

## Fibromyalgia and nutrition, what do we know?

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

Received: 3 December 2009 / Accepted: 12 March 2010 / Published online: 1 April 2010  
© Springer-Verlag 2010

**Abstract** 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. A systematic search has been performed on Medline with a wide range of terms about these nutritional issues. The search has been made during 2009, for articles published between 1998 and 2008. Target population: people suffering from FM. 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. 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.

**Keywords** 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

---

L.-I. Arranz (✉)  
Faculty of Pharmacy, University of Barcelona,  
Joan XXIII, s/n., 08028 Barcelona, Spain  
e-mail: encavifibro@yahoo.es

M.-Á. Canela  
Department of Managerial Decision Sciences,  
IESE Business School, Barcelona, Spain  
e-mail: Mcelona@iese.edu

M. Rafecas  
Department of Nutrition and Food Science,  
Faculty of Pharmacy, University of Barcelona,  
Barcelona, Spain  
e-mail: magdarafecas@ub.edu

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 FM has not been determined using a large or international population base, but it is commonly estimated to affect 1–2% 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 FM in the French population is 1.4% [13]. Women are more likely than men to have FM and patients with FM 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 FM in China is an interesting issue, which could be explained by genetic differences and, maybe, by sociocultural 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 peroxynitrite ( $\text{ONOO}^-$ ) are often said to have a relevant role in this process.  $\text{ONOO}^-$  is a powerful oxidant agent which is the result of the combination of the NO and the superoxide radical ( $\text{O}_2^-$ ). 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 not only to an increase in oxidative stress but also to a decrease in 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 erythrocytes damages them and alters their normal functionality, contributing to the CFS symptoms [27].

Since the discovery of mitochondrial dysfunction, medicine has advanced in the understanding of the roles of these cellular organelles in some diseases and in ageing. 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, thiamine, riboflavin, pantothenic acid, lipoic acid and L-carnitine are all involved. In the electron transport chain, coenzyme 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 feedback 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, peroxynitrite, 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 FM 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 FM 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 serotonin-norepinephrine reuptake inhibitors (i.e., duloxetine and milnacipran), opioids (i.e., tramadol) and the  $\alpha 2$ - $\delta$  ligand pregabalin have recently received the US 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 FM. 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 FM 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 scrutinised 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 alpha-carotenes, lycopene 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 kaempferol were much higher than in the omnivorous controls. Moreover, the clinical outcomes of this intervention for FM 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.

**Table 1** Search criteria

Subjects	Search criteria	Search results medline	
		Total	Selected
Common key word	Fibromyalgia	4,224	87
	Plus		
Other key words			
Nutritional status	Obesity	159	44
	Nutritional status		
	Body mass index		
	Weight loss		
	Eating disorders		
	Deficiency		
	Depletion		
	Osteoporosis		
	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		

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 FM 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 FM 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 7 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 FM 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. Thirty-seven 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 amitriptyline 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 FM.

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 FM, to some changes in faecal flora and in clinical outcome. A total of 51 patients participated and none of the two dietary interventions, in the way they were carried out, led to change, neither in the 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 four FM 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 as 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 FM, developed by the National Fibromyalgia Association (NFA) of the US, and responded to by about 2,500 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 US 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 whether weight gain, experimented in these persons, especially in women with FM, is due to the disease and its accompanying low activity levels, or whether 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 FM 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 FM, without either biochemical alterations in T3, T4 and TSH or clinical manifestations such as goitre and cretinism [57]. It has also been pointed that selenium, zinc, iron or retinoic acid imbalance 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 thalassaemia minor (TM) was diagnosed in a study. Some non-specific 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 non-specific 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 referents. 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 etiopathogenesis [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 [16].

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 [70]. An altered response of IL-6 to a physiologic stressor supported the notion that FM may represent a primary disorder of the stress system [71]. Otherwise we have not found any study comparing the nutritional status with the inflammatory status of these patients.

Fibromyalgia pain has been related to a deficiency of serotonergic 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) [72]. Due to the possible malfunction of energy metabolism of the muscle fibres 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 FM, 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 hangover 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 [73].

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 FM, 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 pyreïnoidosa*, 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 [87]. Positive effects on chronic fatigue syndrome, but not directly on FM, have been described in some studies on different nutritional supplements [88].

Due to the possible relationship between a high oxidative stress and FM, 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

**Table 2** Search results for nutritional supplements and fibromyalgia

Study references	Type of study	Nutritional supplementation	Dose and time	n	Results or conclusions	Assessment tools or clinical variables evaluated
Caruso I, et al. 1990 [74]	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
Putini PS, et al. 1992 [75]	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 [76]	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 group.	Daily pain diary by a visual analogue scale (VAS)
Birdsall TC, 1998 [77]	Review of clinical studies	5-HTP			Significant improvement in symptoms, including pain, morning stiffness, anxiety, and fatigue.	
Merchant RE, et al. 2000 [78]	Pilot study	Chlorella pyrenoidosa	10 g tablets & 100 ml extract daily 2 months	18	Possibly useful	Tender points index, VAS, Health Assessment Questionnaire (HAQ)
Merchant RE, et al. 2001 [79]	Double-blind, placebo-controlled, crossover study	Chlorella pyrenoidosa	10 g tablets & 100 ml 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 [80]	Review of double-blind, placebo-controlled, randomised 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 [81]	Double-blind, multicenter randomised clinical trial, placebo-controlled	Acetyl-L-carnitine (LAC)	Two capsules/day of 500 mg of LAC and one i.m. Injection of 500 mg LAC for 2 weeks, and three capsules/day of 500 mg 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 and musculo-skeletal pain.	Tender points, total myalgic score, Short Form SF-36 Health questionnaire, VAS for stiffness, fatigue, tiredness on awakening, sleep, work status, depression, musculo-skeletal pain, Hamilton Depression Rating Scale (HDRS).
Lister RE. 2002 [82]	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 [83]	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 [84]	Prelimi-nary trial	100 mg ascorbigen + 400 mg broccoli powder/day	30 days	12	Reduction of sensitivity to pain and improvement in quality of life measured.	FIQ, tender points
Jacobson S, et al. 1991 [85]	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 [86]	Review	s-adenosyl-L-methionine	200–600 mg/day/during 2–4 weeks	10–47	Reduced tender point pain	VAS

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 FM 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, hyposerotonergic 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 pyreïnoidosa* algae and ginkgo 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.

**Acknowledgments** This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. We thank Professor Casimiro Javierre and Ramon Segura, from University of Barcelona, for their help and advice during all the revision process to write this article. We are very grateful also to Rebecca Jeffree for her help in the linguistic revision of the text.

**Conflict of interest statement** There are no conflict of interests.

## References

1. Wolfe F, Smythe HA, Yunus MB et al (1990) The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. *Arthritis Rheum* 33:160–172
2. Weir P, Harlan G, Nkoy F et al (2006) The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th revision codes. *J Clin Rheumatol* 12:124–128
3. Maquet D, Croisier JL, Crielaard JM (2000) Fibromyalgia in the year. *Rev Med Liege* 55(11):991–997
4. Lawrence R, Helmick C, Arnett F et al (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 41:778–799
5. Wolfe F, Ross K, Anderson J et al (1995) The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 38:19–28
6. White KP, Speedchley M, Harth M et al (1999) The London fibromyalgia epidemiology study: the prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol* 26(7):1570–1576
7. White KP, Harth M (2001) Classification, epidemiology, and natural history of fibromyalgia. *Curr Pain Headache Rep* 5(4):320–329
8. Valverde M, Juan A, Ribas B et al (2000) Prevalencia de la fibromialgia en la población española. Estudio EPISER 2000. *Rev Esp Reumatol* 27(5):157
9. Carmona L, Ballina J, Gabriel R et al (2001) EPISER study group. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Ann Rheum Dis* 60(11):1040–1045
10. Mas AJ, Carmona L, Valverde M et al (2008) EPISER study group. Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population results from a nationwide study in Spain. *Clin Exp Rheumatol* 26(4):519–526
11. Gamero F, Gabriel R, Carbonell J et al (2005) Pain in Spanish rheumatology outpatient offices: EPIDOR epidemiological study. *Rev Clin Esp* 205:157–163
12. Salaffi F, De Angelis R, Gras W et al (2005) Pain prevalence, investigation group (MAPPING) study. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. *Clin Exp Rheumatol* 23(6):819–828
13. Bannwarth B, Blotman F, Roué-Le Lay K et al (2008) Fibromyalgia síndrome in the general population of France: a prevalence study. *Joint Bone Spine* 24. [Epub ahead of print]

14. Felson DT (2008) Comparing the prevalence of rheumatic diseases in China with the rest of the world. *Editorial. Arthritis Res Ther* 10:106
15. Eisinger J, Plantamura A, Marie PA et al (1994) Selenium and magnesium status in fibromyalgia. *Magnes Res* 7(3–4):285–288
16. Reinhard P, Schweinsberg F, Wernet D et al (1998) Selenium status in fibromyalgia. *Toxicol Lett* 96–97:177–180
17. Ozgocmen S, Ozyurt H, Sogut S et al (2006) Antioxidant status, lipid peroxidation and nitric oxide in fibromyalgia etiologic and therapeutic concerns. *Rheumatol Int* 26:598–603
18. Bagis S, Tamer L, Sahin G et al (2005) Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder? *Reumatol Int* 25:188–190
19. Altindag O, Celik H (2006) Total antioxidant capacity and the severity of the pain in patients with fibromyalgia. *Redox Rep* 11(3):131–135
20. Pieczenik SR, Neustadt J (2007) Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol* 83:84–92
21. Ozgocmen S, Ozyurt H, Sogut S et al (2006) Current concepts in the pathophysiology of fibromyalgia: the potential role of oxidative stress and nitric oxide. *Reumatol Int* 26:585–597
22. Pall ML (2001) Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. *Med Hypotheses* 57(2):139–145
23. Hänninen O, Kaartinen K, Rauma AL et al (2000) Antioxidants in vegan diet and rheumatic disorders. *Toxicology* 155:45–53
24. Donaldson MS, Speight N, Loomis S (2001) Fibromyalgia syndrome improved using a mostly raw vegetarian diet: an observational study. *BMC Complement Altern Med* 1:7
25. Vecchiet J, Cipollone F, Falasca K et al (2003) Relationship between musculoskeletal symptoms and blood markers of oxidative stress in patients with chronic fatigue syndrome. *Neurosci Lett* 335(3):151–154
26. Kennedy G, Spence VA, McLaren M et al (2005) Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radic Biol Med* 39:584–589
27. Richards RS, Wang L, Jelinek H (2007) Erythrocyte oxidative damage in chronic fatigue syndrome. *Arch Med Res* 38:94–98
28. Zhang Z, Cherryholmes G, Mao A et al (2008) High plasma levels of MCP-1 and Eotaxin provide evidence for an immunological basis of fibromyalgia. *Exp Biol Med* 233:1171–1180
29. Wallace DJ, Linker-Israeli M, Hallegua D et al (2001) Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. *Rheumatology* 40:74–749
30. Wallace DJ (2006) Is there a role for cytokine based therapies in fibromyalgia. *Curr Pharm Des* 12(1):17–22
31. Chakrabarty S, Zoorob R (2007) Fibromyalgia. *Am Fam Physician* 15; 76(2):247–254
32. Carville SF, Arendt-Nielsen S, Bliddal H et al (2008) EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* 67:536–541
33. Perrot S, Dickenson AH, Bennett RM (2008) Fibromyalgia: harmonizing science with clinical practice considerations. *Pain Practice* 8(3):177–189
34. Abeles M, Solitar BM, Pillinger MH et al (2008) Update on fibromyalgia therapy. *Am J Med* 121:555–561
35. Goldenberg DL, Burckhardt C, Crofford L (2004) Management of fibromyalgia síndrome. *JAMA* 292(19):2388–2395
36. Nishishinya MB, Rivera J, Alegre C et al (2006) Intervenciones no farmacológicas y tratamientos alternativos en la fibromialgia. *Med Clin* 12(8):295–299
37. Kaartinen K, Lami K, Hyphen M et al (2000) Vegan diet alleviates fibromyalgia symptoms. *Scand J Rheumatol* 29(5):308–313
38. Bennet RM (2002) A raw vegetarian diet for patients with fibromyalgia. *Curr Rheumatol Rep* 4(4):284
39. Azad KA, Alam MN, Hag SA et al (2000) Vegetarian diet en the treatment of fibromyalgia. *Bangladesh Med Res Counc Bull* 26(2):41–47
40. Michalsen A, Riegert M, Lütcke R et al (2005) Mediterranean diet or extended fasting's influence on changing the intestinal microflora, immunoglobulin A secretion and clinical outcome in patients with rheumatoid arthritis and fibromyalgia: an observational study. *BMC Complement Altern Med* 5:22
41. Smith JD, Terpening CM, Schmidt SOF et al (2001) Relief of fibromyalgia symptoms following discontinuation of dietary excitotoxins. *Ann Pharmacother* 35:702–706
42. Geenen R, Janssens EL, Jacobs JWG et al (2004) Dietary glutamate will not affect pain in fibromyalgia. *J Rheumatol* 31:785–787
43. Cairns BE, Svensson P (2005) Dietary glutamate and fibromyalgia. *J Rheumatol* 32(2):392–393; Author reply 393–394
44. Cymet TC (2003) A practical approach to fibromyalgia. *J Natl Med Assoc* 95:278–285
45. Arnold LM, Hudson JI, Keck PE et al (2006) Comorbidity of fibromyalgia and psychiatric disorders. *J Clin Psychiatry* 67:1219–1225
46. Javaras KN, Harrison GP, Lalonde JK et al (2008) Co-occurrence of binge eating disorder with psychiatric and medical disorders. *J Clin Psychiatry* 69:266–273
47. Bennett RM, Jones J, Turk DC et al (2007) An internet survey of 2, 596 people with fibromyalgia. *BMC Musculoskeletal Disorders* 8:27
48. Patucchi E, Fatati G, Puxeddu A et al (2003) Prevalence of fibromyalgia in diabetes mellitus and obesity. *Recent Prog Med* 94:163–165
49. Yunus MB, Arslan S, Aldag JC (2002) Relationship between body mass index and fibromyalgia features. *Scand J Rheumatol* 31:27–31
50. Mengshoel AM, Haugen M (2001) Health status in fibromyalgia—a followup study. *J Rheumatol* 28:2085–2089
51. Shapiro JR, Anderson DA, Noff-Burg S (2005) A pilot study of the effects of behavioral weight loss treatment on fibromyalgia symptoms. *J Psychosom Res* 59:275–282
52. Neumann L, Lerner E, Glazer Y et al (2008) A cross-sectional study of the relationship between body mass index and clinical characteristics, tenderness measures, quality of life, and physical functioning in fibromyalgia patients. *Clin Rheumatol* 27(12):1543–1547
53. Shaver JLF, Wilbur J, Robinson P et al (2006) Women's health issues with Fibromyalgia syndrome. *J Women's Health* 9(15):1035–1045
54. Hooper MM, Stellato TA, Hollowell PT et al (2007) Musculoskeletal findings in obese subjects before and after weight loss following bariatric surgery. *Int J Obes* 31:114–120
55. Ananda A, Catterson I, Sambrook P et al (2008) The impact of obesity on the musculoskeletal system. *Int J Obes* 32(2):211–222
56. Lowe JC, Yellin J, Honeyman-Lowe G (2006) Female fibromyalgia patients: lower resting metabolic rates than matched healthy controls. *Med Sci Monit* 12(7):CR282-9
57. Loevinger B, Muller D, Alonso C et al (2007) Metabolic syndrome in women with chronic pain. *Metab Clin Exp* 56:87–93
58. Verheesen RH, Schweitzer CM (2008) Iodine deficiency, more than cretinism and goiter. *Med Hypotheses* 71:645–648
59. Pamuk GE, Pamuk ON, Set T et al (2008) An increased prevalence of fibromyalgia in iron deficiency anemia and thalassemia minor and associated factors. *Clin Rheumatol* 27:1103–1108
60. Swezey RL, Adams J (1999) Fibromyalgia: a risk factor for osteoporosis. *J Rheumatol* 26(12):2642–2644
61. Al-Allaf AW, Mole PA, Paterson CR et al (2003) Bone health in patients with fibromyalgia. *Rheumatology* 42:1202–1206
62. Plotnikoff GA, Quigley JM (2003) Prevalence of severe hypovitaminosis D in patients with persistent nonspecific musculoskeletal pain. *Mayo Clin Proc* 78:1463–1470
63. Block SR (2004) Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc* 79(12):1585–1591

64. Warner AE, Arnsperger SA (2008) Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol* 14(1):12–16
65. Armstrong DJ, Meenagh GK, Bickle I (2007) Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol* 26:551–554
66. Mouyis M, Ostor AJK, Crisp AJ et al (2008) Hypovitaminosis D among rheumatology outpatients in clinical practice. *Rheumatology* 47:1348–1351
67. Sendur OF, Tastaba E, Turan Y et al (2008) The relationship between serum trace elements levels and clinical parameters in patients with fibromyalgia. *Rheumatol Int* 28:1117–1121
68. Rosborg I, Hyllén E, Lidbeck J et al (2007) Trace element pattern in patients with fibromyalgia. *Sci Total Environ* 385:20–27
69. Eisinger J, Plantamura A, Marie PA et al (1994) Selenium and magnesium status in fibromyalgia. *Magnes Res* 7(3–4):285–288
70. Schwarz MJ, Offenbaecher M, Neumeister A et al (2002) Evidence for an altered tryptophan metabolism in fibromyalgia. *Neurobiol Dis* 11:434–442
71. Torpy DJ, Papanicolaou DA, Lotsikas AJ et al (2000) Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6. A pilot study in fibromyalgia. *Arthritis and Rheumatism* 43(4):872–880
72. Maes M, Verkerk R, Delmeire L et al (2000) Serotonergic markers and lowered plasma branched-chain-amino acid concentrations in fibromyalgia. *Psychiatry Res* 97:11–20
73. Rohr UD, Herold J (2002) Melatonin deficiencies in women. *Maturitas* 41(1):S85–S104
74. Caruso I, Puttini PS, Cazzola M et al (1990) Double-blind study of 5-hydroxytryptophan versus placebo in the treatment of primary fibromyalgia syndrome. *J Int Med Res* 18:201–209
75. Puttini PS, Caruso I (1992) Primary fibromyalgia syndrome and 5-HTP: a 90-day open study. *J Int Med Res* 20:182–189
76. Nicolodi M, Sicuteri F (1996) Fibromyalgia and migraine, two faces of the same mechanism. Serotonin as the common clue for pathogenesis therapy. *Adv Exp Med Biol* 398:373–379
77. Birdsall TC (1998) 5-Hydroxytryptophan: a clinically-effective serotonin precursor. *Altern Med Rev* 3(4):271–280
78. Merchant RE, Carmack CA, Wise CM (2000) Nutritional supplementation with chlorella pyrenoidosa for patients with fibromyalgia syndrome: a pilot study. *Phytother Res* 14:167–173
79. Merchant RE, Andre CA, Wise CM (2001) Nutritional supplementation with chlorella pyrenoidosa for fibromyalgia syndrome: a double-blind, placebo-controlled, crossover study. *J Musculoskeletal Pain* 9(4)
80. Merchant RE, Andre CA (2001) A review of recent clinical trials of the nutritional supplement chlorella pyrenoidosa in the treatment of fibromyalgia, hypertension, and ulcerative colitis. *Altern Ther Health Med* 7(3):79–91
81. Rossini M, Di Munno O, Valentini G et al (2007) Double-blind, multicenter trial comparing acetyl-L-carnitine with placebo in the treatment of fibromyalgia patients. *Clin Exp Rheumatol* 25(2):182–188
82. Lister RE (2002) An open, pilot study to evaluate the potential benefits of coenzyme Q10 combined with Ginkgo Biloba extract in Fibromyalgia Syndrome. *J Inter Med Res* 30:195–199
83. Olson GB, Savage S, Olson J (2000) The effects of collagen hydrolysate on symptoms of chronic fibromyalgia and temporomandibular joint pain. *Cranio* 18(2):135–141
84. Bramwell B, Ferguson S, Scarlett N et al (2000) The use of ascorbigen in the treatment of fibromyalgia patients: a preliminary trial. *Altern Med Rev* 5(5):455–462
85. Jacobsen S, Danneskiold-Samsoe B, Andersen RB (1991) Oral S-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. *Scand J Rheumatol* 20(4):294–302
86. Fetrow CW, Avila JR (2001) Efficacy of the dietary supplement S-adenosyl-L-methionine. *Ann Pharmacother* 35:1414–1425
87. Dykman KD, Tone C, Ford C et al (1998) The effects of nutritional supplements on the symptoms of fibromyalgia and chronic fatigue syndrome. *Integr Physiol Behav Sci* 33(1):61–71
88. Werbach MR (2000) Nutritional strategies for treating chronic fatigue syndrome. *Altern Med Rev* 5(2):93–108