

Role of micronutrients in the symptoms of fibromyalgia: a review of the literature and analysis of an Italian female sample

M.G. TARSITANO¹, G. DOLCINI², C. PANDOZZI³, F. GRECO⁴,
C. IANNUNCELLI², C. CONTE^{5,6}, E. GIANNETTA³, M. DI FRANCO²

¹Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy

²Rheumatology Unit-Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

³Department of Experimental Medicine, "Sapienza" University of Rome, Rome, Italy

⁴Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Rome, Italy

⁵Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome, Italy

⁶Department of Endocrinology, Nutrition and Metabolic Diseases, IRCCS MultiMedica, Milan, Italy

Abstract. – OBJECTIVE: Fibromyalgia (FM) is a multifactorial disease characterized principally by chronic, widespread pain impairing a patient's quality of life. The management of FM requires a multidisciplinary approach that combines pharmacological and non-pharmacological strategies. Growing evidence suggests a potential beneficial role of micronutrients such as minerals and vitamins. Overall, the role of these supplements remains controversial, but clinical trials on vitamin D, vitamin B12, magnesium, and iron supplementation seem to provide promising results. The aim of this study was to investigate their role in an Italian female sample.

SUBJECTS AND METHODS: An exploratory cross-sectional study was done to assess the association of selected micronutrients with symptoms of FM by using the Fibromyalgia Impact Questionnaire (FIQ) in twenty consecutive female patients with FM. A literature review was also conducted.

RESULTS: FIQ results revealed that vitamin D and magnesium deficiency appear to play a role in FM symptoms, mainly in physical function and stiffness. From the literature review, only two studies investigating the role of micronutrients in FM were retrieved.

CONCLUSIONS: Screening for micronutrient deficiencies in FM patients and supplementing them when levels are low might help counteract FM symptoms.

Key Words:

Micronutrients, Vitamin D, Vitamin B12, Magnesium, Fibromyalgia, Symptoms, Italian female sample.

Introduction

Fibromyalgia (FM) is a multifactorial disease characterized by chronic generalized musculoskeletal pain persisting for a minimum of 3 months, commonly associated with cardiovascular risk and metabolic disorder¹⁻⁶. The syndrome is not only related to pain on acupressure of the "tender points"¹, but can also involve several systemic symptoms like fatigue, sleep disorders, cognitive impairment and depression, migraine, irritable bowel syndrome, sicca syndrome, Raynaud's phenomenon, restless legs syndrome, and psychological manifestations². Fibromyalgia is more common in women compared to men, having a prevalence of 2.9% to 4.7% in the general population⁷. The age of onset is around 30-50 years, but it is observed during adolescence or in old age. The etiology and the pathophysiology of FM are not completely understood, the diagnosis is based on the clinical criteria described by the American College of Rheumatology and revised in 2016, including 2 items: Widespread Pain Index (WPI), and Symptoms Severity Scale⁸. According to previous studies⁹, biological factors such as rheumatic disorders, genetic predisposition, lifestyle behaviors (smoking, poor diet, sedentarily, overweight), physical and emotional stressors (physical and/or sexual abuse in childhood, sexual violence in adulthood, depressive disorders) are closely linked with FM. Additionally, a strong consensus has highlighted how poor sleep quality

could become a risk factor for FM development¹⁰. There are no specific laboratory or imaging markers for diagnosis, so it relies on excluding other medical conditions that could cause the same symptoms⁹. The management of FM needs a multidisciplinary approach involving pharmacological and non-pharmacological strategies¹¹. Anti-epileptic drugs and anti-depressants, especially selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are the main pharmacological treatment prescribed. Nevertheless, pregabalin, duloxetine, and milnacipran are the only Food and Drug Administration-approved drugs for FM but not by the European Medicines Agency¹². All the others, including analgesics, opioids, and myorelaxants that are frequently used by FM patients^{13,14}, are off-label. Among non-pharmacological approaches, nutrition plays a cardinal role¹⁵. In particular, nutrients such as minerals and vitamins showed positive effects on chronic pain and other FM symptoms, and clinical trials with vitamin D, magnesium, vitamin B12, and iron supplementation seem to provide promising results¹⁶. We reviewed the available evidence from the literature on the micronutrients most frequently associated with FM symptoms, and presented original data on the association between such micronutrients and FM symptoms, using the Fibromyalgia Impact Questionnaire (FIQ).

Materials and Methods

Clinical Data

We conducted an exploratory, cross-sectional original study to assess the association of selected micronutrients with the symptoms of FM. Twenty consecutive female patients with FM attending the outpatient Fibromyalgia clinic at Policlinico Umberto I, Rome, Italy, were included in the Disease Group (DG). FM was diagnosed according to the 2016 revision of the diagnostic criteria ACR/EULAR 2010/2011. For each participant, we recorded age, body mass index, duration of disease, and blood levels of 25(OH) vitamin D, magnesium, vitamin B12, iron, and ferritin. Twenty age-matched women with no FM, chronic disease, or pain were enrolled as a control group (CG). The study was approved by the Ethics Committee of Sapienza – University of Rome No. Prot. 442/19.

Fibromyalgia Impact Questionnaire

All patients in the DG filled out the FIQ for the assessment of disease severity¹⁷.

The first 10 sub-items focus on the patient's ability to perform daily tasks (e.g., walking, cooking) representing the domain of physical functioning. The score ranges from 0 (always able to do) to 3 (never able to do). The subitems are summed up and divided by the number of valid scores to yield the total physical functioning score. The next two items (days number felt good and the number of workdays missed) refer to the days in which patients felt good and missed work in the past week. The last 7 items are scored from 0 (no impairment) to 10 (maximum impairment). The items concerning physical impairment, "days number felt good", and "days number missed work" were normalized, and their scores can be expressed on a scale ranging from 0 to 10, (10 - greater impairment). The sum of the scores of all items represents the final score, ranging from 0 to 100 (maximum FM impact)¹⁷.

Statistical Analysis

Data are handed out as mean \pm standard deviation (SD) or count (percentage). Differences between groups (DG and CG) were evaluated using the unpaired *t*-test. The Pearson correlation test was used to analyze the correlation between clinical variables and FIQ scores in DG. The level of significance was set at $p < 0.05$. Statistical analysis was conducted using IBM SPSS statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

Results

We assessed the association between the micronutrients described above and FM symptoms. The FIQ-I scores for each domain in the DG are reported in Table I, and the characteristics of subjects in the disease and control groups are reported in Table II. There were no significant differences between DG and CG (Table II). In patients with FM, we found a moderate negative correlation between vitamin D and physical functioning ($r = -0.561$, $p = 0.008$) and between magnesium (Mg) and stiffness ($r = -0.518$, $p = 0.016$) (Table III). Other variables were not associated with FIQ scores (Table III).

Table I. FIQ-I results.

FIQ item	Score
	Mean±SD
Physical functioning	4.9±2.5
No days felt good	7.5±2.6
No workdays missed	2.7±3.3
Ability to do job	7.0±2.3
Pain	7.0±2.0
Fatigue	8.1±2.0
Tiredness	8.0±1.7
Stiffness	7.3±2.6
Anxiety	6.7±2.3
Depression	5.8±3.0
Total FIQ-I	64.9±15.5

FIQ = Fibromyalgia Impact Questionnaire.

Discussion

Review of Literature

PubMed and Scopus databases were searched. The literature was scanned, selecting papers of the last 10 years (the last search was on the 19th of June 2023). The keywords used for the search were: “fibromyalgia” AND “vitamin D”, “magnesium”, “vitamin B12”, “iron”, “ferritin”. Two of the authors (MGT and CP) separately examined and read the selected full papers. We included only articles written in English. We excluded

animal studies and selected clinical trials and randomized clinical trials to obtain considerable literature data. Studies on the micronutrients involved in FM were reviewed, and the search revealed that these were vitamin D, magnesium, vitamin B12, iron, and ferritin.

Vitamin D

Vitamin D supplementation is being considered in the management of FM because approximately 40% of patients are vitamin D deficient¹⁸. Furthermore, several studies^{19,20} have suggested that reduced serum level of vitamin D is associated with chronic pain, depression, and anxiety in patients with FM. The first study about vitamin D supplementation was conducted in 2008 in 90 FM patients with mild vitamin D deficiency (mild to moderate) treated with 50,000 units of cholecalciferol (vitamin D3) per week and placebo in the control group. After 8 weeks, treated patients showed a significant improvement in symptoms²¹. Subsequently, other studies²²⁻²⁶ evaluated the effect of vitamin D supplementation. Although in a smaller sample (between 11 and 48 subjects with FM, all studies including a control group), a beneficial effect of vitamin D supplementation on FM symptoms was described. Only the study by Wepner et al²³ yielded inconclusive results. Several mechanisms may underlie the association of vitamin D with FM symptoms. Vitamin D is involved in brain development and neuronal regulation, it can increase neuronal growth

Table II. Clinical data of DG and CG.

Variable	Group	N	Mean	SD	p-value
BMI (kg/m ²)	DG	21	24.5	4.1	0.310
	CG	21	24.0	2.8	
Age (years)	DG	21	50.1	10.2	0.457
	CG	21	46.7	11.4	
Mg (mg/dL)	DG	21	2.0	0.2	0.318
	CG	21	2.0	0.2	
	CG	21	4.2	0.4	
Vitamin D (ng/dl)	DG	21	27.8	11.3	0.765
	CG	21	31.9	9.3	
Vitamin B12 (pg/ml)	DG	19	395.2	118.6	0.268
	CG	21	423.7	147.6	
	CG	21	1.9	1.0	
Fe (ug/dl)	DG	21	80.5	26.3	0.812
	CG	21	80.8	30.7	
Ferritin (ng/ml)	DG	17	64.9	46.3	0.601
	CG	21	82.1	56.4	

DG = disease group; CG = control group; BMI = body mass index; Mg = magnesium; Fe = iron.

Table III. Correlation analysis between clinical data and FIQ scores (* $p < 0.05$).

Variable	Mg (mg/dL)		Vit D (ng/dL)		Vit B12 (pg/mL)		Fe (ug/dL)		Ferritin (ng/mL)	
	20		20		18		20		17	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Physical functioning	-0.212	0.370	-0.492	0.027*	-0.134	0.597	0.211	0.373	-0.271	0.292
No days felt good	0.213	0.368	-0.128	0.591	-0.217	0.387	-0.269	0.251	0.337	0.186
No workdays missed	0.136	0.568	-0.072	0.762	-0.345	0.160	-0.149	0.529	-0.297	0.247
Ability to do job	-0.010	0.967	-0.380	0.099	0.034	0.894	-0.239	0.310	-0.076	0.773
Pain	-0.079	0.740	-0.138	0.562	-0.033	0.896	-0.039	0.872	0.135	0.606
Fatigue	-0.147	0.535	-0.204	0.388	0.138	0.585	-0.033	0.890	0.283	0.271
Tiredness	-0.166	0.483	0.096	0.688	0.140	0.578	-0.134	0.574	0.218	0.401
Stiffness	-0.516	0.020*	-0.415	0.069	0.160	0.526	-0.179	0.451	-0.474	0.054
Anxiety	-0.201	0.395	-0.019	0.936	-0.221	0.378	-0.016	0.948	-0.256	0.321
Depression	-0.221	0.349	0.006	0.980	0.020	0.938	0.017	0.653	-0.108	0.680
Total FIQ	-0.169	0.476	-0.257	0.274	-0.118	0.641	-0.111	0.641	-0.114	0.662

FIQ = Fibromyalgia Impact Questionnaire; Mg = magnesium; Fe = iron.

factors, reduce neuronal excitability, and supply neuroprotective effects²⁷. Vitamin D upraises the transforming growth factor- β 1 (TGF- β 1), opposing the elevated inflammatory cytokines in FM patients. Furthermore, considering that reduced bone mineral density (BMD) appears to be linked to the severity of FM pain, vitamin D is known to be part of the symptomatology itself²⁷. Finally, vitamin D has several intramuscular actions, such as increasing strength and preserving the mass of the muscle²⁸.

Magnesium

The magnesium deficiency causes muscle weakness, paraesthesia, and low-grade inflammation, which are characteristic symptoms of FM²⁹. A low magnesium intake within the diet is related to a worse pain threshold in patients with FM³⁰. Magnesium is considered the supplement with the highest potential for FM³¹. Unfortunately, only two clinical studies^{32,33} are present in the literature. In the first study, the effect of magnesium, combined with malic acid supplementation, showed little or no effect on pain or depression in 24 women with FM³². The second one compared the treatment with magnesium citrate and amitriptyline vs. amitriptyline alone in 60 female FM patients, showing that amitriptyline and magnesium supplementation was more effective than amitriptyline in single administration³³. A hypothesis of the analgesic effects of magnesium implicates the

inhibition of the N-methyl-D-aspartate (NMDA) receptor and, consequently, the increase of central sensitization and pain hypersensitivity. Moreover, magnesium deficiency is connected to the pain intensity of FM. Therefore, this element can be useful in the management of symptoms in FM patients³⁴.

Vitamin B12

Vitamin B12 is another useful element to investigate in patients with FM. It has a significant role as an acute analgesic and is used to alleviate chronic pain. Some studies^{35,36} highlighted the positive effects of vitamin B12 in patients with chronic non-specific pain (without a specific diagnosis of FM). For example, one of these³⁵ examined the analgesic effects: the patients receiving an intramuscular injection of methylcobalamin three times a week for 2 weeks showed a reduced pain score. Indeed, vitamin B12 inhibits inflammatory mediators and acts on neuronal activity^{35,36}. Interestingly, Munipalli et al³⁷ recently observed an association between vitamin B12 levels and fatigue in patients with FM³⁷. Specifically, this symptom was prevalent in the vitamin B12-deficient group of patients, regardless of whether the cut-off was 400 or 350 ng/L. Long-term effects of vitamin B12 supplementation were identified in a group of patients with myalgic encephalomyelitis/fibromyalgia, indicating a dose-response relationship and a good clinical response³⁸.

Iron and Ferritin

Other studies³⁹⁻⁴² suggested a possible link between iron deficiency and FM. Only one study³⁸ evaluated the effect of iron supplementation on FM symptoms highlighting a general improvement of symptoms reported by the patients. Ortancil et al⁴⁰ evaluated the association between FM and ferritin levels, suggesting that iron might play a role in the etiology of FM⁴⁰. Using a logistic regression model, authors proposed a cut-off of 50 ng/ml below which severe symptoms of restless legs syndrome occurred, although ferritin levels were normal⁴⁰. However, lower ferritin levels were found in patients with FM, suggesting decreased iron stores in these patients. Prescribing iron supplementation could represent a therapeutic strategy in the treatment of FM. Indeed, FM patients have a high prevalence of non-anemic iron deficiency and, if compared with a control group, iron deficiency anemia is significantly more common³⁹. However, in another study⁴³, no associations with anxiety, depression, sleep quality, and physical functioning were found. Individuals with poor sleep quality show more severe depression when they have low ferritin levels. Indeed, iron is a cofactor for several enzymatic synthesis reactions, such as for serotonin dopamine synthesis⁴⁰. Thus, decreased levels of dopamine, norepinephrine, and serotonin were found in the cerebrospinal fluid of patients with FM, suggesting that iron deficiency could alter enzymatically derived hormones with a possible subsequent effect on pain perception⁴⁴. For example, Kucuk et al⁴⁵ considered low ferritin levels to be an independent risk factor for FM. Furthermore, they provided evidence supporting the association between vitamin B12 deficiency and muscle pain. Adequate replacement may decrease the pain. Levels of vitamin B12, vitamin D and ferritin in FM patients appeared significantly lower than those of healthy women. In particular, ferritin and vitamin B12 levels have been identified as able to affect FIQ score and tender points.

Some micronutrients serum levels correlate to FM symptoms. So, the main objective of this paper was to evaluate in the study population the possible correlation between serum levels of vitamin D, magnesium, vitamin B12, iron with the disease state, using the validated FIQ. Moreover, assuming that pronounced symptoms correlate inversely with serum levels of these micronutrients, another purpose was to estimate the impact of these compounds and

their levels on the severity of symptoms, trying to identify cut-offs that could guide clinical practice.

FM is a complex disease with an unknown etiology, occurring more frequently in women and often secondary to an emotional or physical trigger and inflammatory substrate, like other syndromes such as Takotsubo syndrome⁴⁶. FM remains with an unknown etiology in which micronutrient deficiency plays a role, either as a trigger or an aggravating factor. Micronutrients are involved in intracellular and tissue pathways in the development of FM symptoms. So, distinctly, a marked hypovitaminosis D causes fatigue, while iron deficiency correlates with anxiety. Therefore, micronutrient deficiency, such as other factors implicated in chronic pain, should gain the right role in the framework and management of the patient affected by FM. However, the available literature is still relatively scarce, and more clinical studies are needed to understand the correlation between micronutrients and FM symptoms, the possible mechanisms, and the specific role of supplementation in micronutrient-deficient patients. With this in mind, we compared levels of vitamin D, B12, magnesium, iron, and ferritin between FM patients and healthy controls, and analyzed the correlation between micronutrient levels and FM symptoms, as assessed by the FIQ. We did not find differences between the FM patient and the CG in micronutrient levels. However, in the DG, vitamin D levels significantly correlated with physical activity, such as highlighted in the specific FIQ item. It is known that vitamin D has a role in chronic muscle pain, which is the main factor limiting physical activity²⁸. Indeed, vitamin D deficiency is associated with chronic muscle pain, with symptoms improving after supplementation. In patients with FM, this data is less clear. Our findings, albeit from a small, exploratory study, support these data. Our patients scored lower (i.e., better) on physical function if they had higher serum levels of vitamin D.

Secondly, we found a significant negative correlation between Mg and stiffness in FM patients, confirming the role of Mg in muscle function. A reduced level of intracellular magnesium is described in patients with FM³¹. Magnesium deficiency was largely associated with low-grade inflammation, muscle weakness, and paresthesia, which are typical symptoms of FM⁴⁷. In addition, a low dietary intake of magnesium correlates with a worsening of the parameters that evaluate the pain threshold in FM³⁰.

Limitations

The main limitation of the study is the small sample size.

Conclusions

Published evidence and our own data suggest that vitamin D and magnesium deficiency are implicated in FM symptoms, affecting physical function and stiffness, respectively.

Screening for micronutrient deficiencies in FM patients is useful in clinical practice. Supplementation in patients – even when not deficient – should be considered due to the inverse association between vitamin D and magnesium levels and physical function/stiffness. Further studies are needed to make solid recommendations.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

There was no funding for this study.

Availability of Data and Materials

The data and material can be made available from the authors upon request.

Ethics Approval

The study was approved by the Ethics Committee of “Sapienza” University of Rome No. Prot. 442/19.

Informed Consent

All participants provided fully informed written consent at the time of recruitment.

Authors' Contributions

M.G.T., M.D.F., and E.G. planned the study. M.G.T., M.D.F., C.C., C.P., C.I., and G.D. collected the data. C.C. and F.G. did the analysis. M.G.T., M.D.F., and C.C. wrote the draft paper. All authors contributed to and approved the final version of the manuscript.

ORCID ID

M.G. Tarsitano 0000-0002-3500-0591
 G. Dolcini 0000-0002-0503-0343
 C. Pandozzi 0000-0002-7427-1431
 F. Greco 0000-0002-6539-7796
 C. Iannucelli 0000-0003-1428-9725
 C. Conte 0000-0001-7066-5292
 E. Giannetta 0000-0003-3614-6151
 M. Di Franco 0000-0002-5468-2065

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