Nutritional management of rheumatoid arthritis: a review of the evidence

K. L. Rennie,* J. Hughes,† R. Lang* and S. A. Jebb*

*MRC Human Nutrition Research, Elsie Widdowson Laboratory, Fulbourn Road, Cambridge, UK; †Independent Nutrition Consultant, 7 Holmesdale Park, Nutfield, Surrey, UK

Correspondence
Kirsten L. Rennie,
MRC Human Nutrition Research,
Elsie Widdowson Laboratory,
Fulbourn Road,
Cambridge CB1 9NL, UK.
Tel.: 01223 426356
Fax: 01223 437515
E-mail: kirsten.rennie@
mrc-hnr.cam.ac.uk

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Abstract

Rheumatoid arthritis (RA) is a debilitating disease and is associated with increased risk of cardiovascular disease and osteoporosis. Poor nutrient status in RA patients has been reported and some drug therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs), prescribed to alleviate RA symptoms, may increase the requirement for some nutrients and reduce their absorption. This paper reviews the scientific evidence for the role of diet and nutrient supplementation in the management of RA, by alleviating symptoms, decreasing progression of the disease or by reducing the reliance on, or combating the side-effects of, NSAIDs. Supplementation with long-chain n-3 polyunsaturated fatty acids (PUFA) consistently demonstrates an improvement in symptoms and a reduction in NSAID usage. Evidence relating to other fatty acids, antioxidants, zinc, iron, folate, other B vitamins, calcium, vitamin D and fluoride are also considered. The present evidence suggests that RA patients should consume a balanced diet rich in long-chain n-3 PUFA and antioxidants. More randomized long-term studies are needed to provide evidence for the benefits of specific nutritional supplementation and to determine optimum intake, particularly for n-3 PUFA and antioxidants.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease resulting in joint inflammation that is manifested by swelling, pain, functional impairment and muscle wasting and is associated with increased risk of cardiovascular disease (CVD) and osteoporosis. It is characterized by both localized and systemic inflammation with elevated plasma concentrations of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and acute-phase proteins. RA is thought to result from an underlying genetic susceptibility, which is manifest in response to an environmental trigger. However, the exact cause or causes of the disease are unknown.

Poor nutrient status in diagnosed RA patients has been reported in observational studies, with reduced energy intake from carbohydrates, high consumption of saturated fat and poor intake of micronutrients relative to nonaffected controls (Hansen *et al.*, 1996; Morgan *et al.*, 1997; Stone *et al.*, 1997). This may in part contribute to the increased risk of CVD observed in patients with

RA. However, it is not clear why people with RA have poor nutrient status.

Rheumatoid arthritis has a prevalence of about 2% worldwide and is more common in women, with symptoms typically appearing during middle age. The associated complications of osteoporosis and CVD make RA important in public health terms. Rheumatoid cachexia, characterized by a decrease in body cell mass, muscle mass and strength, may be an important contributor to the risk of developing these complications and is associated with the elevated production of the inflammatory cytokines IL-1β and TNF-α (Roubenoff *et al.*, 1994). Conventional treatments for RA, including nonsteroidal anti-inflammatory drugs (NSAIDs), slow-acting anti-rheumatic drugs and corticosteroids, aim to reduce the patients' pain and joint inflammation, minimize loss of function and decrease the progression of joint damage. However, such treatments are rarely, totally effective and some pharmacological therapies have the potential to cause side-effects, such as gastro-intestinal bleeding and bone loss (Sarzi-Puttini *et al.*, 2000). As a result many RA sufferers turn to alternative (self-prescribed) therapies including dietary supplements.

In addition, some drug therapies prescribed to alleviate symptoms of RA have anti-nutrient effects by both increasing the requirement of some nutrients and reducing their absorption. Studies have suggested that diet may play a role in the management of RA, particularly in alleviating the symptoms of the disease and reducing the risk of complications (Darlington & Ramsey, 1993; Danao-Camara & Shintani, 1999).

This paper is not a systematic review but rather provides an overview of the scientific evidence for the role of many different aspects of diet and/or nutrient supplementation in the management of rheumatoid arthritis, by alleviating symptoms, decreasing progression of the disease or by reducing the reliance on, and combating the side-effects of, concomitant medication. Associations between specific nutrients in the diet, both in the form of supplements and foods were examined and changes in diet composition, such as elimination diets, were also considered. It highlights particular nutrients of interest and may form the basis for subsequent systematic reviews.

Polyunsaturated fatty acids

There is much interest in the putative role of n-3 polyunsaturated fatty acids (PUFA) to reduce inflammation and alleviate the symptoms of RA. Dietary n-6 and n-3 PUFA are modulators of the lipid content of membrane phospholipids, where they are able to affect cell function, and precursors for eicosanoid production. Eicosanoids mediate inflammation, cytokine synthesis and cell communication (Volker *et al.*, 2000). Metabolism of n-6 PUFA produces arachidonic acid (AA), leading to the production of leukotrienes, prostaglandins and thromboxanes of the two and four series, whereas metabolism of n-3 PUFA produces docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) which form the respective eicosanoids of the three and five series.

The major sources of n-6 and n-3 PUFA are linoleic and α-linolenic acid (ALNA), respectively. These fatty acids are elongated and desaturated by the same enzymes leading to a competition between these fatty acid groups. In recent years there has been a marked increase in the consumption of n-6 PUFA-rich vegetable oils, such as sunflower oils and spreads, and the ratio of n-6 to n-3 has increased dramatically (Simopoulos, 1991). This has shifted the balance of eicosanoids synthesized to favour those from the AA precursor that have more pro-inflammatory biological actions, over those synthesized from DHA and EPA. DHA and EPA, which are found in fish oil, are able to decrease the production of AA-derived eicosanoids and decrease the production of pro-inflammatory cytokines TNF-α, IL-1β and IL-6, decrease lymphocyte proliferation and reactive oxygen species (Calder & Zurier, 2001). The exact mechanisms through which n-3 PUFA act are still being debated, but it is clear that these oils do demonstrate some anti-inflammatory properties.

A large number of studies have examined the effect of fish oil supplementation in relation to RA. Review papers conclude that the evidence for significant clinical improvements on RA and inflammatory status from fish oils is consistent,

with a reduction in the number of tender joints being the most often observed benefit (Ariza-Ariza *et al*., 1998; Belch & Muir, 1998; Grimble & Tappia, 1998; Simopoulos, 1999; James *et al*., 2000; Kremer, 2000; Calder & Zurier, 2001; Darlington & Stone, 2001). A beneficial clinical effect of dietary supplementation of fish oil on RA has been observed in at least 13 double-blind, placebo controlled studies since 1985 (James *et al*., 2000; Calder & Zurier, 2001).

Calder *et al*. suggested that the effectiveness of fish oils may have been underestimated as RA patients in many studies continued with existing drug therapies in addition to the fish oil supplementation (Calder & Zurier, 2001). Other studies have suggested that NSAIDs therapy could be reduced or stopped in some RA patients (Belch *et al*., 1988; Skoldstam *et al*., 1992; Lau *et al*., 1993; Geusens *et al*., 1994; Kremer, 2000). One study reported a significant reduction in NSAID usage in patients receiving a fish oil supplement compared with those taking a placebo, which persisted throughout the 12-month intervention period [mean requirement (95% CI for mean) intervention 40.6 (24.5–56.6)%; placebo 84.1 (62.7–105.5)% $P < 0.001$] (Lau *et al*., 1993). In a review of fish oil supplementation studies, it was concluded that after 3–4 months of supplementation patients may be able to reduce their NSAIDs dose under the supervision of a physician (Kremer, 2000). Further research is required to investigate these potentially beneficial interactions between drug therapies and long chain n-3 PUFA supplementation.

Most studies of n-3 supplementation have not considered the background dietary intake of n-6 PUFA. In principle, reductions in n-6 would increase the n-3 to n-6 ratio and may, by modulating the balance of eicosanoids, enhance the effect of the n-3 supplements (Calder & Zurier, 2001). One study specifically selected RA patients whose background diet was naturally low (<10 g day^{-1}) in n-6 fatty acids and provided either a fish oil supplementation or a control capsule of 50/50 corn/olive oil (Volker *et al*., 2000). Significant improvements in the number of tender and swollen joints, stiffness, pain and both the patient's and physician's global assessment of arthritis activity were observed in the fish oil group after 15 weeks. No significant improvements in any clinical measure were seen in the control group.

Clinical trials of fish oil supplementation have predominantly been of short duration and more studies are required to investigate the safety of long-term supplementation. There is also a need for studies to further examine the minimum doses and duration required to bring about clinical improvement (Calder & Zurier, 2001) particularly as suppression of cell-mediated immunity has been observed with high doses of fish oil in animal studies (Hinds & Sanders, 1993). One study compared 27 mg kg^{-1} EPA and 18 mg kg^{-1} DHA (low dose) with 54 mg kg^{-1} EPA and 36 mg kg^{-1} DHA (high dose) in RA patients. Both doses were equally effective in improving symptoms over 24 weeks but the improvements reached statistical significance sooner with the high dose (12 weeks versus 18 or 24 weeks) suggesting that high doses may not confer any additional long-term benefit (Kremer *et al*., 1990).

Case–control studies that have examined the effect of fish in the diet on the risk of developing RA have been ambivalent (Linos *et al*., 1991; Shapiro *et al*., 1996; Linos *et al*., 1999) and no studies have specifically assessed the effect of dietary fish on RA symptoms. Studies in healthy individuals have demonstrated that dietary sources of n-3 PUFA can increase n-3 fatty acid tissue concentrations to levels observed with fish oil capsules and can modestly suppress some inflammatory eicosanoids and cytokines (Fahrer *et al*., 1991; Mantzioris *et al*., 2000). However, compared with fish oil capsules, which contain concentrated high doses of n-3 oils, fish, even oily fish, contain less long chain n-3 and are rarely consumed on a daily basis. Further research is needed to establish recommended dietary intakes of n-3 PUFA from foods for patients with RA to confer clinical benefit. At present, the evidence suggests that an increase in long chain n-3 PUFA is associated with beneficial effects for patients with RA. In addition, increases in n-3 PUFA are associated with reduced risk of CVD and other health benefits. There is therefore sufficient evidence to promote fish consumption for patients

with RA in line with general healthy eating recommendations (at least two servings per week, with one or more of the servings as oily fish). Patients who do not consume fish regularly may consider modest fish oil supplements, but, until long-term supplementation trials have been undertaken and further evidence on optimal doses are available, caution should be exercised in the use of concentrated high dose fish oil supplements.

There is little evidence of the relative efficacy of plant sources of n-3 PUFA in the form of ALNA, such as leafy green vegetables, flaxseeds, rapeseeds and canola oils. One study has demonstrated that 18 g of ALNA/day for 8 weeks significantly decreased the stimulation and proliferation of lymphocytes in healthy adults (Kelley *et al.*, 1991). However, this dose was greatly in excess of current average intakes (1–2 g day^{-1} in UK adults) (British Nutrition Foundation, 1999) and would be very difficult for most individuals to achieve through dietary change. Only one randomized trial has investigated the effects of modest levels of ALNA (2 g day^{-1}) alone in healthy subjects with a 12-week supplementation of flax seed oil (Thies *et al.*, 2001). This study reported no change in markers of inflammation or immune response. As the conversion of plant sources of n-3 to EPA is relatively inefficient, it is likely that large doses would be required to effect immunological responses (Calder & Zurier, 2001). No studies examining the effects of ALNA in RA patients were identified.

Many plant oils are rich in n-6 linoleic acid. Metabolism of this acid produces γ-linolenic acid (GLA), which is converted to dihomo-γ-linolenic acid (DGLA) and AA. In human inflammatory cells, GLA is readily converted to DGLA and accumulates in these cells that do not contain the necessary enzymes for the subsequent conversion to AA (Barham *et al.*, 2000). Thus increased dietary GLA reduces the synthesis of potent mediators of inflammation from AA and increases anti-inflammatory action through some of the DGLA-derived eicosanoids (Calder & Zurier, 2001). A number of studies have examined whether certain plant seed oils that contain relatively large amounts of GLA may have anti-inflammatory actions, notably those extracted from the seeds of evening primrose oil (EPO), blackcurrants and borage plants.

A randomized control trial using GLA-rich borage seed oil (BSO) reported a reduction in signs and symptoms of disease activity in RA patients after a 24-week intervention (Leventhal *et al.*, 1993). However, this was a small study ($n = 37$) and the dose of GLA was relatively high (1.4 g day^{-1} GLA). The authors concluded that further controlled trials were required. The biological mechanism for this effect is supported by an uncontrolled human study, in which similarly high doses of BSO (1.1 g day^{-1} GLA) were given to both healthy subjects and patients with RA over 12 weeks (Pullman-Mooar *et al.*, 1990). Significant increases in DGLA were observed in circulating mononuclear cells, with increases in the ratios of DGLA to AA and reductions in the associated pro-inflammatory two-series prostaglandins and four-series leukotrienes. Similar beneficial effects on RA have been reported following a supplementation with blackcurrant seed oil, containing 525 mg day^{-1} GLA (Watson *et al.*, 1993). Two trials examining whether EPO supplements could reduce the clinical symptoms of RA and the dosage of NSAIDs used by patients with RA found mild improvements in symptoms and reduction in NSAIDs (Belch *et al.*, 1988; Brzeski *et al.*, 1991) whereas others have found no positive effects (Hansen *et al.*, 1983; Darlington & Stone, 2001). One of the above trials, reporting a positive effect of EPO, found a reduction in NSAIDs usage in both the placebo and intervention arms (reduction of 400 mg ibuprofen per day) (Brzeski *et al.*, 1991). In this study, olive oil, rich in monounsaturated fatty acids (MUFAs), which may have beneficial effects on RA symptoms itself, was used as the placebo. There is debate over which fatty acids should be used as the placebo in studies of n-3 supplementation because some fatty acids, such as MUFAs, have been suggested to have independent health benefits and thus may reduce the differences between the trial arms and underestimate the effects of the oil on trial.

It is important to note that one small study (nine subjects in the EPO intervention arm) found possible adverse effects of EPO supplementation with increased concentrations of AA and reduced

levels of EPA in the serum with a 20-mL EPO supplement (9% GLA) (Jantti *et al*., 1989). However, although GLA supplementation may decrease AA levels in inflammatory cells, it has been shown to markedly increase serum levels of AA (Barham *et al*., 2000). High serum AA increases the tendency of platelet aggregation, a risk factor for coronary heart disease. Barham *et al*. (2000) have demonstrated that this potentially adverse effect of GLA may be counteracted if the GLA supplement is combined with EPA.

There is no evidence of a specific benefit of n-3 PUFA rich plant oils for patients with RA. There is some evidence of a possible benefit of plant oils rich in GLA, but the majority of studies have been of short duration and only one randomized control trial has examined the effects of these oils on RA symptoms over 12 months with an appropriate placebo (Belch *et al*., 1988). There is a need for trials to explore the potential long-term effects of GLA supplementation.

Monounsaturated fatty acids

When MUFA are present in the diet, they usually replace dietary n-6 PUFA and thus reduce the competition between n-6 and n-3 PUFA, which results in increased incorporation of n-3 fatty acids into cell membranes (Darlington & Stone, 2001). Metabolism of oleic acid, an n-9 MUFA, produces eicosatrienoic acid (ETA), which like EPA competes with n-6 PUFA. One of the principal dietary sources of oleic acid is olive oil.

Studies to examine the effects of olive oil on RA are limited. Two case–control studies found an inverse association between olive oil consumption and risk of RA (Linos *et al*., 1991, 1999). However, only one intervention study has examined the impact in patients with established RA (Brzeski *et al*., 1991). Patients who consumed olive oil capsules (6 g day^{-1}) had significant reduction in pain and articular index at 6 months in relation to a 540-mg day^{-1} dose of GLA and some patients were able to reduce their dose of NSAIDs by 400 mg of ibuprofen a day. As in the fish oil supplementation trials, it is difficult to assess the full impact of the olive oil intervention when another potentially beneficial fatty acid is used in the other arm of the trial. Further studies are required.

Antioxidants

Adequate tissue concentrations of antioxidants may provide an important defence against the increased oxidant stress in patients with RA. Studies have examined the effects of vitamins C, E and selenium on the management of RA.

In general vitamin E (α-tocopherol) deficiency and low tissue vitamin E content enhances components of the inflammatory response and suppresses components of the immune response (Mangge *et al*., 1999; Darlington & Stone, 2001). Dietary vitamin E supplementation has been reported to bring about the opposite effect (Grimble, 1998). However, randomized controlled trials have reported conflicting results, despite all administering similarly high doses of vitamin E (1200 mg day^{-1}) (Edmonds *et al*., 1997; Miehle, 1997; Wittenborg *et al*., 1998). Miehle *et al*. have proposed that free radical production increases in a dose–response manner depending on the severity of the condition and the number of joints affected and that this could explain the graded effects of α-tocopherol in these randomized control trials (Miehle, 1997) which range from a trial in those who were relatively active (Edmonds *et al*., 1997) to those who had been hospitalized because of their RA (Wittenborg *et al*., 1998). To date all the trials of vitamin E supplementation have been of short duration (3–12 weeks).

Recent molecular studies have demonstrated that the anti-inflammatory effects of aspirin are greatly enhanced when combined with α-tocopherol (Abate *et al*., 2000). The formation of the proinflammatory prostaglandin E2 was inhibited 59% by aspirin compared with control and 95% by aspirin when combined with α-tocopherol. This suggests that vitamin E supplementation may reduce the usually high dosage of aspirin needed by patients with RA to relieve joint symptoms, which often causes considerable gastric irritation (Fries *et al*., 1993). Therefore there is currently no substantial evidence to support vitamin E supplementation, but patients with RA should be encouraged to increase their

consumption of vitamin-E-rich cereals, fruit and vegetables.

Vitamin C (ascorbic acid) is an intra- and extracellular scavenger of free radicals and as such, plays an important role in antioxidant defences (Whiteman & Halliwell, 1996). In animal studies biochemical markers of antioxidant defence mechanisms were increased with vitamin C supplementation (Eldin *et al.*, 1992) and infiltration of inflammatory cells into synovial fluid were decreased (Sakai *et al.*, 1999). Only one vitamin C supplementation study in humans was identified, which failed to show any beneficial effect on the synovial inflammatory process (Mangge *et al.*, 1999).

Many studies have investigated the effect of selenium on RA. In the general UK population, selenium intakes are currently below the recommended nutrient intake (Brown & Arthur, 2001). In a prospective study, 28 RA patients were followed for a mean period of 7.3 years (Tarp *et al.*, 1989). Serum selenium fluctuated in most of the patients during the course of the disease, with low levels in periods of high disease activity and normal levels in periods of low activity. It is hypothesized that selenium levels drop in response to inflammation and that supplementation may have anti-inflammatory effects (Tarp, 1995). Animal studies indicate that selenium deficiency leads to a less responsive immune system (Tarp, 1995) but the mechanisms in humans are not fully understood. In immune cells, the major function of selenium appears to control excessive production of perioxidative substrates and it may also down-regulate cytokine signalling (McCarty & Russell, 1999) with high doses possibly causing immunosuppression (Tarp, 1995).

In patients with RA selenium supplementation studies have produced conflicting results, reporting an improvement in RA symptoms (Peretz *et al.*, 1992; Aaseth & Teigen, 1993; Heinle *et al.*, 1997) or no change with supplementation (Tarp *et al.*, 1985; Jantti *et al.*, 1991; Petersson *et al.*, 1991), which may be attributable to differences in study design. The intervention periods of these studies have varied from 8 weeks (Jantti *et al.*, 1991) to 8 months (Aaseth & Teigen, 1993) in 15–70 patients, who were either recently diagnosed, had low inflammatory activity or active RA. The largest study ($n = 70$), a double-blind randomized control trial with a 3-month intervention period, reported a significant decrease in RA symptoms, reduced reliance on cortisone and NSAIDs and a significant decrease in biochemical indicators of inflammation in the group receiving a selenium supplementation of 200 g sodium selenite (Heinle *et al.*, 1997). However, both the supplementation and placebo groups received an additional fish oil supplementation, so the effect of selenium alone cannot be accurately determined. Further well-controlled studies are needed.

The effect of dietary sources of antioxidants has not been examined in subjects with established RA. However, associations between high vegetable consumption and reduced risk of developing RA have been reported in a cross-sectional cohort (La Vecchia *et al.*, 1998) and a case–control study (Linos *et al.*, 1999). Patients with RA should be encouraged to meet the recommended intake of these antioxidants through consumption of plant foods, but the case for nutrition supplementation is unproven.

Folate and other B vitamins

Low plasma levels of pyridoxal-5-phosphate (PLP), the metabolically active form of vitamin B6, have been reported in RA patients (Roubenoff *et al.*, 1995) which may be associated with the elevated TNF-α production and subsequent elevated energy expenditure seen in RA (Roubenoff *et al.*, 1995). It is not clear whether these low levels reflect an intracellular deficiency or whether there is redistribution, rather than an absolute decline, of PLP in RA.

There are no reports of positive effects of oral vitamin B_6 supplements to treat the symptoms of RA (Roubenoff *et al.*, 1997). It has been suggested that vitamin B_6, in conjunction with folate and vitamin B_{12} supplementation, may be beneficial to a subgroup of RA patients with high homocysteine levels, as PLP has an integral role in homocysteine metabolism. Elevated levels of total homocysteine occur commonly in RA patients, and may, contribute to the increased cardiovascular risk associated with the disease (Roubenoff *et al.*,

1997). However, as large doses of vitamin B_6 have known toxic effects, RA patients should be advised to consume dietary sources of vitamin B_6 up to the dietary reference value, until further research is undertaken into the safety and effectiveness of enhanced supplementation.

Methotrexate (MTX), an anti-rheumatic drug, is a known folate antagonist (Dijkmans, 1995; Ortiz *et al*., 2001). Some side-effects of MTX, such as gastrointestinal intolerance, mimic complicated folate deficiency. Folate stores are decreased in RA patients on MTX, suggesting that impaired folate status is indeed related to MTX toxicity (Morgan *et al*., 1994).

A Cochrane review of seven trials reported the effects of folic acid and folinic acid (a one carbon substituted, fully reduced folate) in reducing the mucosal and gastrointestinal side-effects of low-dose MTX in patients with RA (Ortiz *et al*., 2001). A total of 147 patients received folate supplementation in the seven studies (80 with folinic acid and 67 with folic acid). With folic acid, a 79% reduction in mucosal and gastrointestinal side-effects was observed [OR = 0.21 (95% CI 0.10, 0.44)]. For folinic acid a reduction of 43% was reported, which was not statistically significant [OR = 0.57 (95% CI 0.28–1.15)]. No major differences were observed between low and high doses of folic or folinic acid and no consistent differences in disease activity parameters, such as number of tender and swollen joints, were seen when the folic or folinic acid at low or high doses were compared with the placebo. The reviewers concluded that the results support the protective effect of low doses of folic acid supplementation (<5 mg $week^{-1}$) in patients having RA treated with MTX. This exceeds the current recommended nutrient intake for folate (1.4 mg $week^{-1}$) and supplementation may be warranted in this subgroup of patients with RA. However, it is essential to ensure that patients have adequate vitamin B_{12} status before starting any supplementation to prevent any possible masking of vitamin B_{12} deficiency.

Zinc

Low levels of serum zinc have been reported in patients with RA (Helliwell *et al*., 1984) which may not be fully accounted for by low dietary zinc intake (Honkanen *et al*., 1991). It has been postulated that low serum zinc may be caused by elevated IL-1 associated with RA (Svenson *et al*., 1985; Honkanen *et al*., 1991) or by the use of corticosteroids and NSAIDs (Milanino *et al*., 1993). Clinical studies of zinc supplementation yield contradictory results (Mangge *et al*., 1999) and at present do not support a therapeutic use of zinc. There have been no studies examining the effect of dietary sources of zinc on inflammation or the immune function of RA patients.

Iron

Approximately, one-third of cases of anaemia in RA patients may be caused by depletion of iron stores, suggesting that in this population iron deficiency is an important cause of anaemia (Punnonen *et al*., 2000). Iron deficiency anaemia may develop as a result of chronic inflammation, gastrointestinal blood loss caused by RA medications, preferential uptake of iron by inflamed synovial tissue as well as poor dietary intake (Giodano *et al*., 1984). Deferioxamine, an iron-chelating agent, which has possible anti-inflammatory properties, was given to five patients with severe RA for 4 weeks (500 mg five times a week) (Marcus, 1987). After treatment, haemoglobin and serum iron levels increased and this lasted 8 weeks after the cessation of the treatment. However, one patient had significant toxicity and three patients developed gastrointestinal side-effects including vomiting and abdominal pain. No further studies of supplementation have been reported. Since iron deficiency anaemia is relatively common in the general population, an adequate dietary intake to meet the recommended intakes should be encouraged, but there is no evidence for additional routine supplementation for patients with RA.

Calcium, vitamin D and fluoride

Patients with RA are vulnerable to steroid-induced and disease-associated osteoporosis. In RA, vertebral bone density has been found to be 5–15% less than aged matched controls (Adachi *et al.*, 1997). In addition, corticosteroids, used in the treatment of RA, impair intestinal calcium absorption (Reid *et al.*, 1994). It appears that bone loss occurs rapidly within the first 6–12 months of corticosteroid therapy and then slows (Adachi *et al.*, 1998). Low dietary intakes of calcium (Morgan *et al.*, 1997) and vitamin D (Martin, 1998) have been reported in patients with RA. It is not clear why this is the case, but patients with RA should be encouraged to meet the recommended dietary intakes. Studies have examined the effect of calcium and vitamin D_3 supplementation on bone mineral density (BMD) among subjects taking corticosteroids in men and women who were predominantly post-menopausal (Adachi *et al.*, 1996; Buckley *et al.*, 1996; Adachi & Ioannidid, 1999). Calcium prophylaxis alone appears to offer only minimal protection from corticosteroid-induced spinal bone loss (Adachi & Ioannidid, 1999). A 2-year randomized control trial of calcium combined with vitamin D_3 in 65 RA patients taking corticosteroids demonstrated a reduction in BMD loss in both the spine and trochanter, but not the femoral neck (Buckley *et al.*, 1996). However, patients in this trial were only receiving a low dose of corticosteroids. The trial did not find a significant difference with menopausal status, but was not powered to examine any interactive effects with hormone replacement therapy. Other long-term supplementation trials, in those undergoing extended therapy with higher doses of corticosteroids for a variety of inflammatory conditions, did not demonstrate significant beneficial effects on BMD (Adachi & Ioannidid, 1999). No change in BMD with calcium and vitamin D_3 supplementation has been seen in RA patients not receiving corticosteroids (Buckley *et al.*, 1996) and therefore, considering the possible side-effect of hypercalcaemia (Adachi & Ioannidid, 1999) there is no evidence to support calcium and vitamin D supplementation in these patients.

The effects of fluoride supplementation in preventing RA-induced bone loss were examined in a randomized control trial in 38 patients (Adachi *et al.*, 1997). Lumbar spine BMD significantly increased in those treated with 40 mg day^{-1} sodium fluoride relative to a placebo after an 18-month intervention. This suggests that fluoride therapy may increase vertebral bone mass in RA patients. A Cochrane review of fluoride supplementation in post-menopausal women found a consistent increase in BMD at the lumbar spine, but the trials did not demonstrate a reduction in vertebral fractures (Haguenauer *et al.*, 2000). Studies in other conditions have raised concerns of possible gastrointestinal complications following fluoride supplementation (Mamelle *et al.*, 1988). However, in the trial in patients with RA no significant differences were found in adverse events between groups (Adachi *et al.*, 1997). Additional trials are required to confirm this result, and to examine whether fluoride reduces fracture rates in patients with RA.

Foods associated with aggravating symptoms

Patients with RA often claim that their symptoms are alleviated by special diets or by simple elimination of certain foods and it has been proposed that food related antigens, predominantly from protein sources, might provoke hypersensitivity responses, which may increase symptoms of RA (Panush, 1991). Controlled studies, involving the exclusion of foods such as red meat, dairy products, cereals and wheat gluten foods have reported inconsistent results, with either improvements (Darlington *et al.*, 1986; Gianfranceschi *et al.*, 1996) or no change (Panush, 1991; Van de Laar & van der Korst, 1992a) in subjective and objective measures of symptoms. To confirm which foods produce symptoms, blind challenge tests with capsules of the alleged food antigen are essential to overcome possible placebo effects (Darlington & Ramsey, 1993). In this situation, many patients who report an improvement in symptoms during elimination diets, do not show any symptom deterioration with a blinded challenge (Panush, 1990).

However, a small number of patients in these studies experienced an alleviation of symptoms on the elimination diet and a recurrence of symptoms in controlled food challenge conditions (Darlington *et al*., 1986; Panush, 1991). In some cases, further exploration of potential antigens, such as dairy products, in these patients, have resulted in immune tests confirming food allergy (Panush, 1991; Van de Laar *et al*., 1992b). No foods or food groups have been consistently identified as a cause, trigger or aggravating factor in studies where RA patients were unselected (Danao-Camara & Shintani, 1999). It is estimated that probably less than 5% of RA patients do have an actual immune sensitivity to specific foods (Panush, 1991; Danao-Camara & Shintani, 1999; Henderson & Panush, 1999), which is similar to the level found in the general population (Department of Health, 2000).

Other possible biological mechanisms for the reported improvement in symptoms from elimination diets include placebo response, suppression of Type I reaction, reduced gastrointestinal permeability and bacterial antigens and secretory IgA deficiency, or weight loss acting either singly or in combination (Darlington & Ramsey, 1993). Further data are required to explore the impact of weight loss in more detail, independent of potential food intolerances.

Elimination diets are usually preceded by a period of fasting, which may confound the reported improvement in symptoms. Fasting is known to suppress inflammation (Danao-Camara & Shintani, 1999). The mechanism by which this operates is not completely understood, but may involve a reduction in the release of pro-inflammatory cytokines, reduced leukotriene formation (Hafstrom *et al*., 1988) and altered intestinal permeability, which may decrease the penetration of immunostimulants from the intestines (Danao-Camara & Shintani, 1999). Four controlled studies have evaluated the effects of following a vegetarian diet for at least 3 months after an initial period of fasting (Lindberg, 1973; Skoldstam *et al*., 1979; Skoldstam, 1986; Kjeldsen-Kragh *et al*., 1991). Pooled results from these early studies implied that eliminating meat from the diet might be useful in the treatment of RA (Kjeldsen-Kragh, 1999; Muller *et al*., 2001). However, it is difficult to determine what aspect of the diet is responsible for the observed effects on RA symptoms. Benefits may be observed either as a consequence of eliminating meat or the inclusion of fruits and vegetables, naturally rich in antioxidants.

Most of these studies have not been rigorously or completely controlled and should not be interpreted as definitive. As confirmed food intolerance affects only a small number of patients with RA and elimination of potential dietary antigens from the diet offers only limited relief of RA symptoms, it is not a practical strategy for managing the symptoms of this disease in all patients with RA. For a very small number of individuals with clinically diagnosed food intolerance, elimination diets may be a feasible therapy, although long-term efficacy and patient adherence is yet to be determined. Such diets must be developed with expert dietetic support in order to preserve the nutritional quality of the diet. Patients with RA should be discouraged from undertaking self-imposed elimination diets, which may compromise nutritional status.

Conclusions

Studies of the effects of dietary habits and nutrient supplementation on RA are hampered by the inherent variability in the clinical course of the disease and the wide spectrum of clinical phenotypes (Ollier *et al*., 2001). Patients frequently self-prescribe complementary medicine including diet modifications. This makes selecting an appropriate group of patients difficult. Improvement in symptoms may be dependent on the severity of the disease and underlying inflammatory status. More randomized long-term studies are needed to provide clear evidence of the impact of nutritional supplements and specific dietary advice for patients with RA.

In trials of dietary change, compliance is difficult to assess. In addition, it is frequently difficult to implement a double-blind protocol to reduce possible placebo effects. The poor scientific methodology of many diet-manipulation studies, particularly elimination diets, currently gives research in this area poor credibility (Kjeldsen-Kragh, 1999).

Given the often poor nutrient status in people with RA, it is important to ensure adequate nutrient intakes. Dietary advice for patients with RA should be focused on achieving current dietary recommendations for the population at large, with a varied balanced diet containing foods rich in anti-oxidants, providing adequate intake of iron, calcium, vitamin D and the B vitamins and boosting n-3 PUFA intake to reduce the severity of RA symptoms and improve overall health.

This review has identified a number of promising areas that warrant further investigation. There is growing scientific evidence for the use of dietary supplements of fish oils as part of the treatment for inflammatory disorders such as RA. Many anti-inflammatory pharmacotherapies are directed at inhibiting the production of inflammatory mediators, cytokines, which are implicated in the late and painfully destructive phase of the disease. Therapies incorporating n-3 PUFA and possibly MUFA may have similar anti-inflammatory effects (James *et al.*, 2000).

Further studies are needed into the potential effects of nutrients in counteracting side-effects of conventional RA treatments, in particular, the effects of folate in patients taking MTX and nutritional strategies to decrease bone loss accompanying corticosteroid therapy.

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References

Aaseth, J. & Teigen, S.W. (1993) *Eighth International Symposium on Trace Elements in Man and Animals – TEMA 8*. Berlin: Verlag Media Touristik.

Abate, A., Yang, G., Dennery, P.A., Oberle, S. & Schroder, H. (2000) Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. *Free Radic Biol. Med.* **29**, 1135–1142.

Adachi, J.D., Bell, M.J., Bensen, W.G., Bianchi, F., Cividino, A., Sebalt, R.J., Gordon, M., Ioannidis, G. & Goldsmith, C. (1997) Flouride therapy in prevention of rheumatoid arthritis induced bone loss. *J. Rheumatol.* **24**, 2308–2313.

Adachi, J.D., Bensen, W.G., Bianchi, F., Cividino, A., Pillersdorf, S., Sebalt, R.J., Tugwell, P., Gordon, M., Steele, M., Webber, C. & Goldsmith, C.H. (1996) Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year follow-up. *J. Rheumatol.* **23**, 995–1000.

Adachi, J.D., Bensen, W.G. & Civicino, A. (1998) Corticosteroid- induced osteoporosis. *JAMWA* **53**, 25–30.

Adachi, J.D. & Ioannidid, G. (1999) Calcium and vitamin D therapy in corticosteroid-induced bone loss: what is the evidence? *Calcif Tissue Int.* **65**, 332–336.

Ariza-Ariza, R., Mestanza-Peralta, M. & Cardiel, M.H. (1998) Omega-3 fatty acids in rheumatoid arthritis: an overview. *Semin Arthritis Rheum* **27**, 366–370.

Barham, J.B., Edens, M.B., Fonteh, A.N., Johnson, M.M., Easter, L. & Chilton, F.H. (2000) Addition of eicosapentaenoic acid to gamma-linoleic acid-supplemented diets prevents serum arachidonic acid accumulation in humans. *J. Nutr.* **130**, 1925–1931.

Belch, J.J.F., Absell, D., Madhok, R., O'Down, A. & Sturrock, R.D. (1988) Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann. Rheum. Dis.* **47**, 96–104.

Belch, J.J.F. & Muir, A. (1998) n-6 and n-3 Essential fatty acids in rheumatoid arthritis and other rheumatic conditions. *Proc. Nutr. Soc.* **57**, 563–569.

British Nutrition Foundation (1999) *Briefing Paper: n-3 Fatty Acids and Health.* London: British Nutrition Foundation.

Brown, K.M. & Arthur, J.R. (2001) Selenium, selenoproteins and human health: a review. *Public Health Nutr.* **4**, 593–599.

Brzeski, M., Madhok, R. & Capell, H.A. (1991) Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *Br. J. Rheum.* **30**, 370–372.

Buckley, L.M., Leib, E.S., Cartularo, K.S., Vacek, P.M. & Cooper, S.M. (1996) Calcium and vitamin D_3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **125**, 961–968.

Calder, P.C. & Zurier, R.B. (2001) Polyunsaturated fatty acids and rheumatoid arthritis. *Curr. Opin. Clin. Nutr. Metab. Care* **4**, 115–121.

Danao-Camara, T.C. & Shintani, T.T. (1999) The dietary treatment of inflammatory arthritis: case reports and review of the literature. *Hawaii Med. J.* **58**, 126–131.

Darlington, L.G. & Ramsey, N.W. (1993) Review of dietary therapy for rheumatoid arthritis. *Br. J. Rheum.* **32**, 507–514.

Darlington, L.G., Ramsey, N.W. & Mansfield, J.R. (1986) Placebo-controlled, blind study of dietary manipulation therapy in rheumatoid arthritis. *Lancet* **i**, 236–238.

Darlington, L.G. & Stone, T.W. (2001) Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. *Br. J. Nutr.* **85**, 251–269.

Department of Health (2000) *Adverse Reactions to Food and Food Ingredients. A Report from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT).* London: The Stationery Office.

Dijkmans, B.A.C. (1995) Folate supplementation and methotrexate. *Br. J. Rheum.* **34**, 1172–1174.

Edmonds, S.E., Winyard, P.G., Guo, R., Kidd, B., Merry, P., Langrish-Smith, A., Hansen, C., Ramm, S. & Blake, D.R. (1997) Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo controlled double blind trial. *Ann. Rheum. Dis.* **56**, 649–655.

Eldin, A.A., Hamdy, M.A., Shaheen, A.A., Motawi, T.K. & Abd el Gawad, H.M. (1992) Effect of vitamin C administration in modulating some biochemical changes in arthritic rats. *Pharm. Res.* **26**, 357–366.

Fahrer, H., Hoeflin, F., Lauterburg, B.H., Peheim, E., Levy, A. & Vischer, T.L. (1991) Diet and fatty acids: can fish substitute for fish oil? *Clin. Exp. Rheum.* **9**, 403–406.

Fries, J.F., Ramey, D.R. *et al.* (1993) A reevaluation of aspirin therapy in rheumatoid arthritis. *Arch. Intern. Med.* **153**, 2465–2471.

Geusens, P., Wouters, C., Nijs, J., Jiang, Y. & Dequeker, J. (1994) Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. *Arthritis Rheum* **37**, 824–829.

Gianfranceschi, G., Fasani, G. & Speciani, A.F. (1996) Rheumatoid arthritis and the drop in tolerance to foods. *Ann. NY Acad. Sci.* **78**, 379–381.

Giordano, N., Floravanti, A., Sancasciani, S., Marcolongo, R. & Borghi, C. (1984) Increased storage of iron and anaemia in rheumatoid arthritis: usefulness deferioxamine. *Br. Med. J.* **289**, 961–962.

Grimble, R.F. (1998) Modification of inflammatory aspects of immune function by nutrients. *Nutr. Res.* **18**, 1297–1317.

Grimble, R.F. & Tappia, P.S. (1998) Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids. *Z Ernahrungswiss* **37** (Suppl.), 57–65.

Hafstrom, I., Ringertz, B., Gyllenhammar, H., Palmblad, J. & Harms-ringdahl, M. (1988) Effects of fasting on disease activity, neutrophil function, fatty acid composition, and leukotriene biosynthesis in patients with rheumatoid arthritis. *Arthritis Rheum.* **31**, 585–592.

Haguenauer, D., Welch, V., Shea, B., Tugwell, P. & Wells, G. (2000) Fluoride for treating postmenopausal osteoporosis. *Cochrane Database Sys Rev.* **4**, CD002825.

Hansen, T.M., Lerche, A., Kassis, V., Lorenzen, I. & Sondergaard, J. (1983) Treatment of rheumatoid arthritis with prostaglandin E1 precursors cis-linoleic acid and gamma-linolenic acid. *Scand. J. Rheumatol.* **12**, 85–88.

Hansen, G.V.O., Nielsen, L., Kluger, E., Thysen, M., Emmertsen, H., Stengaard-Pedersen, K., Hansen, E.L., Unger, B. & Andersen, P.W. (1996) Nutritional status of Danish rheumatoid arthritis patients and effects of a diet adjusted in energy intake, fish-meal, and antioxidants. *Scand. J. Rheumatol.* **25**, 325–330.

Heinle, K., Adam, A., Gradl, M., Wiseman, M., & Adam, O. (1997) Selenium concentration in erythrocytes of patients with rheumatoid arthritis. Clinical and laboratory chemistry infection markers during administration of selenium. *Med. Klin.* **92** (Suppl.), 29–31.

Helliwell, M., Coombes, E.J., Moody, B.J., Batstone, G.F. & Robertson, J.C. (1984) Nutritional status in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **43**, 386–390.

Henderson, C.J. & Panush, R.S. (1999) Diets, dietary supplements, and nutritional therapies in rheumatic diseases. *Rheum. Dis. Clin. N. Am.* **25**, 937–968.

Hinds, A. & Sanders, T.A. (1993) The effect of increasing levels of dietary fish oil rich in eicosapentaenoic and docosahexaenoic acids on lymphocyte phospholipid fatty acid composition and cell-mediated immunity in the mouse. *Br. J. Nutr.* **69**, 423–429.

Honkanen, V., Konttinen, Y.T., Sorsa, T., Hukkanen, M., Kemppinen, P., Santavirta, S., Saari, H. & Westermarck, T. (1991) Serum zinc, copper and selenium in rheumatoid arthritis. *J. Elem. Electr. Health Dis.* **5**, 261–263.

James, M.J., Gibson, R.A. & Cleland, L.G. (2000) Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am. J. Clin. Nutr.* **71** (Suppl.), 343S–348S.

Jantti, J., Nikkari, T., Solakivi, T., Vapaatalo, H. & Isomaki, H. (1989) Evening primrose oil in rheumatoid arthritis: changes in serum lipids and fatty acids. *Ann. Rheum. Dis.* **48**, 124–127.

Jantti, J., Vapaatalo, H., Seppala, E., Ruutsalo, H.-M. & Isomaki, H. (1991) Treatment of rheumatoid arthritis with fish oil, selenium, vitamins A and E and placebo. *Scand. J. Rheumatol.* **20**, 225.

Kelley, D.S., Branch, L.B., Love, J.E., Taylor, P.C., Rivera, Y.M. & Iacono, J.M. (1991) Dietary alpha-linolenic acid and immunocompetence in humans. *Am. J. Clin. Nutr.* **53**, 40–46.

Kjeldsen-Kragh, J. (1999) Rheumatoid arthritis treated with vegetarian diets. *Am. J. Clin. Nutr.* **70** (Suppl.), 594S–600S.

Kjeldsen-Kragh, J., Haugen, M., Borchgrevink, C.F., Laerum, E., Eek, M., Mowinkel, P., Hovi, K. & Forre, O. (1991) Controlled trial of fasting and one year vegetarian diet in rheumatoid arthritis. *Lancet* **338**, 899–902.

Kremer, J.M. (2000) n-3 fatty acid supplements in rheumatoid arthritis. *Am. J. Clin. Nutr.* **71** (Suppl.), 349S–351S.

Kremer, J.L., Lawrence, D.A., Jubiz, W., DiGiacomo, R., Rynes, R., Bartholomew, L.E. & Sherman, M. (1990) Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. Clinical and immunological effects. *Arthritis Rheum* **33**, 810–820.

La Vecchia, C., Decarli, A. & Pagano, R. (1998) Vegetable consumption and risk of chronic disease. *Epidemiology* **9**, 208–210.

Lau, C.S., Morley, K.D. & Belch, J.J.F. (1993) Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis – a double-blind placebo controlled study. *Br. J. Rheumatol.* **32**, 982–989.

Leventhal, L.J., Boyce, E.G. & Zurier, R.B. (1993) Treatment of rheumatoid arthritis with gamma-linolenic acid. *Ann. Intern. Med.* **119**, 867–873.

Lindberg, E. (1973) Konnen Ernahrungsfaktoren die chronische Polyarthritis beeinflussen? *Z Fur Physiotherapie* **25**, 119–129.

Linos, A., Kaklamani, V.G., Kaklamani, E., Koumantaki, Y., Giziaki, E., Papazoglou, S. & Mantzoros, C.S. (1999) Dietary factors in relation to rheumatoid arthritis: a role for olive oil and cooked vegetables? *Am. J. Clin. Nutr.* **70**, 1077–1082.

Linos, A., Kaklamanis, E., Kontomerkos, A., Koumantaki, Y., Gazi, S., Vaiopoulos, G., Tsokos, G.C. & Kaklamanis, P.H. (1991) The effect of olive oil and fish consumption on rheumatoid arthritis – a case control study. *Scand. J. Rheumatol.* **20**, 419–426.

Mamelle, N., Meunier, P.J., Dusan, R., Guillaume, M., Martin, J.L., Gaucher, A., Prost, A., Zeigler, G. & Netter, P. (1988) Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* **13**, 361–365.

Mangge, H., Hermann, J. & Schauenstein, K. (1999) Diet and rheumatoid arthritis – a review. *Scand. J. Rheumatol.* **28**, 201–209.

Mantzioris, W., Cleland, L.G., Gibson, R.A., Neumann, M.A., Demasi, M. & James, M.J. (2000) Biochemical effects of a diet containing foods enriched with n-3 fatty acids. *Am. J. Clin. Nutr.* **72**, 42–48.

Marcus, R.E. (1987) Treatment of rheumatoid arthritis with deferoxamine: Pilot study. *Arthritis Rheum.* **30**, 595.

Martin, R.H. (1998) The role of nutrition in rheumatoid arthritis. *Proc. Nutr. Soc.* **57**, 231–234.

McCarty, M.F. & Russell, A.L. (1999) Niacinamide therapy for osteoarthritis – does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes? *Med. Hypotheses* **53**, 350–360.

Miehle, W. (1997) Vitamin E in active arthroses and chronic polyarthritis. What is the value of alpha-tocopherol in therapy? *Fortschr. Med.* **115**, 39–42.

Milanino, R., Frigo, A., Bambara, L.M., Marrella, M., Moretti, U., Pasqualicchio, M., Biasi, D., Gasperini, R., Mainenti, L. & Velo, G.P. (1993) Copper and zinc status in rheumatoid arthritis: studies of plasma, erythrocytes and urine and their relationship to disease markers and pharmacological treament. *Clin. Exp. Rheumatol.* **11**, 271–281.

Morgan, S.L., Anderson, A.M., Hood, S.M., Matthews, P.A., Lee, J.Y. & Alarcon, S. (1997) Nutrient intake patterns, body mass index, and vitamin levels in patients with rheumatoid arthritis. *Arthritis Care Res.* **10**, 9–17.

Morgan, S.L., Baggott, J.E., Vaughn, W.H., Austin, J.S., Veitch, T.A., Lee, J.Y., Koopman, W.J., Krumdiek, C.L. & Alarcon, G.S. (1994) Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. *Ann. Intern. Med.* **121**, 833–41.

Muller, H., Wilhelmi de Toledo, F. & Resch, K.-L. (2001) Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. *Scand. J. Rheumatol.* **30**, 1–10.

Ollier, W.E.R., Harrison, B. & Symmons, D. (2001) What is the natural history of rheumatoid arthritis? *Best Pract. Res. Clin. Rheumatol.* **15**, 27–48.

Ortiz, Z., Shea, B., Suarez, A.M., Moher, D., Wells, G. & Tugwell, P. (2001) *Folic and Folinic Acid for Reducing Side Effects of Patients Receiving Methotrexate for Rheumatoid Arthritis (Cochrane Review).* Oxford: The Cochrane Library. Update Software. 2.

Panush, R.S. (1990) Food induced ('allergic') arthritis: Clinical and serological studies. *J. Rheumatol.* **17**, 291–294.

Panush, R.S. (1991) Does food cause or cure arthritis? *Rheumatic Dis. Clin. N. Am.* **17**, 259–272.

Peretz, A., Neve, J., Duchateau, J. & Famaey, J.P. (1992) Adjuvant treatment of recent onset rheumatoid arthritis by selenium supplementation: preliminary observations. *Br. J. Rheumatol.* **31**, 281–282.

Petersson, I., Majberger, E., Palm, S. & Larsen, A. (1991) Treatment of rheumatoid arthritis with selenium and vitamin E. *Scand. J. Rheumatol.* **20**, 218.

Pullman-Mooar, S., Laposata, M., Lem, D., Holman, R.T., Leventhal, L.J., DeMarco, D. & Zurier, R. (1990) Alteration of the cellular fatty acid profile and the production of eicosanoids in human lymphocytes by gamma-linolenic acid. *Arthritis Rheum.* **33**, 1526–1533.

Punnonen, K., Kaipiainen-Sepranen, O., Riittinen, L., Tuomisto, T., Hongisto, T. & Penttila, L. (2000) Evaluation of iron stores in anemic patients with rheumatoid arthritis using an automated immunoturbidimetric assay for transferrin receptor. *Clin. Chem Lab. Med.* **12**, 1297–1300.

Reid, I.R., Veale, A.G. & France, J.T. (1994) Glucocorticoid osteoporosis. *J. Asthma* **31**, 7–18.

Roubenoff, R., Dellaripa, P., Nadeau, M.R., Abad, L.W., Muldoon, B.A., Selhub, J. & Rosenberg, I.H. (1997) Abnormal homocysteine metabolism in rheumatoid arthritis. *Arthritis Rheum.* **40**, 718–722.

Roubenoff, R., Roubenoff, R.A., Cannon, J.G., Freeman, L.M., Dinarello, C.A. & Rosenberg, I.H. (1994) Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *J. Clin. Invest.* **93**, 2379–2386.

Roubenoff, R., Roubenoff, R.A., Selhub, J., Nadeau, M.R., Cannon, J.G., Freeman, L.M., Dinarello, C.A. & Rosenberg, I.H. (1995) Abnormal vitamin B6 status in rheumatoid cachexia. Association with spontaneous tumor necrosis factor alpha production and markers of inflammation. *Arthritis Rheum.* **38**, 105–109.

Sakai, A., Hirano, T., Okazaki, R., Okimoto, N., Tanaka, K. & Nakamura, T. (1999) Large-dose ascorbic acid

administration suppresses the development or arthritis in adjuvant-infected rats. *Arch. Orthop Trauma Surg.* **119**, 121–126.

Sarzi-Puttini. P., Comi, D., Boccassini, L., Muzzupappa, S., Turiel, M., Panni, B., & Salvaggio, A. (2000) Diet therapy for rheumatoid arthritis. A controlled double-blind study of two different dietary regimens. *Scand. J. Rheumatol.* **29**, 302–307.

Shapiro, J.A., Koepsell, T.D., Voigt, L.F., Dugowson, C.E., Kestin, M. & Nelson, J.L. (1996) Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. *Epidemiology* **7**, 256–263.

Simopoulos, A.P. (1991) Omega-3 fatty acids in health and disease and in growth and development. *Am. J. Clin. Nutr.* **54**, 438–463.

Simopoulos, A.P. (1999) Essential fatty acids in health and chronic disease. *Am. J. Clin. Nutr.* **70** (**3** Suppl.), 560S–569S.

Skoldstam, L. (1986) Fasting and vegan diet in rheumatoid arthritis. *Scand. J. Rheumatol.* **15**, 219–221.

Skoldstam, L., Borjesson, O., Kjallman, A., Seiving, B. & Akesson, B. (1992) Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. *Scand. J. Rheumatol.* **21**, 178–185.

Skoldstam, L., Larsson, L. & Lindstrom, F.D. (1979) Effect of fasting and lactovegetarian diet on rheumatoid arthritis. *Scand. J. Rheumatol.* **8**, 249–255.

Stone, J., Doube, A., Dudson, D. & Wallace, J. (1997) Inadequate calcium, folic acid, vitamin E, zinc, and selenium intake in rheumatoid arthritis patients: results of a dietary survey. *Semin. Arthritis Rheum.* **27**, 180–185.

Svenson, K.L.G., Hallgren, R. & Johansson, E. (1985) Reduced zinc in peripheral blood cells from patients with inflammatory connective tissue diseases. *Inflammation* **9**, 189–199.

Tarp, U. (1995) Selenium in rheumatoid arthritis. *A Rev. Anal* **120**, 877–881.

Tarp, U., Graudal, H., Overvad, K., Thorling, E.B. & Hansen, J.C. (1989) Selenium in rheumatoid arthritis. A historical prospective approach. *J. Trace Elem. Electrolytes Health Dis.* **3**, 93–95.

Tarp, U., Overvad, K., Thorling, E.B., Graudal, H. & Hansen, J.C. (1985) Selenium treatment in rheumatoid arthritis. *Scand. J. Rheum.* **14**, 364–368.

Thies, F., Nebe-von-Caron, G., Powell, J.R., Yaqoob, P., Newsholme, E.A. & Calder, P.C. (2001) Dietary supplementation with gamma-linolenic acid or fish oil decreases T lymphocyte proliferation in healthy older humans. *J. Nutr.* **131**, 1918–1927.

van de Laar, M.A.F.J. & van der Korst, J.K. (1992a) Food intolerance in rheumatoid arthritis. I. A double-blind, controlled trial of the clinical effects of elimination of milk allergens and AZO dyes. *Ann. Rheum Dis* **51**, 303–306.

van de Laar, M., Aalbers, M., Bruins, F., van Dinther-Janssen, A. & Meijer, C. (1992b) Food intolerance in rheumatoid arthritis. II. Clinical and histological aspects. *Ann. Rheum. Dis.* **51**, 303–306.

Volker, D., Fitzgerald, P., Major, G. & Garg, M. (2000) Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *J. Rheumatol.* **27**, 2343–2346.

Watson, J., Byars, M.L., McGill, P. & Kelman, A.W. (1993) Cytokine and prostaglandin production by monocytes of volunteers and rheumatoid arthritis patients treated with dietary supplements of blackcurrant seed oil. *Br. J. Rheumatol.* **32**, 1055–1058.

Whiteman, M. & Halliwell, B. (1996) Protection against peroxynitrite-dependent tyrosine nitration and alpha 1-antiproteinase inactivation by ascorbic acid. A comparison with other biological antioxidants. *Free Radic Res.* **25**, 275–283.

Wittenborg, A., Paetersen, G., Lorkowski, G. & Brabant, T. (1998) Effectiveness of vitamin E in comparison with diclofenac sodium in treatment of patients with chronic polyarthritis. *J. Rheumatol.* **57**, 215–221.