Dietary Modifications and Fibromyalgia

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Fibromyalgia (FM) is a common rheumatic condition characterized by chronic widespread musculoskeletal pain and tenderness in the absence of well-defined musculoskeletal or rheumatic disease. The finding of tenderness in 11 of 18 specified soft-tissue points on digital palpation confirms this diagnosis. In addition to pain and tenderness, patients often present with fatigue, insomnia, cognitive difficulty, and gastrointestinal complaints (Goldenberg, 1999). FM patients present with a wide range of symptom fluctuations and high levels of comorbidity and are met clinically with an absence of curative interventions (Friedberg & Jason, 2001).

FM is a commonly diagnosed rheumatic condition that affects more women than men. The prevalence of FM is approximately 3,400 women and 500 men per 100,000; in women, the prevalence increases with age to more than 7% between the ages of 60 and 79 (Wolfe, Ross, Anderson, Russell, & Hebert, 1995). Although considerable international investigation has been devoted to understanding FM, no single etiologic factor has yet been identified. Although the pathophysiology of FM is far from clear, neuroendocrine abnormalities involving the hypothalamic-pituitary-adrenal axis have been observed (Demitrack & Crofford, 1998). Research indicates that FM patients have elevated levels of substance P (Russell et al., 1994) and decreased levels of serotonin (Wolfe, Russell, Vipraio, Ross, & Anderson, 1997). Patients with FM commonly have one or more comorbid conditions, including migraine headaches, irritable bowel syndrome, chronic fatigue, and depression (Millea & Holloway, 2000). The issue of psychiatric comorbidity being an antecedent or the result of the illness...
remains a matter of much debate (Friedberg & Jason, 2001). Physical trauma is one factor that appears to be associated with the onset of FM (Al-Allaf et al., 2002; Buskila, Neumann, Vaisberg, Alkalay, & Wolfe, 1997).

Treatment of FM often involves low-dose antidepressants, and they can certainly be of benefit. It should be mentioned, however, that no pharmacologic treatment has been associated with significantly improved daily functioning among FM patients (Rossy et al., 1999). Indeed, research is beginning to indicate that a multidisciplinary treatment approach is most appropriate (Bennet, 1996; Littlejohn, 2001; Sim & Adams, 1999).

Patients with FM and other rheumatic disorders frequently use complementary and alternative medicine (CAM) (Dimmock, Troughton, & Bird, 1996; Nicassio, Schuman, Kim, Cordova, & Weisman, 1997; Pioro-Boisset, Esaïelle, & Fitzcharles, 1996). In particular, dietary modification by the inclusion or exclusion of specific foods is one of the most common CAM interventions used by FM patients, with 26% to 38% using dietary modification alone or in combination with other CAM therapies (Dimmock et al., 1996; Pioro-Boisset et al., 1996). More than 70% of FM patients report that a healthy diet is important in managing the illness (Mengshoel & Haugen, 2001).

Therefore, an emergent research area that may prove to be an important part of the multidisciplinary approach is dietary modification. As with the pathogenesis of FM, the exact physiological mechanism of symptom reduction due to dietary alteration remains unknown, although alteration of cytokines, reduced oxidative stress, increased antioxidant potential, improved bowel flora, and central nervous system (CNS) chemical modification may be involved.

VEGETARIAN/VEGAN DIET AND ANTIOXIDANTS

The generation of excess free radicals and/or a deficiency in antioxidant status may play a pathophysiological role in numerous illnesses including FM (Bennet, 1993). Research has shown that FM patients have signs of increased oxidative stress as measured by protein peroxidation (Eisinger, Gandolfo, Zakarian, & Ayavou, 1997). In addition, decreased levels of red blood cell magnesium, plasma selenium, and thiols (essential in antioxidant handling of free radicals) have been observed (Eisinger et al., 1997; Eisinger, Plantamura, Marie, & Ayavou, 1994; Reinhard, Schweinsberg, Wernet, & Kotter, 1998). Magnesium deficiency results in the loss of red blood cell glutathione (Barbagallo, Domínguez, Resnick, & Paolisso, 1999; Mak, Stafford, & Weglicki, 1994), selenium is involved in glutathione peroxidase activity (Aurther, 2000), and thiols are a class of organic sulfur derivatives (including glutathione and alpha lipoic acid) that act as reducing agents (Sen & Packer, 2000).

Diet can have a profound effect on antioxidant levels in the human body. The effect of a vegetarian diet on antioxidant levels has been the source of considerable research in recent years. Plasma total antioxidant status can be significantly increased in people following a vegetarian diet (Krajcovicova-Kudlackova et al., 1995; Nagyova, Kudlackova, Grancicova, & Magalova, 1998) and after consuming a meal high in fruits and vegetables (Cao, Booth, Sadowski, & Prior, 1998). Vegetarian diets are associated with increased magnesium intake (Barr & Broughton, 2000) and plasma glutathione levels (Flagg et al., 1993). The research on the selenium (Se) status of vegetarians is conflicting, with studies showing both an increase of plasma Se (Krajcovicova-Kudlackova et al., 1995) and a decrease in plasma and red blood cell Se levels (Kadrabova, Madaric, Kovacicova, & Ginter, 1995). As grains are quite high in
bioavailable Se but are reflective of Se in the soil, it appears that even within a vegetarian diet, blood Se levels are highly dependent on both the regional soil content and total dietary cereal intake (Shultz & Leklem, 1983).

The first objective findings that indicate a vegetarian diet may benefit FM patients comes from a 1993 study published by Hostmark, Lystad, Vellar, Hovi, and Berg from the University of Oslo, Norway. They placed 10 FM patients on a 3-week vegetarian diet and measured the plasma fibrinogen, serum lipid, and peroxide levels before and after the diet. Mean serum peroxide levels fell from 3.60 (± 0.14) to 2.82 (±0.15) µmol/L, and mean plasma fibrinogen levels decreased from 3.33 (±0.25) to 2.74 (±0.5) g/L. There was also a decrease in serum cholesterol that was positively correlated with reduction in body weight. The authors suggest that the reduction in serum peroxides and plasma fibrinogen may be due to the high concentration of antioxidants in the vegetarian foods. Subjectively, 7 of 10 FM patients reported an increase in health status in the form of improved well-being and reduced pain. It should be noted that the patients were encouraged to perform physical activity such as walking during the 3 weeks, and this may have contributed to the weight loss, improved lipid profile, and subjective improvement (Hostmark et al., 1993).

More recently, there have been three published studies examining the role of the vegetarian or vegan diet in the treatment of FM. The first study (Hanninen et al., 2000) addressed the potential role of antioxidants from a vegan diet in FM and rheumatoid arthritis (RA). The University of Kuopio, Finland, researchers examined living foods (LF), a type of vegan diet consisting of fruits, vegetables, seeds, sprouts, and nuts. Included in the study were 20 long-term LF users, 20 controls, 33 FM patients (divided into LF and omnivore), and 42 RA patients (also divided into LF and omnivore). The patients in the LF groups (LF, LF-FM, LF-RA) were given instructions on how to prepare the LF meals, and compliance to the diet was measured by sodium excretion. Dietary flavonols, polyphenolic compounds with strong antioxidant properties (Hollman & Katan, 1999), were calculated based on daily intake assessments. Over the 3-month period, symptoms were measured using subjective assessments and a relative activity index. Serum cholesterol, urinary lignans, and fecal urease were also recorded.

The results of this study showed that significantly higher levels of serum carotenoids (lutein, lycopene, alpha carotene, and beta carotene) and flavonols (quercetin, kaempherol, and myricetin) were found in the LF groups. FM patients who consumed the LF diet reported significant improvements in joint stiffness, pain, and general health. The authors attribute the beneficial effect of the LF diet to the increased antioxidant and lignan levels as well as to the positive change in intestinal microflora. Daily urinary excretion of lignans increased three- to tenfold while on the LF diet compared to the omnivorous control groups.

The vegan diet caused a reduction in fecal urease and beta-glucoronidase activity. The authors explain that the fiber-rich LF diet may have decreased the time available for the absorption of harmful compounds from the intestinal tract. The resulting reduction in these enzymes lowers the level of ammonia and lipophilic aglycones, thereby reducing the chemical load of the body. Previous research has shown that the vegan LF diet reduces the conversion of aromatic amino acids and endogenous proteins into toxic phenols (Hanninen, Nenonen, Ling, Li, & Sihvonen, 1992). In addition, the vegan diet has also been shown to increase lactobacilli in the stool (Hanninen et al., 1992; Mantere-Alhonen & Ryhanen, 1994). Hanninen et al. (2000) suggested that the positive influence of beneficial bacteria in the intestines may improve immune function among patients on the LF diet. Beneficial changes in fecal microbial flora have been correlated with improvements in disease activity in RA patients on a vegan diet (Peltonen et al., 1997). In addition, lactic acid–producing bac-
teria can protect the human intestinal epithelial barrier (Madsen et al., 2001), possibly reduce the incidence of allergies, and alter inflammatory cytokine production (Cross & Gill, 2001).

Cranberry, blackcurrant, bilberry, and other berries are liberally consumed in the vegan LF diet. The antioxidant potential of berries is quite high, particularly blueberries, which have the highest oxygen radical absorbance capacity (ORAC) of more than 30 fruits and vegetables tested (Cao, Sofic, & Prior, 1996; Wang, Cao, & Prior, 1996). Of the blueberry species, *Vaccinium myrtillus* (bilberry) has the highest anthocyanin and ORAC scores (Prior et al., 1998). A recent double-blind, placebo-controlled trial suggests that the administration of pure anthocyanidins (80 mg daily) may be beneficial in FM patients (Edwards, Blackburn, Christie, Townsend, & David, 2000). Patients in the active treatment group received an anthocyanidin formula derived from cranberry, bilberry, and grape seed. There were small yet statistically significant improvements in the group receiving the anthocyanidins, specifically in reduction of fatigue and improved sleep.

The effect of a 3-month uncooked vegan diet on FM symptoms was also investigated by researchers in Finland (Kaartinen et al., 2000). Again, the diet was understood to be rich in lactobacilli based on the findings of previous LF investigators (Hanninen et al., 1992; Mantere-Alhonen & Ryhanen, 1994). Kaartinen et al. (2000) placed 18 FM patients on a vegan diet, and 15 FM patients continued an omnivorous diet in the control group. Once again, those on the vegan diet reported a significant decrease in pain and morning stiffness and improvement in sleep quality and general health. Patients in the vegan diet intervention group also lost weight over the 3-month trial. Prior to commencing the diet, 50% of the FM patients had a body mass index (BMI) of 25 and greater, but after 3 months on a vegan diet, all had a BMI below 24.

Despite these positive results, it should be pointed out that there were no significant differences among groups on the objective measurements of grip strength and exercise capacity at the conclusion of the trial. In addition, FM symptoms recurred after patients returned to their usual eating habits at the conclusion of the intervention period, an occurrence also noted in the vegan diet study by Hanninen et al. (2000). Kaartinen et al. (2000) commented that the vegan LF diet can be difficult to prepare and despite its favorable effects, may be exhausting to maintain for an already tired patient population.

The most recent investigation into a raw vegetarian diet also had beneficial results (Donaldson, Speight, & Loomis, 2001). All subjects in this study (*N* = 20) were FM patients who participated in a dietary intervention using a mostly raw, pure vegetarian diet. Subjects were instructed to consume fresh fruit, salad, raw vegetables, carrot juice, nuts, seeds, whole grains, tubers, flax seed oil, and extra virgin olive oil. They were instructed to avoid alcohol, caffeine, corn syrup, dairy, eggs, all meat, refined sugar, and hydrogenated oils and were given an unlimited quantity of dehydrated barley grass powder (BarleyGreen). A live instructional or video presentation was made available to all subjects. No further motivational encouragement was given. Validated instruments such as the Fibromyalgia Impact Questionnaire (FIQ) and the SF-36 Health Survey were used in follow-up assessment.

Twenty subjects returned surveys as requested over the course of the 7-month trial. A 33% improvement was noted in FIQ scores after 2 months, and this increased to 46% after 7 months. Quality-of-life scores increased over the course of the intervention, particularly in the areas of recreation, health, socializing, and participation in organization. SF-36 results were significantly higher compared to general population norms, however, after 7 months, the general health, vitality, role emotional, and mental health scores were no longer different. Significant improvement in the areas of physical performance, exercise tolerance, flexibility,
and range of motion were recorded by a physical therapist. Handgrip strength and isometric shoulder endurance did not improve.

It is also interesting to note that in this study, the participants were encouraged to use flax oil, a significant source of omega-3 (n-3) fatty acids, resulting in a mean intake of 6 g daily. This addition could have provided extra symptomatic relief as the n-3 fatty acids have been shown to be competitive inhibitors of cylooxygenase and ameliorate the effects of oxygen free radical attack on the polyunsaturated components of cellular membranes (Masters, 1996). In addition, decreased concentrations of n-3 fatty acids have been correlated with the severity of depressive symptoms (Hibbeln & Salem, 1995). In one open, noncontrolled, nonblinded study, 12 FM patients were given 4.5 g of fish oil daily for 4 weeks (Ozgocmen, Catal, Ardicoglu, & Kamanli, 2000). The results showed marked improvement in pain, fatigue, depression, and tender point counts. Placebo-controlled trials are necessary to validate these findings.

The effect of reduced arachidonic acid intake in the vegetarian diet (Phinney, Odin, Johnson, & Holman, 1990) was not specifically discussed in these FM studies but may be a factor in the positive outcomes via reduced series 2 prostaglandins and series 4 leukotrienes. Although reduced arachidonate may be beneficial, a general lack of vitamin B12 and n-3 fatty acids in the vegetarian diet may be a concern for FM patients. Supplementation with vitamin B12 and n-3 fatty acids may offer additional cardiovascular health benefits in the vegetarian diet (Mezzano et al., 2000) and should be considered clinically and in future research. There has been no research to date that has examined an FM diet in which the exclusion of red and white meat was accompanied by encouraging consumption of fish containing high n-3. It is very likely that compliance would be much higher while on such a diet.

Vegetarian and vegan diets have been and continue to be of interest to those investigating other rheumatic disorders. Previous studies have shown that vegetarian or vegan diets can be of value in reducing RA symptoms (Kjeldsen-Kragh et al., 1991; Nenonen, Helve, Rauma, & Hanninen, 1988). Most recently, a 1-year controlled study involving RA patients showed that a vegan diet (free of gluten) improved symptoms, possibly related to a diminished immune response to exogenous food antigens (Hafstrom et al., 2001). The combined studies suggest that changes in the gut immune system can influence the course of rheumatic symptoms.

**FOOD AND CHEMICAL SENSITIVITY**

The elimination and rechallenge of certain foods or additives is an emerging area of research in FM. Haugen, Kjeldsen-Kragh, Nordvag, and Forre (1991) from the University of Oslo, Norway, surveyed patients with various rheumatic disorders, including FM, on disease symptoms and diet. The results were remarkable, with 42% of the FM group reporting aggravation of disease symptoms including increased pain and stiffness (80%) and joint swelling (29%) after the intake of certain (unspecified) foods. Across all rheumatic groups, 119 patients (64%) attempted dietary manipulation after experiencing symptom aggravation from the intake of certain foods (FM; n = 14), and reported decreased pain (47%), stiffness (46%), and joint swelling (36%) after dietary manipulation. There was no significant difference between the rheumatic groups regarding the efficacy of the dietary manipulation. As mentioned, the specific foods aggravating FM were not specified; however, in the case of RA, the top offending foods were listed as meat, wine, and coffee.
There have been similar findings in the related disorder of chronic fatigue syndrome (CFS), in which 54% of patients surveyed had made dietary modifications to reduce fatigue (Nisenbaum, Reyes, Jones, & Reeves, 2001). Of these individuals, 73% partly attributed dietary changes with a reduction in fatigue, making it one of the most helpful CAM therapies used. A research review on dietary modification and its role in the pathogenesis of CFS has previously been published (Logan & Wong, 2001).

Investigators from the Thomas Jefferson University Hospital in Pennsylvania recently reported the results of a retrospective chart review study of 17 FM patients who completed an elimination and challenge diet (Edman et al., 2001). Half of the FM patients reported a significant reduction in pain during the elimination phase, and 76% reported improvement in fatigue, headaches, and gastrointestinal symptoms. These same symptoms worsened during the challenge phase, with corn, wheat, dairy, citrus, and sugar being among the top offending foods.

Patients with chronic illnesses who report food intolerances have often been dismissed as having a psychiatric illness or as merely manifesting somatization traits (Knibb et al., 1999; Manu, Matthews, & Lane, 1993). A landmark study published in the Lancet validates the symptoms of those with food intolerance and challenges the psychiatric hypothesis (Jacobsen et al., 2000). Patients with perceived food intolerance were challenged with foods they had eliminated, in this case, milk and wheat. After the challenge, researchers found significant elevation in cytokine release (interleukin-4, interferon gamma, tumor necrosis factor alpha), which accompanied and can account for increased abdominal discomfort, headache, and joint and muscle pain. Despite normal routine laboratory testing and no lactase insufficiency, Jacobsen et al. (2000) were able to uncover a more subtle physiological mechanism for the reported complaints. Cytokine elevation has recently been shown to be involved in anxiety, depression, and cognitive deficits in otherwise healthy adults (Reichenberg et al., 2001) and may play a role in the pathogenesis of FM (Maes et al., 1999; Wallace et al., 2001).

For some FM patients, it may not be the foods they are intolerant to but certain added chemicals. In a series of case studies published in the Annals of Pharmacotherapy, researchers from the University of Florida concluded that the elimination of monosodium glutamate (MSG) and aspartame can lead to marked improvement in certain FM patients. Although only four patient cases were described, the results were dramatic, with an almost complete resolution of symptoms within months. Rechallenge with MSG led to significant exacerbation of FM symptoms (Smith, Terpening, Schmidt, & Gums, 2001).

Large amounts of dietary glutamate can normally be consumed without significant adverse effects. Brain glutamate concentrations are kept low despite high plasma levels due to an active transport mechanism at the blood-brain barrier (BBB). The possibility of a defective BBB in FM exists and has been previously hypothesized to account for the neurological findings in CFS (Bested, Saunders, & Logan, 2001). Interestingly, anthocyanidins, particularly those from bilberry, have been shown to protect and repair a compromised BBB in the animal model (Cahn & Borzeix, 1983; Detre, Jellinek, & Robert, 1986; Robert, Godeau, Moati, Miskulin, 1977). It is also important to note that viral infection can enhance the neurotoxic effects of MSG in the animal model (Wu, Gao, Zhao, Wu, & Zhang, 1994). Although no singular viral infection has been consistently found among FM patients, a viral contribution to the pathogenesis has been suggested in the literature (Leventhal, Naides, & Freundlich, 1991; Tyler, 1997; Wittrup, Jensen, Blüddal, Danneskiold-Samsoe, & Wiik, 2001).
Once inside the brain, glutamate in excess acts as an excitatory neurotransmitter via the N-methyl-D-aspartate (NMDA) receptor, where it can lead to neurotoxicity and cellular damage. Aspartate can have similar neurotoxic effects and can have additive detrimental effects when combined with glutamate (Olney, 1994). Smith et al. (2001) speculated that the glutamate could be acting in excess causing the hypothalamic disturbances observed by way of the pain modulation at the NMDA receptor or possibly by a general sensitivity or intolerance. The authors acknowledge that a cause-and-effect relationship cannot be established based on a small number of case studies. Prospective, placebo-controlled trials are necessary to verify the findings. In the meantime, the findings suggest that the elimination of MSG and aspartame may be worthwhile as a low-cost, noninvasive method of FM symptom reduction.

**PAIN-MODULATING FOODS**

The notion that individual foods can modulate pain is also being investigated. Research first published in *Neuroscience Letters* has shown that sensitivity to pain can be attenuated by diet in the animal model (Shir, Ratner, Raja, Campbell, & Seltzer, 1998). Soy-containing diets (85%) preoperatively and postoperatively suppressed the development of mechanical and heat allodynia as well as hyperalgesia. The diet-induced reduction in pain was not correlated with caloric intake, weight gain, or fat and carbohydrate content. The pain-reducing effects of the soy diet have been replicated in different laboratories with varied testing methods (Shir, Sheth, Campbell, Raja, & Seltzer, 2001). The mechanism of pain reduction from a soy-based diet remains unclear; however, the research suggests that dietary modification may play a role in human pain reduction. The authors speculate that phytoestrogens may be mediating pain suppression by enhancing CNS beta-endorphin levels.

**CONCLUSION**

There is increasing evidence that dietary modification may play a role in the reduction of FM symptoms. As with the pathogenesis of FM, the exact physiological mechanism of symptom reduction due to dietary alterations remains unknown. Alteration of cytokines, reduced oxidative stress, increased antioxidant potential, improved bowel flora, and CNS chemical modification may be playing a beneficial role. Obviously, the placebo response cannot be ruled out in many of the studies reviewed, and it should be pointed out that the placebo response is a particularly strong one in FM research (Heymann, Helfenstein, & Feldman, 2001). Dietary modifications can provide FM patients with a feeling that they have a sense of control over the illness, and undoubtedly this has played a role in some of the cited research.

Almost a decade ago, Ann L. Parke (1993) from the Connecticut Health Center, Division of Rheumatic Diseases, published a review article in *Current Opinion in Rheumatology* on gastrointestinal disorders and rheumatic diseases. She stated that clinicians have nothing to lose by pursuing dietary modifications in the treatment of rheumatic illness. Parke made note of the fact that dietary modifications are less toxic than standard therapies and that conventional treatments do not work in all patients. Finally, Dr. Parke also pointed out that dietary modifications were an underinvestigated area of research in rheumatic diseases, a fact that, outside of Scandinavia, remains true today.
Based on this literature review, I concur with Parke that in clinical practice, dietary modification is a low-cost and potentially effective treatment intervention. Of critical importance is proper patient education regarding an appropriate balance of protein, carbohydrate, and fat. Compliance with dietary modifications can be difficult, changes can be time-consuming and place a strain on social life, and improvements must more than compensate for the inconvenience. Providing nutritious, palatable alternatives to even temporarily restricted foods will increase compliance. As research continues to uncover the role of diet in chronic pain and fatigue conditions such as FM, clinicians should consider dietary changes worthwhile.

REFERENCES


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