Mod Rheumatol (2005) 15:87–90
DOI 10.1007/s10156-004-0367-6

REVIEW ARTICLE

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Naturopathic management of rheumatoid arthritis

Received: June 3, 2004 / Accepted: November 9, 2004

Abstract Complementary and alternative medicines (CAM) are widely used by those with pain and/or musculoskeletal problems, and previous research has shown that high proportions of individuals with rheumatoid arthritis have used these therapies. One of the largest CAM modalities is that of naturopathy, which combines nutritional, herbal, and other complementary practices to treat such conditions. In this review, evidence is examined in relation to those factors which naturopaths believe are significant contributors to rheumatoid arthritis, and are hence the main focus of therapeutic management. These factors include food allergy, increased gut permeability, increased circulating immune complexes, excessive inflammatory processes, and increased oxidative stress. Naturopathic treatment attempts to alleviate symptoms by altering these factors through dietary modification, manipulation of dietary fats, and use of antioxidants and proteolytic enzymes. An understanding of the rationale for these treatments and evaluation of the evidence from their use in clinical settings will assist with the integration of complementary and conventional practices in the treatment of rheumatoid arthritis.

Key words Complementary and alternative medicine (CAM) · Food allergy · Intestinal permeability · Naturopath · Rheumatoid arthritis (RA)

Introduction

Complementary and alternative medicine (CAM) encompasses a broad range of healing practices from various health systems[1] together with their accompanying theories and beliefs, and is considered outside the dominant health system of a particular society or culture.[2] Although used for a wide range of conditions, CAM is used particularly by those with chronic pain and/or musculoskeletal problems.[3] Buchbinder et al.[4] found that 73.3% of rheumatoid arthritis (RA) patients attending a community-based rheumatology clinic had used some form of CAM in the past year. In this review we examine the evidence related to factors which naturopaths believe are significant contributors to RA, and the main focus of therapeutic management. These factors are food allergies, increased gut permeability, and increased levels of circulating immune complexes, excessive inflammatory processes, and oxidative stress, with diet being foremost.[5]

Food allergies

Some patients with RA claim that symptoms improve with the elimination of certain foods, but scientific support has been sparse. Bengtsson et al.[6] were able to show that skinprick IgG tests frequently failed to detect obvious food intolerance in patients with gastrointestinal reactions. They assessed whether there was any association between the presence of mucus in stools, joint swelling, arthralgia, and atopic disease, in patients with a history of food intolerance and associated gastrointestinal symptoms, and a control group with signs of allergy (eczema and rhinoconjunctivitis), without gastrointestinal symptoms. No differences were found in serum IgG, IgM, and IgA between the two groups. Seventy-one percent of patients with food related gastrointestinal symptoms had a history of arthralgia ($P < 0.001$ compared with controls) and 44% of joint swelling ($P < 0.05$). There were significantly more circulating immune complexes amongst patients with arthralgia compared to patients without this history ($P < 0.03$). A poor correlation between the skinprick test and onset of symptoms was also found. The exact mechanisms for these reactions are not clear, proposed mechanisms include localized IgE synthesis in the gut, antibody-dependent cellular cyto-

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toxicity, or activation of the complement system.[6] Delayed hypersensitivity reactions to foods cannot be accurately tested by the usual IgE tests; combined IgE and IgG4 enzyme-linked immunosorbent assay-specific antibody tests offered by some private laboratories have also been shown to have low test/retest validity and little improvement on chance.[7] It is also suggested that some foods (e.g., cereals) containing specific epitopes may trigger autoimmune responses.[8]

The protein gluten, found in wheat, rye, barley, and oats, is known to produce celiac disease in some individuals.[5] Lubrano et al.[9] found a high prevalence of articular manifestations in a group of 200 patients with celiac disease, particularly in newly diagnosed patients who were on a regular diet compared with those who were on a gluten-free diet (41% vs 22%, $P < 0.005$), and the arthritis was independent of the duration of the intestinal disease. The joint involvement was most frequently nonerosive, nondeforming oligopolyarthritis and there was an absence of rheumatoid factor. In celiac disease, subclinical mucosal damage is difficult to rule out and could favor activation of the immune system with possible connective tissue involvement.[9] These studies identify the importance of food, its effect on the gut, and possible stimulation of an immune response in susceptible individuals.

No one food is believed to aggravate RA; however, the most common implicated foods are wheat, corn, dairy products, beef, the solanaceae family (tomato, potato, eggplant, peppers, chili, paprika, and tobacco), and some food additives.[5] Naturopaths counseling RA patients may recommend diets low in these foods to help control symptoms.

Dietary modifications

Over a decade ago, a controlled trial of fasting followed by an individually adjusted 1-year vegetarian diet resulted in a sustained clinical, objective, and subjective improvement in RA patients.[10] This study investigated the effect of fasting using vegetable juices for 7–10 days, followed by consumption of an individually adjusted, gluten-free, vegan diet for 3.5 months, and then by an individually adjusted lacto-vegetarian diet for 9 months.[10,11] In the experimental group, the principles of an elimination diet were followed after the fast. Potatoes, carrots, celery, parsley, and beets used during the fast made up the basic diet, with the introduction of a new food every second day. If pain, stiffness, or joint swelling occurred within 2–48 h, the food was omitted from the diet for at least 7 days before reintroduction. If symptoms occurred again, the food was excluded during the study period. The experimental group were not allowed to have dairy products or foods containing gluten, meat, fish, eggs, refined sugar, citrus fruit, salt, strong spices, preservatives, alcohol, tea, and coffee for 3.5 months after which time they were allowed to consume dairy products and foods containing gluten, after being introduced one at a time. After 1 month of treatment, in the experimental group there was a significant decrease in all disease activity variables compared with measures taken prior to the study: pain ($P < 0.0001$), morning stiffness ($P < 0.0002$), health assessment questionnaire ($P < 0.0001$), grip strength ($P < 0.0005$), joint tenderness ($P < 0.0002$), and Ritchie's articular index ($P < 0.0004$). Twelve of the 27 patients in the experimental group showed significant clinical improvement compared with only 2 of the 26 patients in the control group ($P < 0.003$).[11] A significant improvement over baseline in the clinical variables was still evident in some individuals 1 year following completion of the study. Changes in several fatty acids occurred when omnivorous patients consumed a vegan diet, and also when they switched to a lacto-vegetarian diet.[11] Bowel flora were also altered with a change to a vegetarian diet,[12] resulting in a significant decrease in IgG antibody activity against *Proteus mirabilis* that correlated significantly with the decline in disease activity.[11] Peltonen et al.[12,13] have also observed alterations in bowel flora with diet changes.

Proteus mirabilis, a normal commensal organism, has been implicated in RA by other researchers. Ebringer et al.[14] found higher antibody titers to this bacterium in RA patients compared with healthy controls. In a later study they showed that *P. mirabilis* contained a sequence of six amino acids that closely resembles a sequence that is present on human lymphocyte antigen (HLA) DR1 molecule and DR4 subtypes known to be associated with RA.[15] Ebringer et al.[15] have gone on to suggest that RA is a form of reactive arthritis triggered by *P. mirabilis* and that reduction of anti-*Proteus* antibodies, which may activate the complement cascade or natural killer cells, could possibly lead to a reduction in inflammation and arrest the progression of the disease.

Another investigation of an extreme uncooked vegan diet in moderate to severe RA patients failed to show objective improvement, although subjective improvement was noted in the intervention group.[16] These findings may have differed from those of Kjeldsen-Kragh[11] because the diet was not adjusted for possible food intolerance.

Intestinal permeability

Complementary medicine practitioners consider increased intestinal permeability to dietary and bacterial antigens (which is referred to as "leaky gut"), against which the body forms antibodies, as a major contributing factor to RA.[5] Food allergies themselves may contribute to this hyperpermeable state as can the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Bacterial endotoxins are believed to be a source of antigen–antibody immune complexes that characterize RA.[5] The focus of complementary medicine is to advantageously alter gut flora, heal the leaky gut, and in so doing alleviate symptoms. In 1986, Segal et al.[18] found evidence of gastrointestinal lesions in RA patients. Initial work aimed at demonstrating labeled leukocyte uptake in the joints demonstrated localization of pyogenic infection in the gut. This study was undertaken to estimate the frequency of this occurrence and demonstrated

localization of radioactivity in the gut in 46% of the RA patients compared with none in controls. This was particularly evident in the terminal ileum, cecum, and ascending colon, and independent of NSAIDs, suggesting that increased intestinal permeability may be a contributing factor in a number of RA patients.

Dietary fats

Complementary and alternative medicine practitioners also focus on fatty acids in RA, as fatty acids provide precursors for synthesis of the inflammatory molecules.[5] The pro-inflammatory eicosanoid, prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) are derived from the omega-6 (ω-6) fatty acid arachidonic acid (AA) which tends to be at high cellular concentration due to an imbalance in the Western diet, in which there is 20–25 fold more ω-6 fats than omega-3 (ω-3) fats consumed.[19] The essential fatty acid, linoleic acid (LA), an ω-6 fatty acid, is present in high concentrations in soy, corn, safflower, and sunflower oils, and α-linolenic acid (ALA), the essential ω-3 fatty acid, is present in leafy green vegetables, flaxseed, and canola oil. The omega-9 nonessential fatty acid (ω-9) oleic acid, present in olive oil and used heavily in the Mediterranean diet, is also involved in fatty acid balance.[19] Altering the type of dietary fat intake can decrease or increase inflammation. Flaxseed oil contains ALA (18:3ω-3) that can be converted to 20-carbon eicosapentaenoic acid (EPA) (20:5ω-3), found in fish and fish oils, along with 22-carbon docosahexaenoic acid (DHA) (22:6ω-3). Eicosapentaenoic acid is known to act as a competitive inhibitor of AA (20:4ω-6) conversion to PGE2 and LTB4. Eicosatrienoic acid (ETA) (20:3ω-9) in the diet also results in decreased synthesis of LTB4,[19] and could partially account for the benefits of the Mediterranean diet. Daily ingestion of ω-3 fish oils has been consistently shown to reduce the number of tender joints on physical examination and the amount of morning stiffness in RA patients, when 3 g of EPA and DHA acids are taken in combination with medication, although benefits are not apparent until at least 12 weeks.[20] In vitro research which involved culturing monocytes from previous tetanus toxoid-inoculated healthy men and women revealed that when activated by the addition of γ-interferon to upregulate surface molecule expression, in the presence of EPA and DHA the percentages of monocytes expressing various surface molecules were reduced.[21] There were significant decreases in percentages of monocytes expressing the major histocompatibility complex class II molecules HLA-DR and HLA-DP and the adhesion molecules, namely, intercellular adhesion molecule-1, which has been shown to be capable of costimulating an immune response.[21] These cell surface molecules are known to be required for the process of antigen presentation, and alterations in their expression are known to alter the degree of immune responsiveness that an individual has to antigenic stimulation.[21] In this study it was shown that activated monocytes had reduced ability to present antigens to lymphocytes when combined with ω-3 fatty acids at a blood plasma level that could be achieved with the consumption of 3 g of fish oil daily.

Antioxidants

A diet high in the antioxidant nutrients, vitamin C, vitamin E, carotenoids, as well as selenium and zinc, found in fresh fruit and vegetables, berries, green tea, nuts, and seeds,[23] is emphasized in complementary medicine. Antioxidants act to scavenge free radicals or reactive oxygen species, an important factor in RA. Some cytokines, such as tumor necrosis factor α, interferon-γ, interleukin-1, and interleukin-2, increase the activity of the enzyme nitric oxide synthase (NOS) to produce nitric oxide (NO),[24] in synoviocytes and chondrocytes, and gives rise to a highly toxic free radical, peroxynitrite,[25] which increases lipid peroxidation and synthesis of eicosanoids.[24] Macrophages produce large amounts of NO when either stimulated by cytokines or lipopolysaccharides. During states of inflammation, as in RA, there is an upregulation of NO and superoxide radical production, producing oxidative stress, resulting in damage to host tissue and rapid depletion of biological antioxidants such as vitamin C and plasma glutathione. Bland[24] has suggested that the presence of leaky gut and bacterial overgrowth of the small intestine can lead to the liberation of lipopolysaccharides and the activation of hepatic macrophages (Kupffer cells), which further stimulate the release of cytokines and increased NO production.

Rheumatoid arthritis patients have low serum levels of some antioxidant nutrients.[26] In a case-controlled study, nested within a Finnish cohort of 1419 men and women, it was shown that 14 individuals developed RA during the 20-year period and it was found that serum α-tocopherol (vitamin E), β-carotene, and selenium concentrations from stored serum samples of these subjects when matched to controls had low levels of all three nutrients, although not to a statistically significant extent.[26] However, an antioxidant index, calculated as the product of the molar concentrations of all three nutrients, did show significant association. Seropositive RA patients have been shown to have significantly lower serum selenium concentrations compared with normal healthy controls.[27] These findings could be a result of increased oxidative stress and increased activity of the selenium-dependent enzyme glutathione peroxidase, or inadequate intake of dietary selenium. Research has shown that supplementation with vitamin C, vitamin E, and glutathione reduces peroxynitrite reactions, reducing the amounts of oxidative damage[24] and therefore, antioxidants are recommended in the management of RA.

Enzyme therapy

Oral enzyme therapy such as bromelain is recommended by CAM practitioners to reduce inflammation.[5] Several

mechanisms have been suggested for its action, and include the inhibition of proinflammatory compounds, modulation of adhesion molecules, activation of fibrinolysis, and reduction of immune complexes.[28] The analgesic effect is believed to be secondary as pain-inducing factors decrease. Results from a comparative assessment of the efficacy and safety of orally administered enzyme therapy (Wobenzym, Mucos Pharma, Germany) (over a 5-year period) with methotrexate (over a 3-year period) and weekly intramuscular gold injections (over 12 months) showed that all three treatments were equally effective in regard to pain and joint and inflammatory indexes. There was no statistical difference between the groups in terms of clinical and laboratory remission parameters (morning stiffness, pain reduction, erythrocyte sedimentation rate); the main difference found was fewer side effects in the enzyme therapy group.[29] These results indicate that enzyme therapy modulates different links in the immune–inflammatory cascade in RA patients. In an earlier study RA patients who had a reduction in disease activity while taking methotrexate, NSAIDS, and enzyme therapy (Wobenzym) manifested the usual exacerbation of RA on discontinuance of enzyme therapy.[30]

Conclusions

The distinction between CAM and biomedicine is becoming less pronounced. Nursing and family medicine are adopting practices that are more holistic and patient centered. This can be seen in the use of stress management, nutrition, and emphasis on a balanced lifestyle for achieving and maintaining health; the philosophy behind these recommendations is intrinsic to CAM.

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