RESEARCH ARTICLE

Rumeysa Samanci[1]
Merve Dede Akpinar[1]
Volkan Murat Samanci[2]
Safinaz Ataoglu[1]
Tuba Erdem Sultanoglu[1]

[1] Department of Physical Medicine and Rehabilitation, Medical Faculty, Duzce University, Duzce, Türkiye
[2] Republic of Turkey Ministry of Health, Family Health Center No. 8, Duzce, Türkiye

Corresponding Author:
Rumeysa Samanci
mail: rumeysakolukisa@hotmail.com

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Relationship between Serum Homocysteine Levels and Disease Activity in Patients with Fibromyalgia

ABSTRACT

Objective: Fibromyalgia syndrome (FMS) is a rheumatic disorder characterized by a wide spectrum of symptoms. Elevated homocysteine (Hcy) levels have been associated with a variety of conditions including renal dysfunction, cardiovascular disease, vitiligo, cancer, diabetes, ischemic stroke, epilepsy, dementia, autism, and various neurological disorders. This retrospective study aimed to evaluate the role of Hcy in the etiology of FMS and its relationship with disease activity.

Method: This study included 42 female patients diagnosed with FMS according to the American College of Rheumatology 2010 criteria, along with 20 age-matched healthy female controls. Detailed medical history and sociodemographic data were collected from all participants. Hemogram, routine biochemical tests, vitamin B12, folic acid, thyroid function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 25-hydroxy vitamin D, and serum Hcy levels were recorded from medical files in both groups.

Results: Serum Hcy, CRP, and ESR levels were significantly higher in the FMS group compared to controls (p=0.003, p=0.004, and p=0.011, respectively). However, no statistically significant correlation was found between Hcy levels and Fibromyalgia Impact Questionnaire, Visual Analog Scale, Beck Depression Inventory, Pittsburgh Sleep Quality Index, or Short Form-36 scores.

Conclusions: FMS is a complex disease with an unclear etiology. Considering that FMS affects multiple systems and that Hcy plays a role in various physiological processes, further comprehensive studies are warranted to elucidate the relationship between FMS and Hcy.

Keywords: Fibromyalgia, Homocysteine, Disease Activity.

Fibromiyalji Hastalarında Serum Homosistein Düzeyleri ile Hastalık Aktivitesi Arasındaki İlişki

ÖZET

Amaç: Fibromiyalji sendromu (FMS), çok çeşitli semptomları olan bir romatizmal hastalıktır. Yüksek homosistein (Hcy) düzeyleri; böbrek fonksiyon bozuklukları, kardiyovasküler hastalıklar, vitiligo, kanser, diyabet, iskemik inme, epilepsi, demans, otizm ve çeşitli nörolojik bozukluklarla ilişkilendirilmiştir. Bu retrospektif çalışma, FMS'nin etiyolojisinde Hcy'nin rolünü ve hastalık aktivitesi ile ilişkisini değerlendirmek amacıyla yapılmıştır.

Yöntem: Çalışmamıza, Amerikan Romatoloji Koleji 2010 kriterlerine göre FMS tanısı konmuş 42 kadın hasta dahil edildi. Yaşları hasta grubuyla benzer 20 sağlıklı kadın, kontrol grubunu oluşturmuştur. Tüm hastaların ve kontrol grubundaki katılımcıların ayrıntılı anamnez ve sosyodemografik verileri kaydedildi. Tüm hastalarda ve kontrol grubunda hemogram, rutin biyokimya, vitamin B12, folik asit, tiroid fonksiyon testleri, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), 25-hidroksi vitamin D ve serum Hcy düzeyleri hasta dosyasından kaydedildi.

Bulgular: Serum Hcy, CRP ve ESR düzeyleri, FMS grubunda kontrol grubuna göre istatistiksel olarak daha yüksekti (sırasıyla p=0,003, p=0,004 ve p=0,011). Ancak, Hcy düzeyleri ile Fibromiyalji Etki Anketi, Vizüel Analog Skala, Beck Depresyon Envanteri, Pittsburgh Uyku Kalitesi İndeksi veya Kısa Form-36 skorları arasında istatistiksel olarak anlamlı bir korelasyon yoktu.

Sonuç: FMS, etiyolojisi aydınlatılamamış kompleks bir hastalıktır. FMS'nin birden fazla sistemi etkilediği ve Hcy'nin çeşitli fizyolojik süreçlerde rol oynadığı göz önüne alındığında FMS ile Hcy arasındaki ilişkiyi açıklamak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Fibromiyalji, Homosistein, Hastalık Aktivitesi.

INTRODUCTION

Homocysteine (Hcy) is an amino acid that is formed during the conversion of methionine to cysteine (1–3). In healthy individuals, the synthesis and elimination of Hcy are in balance, but if this balance is disturbed, plasma Hcy levels rise, leading to hyperhomocysteinemia (HHcy) (3). Hcy is metabolized in two ways via either the transsulfuration pathway or the remethylation pathway (1). HHcy is caused primarily by nutritional deficiencies in vitamin cofactors such as folate, B12, and B6. It is also caused by genetic mutations in the enzymes methylenetetrahydrofolate reductase (MTHFR) and cystathionine β-synthase (CBS) (4,5).

HHcy may be associated with many organ pathologies. High Hcy levels may be associated with kidney dysfunction, cardiovascular disease, vitiligo, cancer, diabetes, ischemic stroke, epilepsy, dementia, autism and neurological problems (1,2,5,6).

Imbalances in Hcy production and/or catabolism can negatively affect cellular methylation and antioxidant processes. Additionally, Hcy decreases the viability of mitochondria (7). Furthermore, Hcy may affect the vagus nerve and superior cervical ganglion, impairing both parasympathetic and sympathetic regulation of skeletal muscle blood vessels and thus affecting muscle function in the long term (4). Hcy accumulation causes vascular dysfunction, decreases perfusion in muscles and thus can cause musculopathy (3,4). Interestingly, children with severe HHcy exhibit skeletal deformities and do not live to puberty (3).

In the literature, only one study has investigated the relationship between FMS and Hcy (8). In this study, the authors found that all patients had elevated Hcy levels in their cerebrospinal fluid and observed a significant positive correlation between fatigue and Hcy levels (8). However, this study was conducted with a very small sample size and the patient group represented mostly patients with chronic fatigue syndrome. Considering that FMS involves a wide range of symptoms affecting multiple systems, and that Hcy impacts the metabolism of various organs, the hypothesis of this study is that HHcy may contribute to the etiopathogenesis of FMS. For this reason, the present study aimed to investigate the role of Hcy in the etiopathogenesis of FMS and its relationship with disease activity.

MATERIAL AND METHODS

This retrospective, cross-sectional study included patients who were admitted to the Department of Physical Medicine and Rehabilitation outpatient clinic at Düzce University Faculty of Medicine between 2018 and 2022. A total of 42 female patients who were diagnosed with FMS according to the American College of Rheumatology (ACR) 2010 criteria were included in the study. In addition, 20 healthy female subjects of similar age to the patient group constituted the control group. Detailed anamneses and sociodemographic data for all patients and control group participants were obtained from hospital archives and recorded.

Study Subjects: Exclusion criteria for the patient and control groups were as follows: age under 18 years, active smoking, male sex, postmenopausal status, chronic hepatic or renal disease, a history of known vascular events, obesity (BMI >30), malignancy, hypothyroidism or hyperthyroidism, diabetes mellitus, pregnancy, presence of other rheumatological diseases except FMS, use of any vitamin supplements in the last 30 days, and missing data.

Laboratory Investigations: The biochemical parameters of serum 25-hydroxy vitamin D, vitamin B12, calcium, phosphorus, magnesium, alkaline phosphatase, glucose, liver and kidney function tests, C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) were studied via commercial kits (Roche Diagnostics, Germany) and were analyzed (spectrophotometrically) with a ROCHE Cobas 6000 device. The hemogram was studied via commercial kits on a Pentra Dx Nexus (UK) device. Serum Hcy levels were measured via the chemiluminescence immune assay (CLIA) method via an IMMULITE 2000 (Siemens Healthcare Diagnostics AG, Erlangen, Germany) via a SIEMENS Hcy kit, and the serum Hcy levels are expressed in μmol/L.

Data including sociodemographic characteristics (age, occupation, sex, smoking status, menopause status) and laboratory test results were retrospectively obtained from hospital records. The visual analog scale (VAS), short form-36 (SF-36) questionnaire to assess general quality of life, Beck Depression Inventory (BDI) to assess psychological status, Fibromyalgia Impact Questionnaire (FIQ) to assess FMS-specific disease severity, and Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality were recorded at the same visit and retrospectively obtained from hospital file archives.

Statistical Analysis: Power analysis was performed via G*Power version 3.1.9.4 software (Heinrich-Heine-Universität, Düsseldorf, Germany) and in accordance with a similar study (9). The sample size was calculated as 68 participants, with a type 1 error of 0.05 and 80% power. SPSS software (IBM SPSS Statistics for Windows, version 24.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses. The means of age, body mass index, and serum levels of vitamin B12, folic acid and Hcy in the FMS group and controls were compared via the independent samples Student's t test. Both the $\chi 2$ test and Fisher's exact test were used for comparisons of categorical variables. Pearson's correlation analysis was used to explore the relationships between Hcy levels and FIQ, PSQI, BDI,

and VAS scores. P<0.05 was considered statistically significant.

RESULTS

The mean age of patients with FMS was 34.28±8.25 years, and the mean age of the control group was 34.25±7.47 years. The average duration of the disease was 18±5.31 months. 60% of patients used duloxetine for FMS (average duration of drug use: 7±22 months).

Information on the distributions of age, BMI, occupation, education and marital status in the patient and control groups is shown in Table 1.

The serum Hcy, CRP and ESR levels were statistically higher in the FMS group than in the control group (**p=0.003, p=0.004, p=0.011**, respectively). The clinical and biochemical variables of patients with FMS and controls are shown in Table 2.

Table 1. Distribution of age, BMI, occupation, education and marital status in the patient and control groups

	FMS (n=42)	**Controls (n=20)**
Age (years) (mean ± SD)	34.28±8.25	34.25±7.47
BMI (kg/m^2) (mean ± SD)	25.47±3.57	23.49±4.09
Education	n (%)	n (%)
Illiterate	0 (0)	0 (0)
Primary	12 (28.6)	3 (15.0)
Secondary	7 (16.7)	2 (10.0)
High School	11 (26.2)	6 (30.0)
University/ higher education	12 (28.6)	9 (45.0)
Housewife	24 (57.1)	11 (55.0)
Manual laborer	11 (26.2)	3 (15.0)
White-collar worker	7 (16.7)	6 (30.0)
Single	8 (19.0)	6 (30.0)
Married	31 (73.8)	14 (70.0)
Divorced	2 (4.8)	0 (0)
Widow	1 (2.4)	0 (0)
Regular	1 (2.4)	4 (20.0)
Irregular	25 (59.5)	8 (40.0)
Never	16 (38.1)	8 (40.0)

**FMS: Fibromyalgia Syndrome, BMI: Body Mass Index, SD: Standard Deviation*

Table 2. Clinical and in biochemical variables data of patients with FMS and controls

	FMS (n=42) (mean ± SD)	**Controls (n=20)** (mean ± SD)	***P*-value**
Homocysteine (µmol)	10.26±3.27	7.60±2.73	**0.003**
CRP (mg/L)	0.29±0.25	0.14±0.13	**0.004**
ESR (mm/hr)	16.23±9.08	10.25±6.84	**0.011**
Folic acid (ng/mL)	5.83±1.69	6.22±2.24	0.448
Vitamin B_{12} (pg/mL)	318.11±103.75	312.77±150.63	0.887
Vitamin D (ng/ml)	11.96±5.54	13.33±8.40	0.448
BDI	16.73±7.41	8.3±4.5	**0.000**
PSQI	10.64±2.73	4.60±3.10	**0.000**
SF-36 subgroups			
Physical functioning	59.64±23.06	86.00±19.23	**0.000**
Role Limitations due to Physical Problems	38.09±34.58	68.00±37.95	**0.003**
Role Limitations due to Emotional Problems	43.65±39.29	76.67±34.36	**0.002**
Vitality	37.73±22.52	58.50±27.34	**0.002**
Emotional well being	51.33±20.67	69.00±23.96	**0.004**
Social functioning	56.84±25.03	75.62±28.52	**0.011**
Pain	34.22±23.06	50.85±27.11	**0.015**
General health	38.80±17.17	53.50±17.55	**0.003**
VAS (cm)	7.52±1.58		
FIQ	58.55±16.85		

**FMS: Fibromyalgia syndrome, CRP: C reaktif protein, ESR: eritrosit sedimentation rate, BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index, VAS: Visual Analogue Scale, FIQ: Fibromyalgia impact questionnaire, SF-36: Short form-36, SD: Standard deviation. P-value was calculated using independent two-sample t-test*

No statistically significant differences in the serum Hcy, folic acid, vitamin B12 or vitamin D levels were detected between the two groups with PSQI scores above and below 10 (p=0.622, p=0.316, p=0.460, p=0.395, respectively). There was no significant correlation between Hcy levels

and FIQ, VAS, BDI, PSQI or SF-36 scores in the patient group (Table 3).

The cutoff values for FMS were determined via ROC analysis of the serum Hcy values. As the area under the curve value is 0.724 and P=0.005, this value can be considered moderately significant (Figure 1). According to the calculations, the cut-off point for sensitivity and specificity values corresponding to the highest positive likelihood ratio for FMS is 11.9.

Table 3. Correlation between serum homocysteine levels and clinical parameters (FIQ, VAS, BDI, PSQI, SF-36 subscales) in the fibromyalgia patient group

	Homocysteine level	
	r	p
VAS	0.184	0.244
FIQ	0.151	0.339
BDI	0.232	0.139
PSQI	0.019	0.903
SF-36 subgroups		
Physical functioning	-0.264	0.091
Role Limitations due to Physical Problems	-0.229	0.145
Role Limitations due to Emotional Problems	-0.256	0.102
Vitality	0.030	0.851
Emotional well being	-0.060	0.708
Social functioning	-0.199	0.207
Pain	-0.283	0.069
General health	-0.211	0.180

**FIQ: Fibromyalgia Impact Questionnaire, VAS: visual analogue scale, BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index, SF-36: Short form-36, r: Pearson's correlation coefficient, p: Correlation is significant at the 0.05 level (two-tailed)*

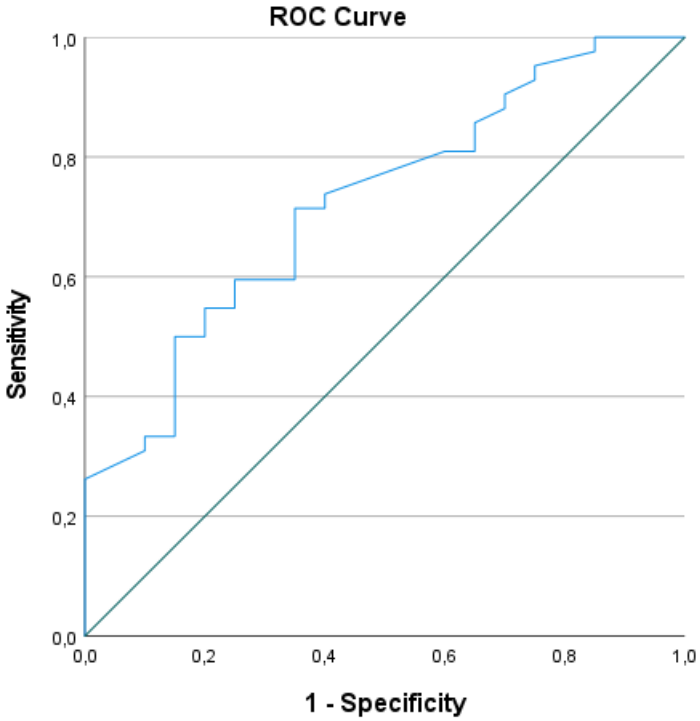


Figure 1. ROC curve analysis identified the optimal plasma homocysteine concentration threshold for use in the evaluation of fibromyalgia

Serum Hcy levels and vitamin B12, folic acid, CRP, ESR, BDI, PSQI, and SF-36 scores were evaluated in all participants, including both patient and control groups. Pearson's correlation analysis revealed weak negative correlations between Hcy and folic acid (r=-0.274, p=0.031) and SF-36 subgroup physical functioning (r=-0.350, p=0.005), role limitations due to physical problems (r=-0.295, p=0.020), role limitations due to emotional problems (r=-0.397, p=0.001) and general health (r=-0.257, p=0.044). The serum Hcy concentration was weakly positively correlated with the CRP concentration (r=0.278, p=0.029) (Table 4).

Table 4. Correlation between serum homocysteine level and Vitamin B_{12}, Folic acid, CRP, ESR, BDI, PSQI, SF-36 in all participants (patients and healthy controls)

Homocysteine level		
	r	*p*
Vitamin B_{12} (pg/mL)	-0.220	0.086
Folic acid (ng/mL)	-0.274	**0.031**
CRP (mg/L)	0.278	**0.029**
ESR (mm/hr)	0.029	0.823
BDI	0.340	0.007
PSQI	0.190	0.140
SF-36 subgroups		
Physical functioning	-0.350	**0.005**
Role Limitations due to Physical Problems	-0.295	**0.020**
Role Limitations due to Emotional Problems	-0.397	**0.001**
Vitality	-0.125	0.331
Emotional well being	-0.208	0.105
Social functioning	-0.168	0.191
Pain	-0.237	0.063
General health	-0.257	**0.044**

**CRP: C reaktif protein, ESR: eritrosit sedimentation rate, BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index, SF-36: Short form-36, r: Pearson's correlation coefficient. p: Correlation is significant at the 0.05 level (two-tailed)*

DISCUSSION

The main finding of this study is that patients with FMS have significantly higher levels of Hcy in their serum than healthy controls.

FMS is a rheumatic disease with poorly understood etiopathogenesis. Chronic and widespread pain is the main feature of FMS, but it can also be associated with other symptoms, such as sleep problems, fatigue, rigidity, irritable bowel syndrome (IBS), headaches and mood disorders (10). There is only one study examining the relationship between Hcy and FMS in the literature (8). In that study, which included 12 patients who met the criteria for both FMS and chronic fatigue syndrome, Hcy levels were higher in the cerebrospinal fluid of all patients, and there was a significant positive correlation between fatigue and Hcy levels. Serum Hcy concentrations were within the normal reference range (<16 μmol/L) except in two patients (8). This study was conducted with a very small sample size, and the group of patients recruited represented mostly patients with chronic fatigue syndrome. HHcy has been reported to cause impaired blood barrier function in both the brain and retina (11). Elevated plasma Hcy concentrations may indicate metabolic dysfunction in the brain. Studies have demonstrated a correlation between elevated concentrations of total Hcy and S-adenosylhomocysteine in the brain (12). Kado et al. emphasized the relationship between HHcy and age-related neurodegeneration (13). Some studies in rats have shown that HHcy causes Parkinson's disease, Alzheimer's disease and seizures (5). However, it is currently unknown whether clinically significant mild elevations in Hcy levels have a neurotoxic effect (13). 'Fibrofog' is a type of cognitive dysfunction that includes the subjectively experienced loss of mental clarity (mental fuzziness) associated with FMS, as well as attention and memory impairment (14). Although the mechanisms responsible for the cognitive impairments observed in FMS are not yet fully understood, it is possible that Hcy plays a role. The serum Hcy pathway is affected by many factors, such as genetic defects in the enzymes controlling the pathway or deficiencies in cofactors (8). Since Hcy metabolism requires folate and vitamin B6, it is unsurprising that each of these nutrients is individually associated with cognitive function (13). There are studies in the literature investigating the role of vitamin B12 and folate in FMS (15,16). Daily supplementation with B12 has been demonstrated to decrease anxiety scores and reduce the severity of FMS (16). Furthermore, a study involving patients with chronic fatigue syndrome demonstrated that long-term treatment with higher doses of vitamin B12 and folic acid led to more pronounced clinical improvement (17).

A study has shown that HHcy causes mild pathological changes in skeletal muscles, such as fragmentation of Z disks and irregularities in myofilaments (18). This study revealed severe and diffuse neuronal loss and cellular damage in the brain (18). Muscle biopsy studies in FMS show that there are no changes that are exclusively specific for FMS (19). In a rat study involving chronic Hcy administration, Hcy was shown to significantly reduce the viability of mitochondria and pyruvate kinase and creatine kinase activities and lead to energy imbalance (20). The fact that serum Hcy levels were greater in our study than in the control group may explain the complaint of fatigue in FMS patients. While central sensitization is frequently observed in FMS, nociceptors in muscles can also be sensitized due to mitochondrial changes, changes in microcirculation, and/or muscle

metabolism, leading to pain, fatigue, and muscle weakness (19).

Studies have reported a negative correlation between plasma Hcy and exercise capacity in older women (21,22). Furthermore, the addition of physical exercise to chronic Hcy administration reversed the effects of glutamate uptake and oxidative stress in rats (23). It is known that exercise is a part of treatment for FMS patients. Therefore, exercise may have many beneficial effects by reducing the negative effects of Hcy.

Reactive oxygen species (ROS) play a significant role in inflammation and are implicated in the pathophysiology of various diseases, such as rheumatoid arthritis, multiple sclerosis and diabetes mellitus. Furthermore, in addition to the presence of oxidative stress, these diseases are also characterized by dysregulated inflammatory responses (24). Hcy may play a role in oxidative stress by increasing the production of reactive oxygen species (25). In some patients, inflammation has been reported to play a role in the pathophysiology of FMS, and it has been suggested that oxidative stress and mitochondrial dysfunction may contribute to the development of inflammation (24,26,27).

A review revealed that the epidemiological association between plasma Hcy levels and migraine is very weak (28). A single study evaluating Hcy in cerebrospinal fluid reported that the concentration of Hcy was significantly in migraine patients than in controls (29). There is a high prevalence of FMS in migraineurs and a high prevalence of migraine and other headaches in FMS patients (30).

In our study, although CRP and ESR laboratory values were within the normal reference range in patients with FMS, they were found to be significantly higher than those in the control group. This result suggests the presence of subclinical inflammation in the pathogenesis of FMS, to which Hcy may also contribute. However, there are conflicting findings concerning whether proinflammatory and anti-inflammatory cytokines are elevated or decreased in FMS (24,31).

Both methionine and Hcy are believed to play significant roles in gut health (32). In a previous study, researchers reported that, compared with control rats, IBS rats presented significantly higher plasma Hcy levels. Researchers have proposed that elevated Hcy levels may contribute to intestinal barrier dysfunction (33). The pathophysiological mechanisms underlying the onset of both FMS and IBS are not fully understood. FMS and IBS often co-occur and share similar symptoms. These findings suggest that there may be a common etiology for both diseases (34).

Studies have reported that Hcy is associated with psychiatric disorders such as autism, schizophrenia, depression and bipolar disorder (35–37). While many questions about psychiatric disorders remain unanswered, it is possible that Hcy may contribute to psychiatric complaints such as anxiety and depression, which are often observed in FMS (38).

The primary limitations of this study are its small sample size and single-center design, which may limit the external validity of the findings. Additionally, that 60% of the patients were taking duloxetine could have influenced the outcomes. Furthermore, although Hcy levels were elevated in patients with FMS, the lack of significant correlations with key clinical outcomes—such as pain severity, functional impairment, and depressive symptoms—limits the clinical applicability and practical relevance of the findings.

FMS is a complex disease with an unclear etiology. Considering that FMS involves a wide range of symptoms affecting multiple systems, and Hcy influences the metabolism of various organs, further studies investigating the relationship between FMS and Hcy would provide valuable insights into the literature.

Ethics Committee Approval: Approval was obtained from the local ethics committee, and written informed consent was obtained from all participants. (Decision no: 2022/30). The study was conducted in accordance with the Helsinki declaration.

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