

AN INTEGRATIVE NUTRITIONAL APPROACH TO THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a condition of great morbidity for which few safe and effective approaches are available. It is an autoimmune disorder characterized by chronic inflammation of the synovial membranes. Although the exact etiology is unknown, some studies suggest that an antigenic response to food-derived proteins can trigger RA in genetically predisposed individuals. In addition, research suggests that changes in the composition of fecal flora and generation of free radicals in synovial fluid also promote symptoms. Modulation of dietary fat intake, manipulation of gastrointestinal flora, and the use of antioxidants may be effective in managing inflammation associated with RA. In this case, a combined approach of nutritional supplementation to support gastrointestinal function was explored in a patient with RA who had previously reacted to many conventional therapies. The combined approach, which included probiotics and botanicals (for balance of fecal flora), fish oil and antioxidants (to balance inflammatory mediators), and a low-allergy potential rice-based medical food (to manage antigenic response to foods) was found to be successful in attenuation of RA symptomatology.

INTRODUCTION

Rheumatoid arthritis (RA)—a systemic autoimmune disorder characterized by chronic inflammation of the synovial membranes—is associated with considerable financial costs and morbidity. Symptoms of RA generally begin as morning stiffness and pain in the small joints of the hands and feet, sometimes progressing to the larger joints and the cervical spine. Permanent deformity is often a result of the disease if symptoms remain untreated. In Caucasian populations of Europe and America, prevalence is approximately 1%, with higher rates among some North American Indians and a lower prevalence in Asian and African populations.

More women than men are diagnosed with RA. Its exact cause is unknown.^{1,2} Studies suggest that RA has a genetic component and, indeed, an association with the human major histocompatibility allele, HLA-DRB1, has been demonstrated to be involved in RA.³ This association accounts for less than half the genetic susceptibility, however, and studies also suggest that several other

genetic factors may contribute to disease presence and severity, as well as response to pharmacological therapies.³⁻⁶ The variety of potential genetic influences supports the clinical observations that indicate RA is a complex, heterogeneous disorder.

Confounding the complex etiology of RA is the observation of a low concordance rate between identical twins, which suggests that environmental factors also have a strong influence in triggering the disease.⁷ Therefore, it is thought that RA develops from an underlying genetic susceptibility, which manifests in response to one or more environmental triggers. These triggers, however, are controversial. One line of intriguing research suggests that RA may occur in predisposed individuals as a secondary response after an antigenic insult, such as from a food-derived protein. Other environmental factors, such as smoking and exposure to toxic metals, pollutants, and pesticides, have also been considered for their effects on RA through modulation of immune-system function.⁸⁻¹⁰

The relationship between RA and the myriad potential environmental triggers is beyond the scope of this report. Instead, this paper addresses the use of a focused nutritional support program and discusses select environmental influences to illustrate the rationale behind this clinical approach. Given the complexity of RA, no one approach can benefit all patients, but it is hoped that the case illustrated here will show how a nutritional program can be personalized, leading to a clinically-beneficial result.

FOOD AND RHEUMATOID ARTHRITIS

Food allergens have long been suggested as causative agents in some RA patients, and this association has led to investigation of dietary regimens as a therapeutic intervention for RA. Early studies in this arena investigated fasting, followed by a vegetarian diet. However, although fasting seemed to improve symptoms in some RA patients, transitioning to a simple lacto-vegetarian diet did not result in extended positive effects.¹¹ Subsequent studies found no statistically significant improvement over “placebo” diet

Key Words: Rheumatoid arthritis, food-derived proteins, probiotics, essential fatty acids, antioxidants

when data were reviewed in total, but significant objective improvement was noted in a subgroup of RA patients during the periods of dietary exclusion when compared to placebo.^{12,13} Diets excluding pulses (eg, beans, peas, lentils), cereals; milk; and non-vegetarian protein foods, as well as elemental peptide diets, have also been reported as beneficial for a subset of RA patients.^{14,15} Though these results suggest that antigenic proteins may act as triggers for RA, all of these trials were of short duration.

Only a few long-term studies of dietary intervention for RA have been reported. For example, a randomized 8-month trial of a hypoallergenic diet vs a “well-balanced” control diet resulted in improvement of several parameters of RA in the hypoallergenic diet group, with 4 assessments showing statistical significance (Ritchie’s index, tender joints, swollen joints, and erythrocyte sedimentation rate).¹⁶ Kjeldsen-Kragh et al published a well-controlled, year-long study assessing the effects of an initial fasting program followed by a vegetarian diet. This randomized, single-blind trial showed statistically significant benefits over 12 months for patients on the exclusion diet, as compared to the control group.¹⁷ Improvement remained a year after patients had completed the trial, and it seems unlikely that a placebo response alone could explain this observation.¹⁸

Hafstrom et al investigated the influence of diet on immunoglobulin G (IgG) status in RA patients by comparing a vegan diet with a normal “wholesome” control diet. They found significant reductions from baseline in anti-gliadin and anti-B lactoglobulin IgG levels in the vegan group, compared to the control group.¹⁹ Moreover, the subset of the vegan group (40%) who complied with the dietary program experienced a significantly positive clinical response, while far fewer (4%) in the non-vegan group responded. And, only those in the vegan group who showed a positive clinical response showed significant decreases in antibodies to gliadin and lactoalbumin. This further supports the idea that improved symptoms may result from a diminished immune response to exogenous food antigens. Other studies have suggested that anti-gliadin antibodies are more commonly found in RA patients than in control groups.²⁰ Not all reports have noted this relationship, however.²¹

Muller et al compiled a review of 31 studies of diet and RA, including 4 controlled studies on fasting and intervention diets lasting at least 3 months. After pooling these studies, the authors found a statistically significant, clinically beneficial long-term effect.²² In summary, there appears to be significant support for the hypothesis that dietary changes can produce a sustained positive response in a subset of RA patients.

ADDITIONAL NUTRITIONAL CONSIDERATIONS

Research studies with RA patients have suggested that the clinical benefits from a dietary “prescription”

may involve more than just the elimination of potentially antigenic proteins. Numerous adjunctive nutritional sources have been explored, and some have shown reproducible, consistent attenuation of symptoms. These include probiotics, fish oils, and antioxidants, which are briefly reviewed below.

Probiotics

Several studies have suggested that changes in the composition of fecal flora may be involved in RA symptomatology, and fecal flora have been observed to be significantly different in RA patients from those in non-RA controls.^{23,24} One mechanism by which microflora may influence conditions like RA relates to the key role these organisms play in supporting the delicate balance between intestinal permeability and host defense. Because nutrients are absorbed through the intestinal wall, some intestinal permeability is associated with food intake, but this is closely regulated in the healthy gastrointestinal tract. Changes in the microflora, however, can disturb this balance and lead to increased absorption and translocation of not only bacterial antigens, but also food proteins, through the intestinal wall.

RA and other spondyloarthropathies have been linked to the indigenous flora of the gut via *molecular mimicry*.^{25,26} Molecular mimicry is a process by which foreign peptides, similar in structure to endogenous peptides, may cause antibodies or T-lymphocytes to cross-react with both foreign and endogenous peptides. It has been shown that microflora share antigenic determinants with normal tissue and produce cross-reactive antibodies, so it is hypothesized that this cross-reactive activity may cause or exacerbate inflammatory processes in the joint in genetically susceptible individuals.²⁷ Bacterial lipopolysaccharide (LPS) found in the cell wall of gram-negative bacteria has also been shown to initiate an immune response and elevate pro-inflammatory cytokines. Therefore, it is proposed that by eliminating dietary elements and changing the microbial flora, the peripheral antigenic stimulus may be reduced, resulting in an improvement in symptoms.²⁸

The 1-year study conducted by Kjeldsen-Kragh et al noted diet-related alterations in the composition of fecal flora. Fecal flora also differed significantly between responders and non-responders in the test-diet group.²⁹ Another study analyzed fecal flora in RA patients on a vegan diet, and compared it to that of participants on a control diet after 1 month. The fecal flora changed significantly only in the vegan-diet group.³⁰ In this study, a significant difference in the flora of good responders vs poor responders was also noted, and the flora reverted back to pre-trial composition when patients discontinued the vegan diet.

Animal studies have suggested that inoculating with certain potentially beneficial strains of commensal bacteria (probiotics) may have a positive effect on the clinical

course of collagen-induced arthritis (a model for RA).³¹ A small human trial investigated this effect on human RA subjects and, although no statistical differences between the treatment group and controls were found, a suggestive difference was noted in subjective well-being.³²

It is clear that resident microflora contain a number of components that can up-regulate immune activation and may, under specific conditions, exert pathologic effects.³³ And, because fecal flora is complex and contains numerous species, a simple inoculation program of one species of bacteria may not be enough to significantly change the bacterial population of the gut. Some studies have implicated specific bacterial species as possible underlying etiological agents. For example, Erbing et al looked at antibodies to *Proteus mirabilis* and found that RA patients have elevated levels compared to controls.³⁴ When these RA patients were placed on a vegetarian diet, they showed a reduction in *Proteus mirabilis* antibody levels. Moreover, a significant correlation between the decrease in antibodies and disease activity was observed.³⁵

Essential Fatty Acids

Various dietary fatty acids, such as arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and gamma-linolenic acid (GLA), are incorporated into the cellular membrane, and their specific concentrations within that membrane can have subtle but pronounced effects on the AA-dependent inflammatory cascade. Arachidonic acid concentration in the cell membrane is an important regulatory step in the synthesis of both inflammatory prostanoids and leukotrienes. EPA acts as an alternative substrate to arachidonate, leading to the formation of the 3 series prostaglandins and 5 series leukotrienes, which can decrease the inflammatory response. Studies indicate that the inflammatory process in RA can be attenuated by dietary fat, and dietary supplementation with EPA has, therefore, been used to decrease the ratio of AA to EPA in the membrane.

Supplementation with fish oils (EPA and DHA) has consistently been shown to reduce both the number of tender joints and the amount of morning stiffness in RA patients. Beneficial clinical effects have been observed in more than a dozen placebo-controlled studies.³⁶ Several investigators have reported that RA patients consuming EPA/DHA supplements are able to reduce or discontinue use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs.³⁷

Although switching to a vegetarian diet can alter the intake of fatty acids, most studies show that the fatty-acid profiles do not differ substantially between diet responders and non-responders, and it is assumed that the clinical effects of various exclusion and vegetarian diets are not primarily due to changes in eicosanoid precursors.³⁸ This is probably because relatively large amounts of EPA/DHA (3-

6 grams daily) are needed to effect changes in neutrophil functions, such as chemotaxis and superoxide radical production.³⁹ These fatty acids have virtually no reported serious toxicity in the dose range used in treating RA patients, and they are generally well tolerated.³⁵ A recent meta-analysis also reported moderate support for the efficacy of the n-6 fatty acid, GLA, in reducing pain, tender joint count, and stiffness in RA patients,⁴⁰ although there is more literature on EPA and DHA.

Antioxidants

Antioxidants have also been used to modulate the inflammatory response. Free radicals appear to play a role in the promotion of inflammatory reactions. In RA, inflammatory cells accumulate in the synovial fluid of joints, and their activation triggers a respiratory burst resulting in excessive generation of free radicals. It is therefore hypothesized that antioxidants may provide an important defense against the increased oxidant stress in RA patients.

A few studies have investigated antioxidant effects when used alone in RA patients and provide some basis for their use as part of a therapeutic program. In one study, pain parameters were significantly decreased after high-dose vitamin E treatment when compared with placebo, although objective laboratory markers were unchanged.⁴¹ High-dose vitamin E and an antioxidant combination (in addition to standard treatment) have also been shown to result in better and earlier control of symptoms, as well as improved markers of oxidative stress.⁴²

Clearly, diet and nutritional support are beneficial in some RA patients; however, the optimal therapeutic program has not been defined. Many underlying imbalances are present in RA, so a nutritional approach of combining many of the aspects described in this brief review is worthy of consideration. The following case study explores this integrated, patient-focused approach (Endnote 1).

CASE REPORT

A 25-year-old white female presented to the clinic with a prior diagnosis of RA. She had complaints of cyclical, migratory pain and bilateral swelling in her hands, knees, ankles, and feet. She said her symptoms had started about 2 years earlier when she developed swelling and pain in her knees. She was initially treated with prednisone, then methotrexate injections and sulindac. After approximately 2 years, she discontinued the methotrexate injections because of the side effects. Gold shots were subsequently administered, but they were also discontinued due to allergic reactions. The patient had recently stopped taking sulindac when her prescription ran out. Three months prior to presentation, she had started seeing a naturopathic physician, who initiated a number of homeopathic remedies and nutritional supplements. On presentation, she was taking the following: EPA/DHA oil, 2

capsules twice a day; calcium, 120 mg twice a day; vitamin C, 2,000-3,000 mg daily; and glucosamine sulfate, 2 tablets twice a day. A food allergy assessment (IgG and IgE) led to the recommendation to avoid certain foods, which she did sporadically.

The patient's past medical history revealed frequent strep infections, a staphylococcus infection (following a tonsillectomy), and treatment with multiple antibiotic regimens during her childhood. She also reported chronic yeast infections in early childhood. She had a history of long-term constipation, with a bowel movement (BM) only 1-2 times a week. Her family history was negative for RA.

At the time of presentation, the patient's physical exam was unremarkable except for swelling in her hands and fingers. Her height was 5' 4"; she weighed 145 lbs; and her blood pressure was 100/70 mm Hg.

Laboratory results were within reference ranges (RR) for routine chemistry and hematology tests. Her complete blood count (CBC) showed slightly depressed white blood cells (WBC) at 3.5 th/mm^3 (RR: $4.0\text{-}12.0 \text{ th/mm}^3$) and slightly elevated eosinophils at 5.6% (RR: 0-5.0%). Stool analysis showed elevations in long-chain fatty acids, total short-chain fatty acids, cholesterol, and pH. Presence of the potential pathogen *Citrobacter freundii* was noted on culture. Ova and parasites were negative, and serum bacterial antibodies were within RR. Intestinal permeability (as measured by lactulose/mannitol ratio) was low-normal at 0.01 (RR: 0.01-0.06), and high-sensitivity C-reactive protein (hs-CRP) was within RR at 0.7 mg/dL (RR: 0-1.0 mg/dL), as was rheumatoid factor (RF) at <10 IU/mL (RR: 0-15 IU/mL).

Initial Assessment/Plan

Several questionnaires were administered to the patient to assess her general quality of life (QOL). The Arthritis Impact Measurement Scales 2 (AIMS2) test scores revealed compromised physical and mental functioning. The MOS 36-Item Short Form Health Survey's Physical Component Summary (MOS-PCS) and Mental Component Summary (MOS-MCS), as well as the Medical Symptoms Questionnaire (MSQ), all indicated some degree of impairment (see Table 1).

Based on her history and the physical exam, the assessment was that this patient fit the criteria for RA. She had evidence of bacterial dysbiosis, possibly secondary to chronic antibiotic use and prednisone. The patient was instructed to discontinue all supplements and was placed on an elimination diet (eliminating common food allergens, including gluten, dairy, beef, pork, and eggs) for an initial 2-week period (see Table 2 and Endnote 2). In addition, she was started on a rice protein-based medical food designed to nutritionally support conditions associated with chronic inflammation, with instructions to gradually increase the dose to 2 scoops twice a day.

At the 2-week follow-up visit, the patient said she was tolerating the medical food and dietary program well. She reported a substantial improvement in joint pain, with a decrease in arthralgias. She was also having daily BMs. She was instructed to continue using the medical food and to gradually introduce 3 additional supplements for improving dysbiosis and decreasing inflammation: a botanical berberine combination, 2 tablets twice a day; a probiotic supplement combination of *Lactobacillus acidophilus* and *Bifidobacterium lactis*, 1 tsp twice a day; and a fish oil supplement providing 600 mg EPA and 400 mg DHA, 3 capsules twice a day.

After 4 weeks, the patient reported feeling about 80% better overall. She still experienced a slight "achiness" in the mornings, which dissipated within about 30 minutes. She was instructed to add 500 mg niacinamide and 200 mg N-acetylcysteine (3 tablets twice a day) for additional antioxidant support. At the 8-week visit, she continued to be very encouraged with the improvement in her pain symptoms and reported no stiffness or "achiness" in her ankles, knees, back, and neck and only slight morning stiffness in her fingers. Several foods had successfully been reintroduced into her diet (she was still maintaining a modified vegan diet), and she was instructed to gradually discontinue the berberine supplement over the course of a month.

At the 12-week follow-up, the patient continued to do very well and reported that she was jogging without pain for the first time in years. She noted only mild morning stiffness, particularly in the shoulders. She had continued to reintroduce foods without noting any reactions. The patient was instructed to remain on the medical food, probiotics, and niacinamide/N-acetylcysteine, to decrease the fish oils to 2 capsules twice a day (she was switched to a lower-potency blend), and to add a fiber supplement, 1 scoop twice a day. A follow-up stool analysis indicated normalized long-chain fatty acids and cholesterol, as well as decreased total short-chain fatty acids. *Citrobacter freundii* was not detected on culture.

The patient was still doing well at her 16-week follow-up visit. She had successfully introduced many foods and had noted reactions only to apples and corn. She was instructed to gradually decrease the medical food to 1 serving per day and continue at the same dosage of the other prescribed products. After 20 weeks, the patient's RA symptoms had almost completely abated. She said she was 100% pain-free and felt only minimal stiffness in her shoulders. Her QOL scores reflected this improvement (see Table 1). She had gradually decreased the medical food to 1 serving per day and had successfully introduced beef, dairy, and eggs into her diet. All of her laboratory stool analyses had normalized except the pH, which remained slightly elevated. No potentially pathogenic bacteria were detectable on stool culture.

TABLE 1
CASE STUDY: PATIENT'S QUESTIONNAIRE DATA

Health Status Components	Possible Score Range	Initial visit	2 Wks	4 Wks	8 Wks	12 Wks	16 Wks	20 Wks	% Change from Initial Visit
MSQ*	<30 = few or low intensity symptoms	--	39	21	12	9	1	2	95% improvement
MOS-PCS† (Physical component summary)	50 or above = healthy function	24.0	26.8	21.4	33.2	46.7	54.5	54.4	Normalized
MOS-MCS† (Mental component summary)	50 or above = healthy function	40.9	49.3	60.2	60.2	55.7	58.0	57.5	Normalized
AIMS2‡: Physical (Physical mobility and self-care)	0-10	2.46	2.79	3.17	1.83	1.71	0	0	100 % improvement
AIMS2: Affect (Tension and mood levels)	0-10	4	2.25	2	1.5	1.75	1.75	1.75	44 % improvement
AIMS2: Symptom (Arthritis pain)	0-10	7.5	9	8.5	4.5	4	0.5	0	100% improvement
AIMS2: Social Interaction (Social activity, family support)	0-10	3.4	3.2	2.9	3.2	2.7	3.4	3.2	9% improvement
AIMS2: Role (Work)	0-10	1.25	0.63	1.25	1.25	0	0	0	100% improvement

* The Medical Symptoms Questionnaire (MSQ) is a clinical tool for the evaluation of general physical symptoms. Total scores above 75 are generally associated with substantial symptomatology and disability; scores below 30 generally indicate few or low-intensity symptoms.

† The MOS SF-36 is a well-validated general quality-of-life questionnaire that summarizes health outcomes in two reliable reproducible scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). On a scale of 0-100, 50 is the US mean. Higher scores are associated with healthier individuals.

‡ The AIMS2 questionnaire is a clinical tool for the evaluation of health status and outcomes of individuals with rheumatic diseases. A low score indicates a high health status, and a high score indicates poor health status.

CONCLUSION

Conventional treatments for RA may be associated with problems, both in terms of safety and efficacy. Several nutritional strategies may help attenuate the signs and symptoms associated with RA. An optimal program takes advantage of the research suggesting that dietary antigens, gastrointestinal flora, and nutritional modulation of inflammation may be important factors in RA. Clearly, all patients with RA cannot be treated in the same manner. Some will respond dramatically to an integrated approach as presented above, whereas others will experience little apparent change in symptoms. The clinician must carefully evaluate both subjective and biochemical responses to determine how each patient's RA condition can best be managed (the simplified flowchart in Figure 1 can be useful in this regard). Conventional treatments may result in

significant side effects, but also may be necessary for some patients. Although not all patients are likely to respond completely to a nutritional approach, a program that comprehensively addresses these areas may be the most cost-effective, safe, and appropriate first course of action for individuals who suffer from rheumatoid arthritis.

ENDNOTES

1. A number of botanicals have also been clinically reported to benefit RA patients. A review of this area is beyond the scope of this paper. See recent reviews by Ho, Soeken, and Gaby.⁴³⁻⁴⁵
2. Specific assessment for IgG was not performed since food sensitivity had been previously tested, showing the patient to be sensitive to some foods. Moreover, it is this practitioner's experience that elimination testing is a more accurate indicator of food sensitivity.

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TABLE 2
ELIMINATION DIET*

Foods to Include	Foods to Avoid
Fruit Whole fruits; unsweetened, frozen, water-packed, and canned fruits; diluted juices	Oranges and orange juice
Dairy and Dairy substitutes Rice, oat, and nut milks (eg, almond and coconut milks)	Milk, eggs, cream, butter, cheese, yogurt and frozen yogurt, cottage cheese, ice cream, non-dairy creamers
Grains and Starches Brown rice, oats, millet, quinoa, amaranth, teff, tapioca, buckwheat, potato	Wheat, corn, barley, spelt, kamut, rye, triticale
Animal Protein Fresh or water-packed fish, wild game, lamb, duck, organic chicken and turkey	Pork, beef/veal, sausage, cold cuts, canned meats, frankfurters, shellfish
Vegetable Protein Split peas, lentils, legumes	Soybean products, including soy sauce, tempeh, tofu, soy milk and yogurt, soybean oil (in processed foods), textured vegetable protein
Nuts and Seeds Walnuts, hazelnuts, pecans, almonds, cashews, nut butters (eg, almond or tahini) and sesame, pumpkin, and sunflower seeds	Peanuts and peanut butter
Vegetables All raw, steamed, sautéed, juiced, or roasted vegetables	Corn and creamed vegetables
Oils Cold-pressed olive, flax, safflower, sesame, almond, walnut, sunflower, canola, and pumpkin oils	Margarine, shortening, salad dressings, mayonnaise, spreads, and processed oils (other than cold-pressed)
Drinks Filtered, distilled, seltzer, and mineral waters, decaffeinated herbal teas	Alcohol, coffee and other caffeinated beverages, colas, soda pop, and soft drinks
Sweeteners Brown rice syrup, stevia, fruit sweeteners, blackstrap molasses	Refined sugar (white/brown sugars), honey, maple syrup, high-fructose corn syrup (HFCS), evaporated cane juice
Condiments Vinegar, all spices including salt, pepper, basil, carob, cinnamon, cumin, dill, garlic, ginger, mustard, oregano, parsley, rosemary, tarragon, thyme, and tumeric	Chocolate, ketchup, relish, chutney, barbecue sauce, teriyaki and soy sauces, and other condiments
*Patient was instructed to eliminate common food allergens, including gluten, dairy, beef, pork, and eggs. In addition, patient was provided with this guide of foods to include and avoid.	

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ACKNOWLEDGMENTS

Metagenics, Inc., provided financial support for this paper. The case study was conducted at the FMRC, the research arm of Metagenics, Inc.

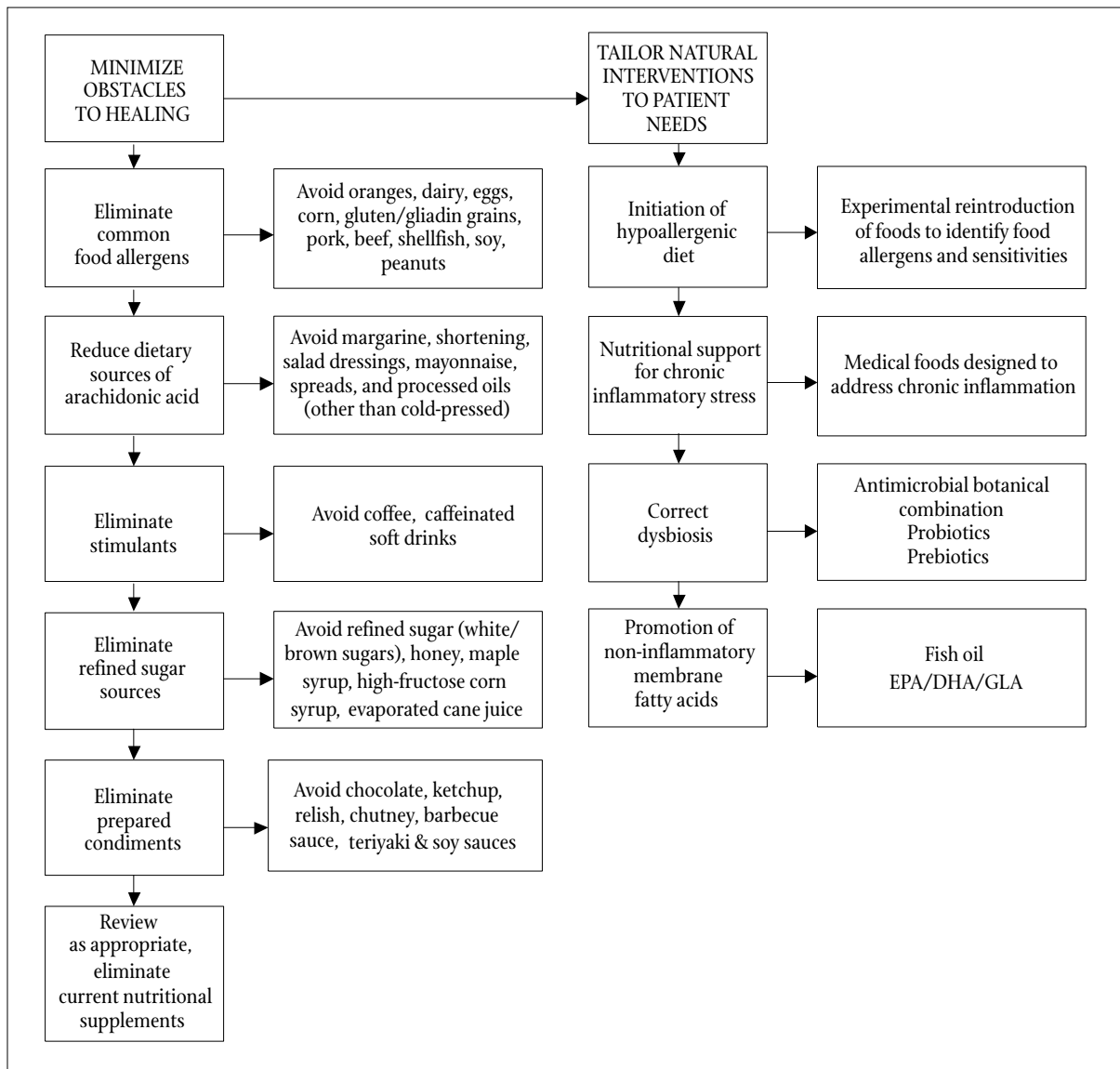


FIGURE 1 AN INTEGRATIVE NUTRITIONAL APPROACH TO THE TREATMENT OF RHEUMATOID ARTHRITIS

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