Review

Fibromyalgia and nutrition: what news?

A. Rossi[1], A.C. Di Lollo[2], M.P. Guzzo[2], C. Giacomelli[1], F. Atzeni[3], L. Bazzichi[1], M. Di Franco[2]

[1]*Department of Clinical and Experimental Medicine, Rheumatology Unit, University of Pisa, Pisa, Italy;*
[2]*Department of Internal Medicine and Medical Specialties, Rheumatology Unit, La Sapienza University, Rome, Italy;*
[3]*IRCCS Galeazzi Orthopaedic Institute, Milan, Italy.*

Alessandra Rossi, PhD
Anna Chiara Di Lollo, MD
Maria Paola Guzzo, MD
Camillo Giacomelli, PhD
Fabiola Atzeni, MD, PhD
Laura Bazzichi, MD
Manuela Di Franco, MD

Please address correspondence to:
Dr Alessandra Rossi,
Dipartimento di Medicina Clinica e Sperimentale,
U.O. di Reumatologia,
Ospedale S. Chiara,
via Roma 67,
56126 Pisa, Italy.
E-mail: alessandra.rossi@unipi.it

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ABSTRACT

Fibromyalgia syndrome (FM) is a chronic, generalised pain condition usually accompanied by several associated symptoms, such as fatigue, sleep disturbance, headache, irritable bowel syndrome and mood disorders. Different medical treatments are used to treat fibromyalgia and the recent guidelines suggest that the optimal treatment consists in a multidisciplinary approach with a combination of pharmacological and non-pharmacological treatment modalities. Among non-pharmacological treatment, nutrition is a promising tool for FM patients.

The aim of this review is to update the present knowledge about fibromyalgia and nutrition by means of a systematic search performed on Medline from January 2000 to December 2014. Nutritional deficiencies have been described in FM patients and the benefits of specific diet and nutritional supplementation are shown. Obesity and overweight, often present in FM patients, are related to the severity of FM worsening the quality of life in terms of higher pain, fatigue, worsened sleep quality and higher incidence of mood disorders. Weight control is thus an effective tool to improve the symptoms. Moreover, it seems reasonable to eliminate some foods from the diet of FM patients, for example excitotoxins. Non-coeliac gluten sensitivity is increasingly recognised as a frequent condition with similar manifestations which overlap with those of FM. The elimination of gluten from the diet of FM patients is recently becoming a potential dietary intervention for clinical improvement.

In summary, this review reveals the potential benefit of specific dietary interventions as non-pharmacological tools as part of a multidisciplinary treatment for FM patients.

Introduction

Fibromyalgia (FM) is a syndrome, with unknown aetiology, characterised by chronic widespread pain and several associated non-specific symptoms such as fatigue, sleep disorders, depression, anxiety and cognitive impairment.

It is the second most common cause of visits to rheumatologists after osteoarthritis and it affects approximately 2–3% of the general population with more than 90% of patients being female (1).

The pathogenesis of FM is uncertain but among several mechanisms, central sensitisation plays a fundamental role. In particular, central nervous system sensitisation is considered the basis of increased pain perception and autonomic nervous system (ANS) dysfunction, with a sympatethic / parasympathetic imbalance, could partially explain several of the FM multisystem features. Moreover, some studies revealed high levels of oxidative stress and a lower antioxidant capability as demonstrated by the low levels of some nutrients such as magnesium and selenium, so it was supposed that free radicals could contribute to the development of FM.

As regards therapy, currently only three drugs have approval for use in FM in the USA: milnacipran, pregabalin and duloxetine. However, pharmacological therapies are often insufficient to control pain in FM patients and the European League Against Rheumatism (EULAR) underlined the importance of a multimodal approach, combining pharmacological and non-pharmacological interventions (2).

Among non-pharmacological interventions, nutrition is becoming an important complementary therapeutic approach for fibromyalgia. The correlation between nutrition and health is well known, and several studies have

demonstrated the importance of specific dietary patterns on the well-being of the population (3).

Food can play a critical role in the prevention of diseases; indeed the World Health Organization supports a key function of diet in preventing non-communicable diseases (4).

The aim of this review is to update the scientific literature regarding fibromyalgia and nutrition. Studies were identified through a computerised search of MEDLINE and the range of publication date was from January 2000 to December 2014.

The search terms used were: fibromyalgia in combination with: nutrition, diets, food intake, dietary patterns, food intolerance or allergy, nutritional deficiencies, nutritional supplementation, antioxidants, obesity, body mass index, gluten sensitivity, and eating disorders.

Nutritional deficiencies

Antioxidants

In the last few years, the theory that oxidative stress may be implicated in the pathophysiology of FM is gaining more weight, however, although it is thought that oxidative and nitrosative stress take part in the pathogenesis of pain, it is not clear whether they are the cause or the consequence of FM (5, 6). Superoxide radicals induce an alteration of nociception through peripheral and central nervous system sensitisation and are implicated in the activation of several cytokines such as TNF-α and IL-1β which are involved in inflammatory pain (7, 8).

Larson *et al*. (9) have hypothesised an enhanced synthesis of nitric oxide (NO) in FM patients through the analysis of some amino acids in the cerebrospinal fluid and its correlation with pain intensity. Bagis *et al*. (10) have reported increased malondialdehyde (MDA) levels and decreased superoxide dismutase (SOD) enzyme activity in 85 FM patients compared to 80 controls.

A relationship between the balance of oxidants/antioxidants and symptoms of FM was also demonstrated by Ozgocmen (11, 12), Altindag (13) and Sendur (14).

The most recent published studies have confirmed the higher oxidative status of FM patients and its possible relationship with FM (15-17).

Antioxidant defense system enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX) prevent oxidative stress through inactivation of reactive oxygen species (ROS). Higher SOD enzyme activity and unchanging total GPX1 activities were found in FM patients by Akbas *et al*. (18). They also studied for the first time genotype and allele frequencies of Ala-9Val polymorphism of MnSOD2 and Pro198Leu polymorphism of GPX1 but no associations were found between them and FM.

La Rubia *et al*. (19) recently performed an exhaustive study of the oxidative/antioxidative status in FM patients investigating lipid and protein peroxidation, oxidative DNA damage, total antioxidant capacity (TAC) and antioxidant enzyme activities. They concluded that the lower antioxidant enzyme activities may lead to oxidative stress through the oxidation of DNA and proteins, which may affect the health status of FM patients.

It is hypothesised that ROS, by inhibiting mitochondrial function, can be involved in muscle pain and central sensitisation, as typically seen in these patients. Increased ROS, resulting in impaired mitochondrial function and reduced ATP in muscle and neural cells, might lead to chronic widespread pain in FM patients. Therefore, targeting increased ROS by antioxidants and targeting the mitochondrial biogenesis could offer a solution for the chronic pain of FM patients (20).

Ferritin and iron

Ferritin and iron deficiency have been explored in FM patients. In a recent study Ortancil *et al*. (21) showed that FM patients had ferritin levels lower than the control group and having a serum ferritin level <50 ng/ml caused a 6.5-fold increased risk for FM. Iron is an important cofactor for enzymes involved in the serotonin and dopamine synthesis and may have a role in the aetiology of FM. Pamuk *et al*. (22) found that the prevalence of FM in subjects with iron deficiency anemia and thalassemia minor was higher than in the control group. Mader *et al*. (23), on the contrary, did not find reduced serum levels of iron or surrogate markers of iron stores in FM patients and concluded that, at present, there is no evidence to support iron supplementation in the treatment of FM.

Trace elements

Some trace elements, like selenium, zinc and magnesium, are essential for the redox balance in cells and are also important for ATP production. The literature reports contradictory results regarding trace elements in biological samples of FM patients.

Rosborg *et al*. (24) found higher concentrations of Cd, Co, Cu, Fe, Se, Sn and Zn in whole blood and increased urinary excretion of Ag in the FM patients, but all the concentrations of the studied elements in blood and urine samples were within reported reference intervals in non-occupationally exposed populations. The authors concluded that the investigation could not demonstrate abnormal levels of trace elements in blood or urine of FM-patients and, thus, does not support the hypothesis that trace element abnormalities play a significant role in the development of FM.

In addition, Sakarya *et al*. (25) did not find any significant differences in the levels of serum Mg between control subjects and patients with FM, nor statistically significant correlations with the number of Tender Points (TP), Visual Analogue Scale (VAS) scores, Fibromyalgia Impact Questionnaire (FIQ), and Beck Depression Inventory (BDI) in patients with FM. According to the results of this study, it was asserted that other complex mechanisms may play an important role in the pathophysiology of FM without Mg levels. Others, on the other hand, supported the hypothesis that an impairment of trace element might be important in the pathophysiology of FM. Sendur *et al*. (26) observed that serum levels of zinc and magnesium were significantly decreased in FM groups, whereas there was no considerable difference in the selenium levels of both groups. Moreover, serum Zn and Mg levels were associated with tender points and fatigue.

Kim *et al*. (27) found that the concentrations of calcium, magnesium, iron, and manganese in the hair of female patients with fibromyalgia were lower than in the controls, while Bazzichi *et al*. (28) reported a trend towards higher calcium concentrations together with a significant increase in magnesium levels in platelets of FM patients, suggesting that disturbances in the homeostasis of platelet calcium-magnesium might be relevant in the pathogenesis of FM.
Verheesen *et al*. (29) observed that fibromyalgia is characterised by a complex of symptoms resembling hypothyroidism, but without the marked TSH increase. They hypothesised that iodine deficiency may give rise to a subtle impairment of thyroid function leading to clinical syndromes resembling hypothyroidism and it might be a crucial, but not investigated factor in hypothyroidism.

Amino acids

Patients with fibromyalgia have significantly lower plasma concentrations of the three branched amino acids (BCAAs) (valine, leucine and isoleucine) and phenylalanine than normal controls. It is hypothesised that the relative deficiency in the BCAAs may play a role in the pathophysiology of FM, since the BCAAs supply energy to the muscle and regulate protein synthesis in the muscles (30). Bazzichi *et al*. (31) confirmed the significant lower plasma concentrations of BCAAs, and highlighted a possible impairment of the cathecolaminergic system suggesting a probable defect of gut malabsorption or a low intake of certain important groups of amino acids: essentially, the ergogenic BCAA and the sulfur-containing amino acids in FM.
The possible tryptophan (TRP) deficiency by means a TRP depletion (TD) in patients with FM was also investigated (32). An altered TRP metabolism and an activation of 5-HT metabolism and IL-6 production emerged in a subgroup of FM patients.

Micronutrients supplementation

The literature describes benefits gained from the supplementation of the diet of FM patients with micronutrients.
Arranz *et al*. (33) conducted a survey on 101 FM patients regarding diet, food intolerance or allergy and nutritional supplement (NS) consumption with the aim to assess patient's awareness of diet in FM treatments. They found that 30% of participants changed their diet after diagnosis. As regards nutritional supplementations, most patients (73%) were NS users and of these 61% became users after disease onset. They described a large variety of NS among whom multi-mineral/multi-vitamin products were the most used, followed by magnesium, anti-oxidants and poly-unsaturated fatty acids. In particular, they noted that magnesium was the most recommended by physicians.
As mentioned above, recent data suggest that the oxidant/antioxidant balance may play a role in FM aetiology, although the mechanism is not entirely clarified. For this reason it has been proposed that FM patients may benefit from supplementation of micronutrients with antioxidant function.
In two consecutive clinical trials, Merchant *et al*. have described an improvement in body function and quality of life after a regular intake of Chlorella pyrenoidosa (34, 35). Chlorella pyrenoidosa is an unicellular green algae that contains high concentration of chlorophyll, cell walls, b-carotene, vitamins and minerals, as well as dietary fibre, nucleic acids, amino-acids, enzymes and other substances.
Cellfood is an antioxidant nutritional supplement containing 78 ionic/colloidal trace elements and minerals combined with 34 enzymes and 17 amino acids, all suspended in a solution of deuterium sulphate, and is efficacious in protecting against oxidative damage *in vitro*. It is a helpful antioxidant treatment not only for FM patients but also for patients affected by neurodegenerative diseases (36, 37).
In an open pilot study, Lister showed a significant improvement in quality of life of FM patients after assumption of CoQ10 and Ginkgo biloba for 84 days (38).
Coenzyme Q10 (CoQ10) or ubiquinone was known for its key role in mitochondrial bioenergetics as an electron and proton carrier and its antioxidant role has been extensively investigated. Recently Garrido-Maraver *et al*. (39) affirmed that many neurodegenerative disorders, diabetes, cancer, muscular and cardiovascular diseases and also fibromyalgia, have been associated with low CoQ10 levels, and oral CoQ10 treatment represents a frequent mitochondrial energiser and antioxidant strategy in many diseases that may provide a significant symptomatic benefit. Several recent papers have confirmed the therapeutic effect of oral supplementation with coenzyme Q10 in FM patients (40-44).
Creatine supplementation increased intramuscular phosphorylcreatine content and improved lower- and upper-body muscle function, with minor changes in other fibromyalgia features. These findings introduce creatine supplementation as useful dietary intervention to improve muscle function in fibromyalgia patients (45).
Lower levels of melatonin and urinary metabolites as 6-sulphatoxymelatonin (6-SMT) were found in FM patients (46-49) and the more recent works seem to agree on the efficacy of melatonin in the management of pain in fibromyalgia (50, 51).
In the last few years, many authors have suggested an association between chronic muscular pain and vitamin D deficiency and these observations have stimulated a great deal of research exploring whether a relationship exists between muscle pain and low vitamin D serum levels (52-57). Although some researchers suggest that vitamin D deficiency should be considered in the management of fibromyalgia syndrome (58-60), there are contrasting data regarding benefits on FM symptoms after vitamin D supplementation.
Jesus *et al*. (61) reviewed studies on the treatment with vitamin D in FM patients and concluded that the data were inconclusive. Nevertheless, they emphasised the importance of testing vitamin D serum level, when risk factors for its deficiency are present, to possibly recommend supplementation.
In a recent review, magnesium, L-carnitine, and *S*-adenosylmethionine are considered non-pharmacological supplements with the most potential for FM (62).

Diet in FM patients

A great deal of non-scientific information addressed to patients points to the benefits of nutrition and many FM patients report that they modified their diet after diagnosis with the aim to control symptoms even without an official guide by physicians (63).

In the literature, clinical trials have been carried out with the purpose of studying the effects of a particular type of nutrition or diet on the symptoms of FM patients.

In particular, evidence of clinical improvement in FM symptoms after a diet rich in anti-oxidants nutrients are reported (64-68) (Table I).

Among the different dietary interventions tested in FM patients there is the excitotoxin elimination diet, which considers that excitotoxins is a substance that can excite neurons in a abnormal and harmful manner (Table I). Glutammate is the most diffuse excitatory neurotransmitter in the central nervous system and at high concentrations it can overexcite and cause neuron death. Several authors have hypothesised that the excitotoxin elimination diet could affect central sensitisation by altering excitatory neurotransmission in the CNS and also the exclusion of aspartame from the diet resulted in a complete regression of FM symptoms (69-71). Vellisca *et al*., on the other hand, in a controlled study showed that the discontinuation of dietary monosodium glutamate (MSG) and aspartame did not improve clinical symptoms significantly (72). However, future research on the role of dietary excitotoxins in FM is warranted.

It is known that FM patients often complain of gastrointestinal symptoms such as abdominal pain, bloating and abdominal distension and diarrhoea or constipation, which are typical symptoms of irritable bowel syndrome (IBS). IBS has been found in 25–81% of people with FM (73).

Some authors suggest the importance of investigating the existence of coeliac disease (CD) or non-coeliac gluten sensitivity in these patients. The available data suggest an elevated prevalence of fibromyalgia among patients with CD (74), whereas the prevalence of CD in fibromyalgia is not different from that of the general population (75). However, some authors suggest that at least a subgroup of patients with fibromyalgia could experience subclinical CD or non-coeliac gluten intolerance and describe the benefit of a gluten-free diet on FM symptoms (76-78). (Table I).

It has also been hypothesised that non-coeliac gluten sensitivity may be an underlying cause of FM symptoms.

Non-coeliac gluten sensitivity is increasingly recognised as a frequent condition with similar manifestations which overlap with those of FM, and the elimination of gluten from the diet of FM patients is recently becoming a potential dietary intervention for clinical improvement. Nevertheless, further research is needed to clarify the role of gluten sensitivity in FM (79).

FM and eating disorders

In FM patients there is a high rate of co-occurrence of psychiatric symptoms; in particular some studies have demonstrated a stronger association with mood and anxiety disorders in comparison with other diseases characterised by chronic pain. Regarding nutritional status and eating disorders, few studies have focused on this argument.

In 2006, in a clinical trial conducted to assess the co-occurrence of fibromyalgia and psychiatric disorders, the authors evaluated FM patients in comparison with subjects affected by rheumatoid arthritis and described a significant co-occurrence of anorexia nervosa and bulimia nervosa in the first group (80).

In a study evaluating obese or overweight people with history of present or past binge eating disorder (BED), it was found that the medical condition BED had a significant comorbidity with FM and irritable bowel syndrome (81).

More recently, some researchers, after evaluating different features of obese and non-obese FM patients, have found that depression was more frequent in obese subjects, and have underlined the role of eating disorders such as BED and nocturnal eating, weight and shape concern and poor sleep as mediators of the relationship between obesity and depression in FM patients. Besides they suggest that focusing on stabilising eating behaviour, in order to reduce or stop binging, might be very important in treating obese patients with fibromyalgia (82).

There is only one study that assesses nutritional status and the presence of eating disorders in paediatric patients. This is a control-group study evaluating female adolescents with or without FM. The authors did not observe significant differences between the FM and the control group, but in the FM patients a significant correlation was found between the adiposity indexes and the symptoms of disordered eating, therefore, the authors emphasise the importance of early nutritional intervention in FM patients (83).

Nutritional status of FM patients

Obesity and overweight are two common co-morbidities in women diagnosed with FM and their prevalence in this population is higher than the national reference values (84-90). Past research suggests that obesity may be related to the severity of FM, thus worsening the quality of life of patients and triggering metabolic changes (91-96).

At present it is not possible to ascertain whether obesity is cause or consequence of fibromyalgia. Among mechanisms proposed to explain the “hidden link” there are: impaired physical activity, cognitive and sleep disturbances, psychiatric comorbidity and depression, dysfunction of thyroid gland, dysfunction of the GH/IGF-1 axis, impairment of the endogenous opioid system (97, 98).

Recent studies have highlighted the association between body mass index (BMI) and clinical features in FM patients. Yunus *et al*. (91) found significant correlation between Health Assessment Questionnaire (HAQ) scores and BMI, and that FM patients with the greater BMI had greater fibromyalgia-related symptoms with worse FIQ subscales and total scores.

Neumann *et al*. (99) found that BMI correlated negatively with quality of life (QoL) assessed by SF36 and tenderness threshold, and positively with physical dysfunctioning and tender point count.

Table I. Fibromyalgia and nutritional interventions.

Kaartinen *et al*. Scand J Rheumatol 2000	18 FM patients receiving a low salt uncooked vegan diet rich in lactobacteria were compared with 15 FM controls receiving an omnivourus diet. The study group showed an improvement of clinical symptoms and a decrease in BMI, sierical levels of cholesterol and urine sodium
Hanninen *et al*. Toxicology 2000	FM patients received an uncooked vegan diet. There was an improvement of their self-experienced health and a decrease in their joint stiffness and pain
Azad *et al*. Bangladesh Medical Research Council Bulletin 2000	In 37 FM patients receiving a vegetarian diet there was an improvement of their clinical symptoms (significant only for pain score) but this was smaller than in a control group of patients receiving amitriptyline
Donaldson *et al*. BMC Complementary and Alternative Medicine 2001	30 FM patients improved after a mostly raw pure vegetarian diet
Michalsen *et al*. BMC Complementary and Alternative Medicine 2005	51 patients (16 RA and 35 FM) were divided into two groups: one receiving a mostly vegetarian Mediterranean diet and the other one following a fasting regimen. Fasting FM did not show significant greater clinical improvements than non-fasting (p=0.25)
Smith *et al*. Ann Pharmacotherapy 2001	4 FM patients ameliorated after eliminating monosodium glutamate (MSG) or MSG plus aspartame from their diet
Holton *et al*. Clinical and Experimental Rheumatology 2012	84% of 36 patients with FM and IBS reported >30% remission of symptoms after an excitotoxin elimination diet. There was a significant return of symptoms after the MSG challenge.
Ciappuccini *et al*. Clinical and Experimental Rheumatology 2010	Case report of 2 patients with aspartame induced fibromyalgia chronic pain
Vellisca, Latorre. Rheumatology International 2014	36 FM patients following a MSG and aspartame elimination diet were compared with 36 controls. The experimental group did not show significant improvement of FM symptoms
Rodrigo *et al*. BMC Gastroenterology 2013	Improvement of clinical symptoms (VAS pain, Tender Points, HAQ, SF36, FIQ) and tissue transglutaminase serum levels in 7 patients with coeliac disease, IBS and FM after 1 year of gluten free diet.
Isasi *et al*. Rheumatology International 2014	20 FM patients without CD who improved when placed on a gluten-free diet for a mean of 16.4 months. They observed remission of FM pain criteria, return to work, return to normal life, opioid discontinuation. For some patients the clinical improvement after starting the gluten-free diet was observed after only a few months, for other patients improvement was very slow and was gradually observed over many months of follow-up.
Rodrigo *et al*. Arthritis Research & Therapy 2014	97 IBS plus FM adult females of whom 58 with lymphocytic enteritis improved after 1 year of gluten-free diet (HAQ, SF36, VAS pain, TP, FIQ).

BMI: Body Mass Index; HAQ: Health Assessment Questionnaire; SF36: The Short Form (36) Health Survey Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; IBS: irritable bowel syndrome; CD: coeliac disease; TP: tender point.

Moreover, Shaver (100), Przekop (101) and Timmerman *et al*. (102), supported the association between BMI and QoL. Kim *et al*. (103) analysed differences in QoL and FM impact between moderately obese and severely obese subjects and showed that symptom severity is more pronounced when obesity is more severe.

The studies which examined the association between weight status and functional capacity of FM patients (104, 105) showed that obesity is associated with reduced strength and flexibility.

Arranz *et al*. (106) showed that women affected by FM had a very specific body composition profile, with an increased fat mass and a decreased lean mass. Almost 75% of patients had a fat mass over the normal range and high BMI values. Moreover, it was shown that the fat mass had a negative correlation with SF-36 bodily pain, and the lean mass almost with all SF-36 scores. This is the first study to investigate the relationship between fat mass, lean mass and QoL in FM patients.

It has been demonstrated that the expanded adipose tissue mass is the site of synthesis of a variety of proteins/peptides that are intimately involved in the regulation of inflammation (107, 108). Pain sensitivity of obese patients may be influenced by centrally modulated pain sensitivity, in addition to the mechanical loads of having to carry extra weight.

Recently, it has been suggested that increases in BMI contribute to increased circulating levels of proinflammatory cytokines in FM patients (109, 110) and significant relationships between serum CRP, BMI and cytokines have also been demonstrated (111), suggesting that inflammation may contribute to the symptoms in some FM patients, particularly in those who are obese.

Obesity and physical inactivity predispose to the development of dyslipidemia and patients with fibromyalgia might be at greater risk for metabolic distur-

bances. Increased levels of triglycerides and cholesterol (total and LDL) have been observed in FM patients (112-114). Cordero *et al*. (96) found that BMI, total cholesterol and triglycerides are highly associated with some clinical parameters. In particular, they found a positive correlation between total cholesterol and disease duration and hypothesised that it could be an interesting data on the role of hypercholesterolemia in the prolongation of FM. In a recent study (115), it has been hypothesised that insulin resistance may represent a risk factor for memory impairment in FM patients.

FM patients who are obese are at greater risk of developing depression and anxiety disorders (116-120). Moreover, obese FM patients exhibit a more disturbed sleep, both the quantity and quality of sleep are adversely impacted by obesity (95, 104), which could influence the severity of FM also via worsened sleep (121).

Weight loss in obese patients with FM, through energy-restricted diet, leads to significant improvement in the quality of life, depression, sleep quality, and tender point count, and patients who lost weight had significantly lower interleukin 6 and C-reactive protein levels (122, 123).

Weight loss after laparoscopic Roux-en-Y gastric bypass reduced BMI and pain in ten FM patients (124). In addition, the weight reduction after the bariatric surgery of twelve FM patients caused fewer musculoskeletal symptoms (125). Thyroid dysfunction could contribute to the link between fibromyalgia and obesity (126-128). Some authors have hypothesised that FM patients could be hypometabolic due to hypothyroidism. Lowe *et al*. (129) showed that FM patients are hypometabolic compared to controls. Sener *et al*. (130), on the contrary, did not find any differences between the resting metabolic rate of FM patients and controls.

Conclusions

The most appropriate approach for the treatment of fibromyalgia is multidisciplinary and among alternative therapies nutrition has becoming increasingly important.

A treatment programme including weight loss strategies, nutritional education, specific dietary interventions and the use of targeted nutritional supplements is recommended for patients suffering from fibromyalgia.

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