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El hambre oculta y la fibromialgia: Una revisión sistemática

The hidden hunger and fibromyalgia: A systematic review

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RESUMEN

Recientemente há sido discutida la posibilidad de una relación causal entre la fibromialgia (FM) y la deficiencia de micronutrientes, un tipo de deficiencia nutricional conocida como "hambre oculta". Sin embargo, los estudios son pocos y los resultados controversiales, lo que genera debates sobre la influencia real del "hambre oculta" en el proceso de la enfermedad en las personas con fibromialgia. En está revisión se presentan y discuten evidencias científicas relacionadas con la deficiencia de micronutrientes y FM, destacando los principales micronutrientes relacionados. El levantamiento de información fue realizado en los bases de datos de PubMed y Science Direct en estudios observacionales publicados entre los años 2000 y 2017. Fueron seleccionados 14 estudios, ocho dirigidos a la asociación de la deficiencia de vitamina D y la presencia de FM y seis enfocados en la asociación de la deficiencia de minerales con FM. Se sugiere una relación entre la deficiencia de vitamina D y el aumento de la sensibilidad al dolor en la FM. Aunque esa insuficiencia también está asociada a otras enfermedades muscoesqueléticas crónicas. Además, parece que la deficiencia mineral (p.ej.o., hierro, magnesio, zinc y calcio) también desempeña un papel importante en el inicio de la FM y sus principales síntomas.

Palabras clave: Deficiencia de micronutrientes; Deficiencia de mineral; Deficiencia de vitamina; Fibromialgia; Hambre oculta.

ABSTRACT

Recently the possibility of a causal link between fibromyalgia (FM) and micronutrient deficiency , a type of malnutrition known as "hidden hunger", has been suggested. However, the results are controversial, which raises questions and debates on the actual influence of "hidden hunger" on the development of FM. In this review, we present and discuss scientific evidence related to micronutrient deficiencies and FM, highlighting key micronutrients involved. We searched PubMed and Science Direct databases for all observational studies published between 2000 to March 2017. We selected fourteen observational studies, eight studies aimed at linking vitamin D deficiency to the presence of FM and six studies focused on the association of mineral deficiency with FM. The association between vitamin D deficiency and increased pain sensitivity in FM is suggested, although such insufficiency is also associated with other chronic musculoskeletal disorders. It appears that mineral deficiency (e.g., iron, magnesium, manganese, zinc and calcium) plays an important role in the onset of FM and its main symptoms.

Keywords: Fibromyalgia; Hidden hunger; Micronutrient deficiency; Mineral deficiency; Vitamin deficiency.

INTRODUCTION

Fibromyalgia (FM) is a clinical syndrome characterized by chronic widespread pain, fatigue, non-restorative sleep, weakness, morning stiffness, numbness in extremities and

cognitive disorders[1]. The condition affects around 1-4% of the population, with the highest prevalence among women 30 to 55 years of age[2]. The clinical diagnosis of FM is confirmed by the presence of pain on digital palpation of 11 out of 18 specific soft tissue points called "tender points" in conjunction with the symptom severity scale (score SS 2A and 2B)[3].

Although the pathophysiology of FM is not completely understood, it has been related to neuroendocrine abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis and deficiencies in the endogenous pain modulation systems[4]. Low serotonin levels and high levels of "Substance P" found in the cerebrospinal fluid of patients with FM suggest changes in the excitatory and inhibitory neurotransmitters in the central nervous system (CNS), leading to variations in response to central pain[4,5,6,7].

Recently, a potential causal link between FM and micronutrient deficiency has been suggested. This type of malnutrition, known as "hidden hunger ", is an implicit lack of one or more nutrients, a phase prior to the appearance of clinical signs of deficiencies, and not necessarily associated with clearly defined pathologies[8]. Therefore, "hidden hunger" produces minimal physiological changes and adverse health consequences, which are imperceptible in routine examination, due to the lack or marginal consumption of micronutrients[9].

Some studies have demonstrated an association between low levels of vitamin D and diffuse musculoskeletal pain, including FM, although the results appear inconclusive. In addition, reduced serum levels of zinc (Zn), magnesium (Mg), calcium (Ca), copper (Cu), iron (Fe) and manganese (Mn) have been observed among FM patients and are related to clinical symptoms such as fatigue, weakness and cognitive impairments[10,11,12,13].

The association between the deficiency of vitamins and minerals and the development of chronic pain syndromes has been studied. However, the results are controversial thus raising debate on the actual influence of "hidden hunger" on the development of such syndromes. In this sense, uncertainties exist regarding which vitamins and minerals are associated with the development of FM. Therefore, in this review we present and discuss the scientific evidence related to micronutrient deficiencies and FM, highlighting the key micronutrients involved.

METHODS

Information Sources and Search Strategies

We searched PubMed and Science Direct databases for all observational studies from January 2000 to March 2017. The search was performed using the following medical search headings: 'fibromyalgia', 'micronutrients', 'vitamin', 'vitamin deficiency', 'minerals', 'trace element', 'zinc', 'iron', 'calcium', 'potassium', 'iodine', 'sodium', 'magnesium', 'selenium', 'manganese', 'fluoride' and 'phosphorus'. Regarding the search on PubMed, we used the following search limits: Title/abstract; Published between 2000 and 2017; Full text; Abstract; Humans; Written in English; Observational studies. In Science Direct, we used the advanced search option, crossing the keywords listed above and pre-selecting all observational studies.

Eligibility Criteria

The following exclusion criteria were used: 1) non-clinical studies; 2) studies on nutritional supplementation and drug therapy; and 3) studies whose participants have FM associated with comorbidities (psychiatric and somatic) and musculoskeletal pain or fatigue.

All participants were adults (male and female aged ≥18 years) diagnosed with FM according to the American College of Rheumatology (ACR) criteria[3], with no clinical signs of micronutrient deficiency. All studies included in this review were observational studies (case-control, cross-sectional and cohort study).

Study Selection Process

The identification and selection of articles were based on title and reading through the abstracts. All duplicate studies in different databases were counted only once. From the selected articles, a reverse citation search to find other relevant studies was done. The full texts of all relevant articles were read.

Data Extraction and Quality Assessment

All eligible reports were independently reviewed by two authors. For the characterization of the articles, the following information was extracted using an excel datasheet: lead author, year of publication and country where the study was conducted; study design; participants, criteria for diagnosing FM syndrome, characteristics and size of sample; indicator and cut-off point, limitations and main results.

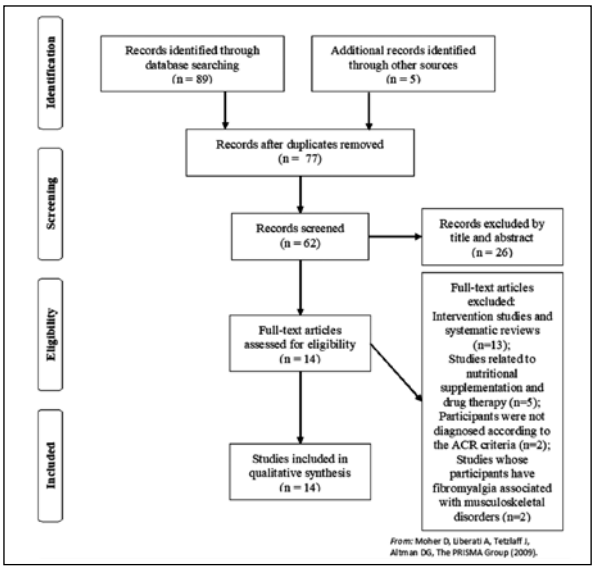
The methodological quality of each article was evaluated according to the Downs & Black checklist[14] for measuring quality. This checklist contains 27 questions divided into four groups: presentation (evaluates items such as clarity in the description of objectives, existence of confounding variables, probability values); external validity (related to the extrapolation of data from the planned sample to a population); internal validity (bias analysis, reliability of measurements of exposure and outcome); and statistical power of the study.

In this study, items 4, 8, 12, 14, 15, 19, 23, 24 and 27 were excluded because they refer to clinical trials. Thus, only 19 items were evaluated, with a maximum score of 20 points. The scale questions allow for objective evaluation of an article under analysis regarding whether or not it answers the questions posed. For each item, the zero score (0) is assigned if the article does not conform to what is being evaluated. On the contrary, score one (1) is assigned when the article provides an answer. Only item 5 assigns a score of 2, if the question is answered by the article.

RESULTS

Characteristics of Included Studies

During the initial database search, we pre-selected 94 studies with 17 repeated in the searched databases. After reviewing the titles/abstracts and reading the articles, only 14 articles[12,13,15-26] met the eligibility criteria adopted and correlated micronutrient deficiency to the presence of FM (Figure 1).



The parameters evaluated in each study and the characteristics of the participants are presented in tables 1 and 2.

Observational studies such as cross-sectional (n= 13) and cohort (n= 1), conducted in South America (n= 1), Europe (n= 3) and Asia (n= 10) were selected. The 14 studies included comprised of 713 FM patients with ages between 20 and 75 years, and 722 control participants with ages between 22 and 71 years. Most studies enrolled people with no pain symptoms as controls; only one study recruited patients with lower back pain and/or tendinitis[15]. Twelve studies focused on women and two included both sex[22,25]. The threshold defined for vitamin D deficiency varied among citations; with 20 ng/mL being the most utilized.

The indicators and cutoff points for mineral deficiency varied among the studies and only one study defined a cutoff point for Fe deficiency[23].

Eight studies linked vitamin D deficiency to the presence of FM[15,16,17,18,19,20,21,22]. However, only two papers found a positive correlation between low serum levels of vitamin D and FM. A case-control study conducted in Egypt18 observed that vitamin D

Table 1. Observational studies of vitamin deficiency.

Author/Location	Study Design	Patients Characteristics	Control Characteristics	Indicator/ Cut-off	Association
Aksoy et al.[15] Turkey	Cross-sectional, observational	N= 53 FM, female Age: 48,2 ± 9,6 yrs	N= 47 Healthy, female Age: 44,4 ± 7,6 yrs	25-OHD <30 ng /mL	There was an association between pain and vitamin D levels in fibromyalgia.
Maafi et al.[16] Iran	Cross-sectional, observational	N= 74 FM, female Age: 37,96 ± 9,8 yrs	N= 68 Healthy, female Age: 32,63 ± 10,1 yrs	25-OHD <20 ng /mL	There was no intrinsic association between FM and vitamin D deficiency.
Okumus et al.[17] Turkey	Cross-sectional, observational	N= 40 FM, premenopausal female Age: 41,23 ± 4,8 yrs	N= 40 Low back pain and/or tendinitis premenopausal female Age: 39,48 ± 4,08 yrs	25-OHD <15 ng /mL	Vitamin D deficiency was not more common in premenopausal patients FMS than in the control group without FM. There was an association between pain and vitamin D levels in fibromyalgia.
Olama et al.[18] Egypt	Case-control, observational	N= 50 FM, premenopausal female Age: 32,3 ± 9,4 yrs	N= 50 Healthy, premenopausal female Age: 33,1 ± 9,7 yrs	25-OHD <20 ng/mL	FM patients have significantly lower serum levels of 25 - OHD that controls.
Ulusoy et al.[19] Turkey	Cross-sectional, observational	N= 30 FM, premenopausal female Age: 20-40 yrs	N= 30 Healthy, premenopausal female Age: 22-38 yrs	25-OHD ≤20 ng /mL	The frequency of vitamin D deficiency in FMS patients was not different from the rest of the population.
Tandeter et al.[20] Israel	Cross-sectional, observational	N=68 FM, premenopausal female Age: 43,8 ±7,6 yrs	N= 82 Healthy, premenopausal female Age: 40,4 ± 9,8 yrs	25-OHD <30 ng /mL <20 ng /mL <15 ng /mL	There was no significant difference in levels of 25-OHD between groups.
Velozo et al.[21] Argentina	Cross-sectional, observational	N=60 FM, premenopausal female Age: 47,3 ± 8 yrs	N= 58 Healthy, premenopausal female Age: 47,3 ± 8 yrs	25-OHD <10 mg/dL	There was no difference in the levels of 25-OHD between FMS and control. FMS patients had higher PTH levels than the control suggesting prolonged exposure to low levels of vitamin D.
Armstrong et al.[22] Northern Ireland	Cohort, observational	N= 75 FM, 70 female and 5 male Caucasian Age: 21-75 yrs	Absent	25-OHD <10ng /mL	Vitamin D deficiency was common in fibromyalgia patients. It occured most frequently in patients with anxiety and depression.

Note: Abbreviation: FM, fibromyalgia; yrs, years; 25-OHD, 25-hydroxyvitamin D; PTH: parathyroid hormone.

deficiency (using a cutoff of < 20 ng/mL for levels of 25-OHD) is common in premenopausal women with FM (age: 32.3 ± 9.4) and occurs more frequently in patients with anxiety and depression. A cohort study in Northern Ireland[22] found an association between pain levels and vitamin D deficiency in patients with FM, based on the investigation of 75 patients (70 women and 5 men aged 21-75 years). Two other studies found an association between pain and vitamin D levels in patients with FM[15,17].

Table 2. Observational studies of mineral deficiency.

Author/Location	Study Design	Patients Characteristics	Control Characteristics	Indicator/ Cut-off	Association
Mader et al.[23] Israel	Cross-sectional, observational	N= 84 FM, female Not anemic Age: 52 ± 12 yrs	N= 87 Healthy, female Not anemic Age: 48 ± 12 yrs	Hemoglobin <12 g/dL, Serum Fe <40 µg/dL, Serum ferritin ≤30 ng/mL, Serum sTfR >28.1 nmol/	FM patients did not have reduced levels of Fe and other Fe storage markers.
Sakarya et al.[12] Turkey	Cross-sectional, observational	N= 40 FM, premenopausal female Age: 33.6 ± 7.6 yrs	N= 40 Healthy, premenopausal female Age: 31.7 ± 7.0 yrs	Mn No cut-off values	There was no significant difference in the levels of Mg between control subjects and FM patients. There was no statistically significant correlation between serum levels of Mg and pain, functional ability and depression in patients with FM.
Kim et al.[13] South Korea	Cross-sectional, observational	N= 44 FM, female Age: 42.5 ± 6.9 yrs	N= 122 Healthy, female Age: 44.2 ± 8.3 yrs	Analysis of hair minerals: Ca, Mg, Na, K, Zn, Mn, Se, Cr, P, Fe, Cu No cut-off values	The FM patients showed significantly lower levels of Ca, Mg, Fe and Mn
Sendur et al.[24] Turkey	Cross-sectional, observational	N= 32 FM F Age: 42.9±7.7 yrs	N= 32 Healthy F Age: 41.3 ±9.7 yrs	Serum concentration of Mg, Zn and Se. No cut-off values	Serum Zn and Mg were significantly lower in the group of patients FMS The associations between serum levels of Zn and the number of tender points, and fatigue and Mg levels were statistically significant.
Bazzich et al.[25] Itally	Cross-sectional, observational	N= 25 FM 24 F and 1 M Age: 48,8±9,3 yrs	N= 25 Healthy 24 F and 1 M Age matched	Ca e Mg No cut-off values	There was a tendency of higher levels of Ca with significant Mg increases in FM patients compared to controls.
Rosborg et al.[26] Sweden	Cross-sectional, observational	N= 38 FM Female Age: 31-71 yrs	N= 41 Healthy Female Age: 28-71 yrs	Ca, Cu, Fe, K, Mg, Mn, Na, Zn Ag, B, Ba, Br, Cd, Co, Cs, Hg, I, Li, Mo, Pb, Se, Rb, Sn; Sr, U, V No cut-off values	There were significant differences in urinary concentration of Ag betwee n FM patients. The study did not show abnormal levels of trace of patients with FM in accordance with the reference values for the population.

Note: Abbreviation: FM, fibromyalgia; yrs, years; sTfR, serum transferrin receptor, iron (Fe), manganese (Mn), calcium (Ca), magnesium (Mg), sodium (Na), potassium (K), zinc (Zn), selenium (Se), chrome (Cr), phosphorus (P), copper (Cu), silver (Ag), boron (B), barium (Ba), bromine (Br), cadmium (Cd), cobalt (Co), cesium (Cs), mercury (Hg), iodine (I), lithium (Li), molybdenum (Mo), lead (Pb), rubidium (Rb), tin (Sn), strontium (Sr), uranium (U), vanadium (V).

Six studies related mineral deficiency to FM[12,13,23,24,25,26]. Two studies identified an association between mineral deficiency and FM. Sendur et al.[24] observed lower levels of Zn and Mg in the blood of Turkish women with FM (age: 42.9 ± 7.7 years). Low Zn levels were associated with the number of tender points and fatigue was associated with low Mg levels. A study conducted in South Korea13 found positive associations between FM and low levels of Ca, Mg, Mn and Fe measured in the hair of patients aged 42.5 ± 6.9 years (Table 2).

Quality of selected studies

The scores of the studies according to the Downs & Black checklist[14] varied from 14 to 18 points (average: 16 points). Regarding presentation, all studies scored positively in the description of objectives, methods of measurement and presentation of main results. Only eight studies scored points for external validity and the vast majority had low scores for internal validity.

DISCUSSION

I. Vitamin deficiency in Fibromyalgia

Vitamin deficiency has been directly linked to the pathophysiology of several chronic non-communicable musculoskeletal diseases, including osteoporosis, myofascial pain syndrome, chronic fatigue syndrome, myositis, and FM[10,27,28,29,30].

Patients with myofascial pain syndrome exhibit a high prevalence of vitamin inadequacy or deficiency[27]. Folic acid and vitamin B_{12} deficiency reduces red blood cell production, leading to reduced oxygen transport. The consequent dysfunctions in muscle energy metabolism at the motor end plates results in painful muscular regions known as trigger points[27].

In this review, two studies identified a positive correlation between vitamin D deficiency and the presence of FM[18,22] and two others identified an association between pain levels and vitamin D levels in FM[15,17].

Recent studies have indicated vitamin D deficiency as the main trigger factor for diseases related to chronic diffused pain, myofascial pain, joint pain, muscle weakness and fatigue[10,11,30,31]. According to Schinchuk and Holick[28], vitamin D deficiency causes osteopenia, and it precipitates and exacerbates osteoporosis, leading to osteomalacia, a painful bone disease. In addition, vitamin D deficiency reduces the strength of proximal muscles and postural balance, and should therefore be considered in the diagnosis of FM.

Vitamin D from the skin and diet is metabolized in the liver to 25-OHD, which is used for determining vitamin D status in the blood[32]. 25-OHD is then metabolized in the kidneys by the enzyme 25-hydroxyvitamin D- 1alpha-hidroxylase (CYP27B1) in its active form, 1.25 (OH)2D. Renal 1.25(OH)2D is regulated by the plasma levels of parathyroid hormone and the serum levels of Ca and phosphorus. In this sense, Lewis et al.[33] believed that FM could be the result of a physiological blockade within the parathyroid axis due to suppressed parathyroid hormone secretion and/or renal excretion of phosphorus with subsequent interruption of the final steps in vitamin D activation and systemic action.

The biological actions of vitamin D in the nervous system include the biosynthesis of neurotrophic factors and synthesis of neurotransmitters, in addition to playing a role in brain detoxification (e.g.: inhibition of nitric oxide synthesis)[34].

Studies have related FM to neuroendocrine abnormalities involving the HPA axis and deficit in the endogenous pain modulation systems[4,5]. The main aspect related to the symptoms of FM is the presence of chronic widespread pain. Chronic pain has been associated with changes in brain anatomy, particularly related to the reduction of gray matter in patients. These changes would affect the regions of pain and stress modulation, reinforcing the theory that FM is associated with hypersensitivity of pain pathways in the CNS[35].

The neuroprotective and immunomodulatory effects of vitamin D have also been described in some experiments, indicating a potential pharmacological value of analogs of 1.25 (OH)2D for the treatment of neurodegenerative and neuroimmune diseases[34]. In this context, both the reduced production of active vitamin D and the micronutrient deficiency of vitamin D may be associated with the pathophysiology and clinical symptoms of FM. Thus, supplementation with vitamin D has shown significant improvement of pain and functional capacity in patients with FM. For example, Bilal et al.[36] observed that Pakistani patients with FM with vitamin D deficiency had a significant beneficial effect on their symptoms after replacement of vitamin D.

Similarly, Matthana[11] established a strong association between low serum vitamin D levels and FM in Saudi women. They reported that after vitamin D supplementation, 42 out of 61 women showed significant improvement in pain and functional capacity. In addition, statistically significant data were found in relation to the other symptoms of FM, except cognitive symptoms.

The study by Olama et al.[18] reported significant differences in bone mineral density of the lumbar spine between FM and control patients, with 30% of the FM patients presenting osteopenia and 8% presenting osteoporosis. Similarly, Al-Allaf et al.[38] concluded that FM patients have a high propensity for poor bone health in the future because of their susceptibility to low vitamin D levels and poor lifestyle factors; therefore, these patients should be screened and supplemented.

Although vitamin D deficiency is common in patients with FM, it occurs more frequently in patients with anxiety and depression[22]. Accordingly, Velozo et al.[21] observed that patients with FM and vitamin D deficiency are prone to depression.

Anxiety and depression are comorbidities often present in patients with FM and appear to be associated with reduced levels of serotonin. This central neurotransmitter is known to influence several behaviors, as well as physiological and cognitive functions[39]. Vitamin D receptors are found in the

neurons, in the glia cells, and in the pituitary gland, however their exact function remains unknown. The distribution of vitamin D receptors suggests that vitamin D may also act in the same way as other neurosteroids[40].

Two studies in this review[17,21] found no correlation between low serum levels of 25-OHD and FM, although they observed significant associations between serum levels of parathyroid hormone and pain perception in vitamin D deficient patients. According to Okumus et al.[17], their findings are in agreement with several studies reporting vitamin D deficiency in patients with musculoskeletal pain[22,30,41,42,43].

Therefore, even though studies suggest an association between vitamin D levels and the presence of FM, it is difficult to confirm this hypothesis. We have to consider the limitations of studies such as the absence of control groups or the use of unhealthy controls; and the lack of adjustments for confounding factors related to vitamin D deficiency, such as body mass, sun exposure time, skin pigmentation and the use of medication and supplements. Additionally, the variability of the studied populations (ethnicity, latitude of the location of the study) alongside small samples, different definitions for vitamin deficiency and different cut-off points of plasma levels of vitamin D (usually <20 ng/mL) make difficult the comparisons between studies and the validation of external results. Despite that, there seems to be an association between vitamin D deficiency and increased pain sensitivity, which is a symptom characteristic of FM.

II. Mineral Deficiency and Fibromyalgia

The association between FM development and mineral deficiency has been investigated. For example, Romano and Stiller[44] indicated that Mg participates in ATP synthesis and it is important for muscle metabolism, thus its reduction would contribute to the progression of FM. The serum levels of selenium (Se) in FM patients were lower compared to their controls of the same age and sex[45]. In a recent study, Seferoglu et al.[46] noted that the Se levels were lower the serum of patients with FM than in healthy controls, though the serum levels of Cu, Zn and Mg were normal in controls. Furthermore, they observed a significant correlation between Se levels, the duration of the disease, pain severity and the number of "tender points".

In this review, only two studies observed a positive correlation between mineral deficiency and the presence of FM[13,24]. Among the assessed minerals, evidence was found only for Ca, Fe, Mg, Zn, Mn and Cu deficiencies. Besides mineral deficiency, the authors also sought to identify a correlation between possible toxic levels of trace elements in FM development and clinical signs such as pain, fatigue, functional capacity and other symptoms associated with FM.

The studies by Sendur et al.[24] and Kim et al.[13] indicated that serum Mg levels were lower in FM patients than in their controls, and there was a strong association between serum levels of Mg and fatigue.

According to Abraham et al.[47] and Romano and Stiller[44], Mg deficiency can lead to significant reductions in muscle ATP levels, and may play an important role in the development of FM. As Mg levels decrease, energy levels also decrease, resulting in an increased sensation of fatigue[24]. In an intervention study where patients with FM were treated with Mg citrate, low Mg levels correlated with pain intensity, number of tender points, functional capacity, depression and anxiety as well as with fatigue, sleep disturbances, headache and gastric disorders[48]. Other studies[49,50] also demonstrated a correlation between Mg and clinical symptoms of FM, reinforcing that Mg plays an important role in the development of this syndrome.

The association between serum Zn levels and the number of tender points in patients with FM was found by Sendur et al.[24]. Similarly, Eisinger[51] found low Zn levels in patients with FM. The importance of Zn to counteract oxidative stress has been related to its participation as a cofactor for many antioxidant enzymes[51,52,53]. It should also be pointed out that the imbalance of antioxidant enzymes plays an important role in the etiology of FM[54].

Regarding Ca deficiency, a positive association was reported between Ca levels in the hair of women with FM[13]. The authors also pointed out that most patients with muscle pain, including FM, showed normal serum Ca levels but that intracellular Ca concentration can be different and should be investigated. According to Magaldi et al.[55], intracellular Ca levels in patients with FM are lower when compared to healthy controls and may potentially be responsible for muscle hypertonus, which would explain muscle pain related to the symptoms of FM.

Only one study identified low Mn levels in FM patients[15]. However, recent studies reported that alterations in the balance between oxidants and antioxidants may be associated with the presence of FM[48,54]. Antioxidant enzymes, such as superoxide dismutase 2, which contains Mn in its composition, play an important role in antioxidant defense inside the mitochondria[56]. In this sense, considering that the oxidant-antioxidant balance may be altered in patients with FM, Mn deficiency could be related to the pathophysiology of FM.

Iron deficiency has also been associated with clinical symptoms of FM. An increase in the prevalence of FM in patients with anemia due to Fe deficiency has been reported[57]. However, it has been suggested that the presence of anemia cannot explain the clinical manifestations of FM, since both the symptoms and the serum Fe levels do not differ between patients with FM and Fe deficiency anemia, and patients without FM. Thus, Fe deficiency without anemia has also been linked to the presence of FM, and Fe supplementation in such condition attenuated fatigue and improved cognitive and physical states[58,59].

The study by Mader et al.[23] evaluated the association between serum Fe, ferritin, transferritin and FM, but found no significant reduction in these markers in the blood of patients with FM. However, a study by Kim et al.[13] reported significant reductions in Fe levels in the hair of FM patients, although comparisons of this result with those from serum

levels cannot be made. This limitation makes it difficult to validate their results.

Thus, the number of studies on the influence of mineral deficiency in the pathophysiology of FM is still limited and the results are controversial. Observational studies also find it difficult to adjust all confounding factors related to the status of minerals in the body. Serum levels of trace elements in the body seem to vary constantly in a dynamic environment influenced by hormonal factors, environment, eating habits and others.

Finally, factors related to the study designs including duration, characteristics and sample size also hinder comparisons among studies and extrapolation of results. However, some minerals such as Mg, Ca, Zn, Fe and Mn appear to be associated with some of the most common clinical signs of FM (i.e. fatigue, weakness and pain), and may play an important role in the pathophysiology of this syndrome.

CONCLUSIONS

The positive association between vitamin D deficiency and increased pain sensitivity characteristic of FM is suggested, although such vitamin insufficiency is also associated with other chronic musculoskeletal disorders.

It appears that mineral deficiency (e.g., Fe, Mg, Mn, Zn and Ca) plays an important role in the onset of FM and its main symptoms. For instance, Mg and Fe deficiency is associated with fatigue, weakness and cognitive impairments. In addition, lower intracellular Ca is linked to increased muscle tone and tension, and hence muscular aches. Moreover, Zn and Mn deficiencies are related to changes in the oxidative cellular balance.

Finally, intervention studies on the influence of "hidden hunger" or micronutrient deficiency on the etiology of FM are necessary. Such findings in the field of nutritional science would contribute to the creation of more efficient and low cost therapeutic strategies following the preventive therapeutic principle.

REFERENCES

1. *Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol. 2005; 75(suppl 1): 6-21.*
2. *Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995; 38: 19-28.*
3. *Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010; 62: 600-610.*
4. *Dadabhoy D, Crofford LJ, Spaeth M, et al. Biology and therapy of fibromyalgia: evidence-based biomarkers for fibromyalgia syndrome. Arthritis Research & Therapy 2008; 10: 11.*
5. *Sluka KA. Pain syndromes: myofascial pain and fibromyalgia. In: Sluka KA. Mechanisms and management of pain for the physical therapist. Seattle: IAPS Press; 2009. P. 279-297.*
6. *Larson AA, Giovengo SL, Russell IJ. Changes in the levels of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. Pain 2000; 87: 201-211.*
7. *Russell IJ, Orr MD, Littman B. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum 1994; 37: 1593-601.*
8. *Kennedy E, Meyers L. Dietary reference intakes: development and uses for assessment of micronutrient status of women-a global perspective. Am J Clin Nutr. 2005; 81 (suppl 1) 1194S-1197S.*
9. *Underwood BA. Long-term strategies for the control of micronutrient deficiencies. Vitamin A Field Support Project (VITAL) IN-14, Arlington, Virginia: USAID; 1993. P.70-76.*
10. *Okumus M, Ceceli E, Tuncay F, et al. The relationship between serum trace elements, vitamin B12, folic acid and clinical parameters in patients with myofascial pain syndrome. J Back Musculoskelet Rehabil 2010; 23: 187-191.*
11. *Matthana MH. The relation between vitamin d deficiency and fibromyalgia syndrome in women. Saudi Med J 2011; 32: 925-929.*
12. *Sakarya ST, Akyol Y, Bedir A, et al. The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome. Clin Rheumatol. 2011; 30: 1039-1043.*
13. *Kim YS, Kim KM, Lee DJ, et al. Women with fibromyalgia have lower levels of calcium, magnesium, iron and manganese in hair mineral analysis. J Korean Med Sci 2011; 26: 1253-1257.*
14. *Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of healthcare interventions. J Epidemiol Community Health 1998; 52: 377-384.*
15. *Aksoy MK, Altan L, Metin BO. The relationship between balance and vitamin 25 (OH)D in fibromyalgia patients. Mod Rheumatol 2016; 26: 1-7.*
16. *Maafi AA, Parsa BG, Haghdoost A, Aarabi Y, et al. Serum vitamin D status in iranian fibromyalgia patients: according to the symptom severity and illness invalidation. Korean J Pain 2016; 29(3): 172-178.*
17. *Okumus M, Koybasi M, Tuncay F, et al. Fibromyalgia syndrome: is it related to vitamin D deficiency in premenopausal female patients? Pain Management Nursing 2013; 14: 56-163.*
18. *Olama SM, Senna MK, Elarman MM, et al. Serum vitamin D level and bone mineral density in premenopausal Egyptian women with fibromyalgia. Rheumatol Int. 2012; 33: 185-192.*
19. *Ulosoy H, Sarica N, Arslan S, et al. Serum vitamin D status and bone mineral density in fibromyalgia. Bratisl Lek Listy. 2009; 111: 604-609.*
20. *Tandeter H, Grynbaum M, Zuili I, et al. Serum 25-OH vitamin D levels in patients with fibromyalgia. IMAJ. 2009; 11: 339-342.*
21. *Velozo E, Recalde MC, Rafaelli BS, et al. Vitamin D levels on patients with fibromyalgia. Bone 2008; 43(6): S128-S136.*
22. *Armstrong DJ, Meenagh GK, Bickle I, et al. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. Clin Rheumatol 2007; 26: 551-554.*
23. *Mader R, Koton Y, Buskila D, et al. Serum iron and iron stores in non-anemic patients with fibromyalgia. Clin Rheumatol. 2012; 31: 595-599.*
24. *Sendur OF, Tastaban E, Turan Y, et al. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. Rheumatol Int. 2008; 28: 1117-1121.*
25. *Bazzichi L, Giannaccini G, Betti L, et al. ATP, calcium and magnesium levels in platelets of patients with primary fibromyalgia. Clinical Biochemistry 2008; 1084-1090.*

26. Rosborg I, Hyllén E, Lidbeck J, et al. Trace element pattern in patients with fibromyalgia. Science of the Total Environment. 2007; 20-27.
27. Gerwin RD. Systemic perpetuating factors in myofascial pain syndromes. In: Simons DG, Travell JG and Simons LS. Myofascial pain and dysfunction: the trigger point manual 2nd ed, Baltimore: Williams and Wilkins; 1999. P. 178-228.
28. Shinchuk L, Holick MF. Vitamin D and rehabilitation: improving functional outcomes. Nutr Clin Pract. 2007; 22: 297-304.
29. Mouyis M, Ostor AJ, Crisp AJ, et al. Hypovitaminosis D among rheumatology outpatients in clinical practice. Rheumatology (Oxford). 2008; 47: 1348-1351.
30. Badsha H, Daher M, Ooi Kong K. Myalgias or non-specific muscle pain in Arab or Indo-Pakistanipatients may indicate vitamin D deficiency. Clin Rheumatol. 2009; 28: 971-973.
31. Whitehurst JL, Reid CM. Vitamin D deficiency as a cause of chronic pain in the palliative medicine clinic: two case reports. Palliative Medicine. 2014; 28(suppl 1): 87-89.
32. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-281.
33. Lewis JM, Coley JLB, Frontrier TH. Fibromyalgia syndrome and vitamin D. J Musculoskeletal Pain. 2011; 19: 164-166.
34. Garcion E, Wion-Barbot N, Montero-Menei CN, et al. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metabol. 2002; 13: 100-105.
35. Valença MM, Medeiros FL, Martins HA, et al. Neuroendocrine dysfunction in fibromyalgia and migraine. Curr Pain Headache Rep 2009; 13: 308-313.
36. Bilal A, Khan S, Irfanliqbal M, et al. Effect of vitamin D replacement in patients of fibromyalgia. A.P.M.C. 2009; 3: 51-58.
37. Abokrysha NT. Vitamin D deficiency in women with fibromyalgia in Saudi Arabia. Pain Medicine 2012; 13: 452-458.
38. Al-Allaf AW, Mole PA, Paterson CR, et al. Bone health in patients with fibromyalgia. Rheumatology (Oxford). 2003; 42: 1202-1206.
39. Manocha M, Khan WI. Serotonin and GI disorders: an update on clinical and experimental studies. Clinical and Translational Gastroenterology 2012; 3: 1-6.
40. Perez-Fernandez R, Alonso M, Segura C, et al. Vitamin D receptor gene expression in human pituitary gland. Life Sci. 1997; 60: 35-42.
41. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clinic Proceedings 2003; 78: 1463-1470.
42. Bhatty SA, Shaikh NA, Irfan M, et al. Vitamin D deficiency in fibromyalgia. Journal of the Pakistan Medical Association. 2010; 60(suppl 11): 949-951.
43. Heidari B, Shirvani S, Firouziahi A, et al. Association between nonspecific skeletal pain and vitamin D deficiency. International Journal of Rheumatic Diseases 2010; 3(suppl 4): 340-346.
44. Romano TJ, Stiller JW. Magnesium deficiency in fibromyalgia syndrome. J Nutr Med 1994; 4: 165-167.
45. Reinhard P, Schweinsberg F, Wernet D, et al. Selenium status in fibromyalgia. Toxicology Letters 1998; 97: 177-180.
46. Seferoglu B, Baykal T, Altas EU, et al. Trace element profile in patients with fibromyalgia syndrome. EFIC & ESPRM / Annals of Physical and Rehabilitation Medicine 2014; 57S: 260-261.
47. Abraham GE, Glechas JD. Management of fibromyalgia: a rationale use of magnesium and malic acid. J Nutr Med 1992; 3: 49-59.
48. Bagis S, Karabiber M, As I, et al. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? Rheumatol Int 2013; 33: 167-172.
49. Eisinger J, Plantamura A, Marie PA, et al. Selenium and magnesium status in fibromyalgia. Magnes Res 1994; 7(3-4): 285.
50. London M. The role of magnesium in fibromyalgia. MIT [internet]. 1994 [accessed March 21, 2016]. Available in: http://web.mit.edu/london/www.magnesium.html.
51. Eisinger J. Reactive oxygen species, antioxidant status and Fibromyalgia. J Musculoskeletal Pain. 1998; 5: 5-15.
52. Bray TM, Bettger WJ. The physiological role of zinc as an antioxidant. Free Radic Biol Med 1990; 8: 281-291.
53. Powell SR. The antioxidant properties of zinc. J Nutr. 2000; 130: 1447-1454.
54. Ozgocmen S, Ozyurt H, Sogut S, et al. Current concepts in the pathophysiology of Fibromyalgia: the potential role of oxidative stress and nitric oxide. Rheumatol Int 2006; 26: 585-559.
55. Magaldi M, Moltoni L, Biasi G, et al. Role of intracellular calcium ions in the physiopathology of fibromyalgia syndrome. Boll Soc Ital Biol Sper 2000; 76: 1-4.
56. Bendich A. Antioxidant micronutrients and immune responses. Ann N Y Acad Sci 1990; 587: 168-180.
57. Pamuk GE, Pamuk ON, Set T, et al. An increased prevalence of fibromyalgia in iron deficiency anemia and thalassemia minor and associated factors. Clin Rheumatol 2008; 27: 1103-1108.
58. Patterson AJ, Brown WJ, Roberts DCK. Dietary and supplement treatment of iron deficiency results in improvements in general health and fatigue in Austrian women of childbearing age. J Am Coll Nutr 2001; 20: 337-342.
59. Verdon F, Burnand B, Fallab Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ 2003; 326: 1124.