

Magnesium and Fibromyalgia: A Literature Review

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Abstract

Fibromyalgia, a widespread chronic pain disorder, imposes a multitude of hardships on patients and their communities. Supplements, specifically magnesium supplements, have been widely used by fibromyalgia patients in an attempt to control their symptoms. The aim of this work is to investigate if the widespread use of magnesium in fibromyalgia is supported by evidence in the literature. This review provides a layout of the studies examining the correlation between body magnesium levels and fibromyalgia. Furthermore, it elaborates on the trials testing the effectiveness of magnesium in treating different clinical parameters of fibromyalgia.

Keywords

fibromyalgia, pain, chronic pain, magnesium, supplements, literature review

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Introduction

The term fibromyalgia is derived from the Latin “fibra,” meaning fibrous tissues; the Greek “mys,” meaning muscles; and “algia,” meaning pain. It is a complex widespread pain disorder.¹ Pain is considered widespread when it involves both sides of the body, above and below the waist, and along the axial skeleton.² Fibromyalgia is often associated with sleep difficulties, memory impairment, mood disturbance, irritable bowel syndrome, and fatigue.³

Fibromyalgia is a common chronic pain disorder.^{4,5} It is the third most common rheumatic disorder after low back pain and osteoarthritis.⁶ Fibromyalgia exhibits an immense burden at the individual and the society levels. Daily living activities of an individual can be profoundly impacted by fibromyalgia.⁷ Medical and pharmaceutical claims along with the annual total medical costs are significantly greater among fibromyalgia claimants than the overall population.⁸ High disability rates have been associated with fibromyalgia.⁹ Due to the healthcare costs along with the loss of productivity and work, fibromyalgia poses a significant social strain.

The underlying etiology for fibromyalgia remains obscure.³ While genetic and hormonal factors among others are thought to play a role in fibromyalgia patients, central sensitization is considered to be the main mechanism.¹⁰ Magnesium is known to play an important role in the prevention of central sensitization by blocking N-methyl-D-aspartate (NMDA) receptors in

a voltage-dependent manner.¹¹ Magnesium deficiency has been largely associated with muscle pain along with fatigue, sleep difficulties, and anxiety; all of which are common symptoms of fibromyalgia.^{12,13} In some studies, it is thought that magnesium deficiency, through reductions in muscle ATP levels, may play a role in the development of fibromyalgia.¹⁴ Other studies correlate increased levels of substance P (a neurotransmitter known for its role in pain perception) with magnesium deficiency as well as pain intensity in fibromyalgia, raising the question of a possible correlation between magnesium deficiency and fibromyalgia.^{15–17} While some estimates suggest that about half of the population in the United States consume inadequate amounts of magnesium, studies have shown that magnesium is one of the most widely used supplements by fibromyalgia patients.^{18–23} At the Mayo Clinic fibromyalgia treatment program, 2 studies (years 2003, 2017) were performed to evaluate the frequency and pattern of complementary and alternative medicine (CAM) use in fibromyalgia patients.^{22,23} Both studies found that magnesium was one of

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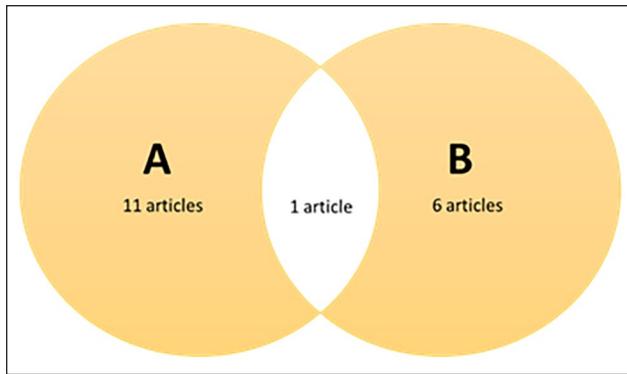


Figure 1. Articles correlating between body magnesium levels and fibromyalgia (A) and articles studying the effect of magnesium on fibromyalgia parameters (B).

the most frequently used supplements in fibromyalgia. This review aims to explore and summarize the possible relationship between magnesium and fibromyalgia in the literature and hence determine the validity of magnesium use in fibromyalgia.

Materials and Methods

We searched the medical literature through Cochrane and PubMed databases using the terms “fibromyalgia” and “magnesium.” The search covered published articles through December 31, 2020. Bibliographies of relevant articles were searched as well. Inclusion criteria were articles written in English language that investigated a form of correlation between magnesium and fibromyalgia or tested the effect of use of magnesium in fibromyalgia.

Results

A total of 18 relevant articles that met the inclusion criteria were found (Figure 1). These articles covered 2 main aspects: the correlation between magnesium levels in the body and fibromyalgia; the effect of magnesium supplementation on clinical parameters of fibromyalgia.

Studies Exploring the Correlation Between Magnesium Levels and Fibromyalgia

Studies correlating magnesium levels (including those of the serum, erythrocyte, leukocyte, platelet, and hair levels) to fibromyalgia have shown varying results (Table 1).

Some studies showed decreased magnesium levels in several tissue compartments in fibromyalgia patients along with a negative correlation between magnesium levels and the clinical parameters of fibromyalgia.²⁴⁻²⁷ Bagis et al²⁴ reported significantly lower serum and erythrocyte magnesium levels in patients with fibromyalgia compared to controls, along with a negative correlation between the magnesium levels

and fibromyalgia symptoms. In Kasim’s²⁵ study, serum magnesium levels were significantly lower in patients with fibromyalgia when compared to normal healthy individuals. Kim et al²⁶ found that concentrations of magnesium in the hair of female patients with fibromyalgia are significantly lower than of controls, even after adjustment of potential confounding factors. Sendur et al²⁷ reported significantly decreased serum levels of magnesium by fibromyalgia groups along with a meaningful association between magnesium level and fatigue in fibromyalgia patients.

Several reports showed no difference in magnesium levels between fibromyalgia and control subjects, with no correlation between magnesium levels and fibromyalgia parameters.²⁸⁻³¹ Andretta et al^{28,29} and Sakarya et al³⁰ found no significant differences in the serum levels of magnesium between fibromyalgia patients and control subjects.²⁸⁻³⁰ One of the studies performed by Andretta et al,²⁸ showed no correlation between serum magnesium levels and pain, quality of life, and depression risk in the fibromyalgia group. Sakarya et al did not find significant correlations between the mean levels of serum magnesium and number of tender points, scores of visual analog scale (pain intensity measurement), Fibromyalgia Impact Questionnaire (functional status evaluation), and Beck Depression Inventory (depression level assessment) in fibromyalgia patients. The study of Prescott et al³¹ also showed no difference in red blood cell or plasma magnesium levels between fibromyalgia patients and controls.

Few investigators reported increased levels of magnesium in patients with fibromyalgia.^{32,33} Bazzichi et al³² found significantly higher magnesium levels in the platelets of fibromyalgia patients compared to controls. Unlike Kim et al,²⁶ Ng reported significantly increased hair magnesium levels in fibromyalgia patients.³³

In some studies, different laboratory assays within the same study showed varying results of magnesium levels.^{13,34} Eisinger et al³⁴ evaluated leukocyte, erythrocyte, and serum magnesium levels in fibromyalgia patients in comparison to controls. They reported significant increase in leukocyte magnesium level in fibromyalgia patients with slight non-significant decrease in erythrocyte magnesium level and no difference in serum magnesium level, compared to control subjects. Romano et al¹³ measured plasma and red blood cell magnesium levels in fibromyalgia patients and compared them with those of osteoarthritis control subjects. They found that fibromyalgia patients, compared to reference laboratory and osteoarthritis controls, had significantly lower red blood cell magnesium levels but no difference in plasma magnesium levels.

Studies Investigating the Effect of Magnesium on Clinical Parameters of Fibromyalgia

Bagis et al²⁴ investigated the effect of magnesium citrate treatment on fibromyalgia symptoms. The study included

Table 1. Studies Assessing Magnesium Levels in Fibromyalgia.

Investigators	# of fibromyalgia patients	# of controls (matching criteria)	Mg lab measures	Mg levels in fibromyalgia versus controls	Mg levels and fibromyalgia clinical parameters
Bagis et al ²⁴	60 (females)	20 (age, sex, wt.)	Serum Erythrocytes	↓	Negative correlation
Kasim ²⁵	25 (females)	25 (age, sex)	Serum	↓	
Kim et al ²⁶	44 (females)	122 (age, sex, BMI)	Hair	↓	
Sendur et al ²⁷	32 (females)	32 (sex) ⁺ age	Serum	↓	Negative correlation
Andretta et al ²⁹	53 (females)	50 (sex) ⁺⁺ age, BMI	Serum	No difference	No correlation
Andretta et al ²⁸	53 (females)	50 (sex) ⁺⁺ age, BMI	Serum	No difference	No correlation
Sakarya et al ³⁰	40 (females)	40 (age, sex, geographic location)	Serum	No difference	No correlation
Prescott et al ³¹	13	11 (age, sex)	Plasma Red blood cells	No difference	
Bazzichi et al ³²	25	25 (age, sex)	Platelets	↑	
Ng ³³	12	12 (age, sex)	Hair	↑	
Eisinger et al ³⁴	22	23 (age)	Serum Erythrocytes	No difference Non-significant ↓	
Romano and Stiller ¹³	100	12	Leukocytes Plasma Red blood cells	↑ No difference ↓	

Abbreviations: Mg, magnesium; wt., weight; BMI, body mass index.

⁺Age: no significant difference in age between fibromyalgia patients and controls.

⁺⁺Age, BMI: average age and BMI were equivalent in fibromyalgia and control groups.

↓ or ↑, significantly lower or higher Mg levels in fibromyalgia patients compared to controls.

No difference, no difference in Mg levels between fibromyalgia and control groups.

Negative correlation, negative correlation between Mg levels and one or more of the clinical parameters of fibromyalgia.

No correlation, no correlation between Mg levels and one or more of the clinical parameters of fibromyalgia.

60 premenopausal women diagnosed with fibromyalgia. The patients were divided into 3 groups. The magnesium citrate (300mg/day) was given to the first group (n=20), amitriptyline (10mg/day) was given to the second group (n=20), and magnesium citrate (300mg/day) with amitriptyline (10mg/day) treatment was given to the third group (n=20). Pain intensity, pain threshold, the number of tender points, the Tender Point Index, the Fibromyalgia Impact Questionnaire, the Beck depression and Beck anxiety scores, and the patient symptoms were evaluated in all the women. All parameters were reevaluated after the 8 weeks of treatment. The number of tender points, Tender Point Index, the Fibromyalgia Impact Questionnaire, and beck depression scores decreased significantly with the magnesium citrate treatment. The combined amitriptyline with magnesium citrate treatment proved effective on all parameters except numbness, more effective in all measured outcomes than amitriptyline alone (Table 2). The authors suggested that magnesium might have a beneficial effect in patients with fibromyalgia.

Engen et al³⁵ performed a pilot study to collect preliminary data concerning the effect of transdermal magnesium on fibromyalgia patients through a patient questionnaires and survey in a fibromyalgia clinic at a tertiary medical center.

The study enrolled 40 female patients with the diagnosis of fibromyalgia; 24 patients completed the study (mean [SD] age, 57.2 [7.6]years; white, 95%; mean body mass index, 31.3 kg/m²). Each participant was provided a spray bottle containing a transdermal magnesium chloride solution and asked to apply 4 sprays per limb twice daily for 4 weeks. At baseline, week 2, and week 4, participants were asked to complete the Revised Fibromyalgia Impact Questionnaire, 36-Item Short Form Version 2 Health Survey, and a quality-of-life analog scale. The Revised Fibromyalgia Impact Questionnaire subscale and total scores were significantly improved at week 2 and week 4. The authors suggested that transdermal magnesium chloride may be of beneficial use in fibromyalgia.

Martínez-Rodríguez et al³⁶ conducted a randomized, controlled trial, to determine the effects of tryptophan and a magnesium-enriched Mediterranean diet on psychological variables and sleep in women with fibromyalgia. The study included 22 women diagnosed with fibromyalgia. Participants were randomly allocated into experimental (EG) and control (CG) groups (EG: Age=48 ± 4 years old and body mass index [BMI]=28.2 ± 3.7 kg/m²) (CG: Age=50 ± 5 years old and BMI=28.6 ± 5.1 kg/m²). The experimental group received a Mediterranean diet enriched with high doses of tryptophan and magnesium (60 mg of

Table 2. Studies Testing the Effect of Magnesium on Fibromyalgia.

Investigator	Intervention	Effect
Bagis et al ²⁴	Magnesium (300 mg/day) + amitriptyline (10 mg/day) (n = 20) (n = 20) versus amitriptyline (10 mg/day) (n = 20) versus magnesium (300 mg/day) (n = 20)	Improvement in VAS, fatigue, sleep, irritability, TP, TPI, dolorimetry score, FIQ, MCGILL, Beck depression, Beck anxiety ($P < .05$) Improvement in VAS, fatigue, sleep, irritability, TP, TPI, MCGILL, Beck depression, Beck anxiety ($P < .05$) Improvement in TP, TPI, FIQ, Beck depression ($P < .05$)
Engen et al ³⁵	Transdermal magnesium chloride solution (n = 24)	Improvement in FIQR ($P = .001$)
Martínez-Rodríguez et al ³⁶	Tryptophan and magnesium enriched mediterranean diet (n = 11) versus standard mediterranean diet (n = 11)	Improvement in trait anxiety, self-image perception, mood state, eating attitudes ($P < .05$)
Gaby ³⁷	Infusions of Myers' cocktail (magnesium + calcium + B Vitamins + Vitamin C) (n ≈ 30)	Improvement in half of the patients; no parameters specified
Ali et al ³⁹	Infusions of Myers' cocktail (n = 16) versus infusions of lactated Ringer's solution (placebo) (n = 18)	No difference in TPI, VAS, FIQ, Beck depression score, HSQ
Abraham and Flechas ¹⁴	Magnesium (300-600 mg/day) and malate (1200-2400 mg/day) versus placebo (crossover trial n = 15)	Improvement in TPI ($P < .001$) and myalgia symptoms
Russell et al ⁴⁰	Super malic (magnesium [50 mg] and malic acid [200 mg]/tablet) 3 tabs BID versus placebo (crossover trial n = 20)	No difference in VAS, TPI, TPA, HAQ, depression scale score, HSS

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; FIQR; Revised Fibromyalgia Impact Questionnaire; HAQ, Health Assessment Questionnaire; HSQ, Health Status Questionnaire; HSS, Hassle Scale score; MCGILL, McGill Pain Questionnaire; TP, tender point count; TPA, tender point average; TPI, Tender Point Index; VAS, visual analog scale.

tryptophan and 60 mg of magnesium). The control group received the standard Mediterranean diet. Before and 16 weeks after the intervention, participants completed Pittsburgh Sleep Quality Questionnaire, Body Shape Questionnaire, State-Trait Anxiety Inventory, Profile of Mood States Questionnaire, Eating Attitudes Test-26, and Trait Anxiety Inventory. Significant differences were found between groups after the intervention for the mean scores of trait anxiety, self-image perception, mood disturbance, and eating disorders. The authors concluded that tryptophan and magnesium-enriched Mediterranean diet improve body image satisfaction, mood state, anxiety symptoms, and eating disorders but do not modify sleep quality in women with fibromyalgia.

In a review, Gaby³⁷ describes his clinical experience with the therapeutic use of intravenous nutrients in fibromyalgia. He gave the modified Myers' cocktail to about 30 patients with fibromyalgia. The modified Myers' cocktail consists of magnesium, calcium, B vitamins, and vitamin C. Half of the patients have experienced a significant improvement mostly after 3 or 4 treatments. In his review, Gaby refers to a study that was published only as an abstract in which 86 patients with chronic muscular complaints received intramuscular or intravenous injections of magnesium, either alone or in combination with calcium, B vitamins, and vitamin C, with 74% of the patients demonstrating improvement in their symptoms.³⁸

Ali et al³⁹ devised a randomized, double-blind, placebo-controlled pilot study to assess the feasibility, safety, and

provided insights into the efficacy of Myers' Cocktail. The study included 34 adult fibromyalgia patients. Subjects were randomly assigned either to treatment (weekly infusions of Myers' Cocktail) or to placebo (weekly infusions of lactated Ringer's solution) for 8 weeks. Primary outcome was the change in the Tender Point Index, assessed 8 and 12 weeks after initiation. Secondary measures included a visual analog scale to assess global pain, and validated measures of physical function (Fibromyalgia Impact Questionnaire), mood (Beck Depression Index), and quality of life (Health Status Questionnaire 2.0). No statistically significant differences were seen between the treatment and placebo groups, in any outcome measure, at 8 and 16 weeks. The authors concluded that the efficacy of Myers' Cocktail for fibromyalgia, relative to placebo, remains uncertain.

Abraham and Flechas¹⁴ treated 15 fibromyalgia patients for an 8-week period with a combination of magnesium (300-600 mg) and malate (1200-2400 mg) in a randomized, placebo-controlled, open-label, crossover trial. The treatment group demonstrated improvement in the Tender Point Index scores as well as the myalgia symptoms.

Russell et al⁴⁰ assessed the efficacy of Super Malic (contains 200 mg of malic acid and 50 mg of magnesium/tablet, given as 3 tablets twice a day) in treatment of primary fibromyalgia syndrome. The study included 24 participants with primary fibromyalgia. The participants were randomized to compare the combination of malic acid and magnesium to placebo in a 2-period (4 weeks per period), double blinded, cross-over design trial. The 20 participants who completed

the study were analyzed for efficacy through 3 primary and 3 secondary outcome measures. The 3 primary outcome measures assessed pain and tenderness. Measurements included were a patient self-assessment of pain on a 10 cm visual analog scale, the Tender Point Index, and the tender point average. The 3 variables of secondary importance were functional and psychological measures. Variables included the Health Assessment Questionnaire score, the Center for Epidemiologic Studies-Depression Scale score, and the Hassle Scale score. In the blinded trial, there was no significant improvement during the Super Malic treatment period compared to the placebo treatment period.

Discussion

Only 0.8% of magnesium is found in the blood (out of which 0.3% is in the serum), with the rest being in the soft tissues, muscles, and bones.¹⁹ Due to the way magnesium is distributed, its concentration in 1 compartment (eg, serum) may not accurately reflect the whole-body magnesium status prompting challenges in determining the magnesium status of the body. Moreover, due to the narrow range of magnesium in the blood that is easily maintained by the exchangeable pool of magnesium, blood magnesium levels can be misleading through masking a deficient magnesium body status. This is reflected in the study of Andretta et al²⁸ where the mean (\pm SD) magnesium intake in the fibromyalgia group (132.8 ± 53.76 mg) was significantly lower than the control group (155.52 ± 53.42 mg) ($P=.03$), yet there was no significant difference in the mean (\pm SD) serum magnesium level between the fibromyalgia group (2.22 ± 0.14 mg/dL) and the control group (2.2 ± 0.19 mg/dL) ($P=.577$). Some literature suggests that examining for magnesium retention following a magnesium load is a more sensitive test to determine the body magnesium status compared to simple serum or other body level assays.^{41,42} The challenges in assessing the magnesium status of the tissues have led to inconsistent relationships between magnesium levels and fibromyalgia with some studies showing no difference in magnesium levels between fibromyalgia patients and controls, others showing decreased levels and a few showing increased levels.²⁴⁻³³

In most of the trials that explored the effect of magnesium on fibromyalgia, magnesium was given along with other interventions.^{14,36,37,39,40} Only a few studies used magnesium as a single intervention.^{24,35} Nevertheless, none of these few studies was designed as a blinded randomized controlled study. This adds to the uncertainty about the role of magnesium in fibromyalgia.

Conclusion

Our study draws conclusions that are relevant to both clinical researchers and clinicians.

For clinical researchers: Serum and other magnesium levels (including erythrocytes, leukocytes, platelets, and hair magnesium levels) may not reflect the whole-body magnesium status. Utilizing these levels to compare magnesium status of fibromyalgia patients and healthy controls can be misleading. Similarly, employing magnesium levels to assess the effect of magnesium on different parameters of fibromyalgia should be avoided.

For clinicians: Some intervention studies in the literature suggest a benefit from magnesium use in fibromyalgia. Yet this beneficial role is not certain as none of these trials was a blinded randomized placebo-controlled study conducted with magnesium as a single therapy intervention in fibromyalgia.

Declaration of Conflicting Interests

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