

## EFFICACY of ORAL MAGNESIUM TREATMENT on PRIMARY FIBROMYALGIA SYNDROME

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### SUMMARY

**Objective:** The aim of this study was to investigate the effects of oral magnesium treatment on clinical findings such as number of sensitive points, severity of pain and functional capacity in primary Fibromyalgia syndrome patients.

**Material and Methods:** Twenty-five primary fibromyalgia syndrome patients (24 female, 1 male) were enrolled to the study. Patients were examined in terms of pain in rest and activity, number of sensitive points and functional capacity. Fibromyalgia Impact Questionnaire and Visual Analogue Scale (VAS) were used for functional assessment and pain respectively. Serum and twenty-four hour urine magnesium levels were measured. The serum and urine magnesium levels were measured by original kits of Abbott Aeroset autoanalyzer (Abbott Laboratories, Abbott Park, IL, 60064, USA). Patients were administered magnesium citrate (Magnesium Diasporal 600 mg sachets b.i.d. orally) therapy for two months. At the end of two months, patients were re-examined in terms of recorded clinical and laboratory findings.

**Results:** The mean age of patients was 44.8 (SD=7.4) years and the mean duration of disease was 25.4 (SD=19.2) months. There was a significant improvement in number of sensitive points, pain and Fibromyalgia Impact Questionnaire score at the end of two-month therapy ( $p<0.001$ ). In the end of the treatment period, the levels of the serum and 24-hour urine magnesium levels remained within normal ranges and the changes could not reach statistical significance ( $p>0.05$ ).

**Conclusions:** In the treatment of Fibromyalgia syndrome, magnesium citrate therapy was found to be safe and efficient on number of sensitive points, pain and functional state.

**Key words:** Fibromyalgia syndrome, magnesium, trace element, clinical findings

### Primer Fibromiyalji Sendromunda Oral Magnezyum Tedavisinin Etkinliği

### ÖZET

**AMAÇ:** Bu çalışmanın amacı, primer fibromiyalji sendromu olan hastalarda oral magnezyum tedavisinin hassas nokta sayısı, ağrı şiddeti gibi klinik bulgular ve fonksiyonel kapasite üzerine olan etkilerini araştırmaktır.

**GEREÇ ve YÖNTEMLER:** Yirmi-beş primer fibromiyalji sendromu olan hasta (24 bayan 1 erkek) çalışmaya dahil edildi. Hastalar istirahat ve aktivite ağrıları, hassas nokta sayısı ve fonksiyonel kapasite açısından değerlendirildi. Fibromiyalji etkinlik sorgulaması ve vizuel analog skala (VAS), sırasıyla fonksiyonel durum ve ağrı şiddetini değerlendirmek için kullanıldı. Serum ve 24 saatlik idrarda magnezyum seviyesi ölçüldü. Serum ve idrar magnezyum düzeyleri Abbott Aeroset autoanalyzer orjinal kiti (Abbott Laboratories, Abbott Park, IL, 60064, USA) ile ölçüldü. Hastalar iki ay boyunca magnezyum sitrat (Magnesium Diasporal 600 mg saşe b.i.d. oral) tedavisi aldılar. İki ayın sonunda, tekrar muayene edilip klinik bulguları kaydedildi.

**BULGULAR:** Hastaların yaş ortalaması 44.8 (SS=7.4) yıl ve hastalık süresi ortalama 25.4 (SS=19.2) aydı. Hassas nokta sayısı, ağrı ve fibromiyalji etkinlik sorgulaması skorunda tedavi öncesine göre ikinci ayın sonunda anlamlı iyileşme olduğu gözlemlendi ( $p<0.001$ ). Tedavi periyodunun sonunda, serum ve 24 saatlik idrardaki magnezyum düzeyleri normal sınırlar içinde kaldı ve değişiklikler istatistiksel olarak anlamlı düzeye ulaşamadı ( $p>0.05$ ).

**SONUÇ:** Fibromiyalji sendromunun tedavisinde magnezyum sitrat tedavisi hassas nokta sayısı, ağrı ve fonksiyonel durum üzerinde etkili ve güvenli olarak bulundu.

**Anahtar kelimeler:** Fibromiyalji sendromu, magnezyum, eser element, klinik bulgular

Fibromyalgia syndrome (FMs) is a chronic pain syndrome characterized by disseminated pain and stiffness, multiple tender points, and fatigue.<sup>1</sup> This pain syndrome has an incidence of 2% in the general population and occurs with higher frequency among women in middle age.<sup>2</sup> FMs is categorized as primary or secondary. In primary fibromyalgia the causes are

not known, and in secondary fibromyalgia the causes such as trauma, cancer, thyroid diseases and pathologies of rheumatic and connective tissues can be identified. Primary fibromyalgia is the more common form. Since the etiology of FMs is not clarified exactly, the treatment is generally symptomatic. Recently, the treatment of FMs is

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focused on the mechanisms such as sleep disorders, neurochemical differentiations, abnormal pain perception and muscle hypo perfusion due to regional vasomotor dysregulation.<sup>1</sup> It is considered that decrease in blood flow beneath the sensitive points, decrease in ATP and local hypoxia is of importance in the development of symptoms in FMs.<sup>2</sup> Magnesium is a trace element which plays a considerable role in ATP synthesis and extremely important for adequate muscle metabolism and function together with calcium. There are several reports suggesting the magnesium level of the patients with FMs is below the normal range.<sup>3, 4</sup> It was reported that magnesium therapy, combined with malic acid, was effective in improving the pain and number of sensitive points in patients with FMs.<sup>3</sup> However, clinical efficacy of magnesium therapy alone in FMs patients has not been investigated sufficiently.

The aim of this study was to investigate the effects of oral magnesium treatment on clinical findings such as number of sensitive points, level of pain and functional capacity as well as laboratory findings such as serum and urine level of magnesium in patients with primary Fms.

## MATERIALS and METHODS

After receiving approval of the local ethics committee and informed consent of the patients, 25 patients (24 women and one man) who had a FMs diagnosis according to 1990 criteria of American College of Rheumatism (ACR)<sup>5</sup> were recruited to the study. The demographic features, disease durations and accompanying symptoms (arthralgia, myalgia, anxiety, forgetfulness, sleep problems and fatigue) of the patients were documented. Visual analogue scale (VAS; 10 cm) was used for the evaluation of the day and night pain of the patients. The sensitive points defined by ACR were determined by applying a 4 kg pressure by thumb on the specific points of body and the number of sensitive points on whole body was recorded.

The Fibromyalgia Impact Questionnaire (FIQ)<sup>6,7</sup> adjusted for the Turkish population was used for the functional evaluation of the patients. The FIQ was developed by Burkhardt et al. to evaluate the health condition of the FMs patients. This scale includes 10 items. The first item concerns with the daily activities and is composed of Likert type 10 questions each scored between 0-3. In the second and third items the impact level by disease and the number of days that the patient couldn't go work were recorded. The remaining 7 questions assess difficulty in performing work, pain, fatigue, morning stiffness, anxiety and depression. The highest score is 100 and indicates the worst functional condition.

In laboratory evaluations, the total blood count, erythrocyte sedimentation rate (ESR) (standard Westergren method), C-reactive protein (CRP) level

(nephelometry), routine biochemical tests and thyroid function tests were recorded. Those with any systemic disease (diabetes mellitus, hypertension, liver-kidney function disorders, thyroid function disorders, anemia, active infection, inflammatory rheumatic disease) were excluded from the study.

The serum and urine magnesium levels were measured by original kits of Abbott Aeroset autoanalyzer (Abbott Laboratories, Abbott Park, IL, 60064, USA). The principle of the study is based on measuring the absorbance of the magnesium-Arsenazo stain complex at 572 nm. Absorbance and the magnesium concentration are proportional to each other. The intraassay CV% of the measurement is 2.6% for serum whereas the interassay CV% is 0.6%. For urine, these values are 3.8% and 0.0%, respectively. The normal range of serum magnesium is 1.6-2.6 mg/dl and the normal range of 24hour urine magnesium level is 6-10 m Eq/l.

Oral magnesium citrate (Magnesium-Diasporal sachets b.i.d) 600 mg/day was administered to the patients for two months. The patients were not allowed to take any analgesic drugs during treatment. The day and night pain, sensitive point count, functional capacity, serum and 24-hours urine magnesium levels recorded pre-treatment and two months post-treatment were compared.

### Statistical Analysis

The software package for Social Sciences (SPSS) 11.0 was used for the purpose of statistical analysis. Descriptive values were presented in numbers and percentages via mediums and standard deviations. The comparison of the pre-and post-treatment clinical findings was performed by Wilcoxon signed ranks test.

## RESULTS

The mean (SD) age of the patients was found to be as 44.8 (7.4) years, the mean duration of the disease 25.4 (19.3) months, and Body Mass Index (BMI) 26.3 (4). The socio-demographical data of the patients were given in table 1. As shown in table 2, the most frequently encountered symptoms accompanying

**Table 1:** Some of the clinical characteristics of fibromyalgia patients

Age [year, mean (SD)]	44.8(7.4)
Sex (F/M)	24/1
BMI [kg/m <sup>2</sup> , mean (SD)]	26.3(4.0)
Education level: n (%)	
Uneducated	4(16)
Elementary school	19(76)
High school	2(8)
Disease duration [month, mean (SD)]	25.4(19.3)
Rest pain [cm, mean (SD)]	6.2(3.2)
Activity pain [cm, mean (SD)]	7.1(1.8)
FIQ score [mean (SD)]	72.4(12.2)

F/M: Female/Male

FMs patients were arthralgia, myalgia, anxiety, forgetfulness, sleep disturbance and fatigue. Clinical and laboratory findings in patients with FMs pre- and post- oral magnesium therapy were given in table 3. Statistically significant ( $p < 0.001$ ) decreases were found at the post-treatment 2nd month in terms of day and night pain, sensitive point count and FIQ score when compared to the pre-treatment period. No statistically significant changes were detected in serum and 24-hours urine magnesium levels at the end of the 2nd month compared to the pre-treatment period ( $p > 0.05$ ). No adverse effects were observed in patients due to the medication.

**Table 2:** Common signs and symptoms of our patients with fibromyalgia

SIGNS AND SYMPTOMS	FREQUENCY (%)
Myalgia	96
Fatigue	100
Sleep disorders	76
Concentration disturbance	48
Forgetfulness	80
Irritable bowel syndrome	60
Irritable bladder syndrome	48
Raynaud phenomena	20
Legs cramp	60
Anxiety	96

## DISCUSSION

In our study, significant improvements were achieved in clinical pain, sensitive point count and functional capacity of the FMS patients by administration of oral magnesium citrate for the duration of two months. Some evidence exists supporting the possibility of deficiency of components required for ATP synthesis in etio-pathogenesis of FMs.<sup>3</sup> Oxygen, magnesium, substrate, ADP and phosphate are required for ATP synthesis. In case each of these is in optimal concentrations, a healthy mitochondrial respiration and a concurrent biological energy production can occur. On the other hand, their deficiencies result in decelerating of crebs cycle, increase of anaerobic glycolysis, increase in lactic acid formation, and decrease of the maximum lung capacity. The combination of these factors may cause fatigue, depression and muscle pain symptoms.<sup>8</sup> Some evidence exist supporting the fact that magnesium is one of the most critical elements for ATP synthesis and

may be below normal limits in FMs patients.<sup>3,4</sup> The mitochondrial uptake and accumulation of magnesium is directly associated to uptake of the required phosphate for ADP phosphorylation. Therefore, the completion of the crebs cycle is a magnesium-dependent mechanism and even a mild deficiency of magnesium can impair the optimal function. The associated problems due to magnesium deficiency include mitochondrial swelling, increase in the membrane permeability, decrease in the selectivity of the mitochondrial inner membrane, uncoupling of oxidative phosphorylation and a possible aluminum toxicity.<sup>8,9</sup> Similar mitochondrial anomalies were reported from the muscle biopsies obtained from painful points of FMs patients.<sup>10</sup>

The most frequently observed symptoms in FMs are myalgia<sup>11</sup>, chronic fatigue syndrome<sup>12</sup>, irritable bowel syndrome<sup>13</sup>, mitral valve prolapsus<sup>14-16</sup>, stress-dependent headache<sup>17</sup> and dysmenorrhea<sup>18</sup>. Several symptoms similar to those of FMs were reported to occur also in magnesium deficiency.<sup>7</sup> Moreover, Abraham et al<sup>19</sup> claimed that a possible mechanism responsible for pain in FMs patients is the magnesium deficiency. However, a few of studies were present investigating the magnesium deficiency in the patients with FMs. In these studies, it was also reported that the serum magnesium level was not changed.<sup>4, 8-10, 20-22</sup> Consistent with all these studies, the pre-treatment and second month post-treatment serum and 24-hours urine magnesium levels of the patients in our study were within normal ranges and the levels did not undergo any significant changes. Magaldi et al<sup>22</sup> reported that the plasmatic magnesium level was normal in FMs patients and the intracellular magnesium level was responsible from the pathophysiology of the disease. In the similar studies, Eisinger et al<sup>20,21</sup> reported that they found the erythrocyte magnesium levels were markedly low in FMs. Therefore, the magnesium levels in blood cells or sublingual cells provide more accurate results.<sup>23</sup> However, it would be difficult to interpret the results of our study since we couldn't able to measure the intracellular magnesium level technically.

The most frequently observed additional symptom in our patients was fatigue (100%). Fatigue is among the most frequent symptoms in FMs patients. The patients generally feel fatigue all day long and its severity is at significance levels.<sup>24</sup> Magnesium plays an important role in enzymatic reactions that

**Table 3:** Clinical and laboratory findings in patients with fibromyalgia pre- and post- trace element therapy

	Pretreatment Mean(SD)	Post-treatment Mean (SD)	P*
Activity pain (VAS, cm)	7.1(1.8)	4.2(2.4)	<0.001
Rest pain (VAS, cm)	6.2(3.2)	3,3(3,0)	<0.001
Number of sensitive points (n)	14.3(2.3)	9.4(3.3)	<0.001
FIQ score	72.4(12.2)	45.5(21.7)	<0.001
Serum Mg level (mg/dl)	2.2(0.1)	2.1(0.2)	>0.05
Urine Mg level (mEq/lt)	8.6(5.1)	8.3(4.4)	>0.05

especially function in energy production. As the magnesium levels decline the energy levels also decline and consequently fatigue may occur.<sup>25</sup> Magnesium supplementation may benefit in the treatment of chronic fatigue.<sup>25,26</sup>

We did not encounter any studies in the literature that research the efficacy of magnesium therapy individually in FMs patients. However, Abraham et al<sup>19</sup> studied the efficacy of the combined oral magnesium and malic acid therapy in 15 FMs patients. They administered both 1200-2400 mg/day malic acid and 300-600 mg/day magnesium to patients for 4-8 weeks. As a consequence of the study they found that a significant pain relief was gained at 48 hours of the treatment and statistically significant decrease in sensitive point count in 4-8 weeks in all the patients. At the end of 8 weeks only 6 patients underwent a placebo therapy for two weeks and a statistically significant increase was observed in sensitive point count. In our study, we also detected a marked decline in day pain, night pain and sensitive point count following the 600 mg/day oral magnesium therapy ( $p < 0.001$ ). In another study<sup>27</sup>, magnesium, massage therapy, vitamin supplement and a weight reduction program were applied to FMs patients and this combined treatment seemed to be useful. Holdcraft et al<sup>28</sup> also reported that acupuncture, massage therapy and some nutritional support accompanying magnesium treatment to be effective in FMs patients. Similarly, Sarac et al<sup>29</sup> emphasized that magnesium supplement, massage therapy and nutritional support to be effective on the disease.

We administered FIQ for the functional assessment of our patients. FIQ is a scale which is able to assess the most frequently complained symptoms by FMs patients such as physical work, depression, anxiety, sleep, pain, stiffness, fatigue and uncomfortable feeling.<sup>6,7</sup> In our study, a statistically significant improvement was observed in FIQ score at the end of two month therapy ( $p < 0.001$ ). Since we didn't come across such a study concerning this topic, according to our data we may suggest that the pronounced improvement in FIQ indicates the real efficacy of the treatment.

In conclusion, administration of oral magnesium citrate 600 mg/day was found to be effective and safe on sensitive point count, pain and functional capacity in FMs treatment. Therefore, oral magnesium therapy may be advised to FMs patients. We suggest that this inference should be supported by placebo controlled studies.

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