

EDITORIALS

RHEUMATOID ARTHRITIS AND THE BALANCE OF DIETARY N-6 AND N-3 ESSENTIAL FATTY ACIDS

RHEUMATOLOGISTS generally regard diet as having little consequence in relation to either the pathogenesis or the treatment of rheumatoid arthritis (RA). It is, therefore, understandable that enquiries from their patients about diet can be considered a nuisance. However, a dismissive or negative response wastes opportunities for conveying positive health messages and encouraging self-efficacy. Furthermore, published epidemiological, clinical and mechanistic studies provide a basis for pertinent health-enhancing dietary advice.

The central thesis is that the contemporary Western diet is hyperabundant in n-6 polyunsaturated fatty acids and sub-optimal in dietary n-3 fatty acids, particularly in relation to risk for thrombotic vascular disease, arrhythmias and inflammatory disorders [1]. From a biological perspective, this diet has recent origins which date to the invention of the seed press in the mid-19th century. Our modern diet is rich in total fat, yields n-6 fatty acids at >50-fold excess of essential requirements and delivers a ratio of n-6 to competitor n-3 fatty acids of 25:1 compared to a ratio of <2:1 in pre-industrial diets [1]. This shift is important because the dietary n-6/n-3 ratio is a determinant of the leucocyte n-6/n-3 ratio of fatty acids. The two classes of fatty acids, n-6 and n-3, are metabolized competitively, including conversion of their 20-carbon homologues by oxygenase enzymes to homologous families of eicosanoids (eicosa is Greek for 20).

The eicosanoids include the prostaglandins, thromboxanes and leukotrienes that mediate platelet vascular homeostasis and inflammation. Importantly, particular n-6 eicosanoids and their n-3 counterparts can have markedly different biological activities. These differences have been implicated in the greater disposition toward thrombotic vascular events and inflammatory diseases observed in communities ingesting strongly n-6-dominant diets (such as the Western diets) relative to communities ingesting n-3-dominant diets (such as the Eskimo diet) [2]. The different activity of n-6 thromboxane A₂ and n-3 thromboxane A₃ (which is relatively inactive) [3] is reflected in bleeding times typical in Western countries and the longer bleeding times observed in Greenland Eskimos [4].

The effects of dietary n-3 fatty acids on eicosanoids may explain the low incidence of myocardial infarction among Greenland Eskimos and Japanese who have a substantial fish intake. Evidence for a preventive effect of n-6-reduced, n-3-enriched diets on inflammatory diseases is less direct. In mice that are strongly predisposed genetically to systemic inflammatory diseases, both low-n-6 diets [5] and high-n-3 diets [6] have been shown to have a marked preventive effect

and a weaker therapeutic effect on established disease. The Japanese, who consume a diet rich in fish, have a relatively high frequency of HLA-DRw15 (which bears the rheumatoid susceptibility motif), but display a 'paradoxically' low prevalence of RA [7]. The effects of dietary fish oils (or n-3 fatty acids derived from fish oils) have been compared with similarly encapsulated comparison oils in 11 double-blind, controlled studies (reviewed in [8]). In all of these trials, modest anti-inflammatory effects of the fish oil preparations have been seen.

A reduced requirement for non-steroidal anti-inflammatory drugs (NSAIDs) was observed in all three studies in which this was used as an end point. In studies to date, a number of design factors could have militated against more favourable outcomes. These include over-representation of patients with long-standing disease, continuation of conventional therapies (including NSAIDs with which n-3 fatty acids share overlapping biochemical actions), suboptimal study duration, selection of end points that monitor the exudative rather than destructive aspects of RA and unmodified background diets (likely to be rich in competitor n-6 fatty acids).

Attention to the background diet is important because oils and spreads rich in n-9 non-essential fatty acids (a.k.a. monounsaturates, found in olive oil) and the n-3 precursor fatty acid, α -linolenic acid (ALA; C18:3n-3, found in flaxseed), can be used to displace n-6 fats from the diet without increasing undesirable saturated fat intake. These measures have been shown to increase the incorporation into cells of n-3 fatty acids from the diet [9,10]. An important but underappreciated biochemical effect of dietary n-3 fatty acid fortification is significantly reduced synthesis of interleukin (IL-1 β) and tumour necrosis factor- α (TNF- α) by peripheral blood mononuclear cells stimulated *in vitro*. This result has been shown in separate studies in healthy men [11], pre- and post-menopausal women [12], and rheumatoid subjects [13], and has been correlated with cellular levels of eicosapentaenoic acid (EPA; C20:5n-3), the n-3 competitor homologue of arachidonic acid (AA; C20:4n-6) [11]. This outcome was most marked with EPA-rich dietary fish oil supplements, but was also seen with an ALA-rich diet [11]. Our studies into the mechanism of this cytokine inhibitory effect have led to the identification of thromboxane A₂ as an autocrine or paracrine facilitator of IL-1 β and TNF- α synthesis (and therefore a novel target for therapy) [14]. The observed inhibitory effects of n-3 fatty acids on IL-1 β and TNF- α synthesis justify further studies into the possible effects of dietary n-3 fatty acid enrichment in RA in the long

term, with particular reference to measures of function and tissue damage. In these studies, n-6-rich foods should be avoided and n-3 fat intake adjusted on an individual patient basis to achieve and maintain peripheral blood mononuclear cell EPA levels of $\geq 1\%$ in order to reduce IL-1 β and TNF- α synthesis [11]. It may also be productive to assess the possible value of n-6-reduced, n-3-fortified diets as a means of extending the interval to relapse following TNF- α (or IL-1 β) blockade by biological agent therapies.

In summary, sufficient evidence exists to form the basis for positive health messages that can potentially reduce unwanted inflammation and protect against coronary vascular disease and sudden death. The nub of this advice is to choose foods that provide substantial amounts of n-3 fatty acids (fish, products based on n-3-rich seeds and vegetables) and to avoid foods that are very rich in n-6 fatty acids (products based on staple polyunsaturated oils, certain nuts). Variety in n-3-rich and/or n-6-poor foodstuffs and ingredients has increased in recent years to make these dietary changes simple and practical procedures. Fish oil supplements can be added for extra effect. At the very least, this information should be made available to patients seeking advice on ways to improve their health by dietary means, with or without conventional medications.

L. G. CLELAND and M. J. JAMES
Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia

REFERENCES

1. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991;54:438–63.
2. Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland. *Acta Med Scand* 1980;208:401–6.
3. Needleman P, Raz A, Minkes MS, Ferrendelli JA, Sprecher H. Triene prostaglandins: prostacyclin and thromboxane biosynthesis and unique biological properties. *Proc Natl Acad Sci USA* 1979;76:944–8.
4. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis. *Lancet* 1978;ii:117–9.
5. Hurd ER, Gilliam JN. Beneficial effect of an essential fatty acid deficient diet in NZB/NZW F1 mice. *J Invest Dermatol* 1981;77:381–4.
6. Prickett JD, Robinson DR, Steinberg AD. Dietary enrichment with the polyunsaturated fatty acid eicosapentaenoic acid prevents proteinuria and prolongs survival in NZB \times NZW F1 mice. *J Clin Invest* 1981;68:556–9.
7. Shichikawa K, Takenaka Y, Maeda A *et al.* A longitudinal population survey of rheumatoid arthritis in a rural district in Wakayama. *Ryumachi* 1981;21(suppl.):35–43.
8. Cleland LG, Hill CL, James MJ. Diet and arthritis. *Baillière's Clin Rheumatol* 1995;9:771–85.
9. Cleland LG, James MJ, Neumann MA, D'Angelo M, Gibson RA. Linoleate inhibits EPA incorporation from dietary fish oil supplements in human subjects. *Am J Clin Nutr* 1992;55:395–9.
10. Mantzioris E, James MJ, Gibson RA, Cleland LG. Dietary substitution with an n-3 rich vegetable oil increases EPA levels in plasma and neutrophil phospholipids. *Am J Clin Nutr* 1994;59:1304–9.
11. Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor α and interleukin-1 β production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr* 1996;63:116–22.
12. Meydani S, Endres S, Woods MM *et al.* Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between younger and older women. *J Nutr* 1991;121:547–55.
13. Kremer JM, Lawrence DA, Jubiz W *et al.* Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. *Arthritis Rheum* 1990;33:810–20.
14. Caughey GE, Pouliot M, Cleland LG, James MJ. Regulation of tumor necrosis factor alpha and interleukin-1 beta synthesis by thromboxane A₂ in non-adherent human monocytes. *J Immunol* 1997;158:351–8.

Further Information: Eprints including more detailed dietary advice can be obtained by e-mail from: les@field.medicine.adelaide.edu.au.

SHOULD PATIENTS ON HYDROXYCHLOROQUINE HAVE THEIR EYES EXAMINED REGULARLY?

THE antimalarial agents chloroquine and hydroxychloroquine were first used in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) in the 1950s on the basis of uncontrolled observations. Placebo-controlled studies in the 1960s and 1970s established that the drugs had a delayed effect in reducing disease activity in RA at between 12 and 72 weeks [1]. The effect was not always prolonged, but in some instances remission was achieved. No placebo-controlled studies have shown evidence of any effect of either drug on the progression of erosions. Once it had been demonstrated that they were more effective than placebo, studies were introduced to compare anti-

malarials with gold, D-penicillamine and sulphasalazine. The general conclusions of these studies were that the antimalarials were effective in reducing most symptoms and signs of active RA, but significantly less so than the other agents. Withdrawal of hydroxychloroquine treatment was more likely to be due to lack of efficacy or loss of control of the arthritis than to toxicity, when compared with gold [2]. It is generally agreed that no life-threatening side-effects are seen with the presently used daily dose of these drugs (chloroquine 250 mg daily or hydroxychloroquine 200–400 mg daily). There have been no controlled studies of antimalarial agents in SLE.

Even in early studies of RA, however, there was concern and controversy about the incidence and severity of ocular side-effects. It was generally concluded that corneal deposits and changes in accommodation due to effects on the ciliary body were reversible and not serious. With high daily doses of chloroquine, after a delay of between a few months and several years, however, more serious and sight-threatening retinal toxicity was observed [3]. Although studies varied in the definition of the exact nature of the lesion, the so-called bull's eye maculopathy was shown to be due to toxic effects and related to direct concentration of the drug in the pigmented layer of the retina. In some cases, especially if not detected early, the outcome was severe visual impairment and, in a few cases, blindness. These reports led to more cautious dosage regimens; since their introduction, the number of reports of irreversible visual changes has been greatly reduced. The lesser retinal toxicity of hydroxychloroquine may simply reflect the fact that this drug has been used since it was first introduced at relatively lower doses than those at which chloroquine was used during the 1950s and 1960s. Reports of progression of the lesion and worsening visual impairment after stopping the drug have been published [4].

Some individuals with RA appeared to develop similar lesions without ever having been exposed to antimalarial medications [5].

The impression that the early detection of the retinal lesion was associated with a lesser frequency of severe visual impairment, and the observation that some individuals developed moderately severe changes without noticing any visual disturbance, while others noticed patchy visual loss, led to the recommendation that the fundi be examined and a variety of tests be performed both before the use of either drug and at intervals of 3–6 months thereafter, even when the drugs were being used in the low-dose regimens. The best way of detecting the early lesion is generally agreed to be by expert direct fundoscopic examination with or without visual field testing using a red marker and a Snellen chart. It became usual practice, therefore, to monitor patients for visual toxicity and such monitoring is recommended currently in the relevant data sheets. There is a significant economic cost attached to such a practice.

Monitoring for drug side-effects is indicated where a drug produces significant toxicity which can be detected early and which can be reversed or reduced, or halted, by stopping the administration of the drug at this stage.

The cost of monitoring of many anti-rheumatic drugs is high and therefore it is now being asked

whether such procedures can be justified not only on pure health grounds, but also on economic grounds. The normal practice in most rheumatology units of following an ophthalmological monitoring regime for patients on antimalarials has come under question. What is the cost? What is the likelihood of detecting a lesion at today's prevalent doses? What happens to the lesion and, in particular, what happens to visual acuity if the lesion is detected early and the drug discontinued at that time? How should we view evidence-based medicine which asks for statistically proven answers to these questions? It is easy if the evidence is clear cut and available, but when the evidence is not properly controlled or controversial, the position is less clear. Is it reasonable to stop present monitoring practices on the basis that no controlled evidence is available? When should the economic argument become a major player in this decision? With those questions in mind, the Clinical Affairs Committee of the British Society of Rheumatology and the Rheumatology Committee of the Royal College of Physicians sought a scientific review of available data. This is published in this issue of the journal, page 599.

As described in this report, there is insufficient information to address properly the important question 'Should patients on hydroxychloroquine have their eyes examined regularly?'. At the present time, such lack of hard data should not deter the careful clinician from monitoring his or her patients, nor prevent resource-pressed ophthalmology departments from arguing that the justification for monitoring does not exist. Locally negotiated policies are likely to vary.

M. SHIPLEY and A. SILMAN*

*Chairman, Clinical Affairs Committee, British Society for Rheumatology, 41 Eagle Street, London and *ARC Epidemiology Research Unit, University of Manchester, Manchester*

REFERENCES

1. Tett S, Cutler D, Day R. Antimalarials in rheumatic diseases. *Baillière's Clin Rheumatol* 1990;4:467–89.
2. Richter JA, Runge LA, Pinals RS, Oates RP. Analysis of treatment terminations with gold and antimalarial compounds in rheumatoid arthritis. *J Rheumatol* 1980;7:153–9.
3. Heibind P, Carr RE, Segel IM. Early chloroquine retinopathy: Clinical and functional findings. *Arch Ophthalmol* 1964;71:65–73.
4. Brinkley JR, Rubois EL, Ryan SJ. Long term course of chloroquine retinopathy after cessation of medication. *Am J Ophthalmol* 1979;88:1–11.
5. Weise EE, Yarronzzi LA. Ring maculopathies mimicking chloroquine retinopathy. *Am J Ophthalmol* 1974;78:204–10.