-6-ELISA is a solid-phase enzyme-dependent immunosorbent assay performed on a microtiter plate. The OD value of almost every well was determined using a microplate reader set to 450 nm. The results are expressed in ng/mL Cytokine concentrations in serum samples are shown in pg/mL compared with the OD of the standard curve. IL-6: CV(Clauw) = SD/mean x 100, Intra-assay: CV<4.2%, Inter-assay: CV<4.4%; IL-8: CV(Clauw) = SD/mean x 100, Intra-assay: CV<3.6%, Inter-assay: CV<13.1%; TNF-alpha: CV(Clauw) = SD/mean x 100, Intra-assay: CV<6.6%, Inter-assay: CV<4.5%.

Statistical Analysis

Continuous variables are shown as Q2 (Q1-Q3) percentiles, and categorical variables are shown as percentages (Clauw). The Shapiro-Wilk test was used to evaluate the compatibility of the

Table 1
Demographic Characteristics of the Groups

		FMS group (n = 87) Q2 (Q1-Q3)[a]	Control group (n = 87) Q2 (Q1-Q3)[a]	*p*
Age (years)		48 (42-51.75)	47 (41-52)	.613[b]
Height (cm)		160 (164-165)	160 (156-165)	.255[b]
Weight (kg)		73 (65-83)	67 (60-78)	**.010**[b]
BMI (kg/m^2)		28.57 (24.79-32,42)	26.17 (22.77-29.40)	**.002**[b]
Symptom duration (months)		4 (3-5)	-	-
		n	n	
Marital status	Married	77 (87.5)	75 (86.2)	.800[c]
	Single	12 (13.8)	11 (12.5)	
Occupation	Desk job	6 (6.8)	18 (20.7)	**.00**[c]
	Requires physical strength	13 (37.9)	33 (14.8)	
	Housewife	69 (78.4)	36 (41.4)	

Statistically significant *p* values are given in bold ($p < .05$).
FMS = fibromyalgia syndrome; BMI = body mass index.
[a] 50th percentile (25-75).
[b] Mann-Whitney *U* test.
[c] Pearson χ^2 test.

variables with a normal distribution. Since both groups did not show a normal distribution, comparisons between groups were performed using the Mann-Whitney *U* test, and differences between two percentages were compared using the Pearson chi-square test. Correlations between scales were evaluated by the Spearman correlation test. The analyses were performed using the IBM SPSS Statistics 23.0 program]. Both $p < .05$ and $p < .01$ values were considered statistically significant.

Results

Table 1 shows the demographic and clinical characteristics of both groups. There were no significant differences in age and height values. Body mass index (BMI) mean values were found to be significantly higher in the FMS group ($p < .05$). A significant difference was found between the patient and control group in terms of occupational distribution ($p < .05$). It was observed that 78.4% of the FMS group and 41.4% of the control group did not work.

The mean number of trigger points in the patients with FMS was 16.50, and the VAS value was 8. It was observed that all parameters of SF-36 were affected. The mean FIQ was 69.26, and 17% of patients had mild, 28% moderate, and 43% had severe disease-related involvement (Table 2).

Table 3 shows a comparison of vitamin K, IL-6, IL-8, and TNF-alpha levels between the two groups. No statistically significant differences in vitamin K levels were found ($p > .05$). IL-6 and TNF-alpha levels were significantly higher in the FMS group ($p < .05$), but no differences in IL-8 levels were noted ($p > .05$). Table 4 shows the relationships between vitamin K and cytokine serum levels.

Significant positive correlations were found between FIQ and IL-6 levels and between physical role difficulty and TNF-alpha levels ($p < .05$). No correlations were found between other variables ($p > .05$) (Table 5).

Table 2
Clinical Parameters of the Patient Group

		FMS Group (n = 87) Q2 (Q1-Q3)[a]
Tender points		16.50 (12-18)
VAS		8 (7-9)
SF-36	Physical function	52.50 (40-65)
	Physical role difficulty	100 (66.6-100)
	Emotional role difficulty	0 (0-50)
	Energy/Vitality	25 (15-40)
	Mental health	44 (32-60)
	Social functionality	50 (28.12-62,5)
	Pain	23.75 (22.5-45)
	General health	35 (20-45)
FIQ		69.26 (55.11 -80.19)
FIQ score		n
<50 (mild)		17 (19.3)
50-70 (moderate)		28 (31.8)
>70 (severe)		43 (48.9)

[a] 50th percentile (25-75).
FMS = fibromyalgia syndrome; VAS = visual analog scale; SF-36 = Short Form-36; FIQ = Fibromyalgia Impact Questionnaire.

Discussion

In this study, we compared vitamin K levels between patients with FMS and controls and investigated associations between these levels and pain, quality of life, and disease activity. No differences in vitamin K levels were observed between the FMS group and the control group, and we found no relationship between these levels and clinical parameters. IL-6 and TNF-alpha levels were found to be high in the FMS group, but no difference in IL-8 levels was observed. In the FMS group, positive correlations were found between IL-6 levels and FIQ results and between TNF-alpha levels and physical role difficulty parameters. We expected these results based on studies supporting that there may be an increase in inflammation in FMS patients.

FMS is most common in women between the ages of 30 and 50 years (Clauw, 2014), and we conducted our study with female patients. The FIQ and SF-6 are most frequently used to assess the quality of life in patients with FMS, and we preferred these scales in our study. The quality of life of patients with FMS has been found to be affected in all components, which is consistent with results in the literature. Ozcan et al. (2013) reported an FIQ score of 59,49±14,25 for patients with FMS in their study (Ozcan et al., 2013). In our study, this score was 69.26 (55.11-80.19), 19.3% of the FMS patients were mildly affected, and 49.9% were severely affected.

Recent studies on the etiology of FMS have emphasized various potential mechanisms, such as central nervous system sensi-

Table 3
Comparison of Biochemical Markers Between the Groups

	FMS group (n = 87) Q2 (Q1-Q3)[a]	Control group (n = 87) Q2 (Q1-Q3)[a]	*p*
Vitamin K1 (ng/mL)	5.12 (1.4-7.74)	5.36 (1.50-10.17)	.239
Vitamin K2 (ng/mL)	150.29 (99.74-229.13)	151.34 (90.58-449.88)	.823
IL-6 (pg/mL)	143.72 (120.04-209.02)	100.40 (70.61-191.73)	**.00**
IL-8 (pg/mL)	680.83 (680.20-1318.52)	680.83 (680.06-1648.67)	.890
TNF-alpha (pg/mL)	40.06 (35.30-50,78)	20.56 (15.60-42.20)	**.00**

Statistically significant *p* values are given in bold ($p < .05$).
[a] 50th percentile (25-75).
Mann-Whitney *U* test

Table 4
Relationship Between FMS Group Vitamin K and Cytokine Levels

FMS group (n = 88)		IL-6 (pg/mL)	IL-8 (pg/mL)	TNF-alfa (pg/mL)
Vitamin K1	r	0.431	0.157	0.119
(ng/mL)	*p*	**.000**	.145	.271
Vitamin K2	r	0.372	0.178	0.239
(ng/mL)	*p*	**.000**	.096	.025
Control group (n = 87)				
Vitamin K1	r	0.427	0.194	0.003
(ng/mL)	*p*	**.000**	.072	.981
Vitamin K2	r	0.414	0.151	-0.065
(ng/mL)	*p*	**.000**	.162	.547

Spearman Test. Statistically significant *p* values are given in bold ($p < .01$).
FMS = fibromyalgia syndrome; IL = interleukin; TNF = tumor necrosis factor.

Table 5
Relationship Between Clinical Parameters and Biochemical Markers in FMS Group

			Vitamin K1 (ng/mL)	Vitamin K2 (ng/mL)	IL-6 pg/mL	IL-8 pg/mL	TNF-alfa pg/mL
	Tender point	r	0,070	0,007	0,116	-0.002	0.015
		p	,518	,949	,280	.986	.892
	VAS	r	-0,002	-0,080	0,091	-0.035	-0.035
		p	,985	,458	,402	.747	.746
	FIQ	r	0,113	0,092	0,216	-0.061	-0.001
		p	,295	,392	,043	.571	.992
	Physical	r	-0,164	-0,147	-0,154	0.084	-0.100
SF-36	function	*p*	,127	,171	,151	.437	.352
	Physical role	r	0,056	0,101	-0,070	0.175	0.238
	difficulty	*p*	,603	,348	,516	.103	.026
	Emotional role	r	0,039	0,091	-0,003	0.113	0.153
	difficulty	*p*	,718	,397	,979	.293	.155
	Energy/Vitality	r	0,039	0,049	0,071	0.001	0.178
		p	,715	,648	,512	.989	.097
	Mental health	r	0,022	0,090	0,071	0.028	0.131
		p	,839	,407	,510	.798	.225
	Social	r	-0,136	-0,131	-0,029	0.063	0.010
	functionality	*p*	,205	,222	,787	.561	.926
	Pain	r	0,013	0,158	-0,100	0.018	-0.095
		p	,902	,141	,354	.868	.381
	General health	r	-0,149	-0,140	-0,135	0.030	0.090
		p	,166	,192	,211	.783	.404

Spearman test, $p < .05$.
FMS = fibromyalgia syndrome; VAS = visual analog scale; FIQ = Fibromyalgia Impact Questionnaire.

tivity, sleep disturbance, affective disorder, genetic abnormalities, inflammation, neurohumoral dysfunction, and autonomic dysfunction (Clauw, 1995; Lee et al., 2015). The relationship between inflammation and FMS has not been fully demonstrated. Studies in the literature show that in patients with FMS, some cytokine levels are high such as IL-1B, IL-Ra, TNF-alpha, IFN-gamma, IL-8, IL-6, IL-2, and IL-10 (Üçeyler et al., 2011). Wallace et al. (2001) reported that high IL-6 levels were associated with hyperalgesia, fatigue, and depression in patients with FMS, while high IL-8 levels were only associated with sympathetic pain (Wallace et al., 2001). Mendieta et al. (2016) found that high IL-6 and IL-8 levels were associated with FIQ results in patients with FMS (Mendieta et al., 2016). In a meta-analysis of 25 studies conducted by Üçeyler et al. (2011), significant increases in serum IL-1Ra, IL-6, and IL-8 levels were reported, and these increased cytokine levels were speculated to be associated with chronic pain (Üçeyler et al., 2011). Differences in materials, cytokines, and methods used for measurements complicate interpretations of studies and cause conflicting results.

Similar to most studies, we found that IL-6 and TNF-alpha levels were significantly higher in the FMS group ($p < .05$), but we did not find a significant difference between the two groups in terms

of IL-8 levels ($p > .05$). We found positive correlations between IL-6 levels and FIQ scores ($p < .05$) and between TNF-alpha levels and physical role difficulties in the FMS group ($p < .05$), suggesting that the physical activity difficulties of patients with FMS may be due to the effect of inflammation on muscles. We found no relationship between proinflammatory cytokine levels and other clinical parameters and pain ($p > .05$). In addition, BMI values in patients with FMS were significantly higher than in controls in our study. Obesity and overweight are known risk factors for chronic pain conditions such as fibromyalgia (Elma et al., 2020). In addition to the negative effect of obesity on pain, obesity may cause mild chronic inflammation by increasing the release of proinflammatory cytokines from adipose tissue (Dietrich & Jialal, 2005). Studies have shown that CRP, IL-6, and TNF-alpha levels are high in obese people (Cawthorn & Sethi, 2008). The patients with FMS in our study had higher BMI values, which may have caused these high cytokine levels. Regardless of whether inflammation is due to obesity, we think that mild chronic inflammation may contribute to symptom development in patients with FMS.

A multidisciplinary approach including both pharmacologic and nonpharmacologic treatments is required in the management of FMS. Many evidence-based guidelines that include a pharmacologic approach to the treatment of FMS focus on four drug classes. These are antiepileptic, tricyclic antidepressants (TCA), selective seratonin reuptake inhibitors (SSRI), and serotonin-noradrenaline reuptake inhibitors (SNRI). These drugs have undesirable side effects such as gastrointestinal problems, peripheral edema, headache, dry mouth, fatigue, insomnia, and dizziness (Choy et al., 2009). These effects reduce drug compliance and cause patients to seek complementary and alternative treatment methods. It has been reported that patients with FMS most frequently use complementary and alternative treatment methods such as vitamins, massage therapy, meditation, and aerobic exercise (Pfalzgraf et al., 2020). Although it is thought that vitamin and mineral deficiencies may play a role in the pathophysiology of FMS and chronic pain syndrome, its mechanism has not been fully elucidated. Most of the studies suggested that vitamins and minerals act through oxidative stress and inflammation-reducing mechanisms. The number of studies examining this relationship in the literature is insufficient, and the quality of these studies is low. Joustra et al. (2017) published a meta-analysis of 27 studies in 2017. According to this meta-analysis, in studies investigating vitamin B12, folic acid, sodium, potassium, selenium, and iodine levels, no significant difference was found in serum levels compared with the control group. However, in studies evaluating vitamin B1, vitamin A, and magnesium levels, significantly lower serum levels were detected in patients compared with the control group. Although the quality of the study is low, there are studies in which vitamin E levels were found to be low in patients. There were uncertain results in zinc, ferritin, and copper levels (Joustra et al., 2017). Vitamin D is the most studied molecule in patients with FMS in the literature. These patients often have low levels of vitamin D, and it has been determined that there is a decrease in pain and an increase in quality of life after replacement (Özgen et al., 2019).

Vitamin K is a general term for compounds such as phylloquinone (PK, vitamin K1) and the menaquinone series (vitamin K2). Vitamin K1 is the main form we get in the diet, while vitamin K2 is found in fermented foods and intestinal flora. Although vitamin K deficiency due to nutritional deficiency is very rare, it may develop due to malabsorption in conditions such as antibiotic use, gastrointestinal diseases, and liver and gallbladder disorders (Schwalfenberg, 2017). In addition to the effects of vitamin K on the coagulation system, it acts as a cofactor in many biochemical reactions related to the central nervous system, cardiovascular system, metabolism, musculoskeletal system, oxidative stress, and inflammation (Ediz et al., 2010).

Activation of 12-lipooxygenase, an enzyme involved in arachidonic acid metabolism, is one of the production mechanisms of reactive oxygen species (ROS) in the body. It has been reported that vitamin K blocks the activation of 12-lipoxygenase in arachidonic acid-induced oxidative damage to developing oligodendrocytes and protects against oxidative damage caused by glutathione depletion in developing neurons. In addition, vitamin K2 is a well-known powerful antioxidant (Olorunnisola et al., 2019). A review by Popa et al. (2021), reported that vitamin K is effective in preventing aging and age-related diseases due to its anti-inflammatory and antioxidant effects (Simes et al., 2019). There are also studies in the literature showing that vitamin K supplements reduce the production of proinflammatory cytokines and that there is a relationship between low vitamin K levels and high proinflammatory markers((Ohsaki et al., 2006; Shea et al., 2008). Sufficient vitamin K levels are thought to be associated with the prevention of musculoskeletal diseases involving chronic inflammation and pain, such as osteoarthritis, osteoporosis, and rheumatoid arthritis (Simes et al., 2019).

Ediz et al. (2010) hypothesized that high vitamin K levels have a protective effect in the development of complex regional pain syndromes by regulating inflammation via NF-kappaB (Ediz et al., 2010). Khojah et al. (2017) showed that vitamin K1 (PK, MK-4, MK-7) was low in patients with rheumatoid arthritis and negatively correlated with disease markers (Khojah et al., 2017). It has been reported that K vitamins exert these anti-inflammatory effects on the joint by suppressing the production of osteocalcin, metalloproteinase-3, and some proinflammatory cytokines in the cartilage and synovium (Ebina et al., 2013). In the Framingham Offspring Cohort study, negative correlations were found between PK levels and proinflammatory cytokines such as IL-6 (Shea et al., 2008). Wang et al. (2004) found a significant reduction in pain with the injection of vitamin K into acupuncture points in patients with dysmenorrhea (Wang et al., 2004).

Although it is thought that vitamin K has a protective effect on muscles, there are very few studies on this subject. In in vitro studies, MK-4 has been observed to increase the proliferation and migration of bovine muscle cells. It has also been found to reduce lysis in these cells and a secondary decrease in lactate dehydrogenase levels (Rønning et al., 2018). There are studies suggesting that its effect energy metabolism by increasing adenosine triphosphate (ATP) production in muscle cells. Observational clinical studies have found an association between higher vitamin K levels and better physical performance (Alonso et al., 2022). Shea et al. (2018) observed better lower extremity function in patients with knee OA with high vitamin K1 levels (Shea et al., 2018).

The relationship of vitamin K with pain is unknown. However, these vitamins have been shown to increase functional capacity in chronic musculoskeletal disorders by suppressing inflammation, antioxidant effect, and strengthening the muscle/bone structure (Simes et al., 2019). In line with these data, it can be thought that vitamin K may be effective in inflammation and pain.

The main purpose of our study was to compare vitamin K levels between patients with FMS and controls and to evaluate their associations with clinical parameters and inflammation. Although evidence indicates that FMS is associated with inflammation, whether FMS is an inflammatory/autoimmune disease remains controversial. No differences in vitamin K levels were identified between the two groups in our study ($p >$,05), and no relationships were found between vitamin K levels and clinical parameters in the FMS group ($p > .05$). Unlike most studies, we found a positive correlation between vitamin K and IL-6 levels in both the FMS and control groups ($p < .01$). No clinical study has ex-

amined vitamin K levels and their relationships with inflammatory cytokines in patients with FMS. In this context, comparing our results with those in the literature is difficult.

Moreover, no optimized method for serum vitamin K measurement is available. While measurements of some vitamin K-dependent molecules (prothrombin, matrix gla protein, and osteocalcin) allow indirect analyses, direct measurements of serum phylloquinone and menaquinone levels may be more informative. Many different methods can be used for the direct measurement of serum vitamin K levels. Optimization and standardization of these measurement methods are important for obtaining more analytical data (Fusaro et al., 2017). The normal range for vitamin K levels measured by the ELISA method has not yet been determined, therefore healthy age- and sex-matched controls were included in this study. These levels for both groups are within the measurement range determined by the test kit.

A relationship is thought to exist between low vitamin K levels and symptom duration in inflammatory diseases. Lasemi et al. (2018) found lower levels of vitamin K2 in patients with multiple sclerosis with longer symptom duration and speculated that this finding might be related to increased use of K vitamins in the body as inflammation progresses, decreased intake, or impaired absorption in the intestines (Lasemi et al., 2018). Since we evaluated newly diagnosed patients to exclude the effect of the treatment used in our study on inflammation and clinical parameters, the patients' symptom durations were short. In this early period, the inflammation-mediated association between FMS and vitamin K may not be fully developed. These results indicate that the relationship between vitamin K levels and cytokines remains unclear.

Limitations

The limitations of this study are as follows. First, FMS is not an autoimmune/inflammatory disease. Secondly, since those who used drugs for pain were excluded from the study, most of the patients were newly diagnosed and their symptom duration was short. A sufficient inflammatory response may not have occurred in these patients. Third, the study was carri out with a small sample size. Fourth, previous studies have used different methods for vitamin and cytokine measurements. The absence of a standard measurement method makes it difficult to compare the data with the literature. Finally, different ethnic populations display different feeding behaviors. We did not evaluate dietary vitamin K or antioxidant and anti-inflammatory food factors in our study. Without information on the general composition of the diets of patients and controls, reporting blood concentrations of vitamin K is of limited use.

Conclusions

In conclusion, this study is the first to evaluate vitamin K levels in patients with FMS. No significant differences in vitamin K levels were identified between patients with FMS and controls, and these levels were not associated with clinical parameters, pain, or quality of life. However, high IL-6 and TNF-alpha levels suggest that low-intensity inflammation may accompany FMS and have a negative impact on physical activity. To understand the relationship between vitamin K and FMS, methodologically well-designed studies with larger sample sizes examining the late stages of the disease are needed.

Clinical Implications

Nurses are an important professional group involved in pain management. It is recommended to evaluate the effects on pain and functional capacity in nurse practices in primary care and pain clinics. Nurses who approach their patients holistically can provide information and training on supportive treatment methods for chronic pain patients. FMS is a difficult pain disorder to treat. The direct and indirect cost burden associated with this disease is high due to the widespread use of health services and loss of productivity (Pfalzgraf et al., 2020). In addition, the drugs used in the treatment have multiple side effects. Considering the difficulty of treatment, side effects, high cost, and decreased efficiency, patients are in search of alternative treatment. At this stage, nurses should have the knowledge and experience to recommend appropriate alternative treatment methods for patients. This study is the first to examine the relationship between vitamin K levels and FMS. More studies are needed to investigate the effects of vitamin and mineral levels on patients with FMS.

Conflict of interest

The authors do not have any financial conflicts of interest.

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