Diet therapy for the patient with rheumatoid arthritis?

In spite of the great advances that have been made in the development of new drugs for the treatment of rheumatoid arthritis (RA), many patients are interested in alternative treatments like dietary therapy. Although relatively few studies have been carried out on the possible impact of dietary therapy on disease activity in RA, interest in this matter is growing as our understanding of disease pathology and the effect of nutrients on immunity and inflammation increases.

Most clinical dietary therapy studies undertaken so far have focused on some form of dietary elimination. Scandinavian health farms have long promoted fasting and vegetarian diets for patients with rheumatic diseases. In 1979 and 1983, Sköldstam et al. [1, 2] carried out two studies to verify whether diet therapy could alleviate disease activity and symptoms in patients with RA. In one study, 16 RA patients fasted for 7–10 days and followed a lactovegetarian diet for the subsequent 9 weeks. There was a significant improvement in both objective and subjective disease symptoms during the fasting period, followed by rapid deterioration when the patients began on the lactovegetarian diet.

In the second study, 20 patients with RA completed a 7- to 10-day fast, followed by 3 months on a vegan diet (a diet without meat, fish or dairy products). Physician’s general assessment revealed that 11 patients had undergone subjective improvement, seven were unchanged and two were worse after the study period than before. Nineteen patients had lost weight and no improvement was seen in objective variables like erythrocyte sedimentation rate (ESR) and C-reactive protein during the dietary period. However, 5 (25%) of the patients showed both objective and subjective improvement. Several patients complained about the diet and only two patients had continued with a strict vegetarian diet after the study period. This confirms that many patients experience difficulty in implementing strict dietary changes.

In 1983, Panush et al. [3] conducted a study of the then popular Dong diet (which eliminated dairy products, red meat, citrus fruits, tomatoes, alcohol and coffee). This was an elegantly performed clinical dietary study with a double-blind, placebo-controlled design. Twenty-six patients took part, 11 on the experimental diet and 15 on a control diet. Although there was no statistical difference between the experimental and placebo diet groups, two patients in the experimental group improved noticeably. One patient experienced disease exacerbation after eating dairy products and the other after eating meat, spices and alcoholic beverages.

In 1986, Darlington et al. [4] published the results of a single-blinded, placebo-controlled study of 6 weeks of dietary manipulation in 53 patients with RA. During the first week, the patients were only allowed to eat foods they were unlikely to be intolerant to. In the article, it is not stated which food items these were. Other food items were then reintroduced one at a time to see whether any symptoms were elicited by the dietary challenge. Foods producing symptoms were then excluded from the diet. Both objective and subjective variables improved significantly, and a subgroup of 33 patients were graded as good responders. However, the patients were only observed for 6 weeks, which is a weakness in a study undertaken on patients with a chronic disease.

In 1991, we published the results of a single-blinded controlled clinical trial testing the effect on disease activity in patients with RA of dietary elimination combined with the vegetarian diet traditionally practised on Scandinavian health farms [5]. Fifty-seven patients took part in the study, 27 in the diet group and 26 in the control group. The patients were followed for 13 months, making this by far the most comprehensive study undertaken with regard to dietary therapy in RA.

We found statistically significant improvement in both objective and subjective disease variables in the diet group compared with the control group. Twelve patients (44%) in the diet group were responders, according to the Paulus criteria, compared with 2 (8%) in the control group [6]. Ten patients (37%) in the diet group reported aggravation of symptoms after reintake of one or more food items. Eight of these belonged to the responder group.

After 2 yr, we conducted a follow-up study on the same patients and found that the responders had continued with the diet and still had a significant reduction in all clinical disease variables and ESR [7]. In this study, 13 patients (59%) in the diet group reported an increase in disease symptoms after intake of meat, and 10 patients (45%) after intake of sugar and coffee. Of the 10 responders examined in the follow-up study, eight reported an increase in disease symptoms after intake of different kinds of meat, and six after intake of coffee, sweets and refined sugar.

Fasting has been documented to have beneficial effects on both clinical and laboratory variables reflecting disease activity in RA [1, 5, 8]. It thus serves as a useful model for studying the biological changes associated with simultaneous improvement in disease activity. Previous studies in healthy subjects have revealed that fasting decreases mitogen- and antigen-induced lymphocyte proliferative responses [9], and suppresses interleukin-2 (IL-2) production [10]. We have recently shown that a 7 day fast in RA patients also decreases CD4+ lymphocyte activation and numbers, suggesting transient immunosuppression [11]. We also found an

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increase in IL-4 production from mitogen-stimulated peripheral blood cells. Thus, further studies should be carried out to clarify the immunomodulatory mechanism behind fasting.

Evidence suggesting that food allergy, defined as an immunological response to food antigens or to intestinal bacterial flora, might be involved in disease pathology in most patients with RA is weak. However, it is possible that an exogenous agent like a food antigen can initiate a pathological immune process in a genetically susceptible individual [12].

Food antigens, food antibodies and their complexes have been detected in the systemic circulation of healthy subjects [13, 14]. Animal models indicate that the gut is an important trigger of and pathway for the immune response. Encounters with complex proteins, like gluten and milk proteins, lead to either oral tolerance or sensitization and possible loss of self-tolerance to cross-reacting epitopes [15].

An association between a special food item and disease activity has been reported by patients with a variety of rheumatic diseases, such as palindromic rheumatism [16, 17], systemic lupus erythematosus [18, 19], Sjögren’s syndrome [20] and juvenile RA (JRA) [21, 22]. Case reports describing an association between diet and disease activity in RA include both seropositive and seronegative disease [23–25]. Although the extent of food allergy involvement is still not known, it has been suggested that between 5 and 30% of patients with RA may be affected [26, 27].

We found an increase in humoral response in all patients with RA, with a general increase in IgG, IgA and IgM antibodies to various food antigens, like gluten and milk proteins. However, the elevated concentrations of specific immunoglobulins could not be used to predict which food items would aggravate the disease symptoms [28].

Wheat and other rough grain products can elicit an allergic T-cell response through their lectin structures. Lectins are glycoprotein molecules that bind to carbohydrate-specific receptors on lymphocytes with high affinity and thus elicit a significant immune response. Lentils and grain products have a particularly high lectin content. Lectins are fairly heat resistant; for example, lentils have to be cooked for a long time to inactivate the lectins.

While the results of a questionnaire-based survey revealed that 37–43% of patients with rheumatic diseases experienced an increase in disease symptoms after intake of certain food items, no difference could be found between the various diseases [29]. This suggests that diet may influence the inflammatory process in general and is not a specific feature of RA.

One of the mechanisms involved may be the release or secretion of vasoactive amines (bioactive amines) like histamine and serotonin [30]. Several of the food items reported to cause disease aggravation have a high histamine content, like pork and beef sausage, meat, tomato and spinach. Since no immunological response to pork and other meat has been demonstrated, a pharmacological response would explain the often reported increase in symptoms resulting from these foods [31]. Other foods like shellfish, strawberries, chocolate and fish can cause a release of histamine.

Citrus fruits, which contain other vasoactive amines (octopamine and phenylephrine), are often said to aggravate symptoms [30]. Consumption of both coffee and alcohol has been shown to liberate adrenaline and/or noradrenaline, which suggests that they have a pharmacological effect [30, 32]. Consumption of alcohol can also result in the release of histamine, and certain red wines have in addition a high concentration of histamine, which may explain the frequently reported intolerance.

A pharmacological reaction would also explain why the patients reported immediate reactions to these food items, as opposed to the more delayed reactions to dairy products and gluten. This may mean that a different mechanism is involved in symptom aggravation. The reported aggravation of symptoms after intake of refined sugar and sweets in patients with RA may have a metabolic explanation, such as an increased concentration of blood glucose due to impaired glucose handling [33–35].

Gut involvement in the pathogenesis of rheumatic diseases was proposed by Rea Smith [36], who reported that surgical removal of intestinal segments with focal infection had a beneficial effect on disease activity. Monroe and Hall [37] reported differences in the stools of 142 patients with chronic arthritis as compared with controls. Månsson and Olhagen [38] found not only an abnormal faecal flora, with an increase in Clostridium perfringens in patients with RA, systemic lupus erythematosus and psoriatic arthropathies compared with healthy controls, but also a higher level of alpha-antitoxin in the serum of these patients. Alpha-toxin (phospholipase-C) is produced by a special strain of C. perfringens often found in RA patients. Månsson and Olhagen [38] found a rise in alpha-antitoxin titre in 75% of the patients with RA in the study, but in none of the controls.

A significantly higher carriage rate of C. perfringens in patients with RA than in healthy controls has also been documented by Shinebaum et al. [39]. An altered intestinal bacterial flora has been reported in patients with seropositive erosive RA compared with patients with seronegative RA and controls [40]. An increased concentration of antibodies to Proteus has been described in patients with active RA [41, 42] and to Klebsiella in patients with ankylosing spondylitis [43]. Several of these reports have suggested that RA and ankylosing spondylitis could be mediated by cross-reactivity between self and bacterial antigens.

The intestinal bacterial flora is known to be affected by diet [44–46], and it has been suggested that a diet which could alter the intestinal flora might have an effect on disease activity. This theory was supported by the finding that changes in disease activity correlated with alterations in the intestinal flora measured in patients who switched from an omnivorous to a vege-
tarian diet [47]. The effects of the intake of functional foods (i.e., food as medicine; in this case, food which promotes the growth of health-promoting bacteria in the intestine or food items that contain natural healthy intestinal bacteria) should be an interesting field for further research.

Much interest has been taken in recent years in the immunomodulatory effects of polyunsaturated fatty acids (PUFAs) and their therapeutic potential as anti-inflammatory agents [48]. Both clinical and in vitro studies have established that long-chain n-3 and n-6 fatty acids inhibit T-lymphocyte function [49–52]. Research suggests that manipulating the balance of dietary fatty acids in favour of increased n-3 fatty acids and decreased n-6 fatty acids may have a beneficial effect on disease activity in RA [49, 53–56]. These studies have shown that long-chain n-3 fatty acids can diminish peripheral blood mononuclear cell proliferation and reduce the production of IL-1, IL-2, IL-6, tumour necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). However, clinical studies on supplementation of n-3 fatty acids have not supported the expectations raised by the laboratory findings [53–57].

The balance between unsaturated and saturated fatty acids may also affect lymphocyte proliferation (in vitro) [58]. The practical implications of these observations for the in vivo situation are currently unclear, but suggest that a diet which is high in unsaturated fatty acids and very low in saturated fatty acids may have a stronger immunosuppressive effect than that obtained by only n-3 fatty acid supplementation.

In this respect, the Mediterranean diet, with a low content of red meat and a high content of olive oil, is of interest. Olive oil has been shown to reduce lymphocyte proliferation, natural killer cell activity, adhesion molecule expression on lymphocytes and the production of pro-inflammatory cytokines in animal models [59]. In an intervention study in which dietary saturated fatty acids were partly replaced by olive oil, mononuclear cell expression of ICAM-1 was found to be significantly reduced [60].

It has also been reported that a very low intake of saturated fats is beneficial in multiple sclerosis, where, as in RA, CD4+ lymphocytes are thought to play a pathogenic role [61]. It is thus worth investigating whether a diet low in saturated fats, with a high content of olive oil and with n-3 supplementation, could have immunosuppressive effects in vivo and could thus be of benefit in the treatment of RA.

The pathological hallmark of RA is persistent destructive inflammation in the synovial membranes of joints, which leads to a gradual destruction of the supporting structures of the joints, such as bone and cartilage. Although the aetiology is still unknown, the inflammation resulting from the immunological reaction is quite well described. It is known that neutrophil granulocytes, macrophages and lymphocytes are activated, and that oxygen free radicals are produced [62]. Hence, a low concentration of antioxidants may perpetuate tissue destruction in RA. Free oxygen radicals and oxidative stress may also be of importance for the aetiology and chronicity of the inflammatory rheumatic diseases [63, 64]. Two epidemiological studies have recently suggested that antioxidants may play a protective role [65, 66].

The most important antioxidants known today are vitamin A, vitamin E, vitamin C, beta-carotene, the bioflavonoids, zinc and selenium. The antioxidant properties of vitamin A and vitamin E lead to a reduction in the oxidation catalysed by free radicals [67]. Vitamin E functions as a physiological antioxidant for the cell membrane and is the most important fat-soluble antioxidant in the cell membrane lipids [64, 68]. Zinc plays a significant role in antioxidant protection and immunity because it is a constituent of the cytoplasmic enzyme superoxide dismutase [69]. Selenium, on the other hand, is part of the glutathione peroxidase enzyme, which can react with peroxides formed during inflammation. Beta-carotene is a fat-soluble, chain-breaking antioxidant and a quencher of singlet oxygen, and is known, along with alpha-tocopherol, to be the most important element of the non-enzymatic antioxidant defence in biological systems [70, 71].

Low serum concentrations of selenium and zinc in RA patients were reported as early as 1978 [72] and were further investigated by Tarp et al. [73–75]. Mezes and Bartosiewicz [63] found reduced plasma vitamin A content in patients with RA. Honkanen et al. [76] found lower serum levels of vitamin A and E in patients than in healthy controls. Sklodowska et al. [64] found lower vitamin E concentrations in plasma in children with JRA than in controls. Studies have also shown reduced concentrations of zinc and selenium in children with JRA [77, 78].

The reduced serum concentrations of antioxidants found in patients with inflammatory rheumatic diseases do not appear to be a consequence of reduced dietary intake in these patient groups compared with healthy controls [78–80]. They may, therefore, indicate a high turnover of antioxidants and an increased antioxidant requirement in these patients which is necessary in order to balance the higher production of free radicals.

Although studies of supplementation with a single antioxidant have not shown disease reduction in RA patients, it is still possible that patients with an inflammatory rheumatic disease will benefit from supplementation with a combination of several antioxidants or from a dietary intake that exceeds the recommended dietary allowances.

Studies of immunomodulation have revealed that nutrients other than food proteins and fats also have an impact. The effects of fatty acids, antioxidants and food proteins on immunomodulation need to be investigated further, and so should the question of the involvement of the gut in the aetiology and pathology of rheumatic diseases. More knowledge on the effects of dietary components upon immunological function is necessary.
if the potential use of dietary therapy as a tool in the treatment of RA is to be adequately assessed.

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