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Laura-Isabel Arranz, Miguel-Ángel Canela, Magda Rafecas

FIBROMYALGIA AND NUTRITION, WHAT DO WE KNOW?

Laura-Isabel Arranz[1], **Magda Rafecas**[2], **Miguel-Ángel Canela**[3]

1. Faculty of Pharmacy, University of Barcelona, Spain.
Joan XXIII, s/n. - 08028 Barcelona (Spain)
encavifibro@yahoo.es
Telephone: (+34) 93 403 48 41
Fax number: (+34) 93 403 59 31

2. Doctor, Department of Nutrition and Bromatology. Faculty of Pharmacy, University of Barcelona. Barcelona, Spain. magdarafecas@ub.edu
3. Doctor, Department of Managerial Decision Sciences, IESE Business School, Barcelona, Spain. Mcanela@iese.edu

Abstract

Objective: Many people suffer from fibromyalgia (FM) without an effective treatment. They do not have a good quality of life and cannot maintain normal daily activity. Among the different hypotheses for its ethiopathophysiology, oxidative stress is one of the possibilities. Non-scientific information addressed to patients regarding the benefits of nutrition is widely available, and they are used to trying non-evidenced strategies. The aim of this paper is to find out what we know right now from scientific studies regarding fibromyalgia disease and nutritional status, diets and food supplements. **Design:** A systematic search has been performed on Medline with a wide range of terms about these nutritional issues. **Setting:** the search has been made during 2009, for articles published between 1998 and 2008. **Subjects:** people suffering from FM. **Results:** Vegetarian diets could have some beneficial effects probably due to the increase in antioxidant intake. There is a high prevalence of obesity and overweight in patients, and weight control seems to be an effective tool to improve the symptoms. Some nutritional deficiencies have been described, it is not clear whether they are directly related to this disease or not. About the usefulness of some food supplements we found very little data, and it seems that more studies are needed to prove which ones could be of help. **Conclusions:** Dietary advice is necessary to these patients to improve their diets and maintain normal weight. It would be interesting to investigate more in the field of nutrition and FM to reveal any possible relationships.

Key words: fibromyalgia, nutrition, diet, antioxidants, nutritional supplementation.

Introduction

Over the 1970s fibromyalgia syndrome (FM) began to be identified as a distinct clinical syndrome, different from other rheumatic illnesses. The WHO and all international medical organisations did not recognise it as a disease until 1992. Nowadays it is classified as a rheumatic disease with an unknown aetiology and without an effective medical treatment. FM is a condition characterised by widespread pain in 11 of 18 tender points experienced for at least 3 months [1]. The 1990 American College of

Rheumatology classification criteria are widely used for the diagnosis of fibromyalgia and provide a sensitivity and specificity of nearly 85% differentiating FM from other forms of chronic musculoskeletal pain. As well as pain, patients commonly report some other symptoms such as fatigue, sleep disorders, depression, anxiety, cognitive difficulties, headache, low back pain, and illnesses like irritable bowel syndrome, chronic fatigue syndrome, rheumatoid arthritis, systemic lupus erythematosus, and osteoarthritis. FM has an enormous impact on the quality of life (QOL) of patients who experience a reduced functionality or capacity to carry on the activities of daily living; every day activity becomes more difficult, more time consuming, or simply impossible.

Fibromyalgia syndrome and rheumatoid arthritis are among the most common causes of musculoskeletal pain and disability. The prevalence of fibromyalgia has not been determined using a large or international population base, but it is commonly estimated to affect 1 to 2% of the population [2-5], although some studies show higher figures, even up to 5% [6, 7]. In Spain it is calculated to affect 2.4% of the general population [8-10], although in other studies the Spanish prevalence seems to be around 4% or more [11]. The results in an Italian survey study show a prevalence of 2.2% [12]. Also, a very recent study estimates that the prevalence of fibromyalgia in the French population is 1.4% [13]. Females are more likely than males to have fibromyalgia and patients with fibromyalgia are more likely to have one or more comorbid conditions such as depression, anxiety, headache, irritable bowel syndrome, chronic fatigue syndrome, systemic lupus erythematosus and rheumatoid arthritis [2]. The absence of fibromyalgia in China is an interesting issue, which could be explained by genetic differences and, maybe, by socio-cultural differences. It could be worthwhile to study and compare the prevalence gradients from China to the ones in the western world, which might provide important insights into what causes this disease [14].

Since FMS aetiology and physiopathology are unknown, it is difficult to find an effective and curative treatment, either pharmacological or non-pharmacological. There is an interesting hypothesis about the pathophysiologic mechanism, which is widespread in the scientific literature, the oxidative stress hypothesis. Some studies try to explain how oxidative stress (OE) may be involved in the development and maintenance of this syndrome. For instance, it has been observed that some FM patients had lower levels of some antioxidant nutrients like magnesium and selenium [15, 16]. They also seem to have an insufficient antioxidant status [17], a predominance of a pro-oxidative status [18], and a lower antioxidant capacity [19]. The results indicate that these patients have a high level of oxidative stress and perhaps the high levels of free radicals in their bodies may be involved in the development of the disease. Some studies have investigated thoroughly the mechanisms of cellular oxidation. Nitric oxide (NO) and its derivative peroxinitrite ($ONOO^-$) are often said to have a relevant role in this process. $ONOO^-$ is a powerful oxidant agent which is the result of the combination of the NO and the superoxide radical (O_2^-). These agents seem to act as initiators of an oxidation reactions cycle which is not totally counteracted by the antioxidant defences. This may be a potential cause of the development of FM and also of chronic fatigue syndrome (CFS) [20-22].

Some of the studies indicated above consider that an antioxidant supplementation might be beneficial in the treatment of FM, because of its high oxidative stress status as well as its inflammation level. In relation to this, there are data from nutritional interventions in which antioxidant intake was increased through a vegetarian diet, with positive

results on rheumatic and FMS patients [23-24]. However this is a matter that would need more evaluation.

The case that in CFS patients as well as FM patients there is a high level of oxidative stress seems widely proved. However, it is unknown whether it is a cause or a consequence. The musculoskeletal symptoms are related to an increase in oxidative stress but also to a decrease of the antioxidant defences [25]. OE causes cellular damage, affecting a wide range of levels and functions like the lipidic peroxidation, cell membrane functionality and prostaglandin synthesis [26]. Another study shows that the higher level of OE or prooxidant substances in erithrocytes damages them and alters their normal functionality, contributing to the CFS symptoms [27].

Since the discovery of mythocondrial disfunction, medicine has advanced in the understanding of the roles of these cellular organelles in some diseases and in aging. Some illnesses, like FM and CFS, seem to have common pathophysiological mechanisms, which involve free radicals, their accumulation in mitochondria and DNA damage [20]. More than 90% of cell energy is produced in mitochondria, through oxidative phosphorylation and through the coordination of two close processes, the tricarboxylic acid cycle (or Krebs cycle) and the electron transport chain, involving different reactions, enzymes, coenzymes and nutrients acting as cofactors. In the Krebs cycle cysteine, iron, niacin, magnesium, manganese, thyamine, riboflavin, pantothenic acid, lipoic acid and L-carnitine are all involved. In the electron transport chain, coenzym Q10, flavines, copper and iron among others, are of a high importance. The correct functioning of all these reactions depends on the presence of high enough quantities of these nutrients. During the oxidative phosphorylation process, consumed oxygen is converted into superoxide radicals, but the mitochondria have mechanisms to eliminate this in aqueous form, with the help of the superoxide dismutase (SOD-Mn) and the glutathione peroxidase (GPX). These antioxidant enzymes are very important because mitochondrial lipids, proteins, enzymes and DNA are especially vulnerable to free radical action. The mitochondria may lose functionality when their components are damaged, and this could lead to a feed-back process that causes additional injuries. When the superoxide radical is not sufficiently neutralised by these protective mitochondrial processes, it combines with nitric oxide leading to the more oxidant free radical, peroxinitrite, and therefore to an oxidative stress situation in cells.

Apart from oxidative stress, another theory for the pathophysiologic mechanism of FM is the immunological theory, involving inflammatory cytokines. Although very few studies have shown elevated cytokine levels in FM, the data available suggest that a high chemokine level may play a causative role in this disease [28-29]. Cytokines are known to play a role in diverse clinical processes and phenomena such as fatigue, fever, sleep, pain, stress and aching. A review of the fibromyalgia literature and related studies suggest that IL-1, IL-6 and IL-8 are deregulated in the syndrome. Therefore, therapies directed against these cytokines may be of potential importance in the management of fibromyalgia, and could be more closely studied in the future [30].

In relation to the management of the disease, recent reviews show which interventions are more effective by reducing the symptoms of the disease, mainly pain but also fatigue and cognitive damage, and also reveal the fact that multidimensional approaches are the most appropriate to these patients. Some drugs, physical activity, relaxation techniques, and cognitive behaviour therapy are the most useful tools [31,32]. Although

various pharmacological treatments have been studied for treating FMS, no single drug or group of drugs has proved to be useful in treating the disease as a whole. Several agents, including serotoninorepinephrine reuptake inhibitors (ie., duloxetine and milnacipran), opioids (ie., tramadol), and the $\alpha 2-\delta$ ligand pregabalin, have recently received the U.S. Food and Drug Administration approval for treating the syndrome in the United States. They have been evaluated in clinical trials, showing a positive effect in terms of pain reduction and improvement in core symptoms such as fatigue and sleep disturbance [33,34].

Regarding non-pharmacological therapeutic approaches there are some data from different reviews. Some have demonstrated strong evidence for efficacy, like cardiovascular exercise, cognitive behavioural therapy, patient education, and multidisciplinary therapy. In addition other adjunctive treatments show moderate evidence of efficacy, like strength training, acupuncture, hypnotherapy, biofeedback and balneotherapy [35]. For other non-pharmacological approaches, widely used and potentially beneficial, such as ozone therapy and some food supplements, more investigation is needed [36].

In summary, at present there is no cure for FM and no universally effective treatment, so physicians are searching for the best way to manage fibromyalgia. There are some aspects that could need more investigation like, for example, how nutrition may affect the clinical symptoms of these patients. Since this disease affects a significant proportion of the population, with various degrees of impact on disability and quality of life, it results in a significant number of physician visits, work disability, and medication use. Therefore it is of a crucial relevance to review what is known and to investigate what else could be done to improve health and quality of life in these patients.

The primary purpose of this review is to find out what we know about the possible relationship between nutrition and FM, and to look at the main studies carried out on nutritional evaluation and intervention. In this report we have analysed the current knowledge related to this disease and diet, nutritional status and nutritional supplementation.

Experimental methods

Studies in humans were identified through a systematic and computerised search of MEDLINE. The languages of the studies selected were English as well as Spanish, and the range of publication date from 1998 to 2008. The main terms for the systematic search were fibromyalgia in combination with nutrients, food intake, dietary patterns, nutritional supplementation, complementary medicine, vegan diet, antioxidants, dietary modification, obesity, body mass index, and others indicated in table 1. Only those papers which studied directly or indirectly the relationship we looked for were selected. Reference lists of the included articles were also scrutinized to search for relevant studies, and in some cases led to a new search to get new papers, or to contact authors for further details of their trials, in particular when the full study report was not available.

Results

Fibromyalgia, diet and nutrition

Fibromyalgia, as a rheumatoid disease where chronic inflammation and oxidative stress are main concerns, may have some benefits from diets rich in antioxidants, like those based on uncooked vegan products called living food (LF) [23]. Patients eating LF showed higher levels of beta and alfa-carotenes, lycopen and lutein, vitamin C and vitamin E in their serum, than the controls eating a normal diet. Also, levels of polyphenolic compounds like quercetin, myricetin and kaempherol were much higher than in the omnivorous controls. Moreover, the clinical outcomes of this intervention for fibromyalgic subjects were an improvement in their joint stiffness and pain as well as an improvement in their self-experienced health.

Due to this possibility of benefit from the vegan diet rich in antioxidants in these patients, some other studies evaluated the effects of vegan diets on the symptoms of FM. Two of them compared the effect of changing an omnivorous diet for a vegetarian diet, without making any change in the medical treatment of the patients. The third compared the effect of the vegetarian diet against the effect of a pharmacological treatment with amitriptyline.

The first one [37], a non-randomised and controlled study, evaluated the effect of a strict, low-salt, uncooked vegan diet rich in lactobacteria, on symptoms in 18 fibromyalgia patients, during a 3-month intervention period. A 15-patient control group continued their omnivorous diet during the same time. The results were evaluated with a Visual Analogue Scale (VAS) of pain, joint stiffness and quality of sleep, and with a Health assessment questionnaire (HAQ), General Health Questionnaire (GHQ), and the rheumatologist's own questionnaire, indicating an improvement in the outcomes. Patients showed a reduction in body mass index (BMI), total cholesterol and urine sodium, indicating good diet compliance. In conclusion, the results suggested that a vegan diet has beneficial effects on fibromyalgia symptoms, at least in the short run.

In the second study [24], 30 people participated in a dietary intervention using a mostly raw, pure vegetarian diet, consisting of raw fruits, salads, carrot juice, tubers, grain products, nuts, seeds, and a dehydrated barley grass juice product. The outcomes measured were dietary intake and different disease/health scales such as the Fibromyalgia Impact Questionnaire (FIQ), the short form health survey (SF-36), a quality of life survey, and a physical performance measurement. The intervention was of seven months and after this period all the respondents, 19 out of 30 subjects, had a significant improvement in all measured outcomes, except for body pain. At the end of the study the scores for all the scales, except body pain, were no longer statistically different from healthy women aged 45-54. To carry on the dietary intervention, all the participants were informed at the beginning of the study, but they did not receive regular support meetings for motivational encouragement because the researchers considered that this might make the results less applicable to the general population. This study concluded that this sort of dietary intervention can help fibromyalgia patients.

Considering Donaldson's study, Bennett concluded that many FM patients could be helped by recommending a mostly raw vegetarian diet, but he encouraged the

researchers to repeat the study with a control group. Although it is difficult to design a double-blind placebo control for dietary studies, it would be interesting and possible to use a different diet control group, distinct from the raw vegetarian one [38].

For the third study, since it was known that brain tryptophan is low in FM, and intake of protein rich in large neutral amino acids has been reported to lower it, an open, randomised and controlled study [39], was undertaken to assess whether any reduction of such proteins by exclusion of animal protein from the diet reduced pain and morbidity in FM patients compared with the reduction by a pharmacological agent. 37 subjects with FM were enrolled in a vegetarian diet and 41 in a pharmacological amitriptyline treatment group. The outcome was assessed with the help of a tender point count, and VAS scale of frequencies of fatigue, insomnia, non-restorative sleep and pain. The differences were significant at 6 weeks of treatment, showing improvement in the amitryptyline group. In the vegetarian diet group all of them were insignificant, except in pain score. However, the decrease in the pain score, though significant, was much smaller than in the amitriptyline group. As a result the authors concluded that due to the differences between both groups the vegetarian diet exclusively is a poor option in the treatment of fibromyalgia.

Composition and alterations in the intestinal bacterial flora are believed to be contributing factors to many chronic inflammatory and degenerative diseases, since the flora act as an important immunologic protection barrier. However, the relationship between possible changes in intestinal flora, secretion of immunoglobulin A, and specific illnesses is unknown. One study [40] was performed to test whether a Mediterranean diet and an 8-day fasting period led, in patients with rheumatoid arthritis or fibromyalgia, to some changes in faecal flora and in clinical outcome. 51 patients participated and none of the two dietary interventions, in the way they were carried out, led to change, neither in intestinal microflora nor in the clinical parameters tested. So the impact of dietary interventions on the human intestinal flora and the role of this in rheumatic diseases still need to be clarified.

Monosodium glutamate (MSG) and aspartame could act as excitotoxin molecules in organisms, acting as excitatory neurotransmitters, and may lead to neurotoxicity when used in excess [41]. The elimination of MSG and aspartame from the diets of 4 fibromyalgia patients with multiple co-morbidities produced a resolution of their symptoms within months after the intervention. It is known that intramuscular injection of glutamate into the human masseter muscle evokes muscle pain, which is stronger in women. However, the effect of dietary glutamate consumption on these patients is not well known. When relatively high concentrations of glutamate are ingested without food, a short-lived increase in serum and intramuscular glutamate concentrations is observed. However, the effects on tissue levels of dietary glutamate and the role in the development and maintenance of chronic musculoskeletal pain such as that in patients with FM are not well understood. This suggests that research with larger number of patients with similar conditions is needed to confirm the effectiveness of this dietary treatment [42, 43].

Nowadays the internet has become a major source of information, and lots of patients with FM use some treatments that mostly lack scientific evidence. This is the case of the 'elimination diet', based on identifying and avoiding irritant foods for which these patients may have a subclinical allergy. It consists of a rotation of foods with close

attention to the effects; specific foods are introduced into the diet at the rate of 1 per 5 days. An "oligoantigenic" diet is another method of food therapy without scientific basis, in which modern manufactured foods are removed from the diet and replaced with the palaeolithic equivalents [44]. Moreover, in some websites, journals and books addressed to FM patients, information regarding the potential benefit of macrobiotic diets and foods is frequently found. Despite this, in our search we have not found any article that deals with these issues. On a practical basis some patients are recommended to avoid those foods which cause them subjective worsening of their symptoms.

Mood, anxiety and eating disorders are of a higher prevalence in FM patients. There is a significant co-occurrence of FM with some psychiatric disorders and eating disorders, such us nervous anorexia and bulimia which have a relevant incidence among this people [45]. It has been observed that binge eating disorders co-occurred significantly with FM disease [46]. Therefore, on a practical level, if FM patients are more likely to have these eating disorders, special attention should be given to that when evaluating and treating them.

Fibromyalgia and nutritional status

A study based on an Internet survey addressed to people with fibromyalgia, developed by the National Fibromyalgia Association (NFA) of the United States, and responded to by about 2500 participants, identified several issues for further research such as the prescribing habits of FM health care providers and the impact of obesity among others. In comparison with United States National Census figures, respondents were moderately overweight, 70% had a BMI > 25, and 43% had a BMI > 30; higher figures comparable with the general population [47]. Several other studies have reported obesity problems in FM [48-50] and others had reported that weight reduction provides improvement to these patients [51]. In fact, overweight and obesity are highly frequent in these people, and body mass index has a negative correlation with quality of life and tenderness threshold, and a positive correlation with physical dysfunction and pain point count. Obese FM patients show higher pain sensitivity and lower levels of quality of life [52]. The high prevalence of overweight and obesity was showed also in a health telephonic survey made only on female participants, with and without FM. However, up to now, it does not seem possible from available current data to determine if weight gain, experimented in these persons, especially in women with FM, is due to the disease and its accompanying low activity levels, or if those women are more prone to premorbid obesity than healthy ones [53]. Nevertheless, sound research has offered us results on the improvement for multiple musculoskeletal complaints and function, usually measured as quality of life by a health questionnaire like SF-36, through weight loss in obese people [54]. It is known that obesity is associated with a range of disabling musculoskeletal conditions, like FM, especially in adults. As the prevalence of obesity increases, the social burden of these chronic musculoskeletal conditions, in terms of disability, health-related quality of life, and health-care costs, also increases. Therefore weight reduction is an important tool in ameliorating some of the manifestations of musculoskeletal diseases and improving function and patients' quality of life [55].

Another characteristic found in FM patients is a higher resting metabolic rate (RMR) compared with healthy controls. In both groups RMR was measured by indirect calorimetry, and predicted RMR, by fat-free weight, sex, age, height and weight. This high measured RMR was not correlated with thyroid hormones TSH, FT4 and FT3 [56].

This study began with the hypothesis that FM patients could be hypometabolic due to hypothyroidism, because of some beneficial results found in some thyroid hormone treatment trials. However TSH, T3 and T4 levels did not significantly differ between patients and the control group.

Patients with fibromyalgia commonly have a high body mass index and are physically inactive, which are two main risk factors for metabolic syndrome. Although there is not enough sound knowledge about the relationship between FM and metabolism we found one study conducted on women with chronic pain from FM which concluded that they have an increased risk of suffering from metabolic syndrome. So it recommended that these people should be educated about the benefits of physical exercise and weight loss, to reduce their metabolic risk as well as improve of pain and general health [57].

Another important aspect of nutritional status is the possibility of some nutritional deficiencies. It has been proposed that some of them are involved in FM patient symptoms, although there is no study that globally evaluates them. We have found in this revision isolated studies that focus on the potential role in the pathogenesis of FM of some possible nutritional deficiencies such as for magnesium, iodine, iron, vitamin D, melatonin, and branched chain amino acids.

Iodine deficiency is hypothesised to give rise to subtle impairment of thyroid function leading to clinical syndromes, like those in fibromyalgia, without either biochemical alterations in T3, T4 and TSH or clinical manifestations such as goiter and cretinism [57]. It has also been pointed that selenium, zinc, iron or retinoic acid disbalance could lead to the clinical effects of iodine deficiency due to their role in optimal thyroid function. It is known that the more symptoms of hypothyroidism are present, the more likely the presence of FM becomes [58]. There is not a total evidence of iodine deficiency in FM, but this issue deserves some attention because this nutritional impairment is a worldwide health problem.

Regarding iron, an increased frequency of FM in iron deficiency anaemia (IDA) and in thalassemia minor (TM) was diagnosed in a study. Some nonspecific symptoms of IDA and TM, like impaired cognitive function, fatigue or inability to concentrate, may not be explained by only anaemia, and consequently may not respond to therapy. In these cases considering the possibility of a FM diagnosis is recommended, since in this study the results show higher prevalence of FM in IDA and TM patients [59]. A second step will be to understand the role that iron replacement therapy could play in some cases suffering from FM and IDA or TM at the same time.

A pilot study concluded that FM was frequently associated with osteoporosis, and thus early detection and implementation of appropriate nutritional supplementation with calcium and vitamin D could be useful [60]. Vitamin D deficiency was found to be common in FM women, although they were not at an increased risk of developing osteoporosis or osteomalacia, since bone density in them was comparable with that in controls [61]. On the contrary, the highest prevalence of hypovitaminosis D, over 92.7%, was found in a group of people with nonspecific musculoskeletal pain [62]. Although this study recommended urgent general screenings of FM patients and treatment with vitamin D for replenishment, it was criticised by other authors, which have obtained different and contradictory results [63]. In those, low vitamin D levels were not associated with diffusing musculoskeletal pain, and treatment with this

nutrient did not reduce pain [64]. Recent studies have confirmed that FM patients have vitamin D deficiencies or insufficient levels compared with local healthy references. Even within those with hypovitaminosis D there is a higher prevalence of anxiety and depression. Therefore more clinical studies are needed to fully assess the impact of vitamin D in these patients, in order to reach a consensus and improved guidelines for rheumatologists [65, 66].

Some trace elements have been supposed to have a relevant role in the pathophysiology of FM, especially those related to the redox balance in cells, like selenium, zinc and magnesium. An examination of serum levels of these three elements in FM patients showed that magnesium and zinc levels were decreased, compared with controls, and there was no considerable difference in selenium levels. Moreover, serum magnesium and zinc levels were associated with clinical parameters, indicating a possible role of these two trace elements in FM ethiopathogenesis [67]. However, this study did not evaluate whether there was a nutritional deficiency or a low magnesium or zinc intake from the diet. In our search we have not found any study on the possible deviation of nutrient intake in patients with FM, compared with recommendations for general population. On the other hand, another recent study could not conclude that there are abnormal levels of copper, iron, magnesium, selenium and zinc, among others, in blood or urine of FM patients. Although there were some differences between them and controls, they were of no clinical significance. Therefore, these results gave no support to the hypothesis that trace elements unbalance could play a significant role in the development of this disease [68]. Otherwise, some other data indicated that this is not a clear issue and contradictory results appeared regarding some trace element levels in this disease, showing some normal levels for Se and Mg [69] and others lower levels for Se [70].

Nevertheless, these trace elements are highly important in maintaining the oxidants/antioxidants balance in the body. When the total antioxidant capacity is measured in these patients, it seems that they are exposed to a higher oxidative stress than healthy controls, reinforcing its possible role in etiopathogenesis and the possible positive effectiveness of therapy with antioxidant vitamins such as vitamins C and E [19].

Based on the hypothesis of possible tryptophan deficiency or metabolism disorders, one study investigated this issue by means of a nutritional intervention consisting of tryptophan depletion in patients with FM. The results showed some differences between FM patients and healthy subjects: IL-6 levels markedly increased during tryptophan depletion in FM patients but not in the control group. This increase seemed to be caused by the general setting of the amino acid beverage and not by the tryptophan depletion, as it was detected under this condition and also the sham depletion. Since both are objectively unpleasant, therefore, the IL-6 elevation may reflect the effect of acute stress [71]. An altered response of IL-6 to a physiologic stressor supported the notion that FM may represent a primary disorder of the stress system [72]. Otherwise we have not found any study comparing the nutritional status with the inflammatory status of these patients.

FM pain has been related to a deficiency of serotoninergic function, with a lower total plasma tryptophan concentration, which is known to be its precursor, as well as a lower ratio of plasma tryptophan to the amino acids valine, leucine, isoleucine, phenylalanine

and tyrosine, which compete with tryptophan for the same cerebral uptake mechanism. However, these results have not been confirmed by other studies which evaluated them as well as plasma concentrations of the branched chain amino acids (BCCAs) [73]. Due to the possible malfunction of energy metabolism of the muscle fibers of FM patients, it has been shown that a reduced plasma concentration of the branched chain amino acids, valine, leucine and phenylalanine, exists in these people and could potentially contribute to muscle energy depletion. Although these results are very interesting, more studies are needed to confirm that this deficiency might play a role in the pathophysiology of fibromyalgia, and to clarify whether it is due to a low dietary intake or not, and whether supplementation with BCCAs could help these patients.

Lower levels of melatonin were also found in FM patients compared to normal controls and, although circadian disturbances cannot be the cause of FM, melatonin replacement reduced complaints. Because of the good safety profile of melatonin, without either hang-over or tolerance development, the authors recommended considering using it as treatment, even more in cases when a deficiency may occur, such as in people suffering from FM [74].

Finally, we would like to highlight that although there is no a sound evidence of possible nutritional deficiencies in FM, there is enough data to encourage more investigation in this matter.

Fibromyalgia and nutritional supplementation

Since there is no therapeutic solution for the treatment of fibromyalgia, a substantial amount of non-scientific literature has arisen concerned with the potential benefits of some products based on nutritional ingredients or botanicals. However when scientific information is searched in databases such as Medline, very few studies are found.

Our search was based on the most popular nutritional remedies, and the results are summarised in table 2. The reports found were about the use of Chlorella pyreinoidosa, 5-Hydroxytryptophan (5-HTP), acetyl-L-carnitine, Coenzyme Q10, Ginkgo biloba, collagen hydrolysate, ascorbigen, and S-adenosyl-L-methionine. All of them reported possible benefits for FM patients, ameliorating symptoms such as pain, fatigue, morning stiffness, and quality of life, measured all with similar, but not equal, tests. Regarding 5-HTP we have included three articles dated before 1998, which are out of the time range of this review because they were used in Birdsall's review in 1998. At the moment, these reports are difficult to compare because of the differences in some aspects such as assessment tools, clinical variables evaluated, doses, time for supplementation, among others.

Although there is not enough evidence for all the nutritional supplements mentioned above, these studies point to the possibility of using them to reduce FM symptoms. Therefore, it is generally observed that when some nutritional supplementation is used, whatever it is, patients frequently report positive effects, mainly in pain, fatigue and capacity for carrying on their daily activities, although there is never a total recovery [88]. Positive effects on chronic fatigue syndrome, but not directly on FM, have been described in some studies on different nutritional supplements [89].

Due to the possible relationship between a high oxidative stress and fibromyalgia, some of the reports reviewed in this paper have recommended more investigation about the potential effects of nutritional antioxidants supplementation. Nevertheless in our search we have not found enough studies to thoroughly evaluate this hypothesis.

Discussion

Fibromyalgia reduces the quality of life of many people in the world and is an important current public health issue. It is a chronic rheumatic disease, but its cause is unknown. There is no an effective treatment for this illness, and at the moment all the studies point to a multidimensional approach, recommending some pharmacological remedies as well as physical activity, relaxation techniques, and other tools. In response to the large amount of non-scientific information regarding the possible benefits of some diets, and food supplements for FM, the purpose of this review was to evaluate this hypothesised relationship between fibromyalgia and nutritional factors.

The data reviewed suggest that some nutritional interventions, such as those focused on the maintenance of weight within normal ranges, could help on FM symptoms, even more so when it is known that within this population the prevalence of overweight and obesity, as well as some eating disorders, are higher than in the general population. Vegetarian diets also seem to have a positive effect, but more complete studies are needed to confirm this. Regarding the use and benefits of elimination diets, based for example on identifying and avoiding potentially irritant food for these patients, we have not found any article dealing with these issues.

Some deficiencies have been proposed to be involved in FM patients, although we have not found any study that globally evaluates them. We have found isolated studies which point to possible nutritional deficiencies for magnesium, selenium, zinc, iodine, iron, vitamin D, melatonin, branched chain amino acids, etc. Moreover FM is hypothesised to be associated with osteoporosis, hypothyroidism, anaemia, hyposerotoninergic function, and other metabolism disorders, although for none of them has a clear relationship been established.

The usefulness of some nutritional supplements has been evaluated in some studies, in general terms with positive results. Those we have found propose the use of some botanicals like Chlorella pyreinoidosa algae and gingko biloba, some antioxidants like coenzyme Q10 and ascorbigen, and other substances like acetyl-carnitine, collagen and S-adenosyl-L-methionine. However, none of the studies found are enough to generally recommend the use of a concrete food supplement in FM patients in order to reduce their symptoms. With the current data available it is reasonable to recommend carrying on more clinical trials to evaluate the benefits of a nutritional supplementation on this disease.

Since there is no a whole solution for the treatment of FM, and some of the studies reviewed show possible benefits of diet, it seems reasonable to manage the dietary habits of these patients, to ensure an optimal nutrient intake, avoiding possible deficiencies, and to help them maintain a healthy weight.

In summary, this review reveals a possible benefit of improving dietary behaviour on normal weight maintenance in this population, and even using some nutritional

supplementation to achieve an optimal nutritional status. This is encouraging, and therefore we suggest that more investigation is required in order to understand more details about the potential benefits for FM from nutrition. We conclude that, at the moment, it is necessary to give dietary advice to these patients to improve their diets and maintain a normal weight as well as good health.

We would like also to note that due to our search being restricted to only the Medline database, there could be other relevant studies not evaluated in this paper.

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Table 1. Search criteria.

		Search Results Medline	
Subjects	**Search criteria**	**Total**	**Selected**
Common key word	Fibromyalgia	4224	87
	plus		
Other key words			
Nutritional status	obesity	159	44
	nutritional status		
	body mass index		
	weight loss		
	eating disorders		
	deficiency		
	depletion		
	osteroporosis		
	trace elements		
Nutrition and Diets		52	23
	nutrition		
	diet		
	food intake		
Nutritional supplementation		82	20
	nutritional supplementation		
	complementary and		

alternative medicine

vitamins

minerals

antioxidant supplementation

magnesium

selenium

zinc

tryptophan

coenzym Q10

amino acids

polyunsaturated fatty acids

nutraceuticals

Table 2. Search results for nutritional supplements and fibromyalgia.

Study references	Type of study	Nutritional supplemen-tation	Dose and time	n	Results or Conclusions	Assessment tools or clinical variables evaluated
Caruso I, et al. 1990 [75]	Double-blind, placebo-controlled study	5-HTP	100 mg of 5-HTP three times daily for 30 days.	50	Significant improvement in symptoms, including pain,morning stiffness, anxiety, and fatigue.	Number of tender points, subjective pain severity, morning stiffness, sleep patterns, anxiety ratings, fatigue ratings
Puttini PS, et al. 1992 [76]	Long-term, open study	5-HTP	100 mg of 5-HTP three times daily for 90 days.	49	Significant improvement in symptoms, including pain, morning stiffness, anxiety, and fatigue.	Number of tender points, pain intensity, sleep quality, morning stiffness, anxiety, fatigue.
Nicolodi M, et al. 1996 [77]	No data	5-HTP	400 mg/day and 200 mg/day+IMAO for 12 months	200	Significant pain improvement in 5-HTP group and in the 5-HTP+IMAO	Daily pain diary by a Visual Analogue Scale (VAS).

					group.	
Birdsall TC. 1998 [78]	review of clinical studies	5-HTP			Significant improvement in symptoms, including pain, morning stiffness, anxiety, and fatigue.	
Merchant RE, et al.2000 [79]	pilot study	Chlorella pyrenoidosa	10g tablets &100ml extract daily 2 months	18	Possibly useful	Tender points index, VAS, Health Assessment Questionnaire (HAQ)
Merchant RE, et al. 2001 [80]	Double-blind, placebo-controlled, crossover study	Chlorella pyrenoidosa	10g tablets &100ml extract daily 3 months	34	Dietary Chlorella supplementation may be useful in relieving symptoms of FM	Tender points index, Fibromyalgia Impact Questionnaire (FIQ), VAS
Merchant RE, et al. 2001 [81]	Review of double-blind, placebo-controlled, randomized clinical trials	Chlorella pyrenoidosa			For most subjects with FM, dietary Chlorella supplementation helped to relieve symptoms.	Tender points index and FIQ
Rossini M, et al. 2007 [82]	Double-blind, multicenter randomized clinical trial, placebo-controled	Acetyl-l-carnitine (LAC)	2 capsules/day of 500 mg of LAC and one i.m. Injection of 500 mg LAC for 2 weeks, and 3 capsules/day of 500mg of LAC for 8 weeks	102	"Total myalgic score" and number of positive tender points declined with the treatment. Most VAS scores significantly improved in both groups. Improvements in SF36 questionnaire, depression	Tender points, total myalgic score, Short Form SF-36 Health Questionnaire, VAS for stiffness, fatigue, tiredness on awakening, sleep, work status, depression, muskular-skeletal pain, Hamilton Depression Rating Scale (HDRS).

					and musculo-skeletal pain.	
Lister RE. 2002 [83]	Pilot clinical study	Coenzyme Q10 + Ginkgo biloba extract	200 mg coenzyme Q10 + 200 mg Ginkgo biloba extract daily for 84 days.	25	Improvements of quality of life scores in patients with FM	Dartmouth Primary Care Cooperative Information Project/World Organization of Family Doctors (COOP/ WONCA) Quality of life Questionnaire
Olson GB, et al. 2000 [84]	Clinical study	Collagen hydrolysat	90 days	20	Pain complaint levels decreased significantly, specially patients with fibromyalgia and concurrent temporomandibular joint problems.	Average pain complaints
Bramwell B, et al. 2000 [85]	Prelimi-nary trial	100mg ascorbigen + 400mg broccoli powder /day	30 days	12	Reduction of sensitivity to pain and improvement in quality of life measured.	FIQ, tender points
Jacobsen S, et al. 1991 [86]	Double-blind clinical study	S-adenosyl-L-methionine	800 mg/day/6 weeks	44	Improvements for clinical disease activity, pain, fatigue, morning stiffness and mood.	Tender point score, isokinetic muscle strength, disease activity, VAS, mood parameters
Fetrow CW, et al. 2001 [87]	Review	S-adenosyl-L-methionine	200 to 600mg/day/ during 2 to 4 weeks	10 to 47	Reduced tender point pain	VAS

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