

Foods and Rheumatological Diseases

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KEY CONCEPTS

- There is little convincing evidence for rheumatoid arthritis (RA) occurring as a result of food allergy.
- Patients with RA commonly associate certain foods with increased joint symptoms, although in many cases this is not confirmed by formal assessments.
- Individual patients with RA may have an improvement in disease control on elimination of certain foods from the diet.
- Prolonged periods of fasting or hypocaloric diets should be avoided due to potential adverse outcomes.
- In patients with RA, long-term dietary supplementation with n-3 fatty acids is associated with improvements in disease activity when combined with disease modifying anti-rheumatic drug therapy.

Introduction

Broadly speaking food has been linked to joint symptoms in three ways. Firstly, primary food allergy can be associated with self-limited arthralgia (joint pain) and/or arthritis (joint inflammation) in addition to the other manifestations of allergy such as urticaria [1]. Secondly, reactive arthritis or Reiter's syndrome may be associated with a preceding gastrointestinal infection such as *Campylobacter*, acquired from eating contaminated food products. Thirdly, patients with primary inflammatory arthritis often report a link between certain foods and joint symptoms in regard to both disease timing and severity of symptoms. The causal link between diet and inflammatory arthritis is strongest for gout [2,3]. However, patients with other forms of inflammatory arthritis such as rheumatoid arthritis (RA) sometimes report an association between their symptoms and food. The frequency with which RA occurs as a consequence of true food allergy is uncertain and perhaps not frequent. Notwithstanding, certain foods seem to have a significant impact on disease activity for some individuals with RA and elimination of particular foods may benefit some patients. However, there is currently no easy way to predict who will respond to dietary avoidance strategies. There is more robust evidence for the benefits of dietary supplementation with n-3 fatty acids in RA. The focus of this chapter is the relationship between foods and RA.

Rheumatoid arthritis

RA is a chronic condition which affects 1–2% of the general population. The hallmark of RA is inflammation of the synovial lining of the joints. Early in the course of the disease the inflammation results in joint pain, swelling, and stiffness. Over time, the joints become damaged by erosion of bone and cartilage by inflamed synovial tissue (pannus), which leads to joint deformities and functional impairment. Disease classification criteria for RA rest on the pattern of joint involvement (symmetrical polyarthritis involving the small joints of the hands and feet), presence of rheumatoid factor (RF) in serum, and radiographic evidence of peri-articular erosions. Further laboratory features which aid the diagnosis of RA include elevated C-reactive protein (CRP) and antibodies against cyclic citrullinated peptide (CCP).

The aims of management in RA are reduction of symptoms, prevention of joint damage, and preservation of joint function. Pharmacological therapies, which are the mainstay of treatment, can be broadly classified into three groups:

- 1 Non-steroidal anti-inflammatory drugs (NSAIDs) which act rapidly to reduce pain but have no beneficial effect on long-term disease progression.
- 2 Corticosteroids which rapidly control inflammation and may reduce joint erosion, but are associated with many non-trivial unwanted effects.
- 3 Disease modifying anti-rheumatic drugs (DMARDs) (e.g. methotrexate, salazopyrin, tumor necrosis factor (TNF) blockers) which in general are slow to act but prevent long-term joint destruction and improve functional outcomes.

In addition to these standard medical therapies, patients frequently request information regarding alternative and/or

complementary therapies, including dietary therapies for management of their disease. Up to 75% of RA patients believe food influences their symptoms and it has been reported that as many as 50% try dietary manipulation in an attempt to control their symptoms [4,5]. By contrast, relatively few physicians would regard diet as contributing to the etiology of RA or as having a significant role in the management of RA.

Diet in the etiology of rheumatoid arthritis

A number of genetic factors have been shown to predispose to RA. As heritability is well short of 100%, it follows that environmental factors contribute substantially to etiology. A number of epidemiological studies have examined the role of diet in the etiology of RA. A decreased risk of developing RA has been reported with high consumption of fish, a rich source of n-3 fatty acids [6]. Consumption of β -cryptoxanthin (a carotenoid found in fruit and vegetables) has also been associated with reduced risk for RA [7,8]. Some but not all studies have reported an increased risk of developing RA with high red meat consumption [9–11] and caffeine intake [12–14].

Evidence for an RA-like illness as a result of food allergy is sparse. Panush described two patients who developed subjective and objective evidence of a non-erosive, RF negative, palindromic inflammatory arthritis after exposure to shrimp and nitrites [15].

Genetics in the etiology of rheumatoid arthritis: the potential interaction with food

Twin studies provide a means for assessing the relative extent of contributions by genetic and environmental factors to multi-factorial diseases. In RA, the concordance rate in monozygotic twins is reported to be 12% [16] to 15% [17]. Quantitative genetic analysis using the data from both of these cohorts has demonstrated that the “heritability” or extent to which liability to RA is explained by genetic variation in the population is about 60% [18].

Human leukocyte antigen (HLA) class II alleles are among the most important genetic contributors to RA. HLA antigens are surface membrane molecules that play a central role in specific immunity through their ability to present peptide fragments that have been processed by antigen-presenting cells (APCs). HLA-DR molecules are strongly expressed on APCs, especially dendritic cells. They present peptides derived from both endogenous and exogenous antigens to CD4+ve T-cells. The HLA genes within the major histocompatibility complex (MHC) comprise the class I loci (A, B, and C) and the class II loci (DQ, DR, and DP). The alleles at these respective loci occur in non-random associations known as haplotypes. The strongest allelic associations in RA are with subtypes of HLA-DR4 and HLA-DR1, in particular

HLA-DR*0401, HLA-DR*0404, and HLA-DR*0101. These HLA-DR specificities are determined by the HLA-DR β 1 locus and have a conserved amino acid sequence in the third hypervariable region of the DR β chain, known as the “shared epitope.” The “shared epitope” is situated within the region of the DR β chain that forms part of the peptide-binding groove which presents the antigen. It is this “shared epitope” portion that is thought to confer the risk of RA [19]. The canonical feature of the shared epitope is a positively charged pocket lined by neutral and positively charged amino acids. This configuration is favorable for presentation of peptide fragments with appropriately located negative charge. The “shared epitope” provides a potential mechanism whereby an individual may inherit a susceptibility to RA. According to this scenario, when a predisposed person meets a potentially pathogenic antigen in an appropriate immunological context (with endogenous and exogenous co-stimulatory molecules signaling a “danger” context), a pathogenic immune response may occur directed against either exogenous and endogenous antigens or both. From the perspective of a possible allergic component to RA, it is notable that the HLA-DR4 alleles have been associated with atopy. While food is an abundant source of exogenous antigens, presentation of peptides within the specialized immunological tissues of the gut mucosa generally evokes immunological tolerance rather than responsiveness because “danger signals” that promote the latter are typically lacking.

Food allergy/intolerance in rheumatoid arthritis

A number of case reports link symptom severity with certain foods in RA (Table 45.1). In all of these reports patients responded with an improvement in arthritic symptoms on elimination of the offending food from the diet. Van der Laar *et al.* have also reported on two patients with RA who had raised serum IgE concentrations to several foods, which reduced after elimination of the foods from the diet. This was accompanied by an improvement in clinical symptoms and a reduction in mast cells in both the synovial membrane and proximal small intestine [20]. However, while a number of patients describe food-related aggravation of symptoms, this often is not substantiated by more formal assessment [15].

The concept of food allergy/intolerance in RA has led to studies examining the effects of dietary manipulation on disease activity in RA. Dietary manipulation can be divided into two categories: exclusion diets where foods thought to increase symptoms are removed from the diet and supplementation diets where foods that improve symptoms are added to the diet. In RA, exclusion diets have been shown to be of some value in individual patients only. In comparison, supplementation of the diet with n-3 fatty acids has been shown to benefit groups of patients in randomized controlled trials. In this section we review the evidence for exclusion diets in RA.

Table 45.1 Reports of food allergy/intolerance in RA

Case summary	Allergen	Effect of removal of putative food allergen from diet	Effect of re-introduction of putative food allergen from diet	Reference
RF–ve RA, extra-articular manifestations, ↑ESR, ↑IgE	Cereals (skin prick test positive)	Remission	Recurrence of symptoms	[21]
Erosive RF–ve RA, 11 years duration	Milk and cheese	Significant improvement with ↓ESR, able to stop prednisone	Recurrence of symptoms within 24 hours of re-introduction of dairy products IgE antibodies to milk and cheese became positive during re-challenge	[22]
Active RA, 35 years duration	Corn	Improved, ↓ESR, able to stop DMARDs	Recurrence of symptoms	[23]
RF–ve arthritis elbow and tenosynovitis	Milk (RAST+ve for cow's milk)	Improved	Recurrence of symptoms	[24]
Spondylitis	Milk and wheat (serum-specific IgE+ve for milk and wheat)	Marked improvement	Recurrence of symptoms	[24]
RF+ve inflammatory arthritis	Milk (↑IgG anti-milk antibodies)	Improved	Challenges with milk resulted in deterioration of symptoms	[25]
Juvenile RA, 6 years duration, RF–ve	Cow's milk (lactose intolerant; IgG and IgM anti-milk antibodies)	Marked improvement	Multiple challenges resulted in recurrence of symptoms	[26]
Monoarthritis form of juvenile chronic arthritis, ANA–ve	Milk	Improved but not resolution	Swelling of the affected joint after milk challenge After 2 years patient asymptomatic and tolerating milk	[27]

ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; RAST, radioallergosorbent tests.

Elemental diets

Elemental diets are designed to provide foods in their simplest forms, thus proteins are provided as amino acids, carbohydrates as glucose or small saccharides, and fats as medium chain triglycerides. Such diets are thought to be hypoallergenic and thereby provide a means for determining whether food allergy/intolerance has a role in RA. There have been several studies using such diets in RA. Haugen *et al.* conducted a prospective, double-blind, controlled study in 20 patients with active RA. For 3 weeks patients received either an elemental diet or a control diet consisting of well mixed and blended soup which contained milk, meat, corn, and wheat. In the fourth week of the study all patients returned to their normal diet. While 3/10 patients in the elemental group and 2/7 patients in the control group improved, overall there was no significant difference between the two groups [28]. In a larger study by Holst-Jensen *et al.*, 4 weeks of an artificial elemental peptide diet was compared to normal diet in 30 patients. Patients were assessed at baseline, at the end of the 4 weeks on the study diet and then at 3 and 6 months. While there were improvements in pain and Health Assessment Questionnaire (HAQ) scores at 4 weeks these improvements were lost by 3 months. Only one patient in the elemental

diet group was classified as a “responder” according to their predetermined criteria (ACR20 improvement (see box)) [29]. Similar findings with individual patient improvement, particularly in the more subjective aspects of disease assessment, have been reported by Kavanagh *et al.* [30]. While individual patients may benefit from such elemental diets, there is insufficient evidence to support their routine use in the management of RA. Furthermore, the benefits appear to be short-lived once patients return to a normal diet and the long-term sustainability of such diets is questionable.

ACR20 response

20% improvement in 5 of 7 core set variables, first two required:

- Tender joint count
- Swollen joint count
- Acute-phase reactant
- Patients' pain
- Patients' global assessment of disease activity
- Physicians' global assessment of disease activity
- Physical disability

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Elimination diets

Elimination diets remove foods that are thought to be allergenic or “arthritogenic” in the case of RA, from the diet. An elimination diet needs to be continued for at least 3 weeks and is usually followed by gradual re-introduction of potentially offending foods. Such a diet trial is considered to be positive if elimination of those potentially allergenic foods from the diet results in clinical improvement with a subsequent deterioration after re-introduction. However, such studies are usually single-blind as patients are aware of what they eat, and a double-blind, placebo-controlled food challenge is the only validated test for the diagnosis of food allergy/intolerance.

As with elemental diets, elimination diets have been reported to be of some benefit in individual patients with RA. One such elimination diet, the Dong diet, contains little meat except occasional fish and chicken, no herbs or spices, dairy products, additives or preservatives, and no alcohol. The Dong diet was created by Dr. Dong after his personal experience of remission of arthritis with such a diet and gained widespread popularity among patients [32]. However, a 10-week double-blind, controlled study of the Dong diet in 33 patients with RA showed no overall benefit, although 2/11 patients did improve while on the Dong diet with subsequent deterioration after return to normal diet [33].

To achieve an even more restrictive diet, van der Laar *et al.* used artificial foods in order to remove potential allergens from the diet. Ninety-four patients with RA consumed their normal diet for 4 weeks and were then assigned either to an “allergen-free” (free of all potentially allergenic foods, additives, and preservatives) or “allergen-restricted” diet (contained milk proteins and yellow azo colorings) for 4 weeks, followed by a return to normal diet for the final 4 weeks of the study. Seventy-eight of the 94 patients completed the study and while there were subjective improvements in both groups, there was no difference between the two diets [34].

The majority of patients with RA are treated with DMARDs in an attempt to provide long-term control of the disease. Withholding or stopping DMARD therapy for the purposes of studying the effects of dietary manipulation would no longer be considered ethical. In addition, therapy in the 21st century is far more intensive than even 10 years ago, thus there would be very few patients with RA on no DMARD therapy. However, in the early 1980s Darlington *et al.* examined the effects of an elimination diet in 53 patients with RA receiving no DMARD treatment [35]. Patients were allocated to 6 weeks of dietary therapy immediately or 6 weeks of placebo followed by 6 weeks of dietary therapy. During the first week of the diet therapy phase, patients were only allowed foods thought very unlikely to cause symptoms; during the ensuing 5 weeks other foods considered more likely to cause symptoms, such as cereals, were gradually re-introduced. During the diet therapy phase there

were significant improvements in pain, swollen joint count, and erythrocyte sedimentation rate (ESR). Interestingly, 9/10 (90%) patients with a family history of atopy had a good response to the diet therapy as compared to 24/34 (70.6%) patients with no family history of atopy ($p < 0.05$) [35]. While these results are encouraging, patients who do not require DMARD therapy are likely to have milder disease and the results of dietary studies in these patients may not be generalizable to those with more active or severe disease.

Compliance with such restrictive diets may be problematic, especially in the long term. Beri *et al.* undertook a complex dietary study in 27 patients with RA, whereby an isocaloric diet consisting of fruit, vegetables, sugar, and refined oil was consumed for 2 weeks, followed by stepwise 2 weekly additions of wheat, rice, milk, and finally non-vegetarian foods. Of the 52% of patients who completed the study, 71% sustained clinical improvement. However, only 3/27 patients adhered to the diet for 10 months [36].

These studies demonstrate that individual patients may respond to dietary manipulation and that compliance with dietary therapy is a major limiting factor in many cases. Determining an appropriate diet for an individual might be expected to result in clinical improvements and increased compliance. Skin prick test (SPT) of potential allergens is one means of determining if an allergy exists. In an attempt to “individualize” dietary manipulation, Karatay *et al.* studied 20 patients with RA who had a positive SPT for at least one food and 20 RA patients with negative SPT. All patients had clinically inactive disease at study entry. Initially patients underwent an elimination diet for 12 days in which the most common allergenic foods were avoided. This was followed by a 12-day “challenge phase” during which SPT-positive foods were added and finally a 12-day “re-elimination” phase whereby the SPT-positive foods were removed. In the control SPT-negative group, corn, which is reported to be a common allergenic food in RA, and rice, which is not thought to be an allergenic food, were added in increasing amounts. At the end of the challenge phase, swollen and tender joint counts, pain, patient and physician global assessment, morning stiffness, ESR, and CRP all increased significantly in the SPT-positive group. In the SPT-negative group only pain and patient global assessment increased during the “challenge phase.” This increase in disease activity was observed in 13/18 (72%) SPT-positive patients compared to 3/20 (17%) SPT-negative patients during the “challenge phase” and continued in all but one patient during the “re-elimination” phase [37]. The authors concluded that food allergy may be a triggering factor in RA and that an individualized avoidance diet may be helpful in some patients. SPT may not be practical for many patients; thus in patients who believe their arthritis is due to or worsened by a particular food, objective measures of disease activity

should be undertaken before and after one or more cycles of removal of the putative “food allergen.” The resulting evidence may then be used by both the patient and physician to determine whether long-term avoidance of the “food allergen” is warranted.

Vegetarian and vegan diets

Vegan and vegetarian diets have been the subject of a number of studies in patients with RA. In the largest study, 66 patients with active RA were randomized to either a gluten-free vegan diet or a well-balanced non-vegetarian diet for 12 months. Only 58% of the vegan diet group and 89% of the control group completed at least 9 months of the study. At the 12-month endpoint 41% of the vegan diet group and 4% of the control group achieved an ACR20 response. Radiographic progression was similar in both groups. In those patients on the study diet who achieved the ACR20 response, a significant reduction in serum IgG-anti-gliadin antibodies and IgG- β -lactoglobulin antibodies was observed. The authors suggest a diminished immune response to exogenous food antigens may have had a role in the observed clinical benefits [38].

Other studies of vegetarian/vegan diets have been preceded by a period of fasting. In a 13-month prospective, single-blind trial, 27 patients with active RA were randomized to a 7–10 day fast followed by gradual re-introduction of foods, which were eliminated if they resulted in symptom deterioration. During the first 3½ months a gluten-free vegan diet was allowed with subsequent introduction of milk-based products and gluten. Twenty-six matched control patients with active RA continued their normal diet. In the diet group, improvements were noted as early as 1 month after entry with significant reductions in tender and swollen joint counts, duration of morning stiffness, ESR, and CRP. The improvements persisted throughout the duration of the study [39]. Of note, 10/27 (37%) patients in the diet group and 9/26 (35%) in the control group withdrew during the study period. Disease flare was the cause for withdrawal in 4/10 patients in the diet group and 7/9 in the control group while one patient in the diet group was unable to tolerate the diet. Importantly some patients were consuming cod-liver oil prior to and during the study period, although the exact numbers and doses are not revealed. As discussed below, cod-liver oil is rich in n-3 fatty acids which have been shown to provide a benefit in patients with RA. In those patients taking the cod-liver oil supplement, it is possible that the change in diet produced a more significant alteration in the ratio of dietary n-3/n-6 fatty acids, in favor of the less inflammatory n-3 fats, thereby contributing to at least some of the observed benefits. Ten of the 27 patients in the diet group who identified foods that exacerbated their symptoms were studied further. Of these 10 patients, 8 were classified as responders and 2 as non-responders to the dietary

regimen. However, in 9/10 patients there was no associated antibody activity to the suspected foods. Only one patient who suspected meat aggravated his arthritis symptoms was found to have elevated concentrations of IgM anti-BSA antibody activity, which subsequently reduced dramatically during the study period in parallel with a reduction in disease activity [40].

Living food consists of an uncooked vegan diet, rich in lactobacilli, with no animal products or added salt. Such a diet has been reported to result in subjective improvement in arthritis symptoms but no change in objective measures of disease activity in patients with RA [41]. Furthermore, the diet was poorly tolerated with half of the patients withdrawing due to adverse events (in particular nausea and diarrhea).

It has been suggested that a vegan diet which is also low in all kinds of fats is more likely to provide benefit to RA patients. In an uncontrolled trial, 24 patients with active RA maintained such a diet for 4 weeks. Compliance was not a problem with this diet, and improvements were observed in tender and swollen joint counts as well as pain scores. However, there was no improvement in duration of morning stiffness, ESR, or CRP [42]. Further, longer-term, double-blind-controlled studies of this diet are required.

Overall like elimination and elemental diets, vegetarian/vegan diets may be of benefit in some RA patients. However, restrictive diets are problematic with regard to compliance and there currently is no way to predict which patients will respond.

Mediterranean diet

The Mediterranean diet (MD) is characterized by a high consumption of fruits, vegetables, cereals, legumes and fish, moderate amounts of wine and olive oil as the primary source of fat. Such a diet is thought to be healthy and appears to be helpful in the secondary prevention of coronary artery disease [43]. The MD has been compared to a typical Western diet in 56 patients with active RA. Patients in both groups were provided with lunch and dinner at a hospital cafeteria for the first 3 weeks. During these 3 weeks patients in the MD group were instructed on Mediterranean food and its preparation and were provided with written instructions and recipes to use during the ensuing 9 weeks of the study, during which period they prepared their food at home. At the end of the 12-week study period there was a significant reduction in the disease activity score (DAS28) (see box), HAQ, swollen joint count, and CRP in patients on the MD compared to baseline, while there were no significant changes in the control group [44]. At least some of the improvements may be due to the increased intake of olive oil which is rich in oleic acid, a precursor to eicosatrienoic acid, which like the n-3 fatty acids can inhibit arachidonic acid (AA) metabolism (see below).

Disease activity score (DAS28)

Statistically derived index combining swollen joint counts, tender joint counts, ESR, and global disease activity.

$$\text{DAS28} = (0.56\sqrt{(28 \text{ tender joint count})} + 0.28\sqrt{(28 \text{ swollen joint count})} + 0.70\ln(\text{ESR})) 1.08 + 0.16.$$

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Fasting

Total and sub-total fasting have preceded some studies of vegetarian/vegan diets. In most cases improvements were observed during the fasting period, but rapidly disappeared on re-introduction of food [39,46–48]. Patients with RA frequently lose weight during periods of active disease. However, even patients with well-controlled disease have a lower body cell mass compared to healthy controls [49,50]. Rheumatoid cachexia is a term used to describe the severe loss of body cell mass that may occur (for recent review see [51]). This reduction in body cell mass can occur despite adequate protein and calorie intake and is associated with increased resting energy expenditure and protein catabolism as well as reduced physical activity. Diets which restrict protein and calorie intake may further compound this loss of body cell mass and should be avoided. In this regard, fasting which can only be maintained for short periods may still be detrimental. Given that the benefits of fasting are modest and short-lived when compared with the chronic nature of RA, fasting is an impractical approach to the management of RA.

Potential mechanisms of food intolerance/allergy rheumatoid arthritis

A number of potential mechanisms have been postulated for the observed responses in those patients who respond to elimination of suspected food allergens.

Disease and psychological factors

Patients who are willing to undertake dietary manipulation studies, particularly diets that involve fasting or are severely restrictive, may differ from the general RA population. One study which examined the psychological characteristics of patients participating in a study of a fasting/vegetarian diet, reported that study participants believed more in “alternative” treatments and less in “standard” medical treatments, had a higher perceived ability to control their own health and a lower perception that chance affected their health and response to treatment than non-study participants. Furthermore, those study participants who responded to the diet believed less in ordinary medical treatment than the non-responders [52]. While these data suggest that psychological factors do indeed play a role, one would not usually expect

clinical improvements to last for such an extended period of time (12 months) if this was the sole explanation.

Patients who are prepared to take part in dietary studies may also differ with respect to the severity of disease. In the study by Kjeldsen-Kragh *et al.*, study participants had shorter disease duration and less steroid and DMARD therapy suggesting milder disease compared to a group of non-study participants [52].

Weight loss

In the majority of dietary studies in RA, weight loss has been observed despite the dietary protocols aiming to be isocaloric. In general, weight loss *per se* has not been associated with improved disease control in these studies [35,39]. However, significant associations between reduction in body mass index and reduction in swollen joint count [53] and between weight loss and improved grip strength [31] have been reported. More recently, analysis of data from three previous studies of lacto-vegetarian, vegan, or MD suggests that weight loss *per se* does contribute to the observed improvements in disease control in patients on these kinds of diets [54].

Alterations in pro-inflammatory cytokines

A number of pro-inflammatory cytokines including interleukin (IL)-1, IL-6, and TNF are important in the inflammation and tissue destruction observed in RA.

Serum and synovial fluid IL-6 concentrations are increased in patients with RA. IL-6 has a role in regulation of the acute phase response, activation of T-cells, and may have a role in bone destruction [55]. A significant reduction in IL-6, along with a decrease in ESR and CRP, has been observed after a 7-day fast in 10 patients with RA [56].

IL-1 β and TNF are both implicated in the tissue destruction seen in RA [57–59]. Biological agent therapies that block TNF or IL-1 β activities have been shown to reduce disease activity and prevent joint damage in RA [60,61]. Recently, a small study has examined the effect of allergenic foods on serum TNF and IL-1 β concentrations in patients with RA. In patients challenged with foods, which had previously resulted in a positive SPT, serum TNF and IL-1 β concentrations increased along with an increase in clinical disease activity [62]. The authors concluded that food allergy may be a “triggering” rather than a causative factor in RA and that such allergy may increase the concentration of TNF and IL-1 β .

Alterations in dietary fatty acid composition

Dietary polyunsaturated fatty acids (PUFAs) are subject to remodeling and incorporated into cell membrane phospholipids. The C20 PUFAs are released from cell membranes by phospholipase A₂ and can then be metabolized to inflammatory lipid mediators known as eicosanoids (prostaglandins (PG) and leukotrienes (LT)). The n-6 fatty acid, linoleic acid (LA), is converted to AA, the precursor for the pro-inflammatory eicosanoids PGE₂, PGI₂, thromboxane (TX)A₂,

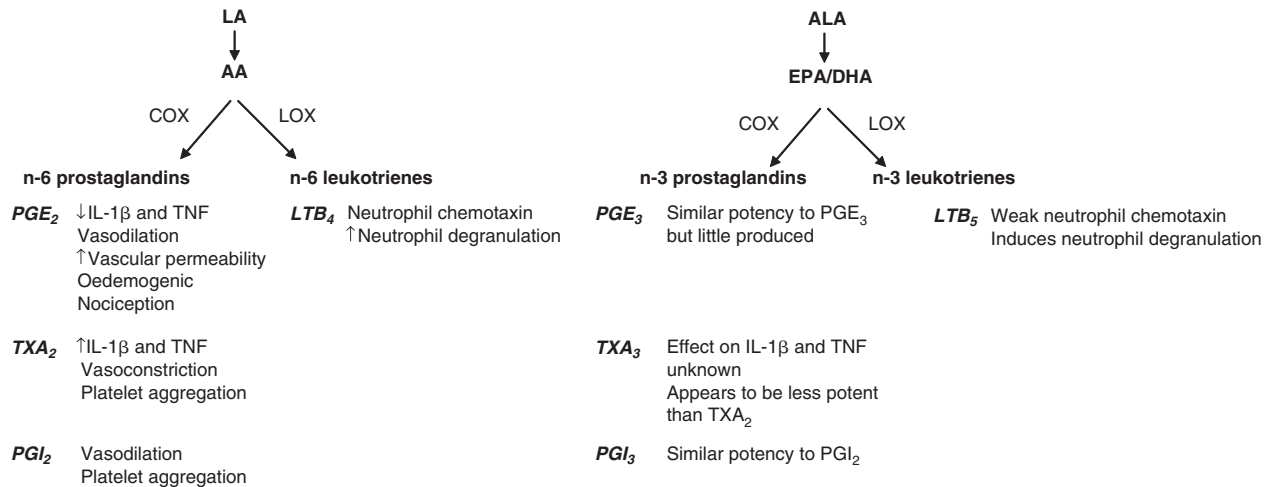


Figure 45.1 Metabolism of LA and ALA.

and LTB₄ (Fig. 45.1). In comparison, the n-3 fatty acid, α -linolenic acid (ALA), can be converted in a limited way to eicosapentanoic acid (EPA). EPA is a substrate inhibitor of AA metabolism to eicosanoids and EPA itself can be converted to the three series eicosanoids (PGE₃, TXA₃, PGI₃, LTB₅), which are generally less inflammatory than the AA-derived eicosanoids (Fig. 45.1). The limited conversion of ALA to EPA within the context of a Western diet has led to the use of dietary supplements of EPA rich fish oils as a means of achieving anti-inflammatory effects. Alteration of dietary fatty acids may therefore modulate inflammatory disease expression (discussed further in section of n-3 fatty acids).

After a 1-week fast, the relative proportion of both AA and EPA has been shown to increase in serum and platelets. Although the increase in AA and EPA was small in neutrophils, there was a reduction in LTB₄ release from stimulated neutrophils *ex vivo* [38]. While plasma AA concentrations have been shown to decrease in patients on a vegan diet, concentrations returned to baseline values when the diet was changed to lacto-vegetarian. In comparison, EPA decreased with both the vegan and lacto-vegetarian diets [63]. However, fatty acid concentrations were no different between diet responders and non-responders, suggesting that other mechanisms must be responsible for the observed benefits of such diets [62].

Alterations in intestinal microbial flora

The intestine is a rich source of microbes and the balance of microbes present contributes to an individual's overall health. Changes in intestinal microbial flora are believed to contribute to many chronic diseases [64]. For example, patients with RA have a high carriage rate of *Clostridium perfringens* compared to healthy controls. Furthermore, those patients with active RA had significantly higher clostridia counts compared to those with inactive disease [65]. Genetic variations in the way individuals respond to normal gut

flora may also contribute. *Proteus mirabilis*, a normal bowel commensal, contains an amino acid sequence similar to that found in the "shared epitope" and patients with RA have higher titers of antibodies directed against this sequence compared to both patients with ankylosing spondylitis and healthy controls [66]. Furthermore, patients with active RA have higher concentrations of anti-*proteus* antibodies compared to patients with inactive RA, healthy controls and healthy HLA-identical same sexed siblings [67].

The diet can have a significant impact on fecal microbial flora and may thus provide a mechanism for alterations in disease activity. With respect to *Proteus mirabilis*, in RA patients who fasted for 7–10 days followed by 1-year vegetarian diet, there was a significant reduction in anti-*proteus* antibodies, which was greater in those patients who responded to the dietary therapy. Furthermore, a correlation was seen between reduced antibody levels and the extent of reduction in disease activity [68]. Alterations in fecal microbial flora, which correlate with improvements in disease activity, have also been observed in patients on a vegan diet, although individual organisms could not be identified with the method employed [69]. However, in a more recent study, neither fasting for 8 days nor a 2-week vegetarian MD altered fecal bacterial counts despite a significant reduction in the DAS28 score in the fasting group [70].

Altered intestinal permeability and gut antigen handling

The gastrointestinal epithelium is a complex structure which allows entry of essential nutrients while at the same time providing a critical barrier which prevents antigens in the lumen gaining access to the circulation. Abnormal intestinal permeability may have a role in the pathogenesis of autoimmune disorders [71]. In a small study of five patients with RA, fasting decreased intestinal permeability and was accompanied by improved disease control. Furthermore,

when patients were started on a lacto-vegetarian diet, intestinal permeability and disease activity both increased [72]. Although limited, such data suggest that alterations in intestinal permeability, which allows increased entry of “arthritogenic” pathogens, may have a role in RA.

In addition to providing a physical barrier, the gut has a highly developed immune system (known as mucosa-associated lymphoid tissue (MALT)), that protects the host from potentially harmful pathogens, while simultaneously “tolerating” or allowing entry of “beneficial” antigens. MALT, which includes Peyer patches, has a preference for production of IgA, in particular secretory IgA, which is released into the gut lumen where it binds and prevents antigens from attaching to intestinal cells and gaining entry. In both patients with RA and healthy controls, short-term fasting has been reported to enhance mucosal antigen-specific B-cell responses but not systemic immune responses [73]. Thus activation of the mucosal immune system may not be reflected in the serum. A recent study has investigated this link among the mucosal immune system, food antibodies, and RA by examining jejunal fluid as well as serum [65]. In comparison to healthy controls, patients with RA had significantly increased concentrations of IgM in jejunal fluid. While there was an increase in IgA and IgG concentrations, this did not reach statistical significance. The activities of jejunal IgA, IgM, and IgG antibodies against a variety of different food antigens were also increased. The authors suggest that mucosal immune activation is important in the pathogenesis of RA, at least in some patients, and that apparent food intolerance may reflect the additive effect of hypersensitivity reactions [74].

Dietary n-3 supplementation and rheumatoid arthritis

n-3 fatty acids, which are abundant in fish and fish oils, have been shown to have a beneficial effect in patients with both early [75] and long-standing RA when combined with standard DMARD therapies (for review see [76]). For maximal benefits of n-3 supplementation to be achieved, the background diet should be low in competitor n-6 fatty acids [77]. Only one study has examined the effects of a diet containing hypoallergenic foods as well as being high in mono- and polyunsaturated fatty acids and low in saturated fatty acids. In this 24-week double-blind randomized, controlled study, 50 patients with RA were randomized to the experimental diet or a balanced control diet. In the experimental diet group, modest improvements were observed in all clinical variables although only ESR and tender joint count improved significantly [78]. The relative contributions of fatty acids and hypoallergenic foods to the outcomes could not be distinguished.

Like most of the DMARDs, there is a latent period of 6–12 weeks before benefits of n-3 supplements are observed

and it is important that patients appreciate the lack of immediate effect when they commence n-3 supplements. The latent period can be shortened with use of higher doses [79–82].

Many patients with RA use NSAIDs on a regular or as required basis. Dietary supplementation with n-3 fatty acids has been shown to reduce NSAID requirements [83–86]. NSAIDs are associated with gastrointestinal toxicity and may contribute to an increase in risk of cardiovascular disease [87–88]. Furthermore, NSAIDs alter the ratio of TXA₂/PGE₂ in favor of TXA₂, which increases monocyte production of the pro-inflammatory cytokines IL-1 β and TNF [89]. Thus the reduction in NSAID requirement associated with n-3 supplementation has a number of additional benefits including reduction in cardiovascular and gastrointestinal risk and potentially less joint damage.

The dose of n-3 fatty acids (EPA + DHA) required for the anti-inflammatory effect is 2.7g/day, which equates to at least nine standard fish oil capsules daily. Perhaps a more efficient way of ingesting sufficient n-3 fatty acids is through bottled fish oil; 15 ml of fish oil, taken on fruit juice is for many patients easier to consume than large numbers of capsules and is significantly cheaper (~45 cents/day compared to ~\$3.00/day for capsules).

Anti-inflammatory mechanisms of n-3 fatty acids

Fish and fish oils are rich in the n-3 long-chain fatty acids EPA (20:5 n-3) and docosahexaenoic acid (DHA; 22:5 n-3). EPA and DHA can be incorporated into cell membranes and tissues and may displace the n-6-derived AA (20:4 n-6). These n-3 and n-6 fatty acids are released from cell membranes and are metabolized by cyclo-oxygenase (COX) or lipoxygenase (LOX) and the terminal synthases to the eicosanoids (PG and TX) and LT, respectively (Fig. 45.1). In general the n-6-derived eicosanoids (PGE₂, TXA₂, PGI₂, LTB₄) are more pro-inflammatory than their n-3-derived counterparts (PGE₃, TXA₃, PGI₃, LTB₅). In humans, dietary supplementation with n-3 fatty acids has been shown to reduce production of PGE₂ [90,91], TXA₂ [91], and LTB₄ [92], and increase production of TXA₃ [93] and LTB₅ [94]. DHA can be converted to C22 oxylipids, which also have anti-inflammatory properties.

In addition to their effects on eicosanoid production, n-3 fatty acids have been shown to decrease production of IL-1 β and TNF, which are important mediators of tissues damage in RA, in both healthy subjects and patients with RA [81,90,91,95,96].

Matrix metalloproteinases (MMPs) have a pivotal role in cartilage degradation and bone erosion in RA. *In vitro* studies have demonstrated that n-3 fatty acids can suppress MMP expression and reduce proteoglycan degradation in IL-1-stimulated bovine chondrocytes [97,98]. Thus n-3 fatty acids may have the ability to reduce cartilage damage in inflamed joints.

As discussed above, class II MHC molecules (HLA-DR) are strongly expressed on APCs and present antigen to T-cells. *In vitro*, the n-3 fatty acids EPA and/or DHA reduce monocyte expression of HLA-DR and HLA-DP molecules [99], and reduce the ability of monocytes to present antigen to autologous lymphocytes [100]. In RA, one could speculate that n-3 fatty acids may inhibit APC function and suppress pathogenic T-cell activation, thereby reducing disease activity.

Cardiovascular risk in rheumatoid arthritis and the benefits of n-3 supplements

Patients with RA have an increased risk of death with a standardized mortality ratio of ~2 and most excess deaths are attributable to cardiovascular and cerebrovascular disease [101]. The risk of non-fatal myocardial infarction is also increased in patients with RA. In the Nurses' Health Study the adjusted relative risk (RR) of myocardial infarction in women with RA compared to women without RA was 2.0 (95% CI: 1.23–3.29). Furthermore, women with RA for >10 years had a RR of myocardial infarction of 3.1 (95% CI: 1.64–5.87) compared to women without RA [102]. There is no increase in traditional cardiovascular risk factors in patients to explain the observed increase [103]. The inflammatory process as well as use of NSAIDs may contribute to the increase risk [104]. In both primary and secondary prevention studies, n-3 fatty acid supplementation has been shown to reduce cardiovascular mortality [105]. To date there have been no studies examining whether n-3 fatty acid supplementation reduces cardiovascular morbidity and mortality in RA. However, a recent study has shown that patients with early RA taking n-3 fatty acid supplementation have lower triglycerides, increased "good" HDL cholesterol, lower CRP, less NSAID use, greater disease suppression, and reduced platelet synthesis of TXA₂ compared to patients not taking fish oil [58]. All of these factors would be expected to reduce cardiovascular risk.

Potential side effects of n-3 supplements

The most common adverse effects of n-3 fatty acid supplements are a fishy after-taste, gastrointestinal upset and nausea. In general these adverse effects are mild and can be controlled by taking the supplement with food. Fish can contain toxins, including methylmercury, polychlorinated biphenyls (PCBs), and dioxins which would accumulate in humans who consume contaminated fish on a regular basis. These toxins are in general reduced to acceptable limits in readily available commercial fish oils during processing.

Summary

Dietary restriction may prove useful in controlling RA in suitably motivated patients. Difficulties encountered in sustaining exclusion and other rigorous diets militate against

a general application. By contrast dietary fish in appropriate doses is relatively easy to take as a dietary additive. The preferred method is to take bottled fish oil on juice with the two glass technique (quickly swallow 15ml of fish oil layered on juice, then begin slowly sipping a juice chaser immediately, followed by food). This is the least expensive and most convenient way to achieve an anti-inflammatory dose of fish oil, since the equivalent dose of capsules is 14 × 1000mg capsules. The symptomatic benefits of fish oil are delayed until the second or third month of treatment and include reduced reliance on NSAIDs, which carry risk for serious gastrointestinal and cardiovascular events. Fish oil in the long term also improves disease control and remission rates with DMARD therapy. There are thus two contrasting approaches, which are not mutually exclusive: elimination of candidate food allergens and arthritogens, while maintaining balance in the diet otherwise, and ingestion of increased amounts of the n-3 fatty acids EPA and DHA in essentially pharmacological, anti-inflammatory doses as a dietary supplement. The latter approach is generally applicable, while the former in practice may be best applied in those who are well disposed to dietary avoidance strategies.

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