The Dietary Treatment of Inflammatory Arthritis: Case Reports and Review of the Literature

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Abstract

Two patients with seropositive inflammatory arthropathies who experienced clinical improvement on the Waianae diet are presented.

The scientific literature validates the usefulness of fasting in the control of joint inflammation. Elimination diets are variably successful. Fasting followed by a vegetarian diet can produce a sustained positive response measured clinically and by laboratory variables of inflammation; the efficacy of such an approach appears to hinge on the alteration of fecal flora. Swaying the balance of dietary fats in favor of the omega 3 and omega 6 fatty acids has an antiinflammatory effect, but does not appear to correct the basic immunologic processes involved in the development of the arthropathies.

Practical guidelines for the application of this information are offered.

Introduction: The Hawaii Diet Program

The Hawaii Diet is a multi-cultural version of the Waianae Diet which is based on traditional Hawaiian foods. The Waianae diet program was developed at the Waianae Coast Comprehensive Health Center in response to the high rates of obesity and chronic disease in the native Hawaiian population. The selection of food consists of items eaten in Hawaii before the onset of Western influence, including such items as taro (a native potato), poi, sweet potatoes, yams, breadfruit, rootcrop greens, fruit, seaweed, fish and chicken. All items are served raw or steamed. The diet contains less than 10% fat, 12 to 15% protein and 75 to 78% carbohydrate. The Hawaii diet is based on the same macronutrient composition but with multi-cultural foods replacing many of the traditional Hawaiian meals. The Hawaii Diet includes as its staples in addition to poi and taro, whole starches such as brown rice, pasta, vegetables, fruit, legumes and a small amount of seafood or poultry.

Both diets have been shown to be effective in the control of high blood pressure, diabetes and hypercholesterolemia.[1] It has not heretofore been reported to positively influence the activity of the inflammatory arthritides.

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Case Reports

Case 1. LS, a 38 year old Japanese female presented with fevers, 20 pound weight loss, joint pain and polyarticular synovitis in the metacarpophalangeal joints and ankles. Antinuclear antibody titer was 1:80 with a speckled pattern, sedimentation rate 53 mm/hr; antibodies to ribonucleoprotein and SSA were present. A presumptive diagnosis of systemic lupus erythematosus (SLE) was made, and the patient was started on low-dose oral prednisone (10 mg/day)supplemented with indomethacin for the control of fever. Hydroxychloroquine 200 mg/day was eventually added as a steroid-sparing agent.

Two years into the disease course, the patient went on the Hawaii Diet. The sedimentation rate dropped from the 70 to 90 mm/hr range to 39 mm/hr. The platelet count, which had been elevated, normalized. The patient lost 10 pounds over 3 months. She reported increased energy, and was able to discontinue indomethacin without recurrence of the fevers. Synovitis disappeared.

The diet was discontinued after three months. Within a month, fatigue, rashes, fevers and joint pain had recurred.

Case 2. HS, a 44 year old female of mixed Hawaiian-European ancestry presented with synovitis in the metacarpophalangeal and proximal interphalangeal joints. She had an antinuclear antibody titer of 1:256, and antibody to DNA of 217 IU/ml (normal < 100 IU/ml). A presumptive diagnosis of systemic lupus erythematosus was made, and the patient was started on prednisone 10 mg/day, hydroxychloroquine 200mg BID and ketoprofen 200 mg/day. The response to oral hydroxychloroquine was less than optimal; this agent was discontinued. Steroid side effects (hyperglycemia, weight gain, fluid retention and Cushingoid facies) prompted the addition of oral methotrexate 10 and then 12.5 mg/week. Prednisone was tapered to 5 mg every other day; doses less than this resulted in disabling synovitis in the small joints of the hands.

The patient went on the Waianae diet program two years into the disease course. Within two months, the patient had discontinued the prednisone. On her own, she also went off the methotrexate a month later. She remained free of pain and synovitis for another month after she went off the diet, at which point both the prednisone and methotrexate had to be restarted.

Neither of these two patients meet strict classification criteria for SLE, but both clearly had an inflammatory arthropathy accompanied by significant serologic markers of autoimmune activity.

The Dietary Treatment of Arthritis

Interest in the impact of nutrition on disease causation, activity and cure is universal among patients with arthritis. The great majority will attempt some form of dietary manipulation, in large part unsupervised by and even unknown to their physician.[2]

Clearly, in gout and saturnine gout, dietary forces have a well-defined role, the first being a disorder of purine metabolism and elimination, and the second a lead intoxication state. Obesity is a risk factor for osteoarthritis, especially in the weight-bearing joints. Reiter's syndrome is a reactive arthropathy triggered in some cases by food pathogens. Beyond these well-defined circumstances, however, the role of food in the arthropathies is controversial.

Arthritis as a Food Allergy

The literature is replete with case reports of arthritis and synovitis being temporally associated with the ingestion of certain foods—dairy products [3,4] gluten[5] and azo dyes[6]. The behavior of the arthropathy in these situations satisfies classical medical criteria for causation—ie. exacerbation with challenge, remission with dechallenge, and reactivation with rechallenge. By and large, however, these cases are seronegative and nonerosive. More importantly, they are sporadic and fairly rare.

Elemental hypoallergenic diets have been studied in patients with rheumatoid arthritis (RA).[7,8,9] As a group, patients on these diets tend to do better subjectively, but objective improvements in the laboratory measures of inflammation do not improve significantly. Certain individuals respond better than others, but the magnitude of the response and the number of patients affected favorably are too small to produce statistical significance. The responders tend to be heavier at outset, and tend to have greater disease activity than the non-responders. Van de Laar et al have obtained synovial membrane and small intestinal biopsies on some of these responders. Mast cells and IgE bearing cells are decreased at these sites during dietary manipulation.[7] The authors postulate that these histologic changes suggest an allergological mechanism underlying the observed arthritis response.

Kavanaghi et al[9] have attempted to sustain improvement by reinstituting feeding selectively. After an elemental diet, patients were refed with one food group at a time. Those food groups followed by a disease flare were eliminated from each individual's maintenance regimen. Even such an individualized approach, however, failed to sustain improvement at 24 weeks.

The Effects of Fasting

Fasting—that is, the voluntary abstention from food for a limited period of time—has been validated as an effective short-term suppressor of inflammation in the arthritides.[10,11,12] Subjective improvement in pain and stiffness starts within three to five days of the initiation of the fast, and is sustained for its duration. Joint inflammation indices as well as acute phase reactants (sedimentation rate, orosomucoid, haptoglobins) decrease. Return to pretreatment disease activity occurs on the day after the fast is discontinued. In the hands of most investigators, no maintenance diet can sustain the benefits of the fast. (An exception to this observation has been reported, and is reviewed below.)

While almost universal relapse at the termination of the fast makes fasting an untenable treatment for RA, understanding the mechanisms underlying the clinical response is instructive.

Lymphocytes are affected by fasting. Antigen-specific B cell responses improve.[13] Suppressor cell activity, usually depressed in RA patients, normalizes with fasting.[14]

Neutrophilic functions are also influenced by food deprivation. Release of the pro-inflammatory chemical leukotriene B4 from neutrophils goes down, as does the ability to generate cytotoxins in vitro.[11] Levels of linoleic and alpha linolenic acids are unchanged; their metabolites, arachidonic and eicosapentaenoic acid increase. Such a profile can be produced by impaired activity of phospholipase and 5-lipoxygenase, enzymes involved in the metabolism of arachidonic acid to leukotriene B4. From these data, Hafstrom et al have postulated stimulus-response decoupling of neutrophil metabolism reduced ability to generate cytotoxins, reduced leukotirene formation) as mechanisms of the antiinflammatory effect of food deprivation.

Fasting also alters intestinal permeability.[15] Polyethylene glycol molecules penetrate intestinal mucosa less well during fasting; this reverses with refeeding of a lactovegetarian diet. If indeed inflammatory arthritis is an allergic or hyperimmune reaction to foreign antigens, the decreased penetration of immunostimulants may explain the temporary relief experienced by patients on a fast.

The Oslo Cohort

In the late 1980s, investigators in Oslo entered a group of 53 patients with RA in a single-blind controlled trial of diet therapy. Twenty-seven patients were randomized in a four-week stay at a health farm. The control group stayed for four weeks at a convalescent home, but ate an ordinary diet throughout the study period.

Treatment started with a 7 to 10 day subtotal fast. After the fast, one new food item was introduced every second day.. If this was followed by an exacerbation in symptoms, the offending food was withdrawn for one week. If a similar exacerbation occurred with later rechallenge, then that food item was permanently removed from the maintenance diet. During the first 14 months, patients were kept on a strict gluten-free vegan diet (ie no meat, fish, eggs, dairy products or food containing gluten). After this period, dairy and gluten were reintroduced. Foods producing a flare in disease activity were recorded in a personal journal. Clinical and laboratory assessments were performed at 1, 4, 7, 10 and 13 months. One year after conclusion of the study (ie 25 months after the intiation of the diet), patients were contacted for follow-up examinations.

The results of this study have been published in a series of related articles covering the clinical, biological, psychosociological and immunologic sequelae of the intervention.[16, 17, 18, 19, 20, 21, 22]

After four weeks at the health farm, the diet group showed significant improvements in the number of tender, swollen joints, pain, morning stiffness, grip strength, sedimentation rate, C reactive protein, and Health Assessment Questionnaire score (HAQ; a standardized instrument measuring the ease with which one performs the activities of daily living). Rest at a health farm did positively influence disease activity; the control group also demonstrated improved pain scores. Subjective improvement was accompanied by statistically significant drops in platelet counts, total IgG, IgM rheumatoid factor, C3 activation products, and complement compo-

nents C3 and C4, all of which are consistent with an amelioration of immunologic hyperactivity.

A little less than half of the experimental group (10 of the 24 evaluable subjects) could be classified as good responders, defined as having a 2-grade improvement on a subjective global assessment scale plus a 20% or better decrease in joint count, pain score, HAQ, and sedimentation rate. These good responders maintained their improvement at the one-year and two-year evaluation points.

Was there anything unique about these responders—ie are there characteristics that can identify which patients are likely to benefit from dietary intervention prior to the fact?
The investigators did determine that:

a. diet responders tended to have had their disease for a shorter time (mean of 6 years versus 14 years for the nonresponders); this is consistent with the response to pharmacologic interventions, implying a more malleable situation in the early inflammatory phases of the disease, before chronic damage is in place,
b. diet responders were more likely to be seronegative (30% versus 58% for the nonresponders); this is reminiscent of the data for RA and food allergies, vide supra,
c. diet responders had a significantly lower belief in the effect of ordinary medical treatment compared with the nonresponders.

The investigators tried to identify laboratory variables that correlated with clinical response. They found that neither immunoglobulin levels nor phospholipid profiles covaried with clinical disease activity. While RA patients were found to have elevated levels of antibodies to food allergens (consistent with generalized B cell hyperactivity), the activity of these immunoglobulins did not correlate with the disease course. Plasma arachidonic acid levels dropped initially and returned to baseline with the lactovegetarian diet; eicosapentaenoic acid levels stayed low throughout the diet. Contrary to findings from the omega fatty acid literature (*vide infra*), plasma phospholipid profiles did not covary with disease activity.

What did appear to be consistently predictive of clinical improvement was a change in fecal flora. Gas-liquid chromatography (GLC) of bacterial cellular fatty acids obtained from stool samples indicated that the microbial profile changes significantly in patients responding to diet therapy.[22,23] Nonresponders do not exhibit this variability. Unfortunately, GLC is a sensitive measure of quantitative changes in cell wall profiles, but is unable to determine specifically which bacterial species are decreasing or increasing.

Other Diet Programs

A calorie-optimized diet enchanced with fish meals and antioxidants has been tested in a single-blind 6 month study in Norway.[24] Compliance was monitored through a diet diary. While the study is confounded by a 26% drop-out rate, those able to follow the diet demonstrated less morning stiffness, fewer swollen joints, less pain, and reduced medication cost. Objective laboratory data, however, did not change.

The Dong diet has also been put forward as a therapeutic diet for arthritis.[25,26] This diet was designed by a southern California dermatologist, Dr. Colin Dong. He came down with RA and cured himself by returning to the traditional Chinese diet of his childhood. The diet consists of fish, little meat and occasional fowl, no fruit, herbs or spices, no dairy products, no alcohol, and no additives or preservatives. The diet was tested by the group of Dr. Richard Panush at the University of Florida in a 10-week randomized double-blind study involving[26] patients.[27] There were no statistically significant differences between the two groups at any point in the study. Interestingly, however, two individuals in the experimental group achieved noteworthy disease control, and elected to remain on the diet after termination of the study. Both had strong personal and family histories of atopy—other than this one observation, nothing else distinguished these remarkable responders from the rest of the subjects.

The Role of Dietary Fats

Fatty acids seem to have some effect on the inflammatory process possibly as a result of their role as precurcors to prostaglandins and leukotrienes. N-3 (the designation refers to the location of the first double bond in the carbon chain, counting from the amino terminus) fatty acids are antiinflammatory. The 20-carbon n-6 and n-3 fatty acids archidonic acid (AA) and eicosapentaenoic acid (EPA) are biosynthetic precursors for n-6 and n-3 eicosanoids of the leukotriene (LT)and prostaglandin (PG) families. The n-6 eicosanoids LTB4 and PGE2 are pro-inflammatory, causing neutrophil chemotaxis and activation as well as increased vascular permeability.[28] The n-3 homologs are either less active (LTB5) or poorly synthesized from

Table 1.—Sources, relationships and inflammatory effects of some metabolically important unsaturated fatty acids (adapted from 32). Abbreviations used: PG - prostaglandin, LT - leukotriene, TNF - tumor necrosis factor, IL - interleukin.

	n-6	n-3
18 Carbon Fatty Acids	Linoleic Acid C18:2	Linolenic Acid C18:3
Sources	Soybean, sunflower and corn oil	Flaxseed, canola oil
20 Carbon Fatty Acids	Arachidonic Acid C20:4	Eicosapentaenoic Acid C20:5
Sources	From meat and ingested linoleic acid	From ingested linolenic acid, and from fish and fish oil
Metabolized to	Proinflammatory n-6 PGs and LTs	Competitive inhibitors of n-6 PGs and LT synthesis
Effect on cytokines	Unknown	Suppression of TNFa and IL1b production

EPA (PGE3). Dietary n-3 fatty acids can increase cellular n-3 content and decrease n-6 eicosanoid synthesis.

Dietary n-3 fats also suppress production of the peptide cytokines interleukin 1beta (IL1B) and tumor necrosis factor alpha (TNFa). These cytokines stimulate PGE2 synthesis and collagenase production, and increase expression of adhesion molecules that allow leukocyte extravasation.[29, 30, 31]

Epidemiologic studies suggest a role for N-3 supplementation in RA. The consumption of baked or broiled fish appears to protect against rheumatoid arthritis,[33] and the use of olive oil seems to have the same effect.[34]

At least 13 prospective studies on the role of fish oils in the symptomatic control of RA have been published in the English-language literature. These are summarized in Table 2.

Table2.—Experimental studies of n-3 fatty acids in RA. Abbreviations used: EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid, PUFA - polyunsaturated fatty acids, gel - morning stiffness, NSAID - nonsteroidal antiinflammatory drug, LT - leukotriene, IL - interleukin, TNF - tumor necrosis factor.

First Author, Year	Subjects, Study Period	Intervention	Results
Kremer, 1985 (35)	37 12 weeks	1.8 gm EPA; diet high in PUFA, low in saturated fats	less pain and joint swelling, but rebound at the end
Kremer, 1987 (36)	40 32 weeks	2.7 gm EPA 1.8 gm DHA	less fatigue and joint swelling, decreased LTB4
Magaro, 1988 (37)	12 30 days	1.6 gm EPA 1.1 gm DHA	less disease activity; less neutrophil chemiluminescence
Van der Tempel, 1990 (38)	16 24 weeks	2.04 gm 20:5 n-3 1.32 gm 22:6 n-3	less gel and joint swelling, decreased LTB4, increased LTB5
Tulleken, 1990 (39)	27 12 weeks	2.0 gm EPA 1.3 gm DHA	less pain and fewer swollen joints
Kremer, 1990 (40)	49 24 weeks	27 mg/kg EPA 18 mg/kg DHA, vs 54 mg.kg EPA 36 mg/kg DHA vs 6.8 gm oleic acid (olive oil)	more improvement with high dose fish oils; decreased LTB4 and IL1; olive oil also helped
Nielsen, 1992 (41)	51 12 weeks	3.6 gm n-3 PUFA	less gel, less tenderness
Skoldstam, 1992 (42)	43 6 months	fish oil 10 gm/day	decreased NSAID consumption
Espersen, 1992 (43)	32 12 weeks	3.6 gm n-3 PUFA	improved Ritchie's index; drop in IL1; TNF and complement activation products unchanged
Kjeldsen-Kragh, 1992 (44)	67 16 weeks	3.8 gm EPA 2.0 gm DHA with doses of naproxen	fish oils mitigated impact of naproxen withdrawal
Lau, 1993 (45)	64 12 months	10 MaxEPA caps/day	decreased NSAID use
Geusens, 1994 (46)	90 12 months	2.6 gm n-3 vs 6 gm olive oil	decreased medication use only in n-3 group
Kremer, 1995 (47)	66 30 weeks	4.6 gm EPA, 2.5 gm DHA diclofenac withdrawal	diclofenac could be stopped without a flare

N-3 fatty acids suppress joint swelling and decrease pain in a dose-dependent fashion. Inflammatory eicosanoid levels go down. The more traditional laboratory measures of RA activity, such as the sedimentation rate and complement degradation products, as well as the titer of rheumatoid factor, are by and large untouched. The clinical effect lasts no longer than four weeks after the supplements are stopped. The magnitude of the response is not impressive—at best, n-3 supplementation may have some drug-sparing properties, allowing the patient to use lower doses of a antiinflammatory or disease-modifier.

The plasma lipid alterations necessary to achieve clinically significant effects require 10 to 15 MaxEPA capsules a day. The same levels can be achieved by including 4 to 6 meals with fish per week.[48]

Some Practical Advice

What should the practitioner say to a patient who asks about the relationship between non-gout inflammatory arthritis and his or her diet? Data support these guidelines:

1. Inflammatory arthritis is a true food intolerance only in a very small number of patients.
These people tend to have seronegative, nonerosive disease.

2. No foods or food groups have been consistently identified as a cause, trigger or aggravating factor in unselected patients. However, if one clearly experiences disease worsening with a particular dietary item, then that item ought to be avoided. Some items that have produced such worsening in a few individuals are dairy products, nitrates, alcohol, simple sugars and azo dyes. Since the ability of these foods and additives to cause disease flares is far from universal, testing one's reaction to each in turn makes better sense than avoiding everything indiscriminately.

3. Fasting clearly suppresses inflammation in the joints. Fasting should not be undertaken without medical supervision for longer than five days. Fasting may be dangerous in the setting of previous or ongoing medication intake, and should be discussed with the medical practitioner. The benefits of fasting are very difficult to sustain, but in some situations can be made to last by switching to a vegan diet. The people who tend to respond favorably to such dietary manipulation tend to be those who have had their disease for a shorter period of time. End-stage, burnt-out disease with severe joint destruction is unlikely to be helped by these measures.

4. Based on the work of Dr. Panush and this current report, reasonable diets to try are the Dong diet and the Hawaii/Waianae diet. Books on both remain widely available in popular bookstores. The responses reported are evident by 10 weeks; there is no data to support staying on these diets longer than that period in the hope of getting a delayed response. It must also be borne in mind that the evidence that these diets work is limited and anecdotal.

5. Omega 3 fatty acids (fish oils) can help suppress joint inflammation. The desired blood levels of the necessary fatty acids can be obtained by eating six fatty fish meal a week. Fish oils are about as effective as an NSAID. They do not reverse the basic immunologic processses underlying RA.

6. The use of olive oil may be of some benefit.[40]

7. While diet can be a useful adjunct in the treatment of the inflammatory arthropathies, there is no reliable and consistent way to use it as monotherapy. It should be part of an integrated approach that pays attention to proper rest and exercise, work modification, family support, stress management and judiciously selected pharmacotherapy.

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