El hambre oculta y la fibromialgia: Una revisión sistemática

RESUMEN
Recientemente ha 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 esta 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. Se seleccionaron 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 musculosqueléticas 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 and 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. The condition affects around 1-4% of the population, with the highest prevalence among women 30 to 55 years of age. 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).

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. 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.

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. 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.

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.

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’, ‘copper’, ‘potassium’, ‘iodine’, ‘sodium’, ‘magnesium’, ‘seledunium’, ‘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.

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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 met the eligibility criteria adopted and correlated micronutrient deficiency to the presence of FM.
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. Twelve studies focused on women and two included both sex. 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.

Eight studies linked vitamin D deficiency to the presence of FM. However, only two papers found a positive correlation between low serum levels of vitamin D and FM. A case-control study conducted in Egypt observed that vitamin D deficiency was not more common in premenopausal female patients with FM than in the control group without FM. There was an association between pain and vitamin D levels in fibromyalgia.

Table 1. Observational studies of vitamin deficiency.

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

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\(^2\) 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\(^1\),\(^3\),\(^7\).

### Table 2. Observational studies of mineral deficiency.

<table>
<thead>
<tr>
<th>Author/Location</th>
<th>Study Design</th>
<th>Patients Characteristics</th>
<th>Control Characteristics</th>
<th>Indicator/_cut-off</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mader et al.(^2)(^3)</td>
<td>Cross-sectional, observational</td>
<td>N= 84 FM, female, Not anemic, Age: 52 ± 12 yrs</td>
<td>N= 87 Healthy, female, Not anemic, Age: 48 ± 12 yrs</td>
<td>Hemoglobin &lt;12 g/dL, Serum Fe &lt;40 μg/dL, Serum ferritin ≤30 ng/mL, Serum sTfR &gt;28.1 nmol/L</td>
<td>FM patients did not have reduced levels of Fe and other Fe storage markers.</td>
</tr>
<tr>
<td>Sakarya et al.(^1)(^2)</td>
<td>Cross-sectional, observational</td>
<td>N= 40 FM, premenopausal female, Age: 33.6 ± 7.6 yrs</td>
<td>N= 40 Healthy, premenopausal female, Age: 31.7 ± 7.0 yrs</td>
<td>Mn No cut-off values</td>
<td>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.</td>
</tr>
<tr>
<td>Kim et al.(^1)(^3)</td>
<td>Cross-sectional, observational</td>
<td>N= 44 FM, female, Age: 42.5 ± 6.9 yrs</td>
<td>N= 122 Healthy, female, Age: 44.2 ± 8.3 yrs</td>
<td>Analysis of hair minerals: Ca, Mg, Na, K, Zn, Mn, Se, Cr, P, Fe, Cu No cut-off values</td>
<td>The FM patients showed significantly lower levels of Ca, Mg, Fe and Mn.</td>
</tr>
<tr>
<td>Sendur et al.(^2)(^4)</td>
<td>Cross-sectional, observational</td>
<td>N= 32 FM F, Age: 42.9 ± 7.7 yrs</td>
<td>N= 32 Healthy F, Age: 41.3 ± 9.7 yrs</td>
<td>Serum concentration of Mg, Zn and Se No cut-off values</td>
<td>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.</td>
</tr>
<tr>
<td>Bazzich et al.(^2)(^5)</td>
<td>Cross-sectional, observational</td>
<td>N= 25 FM, 24 F and 1 M, Age: 48.8 ± 9.3 yrs</td>
<td>N= 25 Healthy, 24 F and 1 M, Age matched</td>
<td>Ca e Mg No cut-off values</td>
<td>There was a tendency of higher levels of Ca with significant Mg increases in FM patients compared to controls.</td>
</tr>
<tr>
<td>Rosborg et al.(^2)(^6)</td>
<td>Cross-sectional, observational</td>
<td>N= 38 FM Female, Age: 31-71 yrs</td>
<td>N= 41 Healthy Female, Age: 28-71 yrs</td>
<td>Ca, Cu, Fe, K, Mg, Mn, Na, Zn Ag, B, Ba, Br, Cd, Co, Cs, Hg, I, Li, Mo, Ph, Se, Rb, Sn; Sr, U, V No cut-off values</td>
<td>There were significant differences in urinary concentration of Ag between FM patients. The study did not show abnormal levels of trace patients with FM in agreement with the reference values for the population.</td>
</tr>
</tbody>
</table>

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 FM12,13,23,24,25,26. 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 checklist4 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

1. 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 FM10,27,28,29,30.

Patients with myofascial pain syndrome exhibit a high prevalence of vitamin inadequacy or deficiency27. Folic acid and vitamin B12 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 points27.

In this review, two studies identified a positive correlation between vitamin D deficiency and the presence of FM10,22 and two others identified an association between pain levels and vitamin D levels in FM15,17.

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 fatigue10,31. According to Schinchuk and Holick28, 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 blood32. 25-OHD is then metabolized in the kidneys by the enzyme 25-hydroxyvitamin D- 1alpha-25(OH)D. 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.31 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 systems41,43. 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 CNS35.

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 diseases34. 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, Matthana31 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 depression22. 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 functions36. 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 review22,24 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.37, their findings are in agreement with several studies reporting vitamin D deficiency in patients with musculoskeletal pain12,30,41,42,43.

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 Stiller44 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.57 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 FM13,24. 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 Stiller44, 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. 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. Other studies49,50 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, Eisinger51 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.42

Regarding Ca deficiency, a positive association was reported between Ca levels in the hair of women with FM.57 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.55 However, recent studies reported that alterations in the balance between oxidants and antioxidants may be associated with the presence of FM.46,54 Antioxidant enzymes, such as superoxide dismutase 2, which contains Mn in its composition, play an important role in antioxidant defense inside the mitochondria.48 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. 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.31 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**


