

# Dietary recommendations for patients with rheumatoid arthritis: a review

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**Abstract:** Dietary interventions can assist with the management of disease symptoms that accompany rheumatoid arthritis (RA), such as pain, tender swollen joints, stiffness, and associated disability and disease progression. Dietary interventions have gained widespread appeal for both clinicians and RA patients. Interventions that promote self-help through education can have significant benefits for patients as they negotiate pain and musculoskeletal disability. There is substantial scientific evidence that demonstrates patients diagnosed with RA may benefit from dietary interventions; however, recent systematic reviews remain uncertain about the therapeutic efficacy of dietary manipulation for RA due to clinical trials with a high risk of bias. However, dietary interventions with plausible therapeutic activity may be indicated for reducing RA-associated symptoms, including elimination of foods that may trigger an allergic or intolerant response, introduction of known anti-inflammatory dietary compounds and correction of food, or drug-induced gastrointestinal tract microbiota abnormalities and permeability.

**Keywords:** diet, rheumatoid arthritis, vegetarian, vegan, Mediterranean, fish oils, probiotics

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune, inflammatory disease with unclear pathophysiology processes. RA may be multiple diseases, currently defined by some common clinical manifestations, and there may not be a single predominant mechanism of initiation or perpetuation.<sup>1</sup> The current view is that inflammation and tissue destruction in the rheumatoid synovium results from complex cell–cell interactions, initiated by antigen-presenting cells and CD4<sup>+</sup> T cells.<sup>1</sup> This is followed by macrophage activation and the release of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) that stimulate synovial fibroblasts and chondrocytes in articular cartilage to secrete enzymes that degrade proteoglycans and collagen, leading to tissue destruction.<sup>1</sup> Autoimmunity and the overall systemic and articular inflammatory load drive the destructive progression of the disease.<sup>2</sup> RA is characterized by joint pain, tenderness, stiffness and swelling, rheumatoid nodules, and destruction of synovial joints, leading to severe disability, reduced quality of life, and premature mortality.<sup>2</sup> Serology is positive for such autoantibodies as rheumatoid factor and anticitrullinated protein antibody, which can precede the clinical manifestation of RA by many years.<sup>2</sup>

Furthermore, rheumatic conditions including RA are associated with an increased prevalence of gastrointestinal tract (GIT) symptoms, particularly dyspepsia (epigastric pain and burning, postprandial fullness, bloating, early satiety, nausea, and belching<sup>3</sup>), mucosal ulceration, and altered bowel habits (constipation/diarrhoea),

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which are associated with reduced quality of life.<sup>4,5</sup> With much interest, evidence has been reported that patients with RA have significant modification of the intestinal microbiota that differs from that of healthy control patients.<sup>6-8</sup> RA patients demonstrate significantly less *Bifidobacterium* species and bacteria of the *Bacteroides-Porphyromonas-Prevotella* group, and a decrease in lactobacteria with various reports of high and low *Clostridium* species. The abundance of opportunistic enterobacteria and staphylococci were also noted to be elevated. Research is now exploring the hypothesis that intestinal microbiota may participate in the aetiopathogenesis of RA.<sup>7,8</sup>

Current research is highlighting the need to define subsets of RA by genetic or serologic markers to enable more concise treatment options for patients. Understanding the multiple predisposing or protective genetic factors provides hope for a new direction,<sup>1</sup> and genetic interaction with GIT microbiota may be the key in developing new treatments or preventive measures based on modulation of the GIT microbiota. The host genotype may guide both the composition of GIT microbiota and immune responses against microbes, and in individuals susceptible for RA, the arthritogenic bacterial antigens may pass from intestines to the joints, causing prolonged immunological response and articular inflammation.<sup>7</sup>

For decades, dietary manipulation has been used by patients diagnosed with RA, in the hope that it may improve their symptoms.<sup>9</sup> Dietary manipulation is still widely used today. There are various commonly used dietary programs utilized for treating RA, such as medically supervised fasting (7–10 days) followed by a vegetarian or vegan diet, vegetarian and Mediterranean diets, elemental diet plans, and elimination diets that are thought to possibly prevent the autoimmune response associated with the pathophysiological process of the disease. A vegetarian eating plan may be varied, as it can be either strictly a vegan diet or a lacto-ovo-vegetarian diet, which allows consumption of dairy products and eggs. The mechanisms of action that dietary manipulation may provide to produce health benefits may result in the rescuing of a potentially dysbiotic GIT that is distorted by sustained proinflammatory metabolites. Plant-based and elimination diets may reregulate the inflammatory process by inducing a more balanced GIT microbiota, leading to a downregulation of inflammation locally and systematically.<sup>10</sup> The effector mechanism may involve a consequent change in the profile of the GIT microbiota that subsequently elaborate secondary metabolites from such diets, which may be seen as beneficial for the host. Vegetarian, vegan, and Mediterranean-type

diets are high in such dietary compounds as those found in vegetables and legumes (eg, phytochemicals, unsaturated fats) which can maintain a regulated anti-inflammatory effect by interacting positively with the GI microbiota, counteracting dysbiosis.<sup>11</sup>

## Methodology

We searched the Cochrane Central Register of Controlled Trials, Medline, EMBASE, AMED, Cinahl, and reference lists of relevant articles up to December 2011. The selection criteria included randomized controlled trials or single- or double-blinded controlled clinical trials where the effectiveness of dietary manipulation was evaluated (Table 1). Dietary supplement studies that included fish oils and probiotics were also included, as the overall aim of this review was to explore the role that diets and functional foods may have in adjusting GIT function and reregulating local inflammatory processes that then could positively influence RA. Studies with individual micronutrients (eg, zinc vitamins) were not included.

## Dietary interventions

### Fasting/vegetarian/vegan diet

Clinical experience suggests that fasting followed by a vegetarian diet may help patients with RA.<sup>11</sup> A 2001 systematic review<sup>12</sup> assessed the available scientific evidence, as patients frequently sought dietary advice, and exclusive pharmacological treatment for RA was often declined due to the side effects the patients may experience. The results of the controlled studies, which reported follow-up data for at least 3 months after fasting, were quantitatively pooled. Thirty-one reports of fasting studies in patients with RA were found. Only four controlled studies investigated the effects of fasting and subsequent diets for at least 3 months. The pooling of these studies showed a statistically and clinically significant beneficial long-term effect. The available evidence tends to suggest that fasting followed by a vegetarian diet may be significantly useful in the treatment of RA pain.<sup>9,11,12</sup>

Once food is reintroduced after fasting, however, most patients with RA present with disease-activity relapses. The effect of a 7–10 day subtotal fast (partial nutrient intake during the fast consisted of herbal teas, garlic, vegetable broth, decoction of potatoes and parsley, and juice extracts from carrots, beets, and celery. No fruit juices were allowed. The daily energy intake during the fast varied between 800 and 1260 kJ) followed by 1 year of a vegetarian diet compared to an ordinary diet was assessed in 53 patients.<sup>13</sup> After 4 weeks of dietary changes, there was a significant improvement in the

Table 1 Dietary and Selected Supplements Clinical Studies and RA

Dietary Recommendation	Study Type [No. Patients]	Duration	Results
Fasting followed by a Vegetarian / Vegan Diet	Systematic Review <sup>12</sup> 4 RCTs  SBRCT <sup>13</sup> [53 RA] 2-year follow-up <sup>14</sup>	7–10 days of fasting followed by an individually adjusted diet. 3.5 mths vegan. 9.0 mths lacto-vegetarian.	→ Fasting followed by vegetarian diets may be useful in the treatment of RA. → Additional studies warranted in order to confirm efficacy.  Test Group → significant improvement after 4 weeks. → ↓ number of tender joints, Ritchie's articular index, number of swollen joints. → ↓ pain score. → ↓ duration of morning stiffness. → ↑ grip strength. → ↓ erythrocyte sedimentation rate; CRP; white blood cell count. → ↑ physical function score. Control Group → only pain score improved. → concluded that compliance with the vegetarian diet was maintained and was efficacious.
Vegan Diet	RCT <sup>15</sup> [26 RA]  RCT <sup>16</sup> [66 RA]  RCT <sup>17</sup> [42 RA] uncooked vegan diet supplemented with fermented wheat drink rich in <i>Lactobacilli</i>	7–10 days of fasting followed by lacto-vegetarian diet.  1 year  2–3 months	Following Fasting → ↑ one-third participants improved objective measures versus control. → ↓ pain, stiffness, consumption of analgesics, Following lacto-vegetarian diet → no significant differences between groups.  → Significantly greater improvement in ACR20 criteria in the vegan group [40.5%] versus non-vegan group [4%] → ↓ IgG antibody levels against gliadin and β-lactoglobulin in the vegan group only.  → Indicators of RA activity did not differ statistically between groups. → Positive subjective effects experienced namely duration of morning stiffness, pain at rest and pain on movement was not discernable. → A composite index showed a higher number of patients with 3–5 improved disease activity measures in the intervention group. → Stepwise ↓ in Disease Activity Scores [DAS28] with <i>lactobacilli</i> -rich and chlorophyll-rich drinks and increased fibre intake.
Mediterranean Diet	RCT <sup>18</sup> [51 RA]	3 months	→ Significant ↓ in DAS28 and Health Assessment Questionnaire scores and QoL. → No significant changes in controls following a regular diet.

(Continued)

Table 1 (Continued)

Dietary recommendation	Study type [no patients]	Duration	Results
	RCT <sup>19</sup> [130 RA]	6 months	→ Women in the intervention group reported a healthier dietary intake and showed significant benefits compared with controls for patient global assessment at 6 months, pain score at 3 and 6 months, early morning stiffness at 6 months and HAQ at 3 months. → The mean DAS28 significantly decreased in both groups with no significant difference between the groups. → VAS showed a consecutive decrease of pain in both study groups that was significantly higher in the fasting group on day 7.
Exclusion Diet	Comparative <sup>20</sup> [50 RA]	7 days fasting followed by reintroduction of foods for 8 days and 13 days Mediterranean diet.	→ Significant objective improvement during periods of dietary therapy compared with periods of placebo treatment. → Explanations for improvement include reduced food intolerance, reduced gastrointestinal permeability, and benefit from weight loss and from altered intake of substrates for prostaglandin production.
	DBRCT <sup>25</sup> [45 RA]	6 weeks of dietary treatment or placebo followed by a further 6 weeks of dietary treatment.	→ Comparison between baseline and subsequent periods showed only subjective improvements. → No differences were seen between the clinical effects of the two tested diets.
	DBRCT <sup>34</sup> [94 RA]	12 weeks intervention consisting of two types of artificial elementary food. One diet was allergen free versus allergen restricted, containing only lactoproteins and yellow dyes.	→ Nine patients (three in the allergen restricted group, six in the allergen free group) showed favourable responses, followed by marked disease exacerbation during re-challenge. • dietary manipulation improved changes in objective disease activity parameters in this sub group of patients. → The existence of a subgroup of patients in whom food intolerance influences the activity of rheumatoid factor seropositive RA deserves serious consideration.
Elemental Diet	Comparative <sup>35</sup> [47 RA]	4 weeks with E028 and foods like chicken, fish, rice, carrots, runner beans, and bananas. The period was followed by reintroduction of food	Elemental diet [E028] improvement some parameters in RA but not sustained by an individualized diet. Significant improvement in the diet group in grip strength and Ritchie score No improvement in ESR, CRP, thermographic joint score or functional score.
	SBRCT <sup>36</sup> [30 RA]	4 weeks of a liquid elemental peptide-diet or continuation of the usual food (control group)	→ Symptom improvement → Transient but statistically significant improvement in the average level of pain, in HAQ-score and a significant reduction in Body Mass Index
	RCT <sup>37</sup> [30 RA]	2 weeks intervention of elemental diet versus prednisolone	→ An elemental diet for 2 weeks resulted: • clinical improvement and was as effective as a course of oral prednisolone 15 mg daily in improving subjective clinical parameters. • study supports the concept that RA may be a reaction to a food antigen(s) and that the disease process starts within the GIT. → significant improvement: • number of tender joints ( $p = 0.04$ ) in the experimental group; • erythrocyte sedimentation rate (ESR) ( $p = 0.03$ ) and in the thrombocyte count ( $p = 0.02$ ) in the controlled group.
	DBRCT-pilot <sup>38</sup> [17]	3 weeks elemental diet intervention versus a control soup	

<p>–results suggest:</p> <ul style="list-style-type: none"> <li>• some RA patients may respond to the elimination of offending food items;</li> <li>• results do not encourage treatment with an elemental diet in unselected RA patients.</li> </ul>		
<p>–by univariate analysis risk of developing RA was inversely and significantly associated only with:</p> <ul style="list-style-type: none"> <li>• cooked vegetables (OR: 0.39)</li> <li>• olive oil (OR: 0.39)</li> </ul>		
<p>→ Study diet adherence demonstrated a significant improvement in the duration of morning stiffness, number of swollen joints, pain status, and reduced cost of medicine, while doctors global assessment, laboratory data, X-ray, and daily activities were unaltered.</p> <p>→ Experimental diet group improved on all the variables considered but only 4 variables (Ritchie's index, tender and swollen joints, and ESR) reached a statistical difference by multivariate analysis.</p> <p>→ Data adjusting for weight variations, the number of tender joints (<math>p = 0.014</math>) and ESR (<math>p = 0.025</math>) remained statistically significant.</p> <p>→ Dietary manipulation, either by modifying food supplements or by reducing weight, may provide some clinical benefit.</p>		
<p>–Statistically significant:</p> <p>→ ↓patient reported joint pain intensity</p> <p>→ ↓minutes of morning stiffness</p> <p>→ ↓number of painful and/or tender joints</p> <p>→ ↓NSAID consumption</p> <p>→ Significant effects were not detected for:</p> <ul style="list-style-type: none"> <li>• physician assessed pain</li> <li>• Ritchie articular index at 3–4 months.</li> </ul> <p>→ The results suggest that omega-3 PUFAs are an attractive adjunctive treatment for joint pain associated with RA, inflammatory bowel disease, and dysmenorrhea.</p>		
<p>→ Fish oil supplementation while taking diclofenac (75 mg twice a day).</p> <p>→ Patients took either 130 mg/kg/day of omega 3 fatty acids or 9 capsules/day of corn oil.</p> <p>→ Patients taking dietary supplements of fish oil exhibited</p> <ul style="list-style-type: none"> <li>• improvements in clinical parameters of disease activity from baseline, including the number of tender joints;</li> <li>• improvements associated with significant ↓ IL-1 beta from baseline;</li> <li>• Some patients who take fish oil are able to discontinue NSAIDs without experiencing a disease flare.</li> </ul> <p>→ Cod liver oil supplements containing n-3 fatty acids demonstrated NSAID-sparing effects in RA patients.</p> <p>→ No differences were observed in clinical parameters of RA disease activity</p> <p>→ No side effects observed.</p>		
<p>–results suggest:</p> <ul style="list-style-type: none"> <li>• some RA patients may respond to the elimination of offending food items;</li> <li>• results do not encourage treatment with an elemental diet in unselected RA patients.</li> </ul>		
<p>–by univariate analysis risk of developing RA was inversely and significantly associated only with:</p> <ul style="list-style-type: none"> <li>• cooked vegetables (OR: 0.39)</li> <li>• olive oil (OR: 0.39)</li> </ul>		

(Continued)

Table 1 (Continued)

Dietary recommendation	Study type [no patients]	Duration	Results
	DBRCT <sup>62</sup> [54 RA, 6 psoriatic arthritis]	12 week duration: 4 groups: Group 1: 3000 mg n-3 LC-PUFA/day Group 2: 3150 mg GLA/day Group 3: 1575 mg n-3 LC-PUFA plus 1800 mg GLA/day Group 4: 3000 mg olive oil	<ul style="list-style-type: none"> <li>→ Supplemented LC-PUFA increased the amount of PUFA in the analysed tissues (plasma lipids, cholesterol esters, erythrocyte membranes) indicating a high bioavailability.</li> <li>→ n-3 LC-PUFA or GLA (3 g/d) resulted in an increased incorporation of the eicosanoid precursor fatty acids (EPA, DHA, DGLA) in plasma lipids and cell membranes</li> <li>→ An improvement in clinical status of patients with RA or psoriatic arthritis was found in n-3 LC-PUFA and GLA (3 g/d) supplemental groups.</li> <li>→ Changes on fatty acid distribution resulted in a reduction of inflammatory eicosanoids from arachidonic acid.</li> <li>→ n-3 LC-PUFA (3 g/d) improved cardiovascular risk factors e.g. AA/EPA ratio and n-3 FA index</li> </ul>
	RCT <sup>63</sup> [19 RA]	Patients were treated with methotrexate, hydroxychloroquine and sulphasalazine. In addition they were randomized to either: Group 1: Fish oil (EPA 2.7 g, DHA 1.8 g/day) Group 2: Fish oil (EPA 270 mg, DHA 180 mg/day). After avoidance of NSAIDs for 10 days and paracetamol for 24 hr, 1 g paracetamol was given. Bloods taken 0 hr, 1 hr.	<ul style="list-style-type: none"> <li>→ No time duration of treatment and intervention with fish oils were given before paracetamol blood sampling was conducted.</li> <li>→ Blood analysis of EPA was conducted on base line bloods and patients were divided into High EPA or Low EPA groups.</li> <li>→ The suppression of eicosanoid measures of COX-1 and COX-2 activity was greater in the High EPA group after paracetamol administration.</li> <li>→ It was found that the combination of paracetamol and high fish oil intake should be the first line treatment over NSAIDs for symptom relief of RA or OA.</li> </ul>
	DBRCT <sup>64</sup> [60 RA = 35 completed]	24 weeks duration Group 1: Diet low in n-6 FAs plus n-3 FA supplement (fish oils) Group 2: Diet low in n-6 FAs plus placebo Group 3: Control group with no special diet or intervention	<ul style="list-style-type: none"> <li>→ At week 18, the fish oil group compared to baseline had: <ul style="list-style-type: none"> <li>• significant ↓ in linoleic acid, CRP and sTNF-p55</li> <li>• significant ↑ in EPA and DHA</li> </ul> </li> <li>→ At week 24, the fish oil and placebo groups had significant reductions in: <ul style="list-style-type: none"> <li>• Interleukin-6</li> <li>• TNF-alpha</li> </ul> </li> <li>→ A low n-6 FA diet and fish oil supplementation was found to decrease sTNF-R p55 and CRP.</li> <li>→ There were no statically significant differences in clinical variables between the 3 groups.</li> </ul>
	DBRCT <sup>65</sup> [83 RA]	3 months (12 weeks) duration: patients allowed conventional drugs Group 1: 1 g/day of fish oil Group 2: no fish oil	<ul style="list-style-type: none"> <li>→ This trial was evaluating if fish oil supplementation would modify the soluble receptor activator of nuclear factor-kappa B ligand (sRANKL) to osteoprotegerin ratio for bone metabolism in RA patients.</li> <li>→ Fish oil supplementation was found to decrease sRANKL, TNF alpha and sRANKL/osteoprotegerin ratio and increase the serum levels of osteoprotegerin.</li> <li>→ Fish oils were found to decrease the inflammatory response by decreasing serum TNF alpha and sRANKL/osteoprotegerin ratio.</li> </ul>



RCT <sup>66</sup> [100 RA]	12 week duration Group 1: indomethacin (75 mg) Group 2: indomethacin (75 mg) with 3 g of omega-3 fatty acids.	<p>→ The combination of indomethacin and omega-3 fatty acids indicated a better improvement in reducing disease activity</p> <p>→ Statistically significant improvement:</p> <ul style="list-style-type: none"> <li>• physical functioning</li> <li>• physical role</li> <li>• body pain</li> <li>• general health</li> <li>• vitality</li> <li>• social functioning</li> <li>• grip strength</li> <li>• duration of morning stiffness</li> </ul> <p>→ Dairy products enriched with n-3 LC-PUFA:</p> <ul style="list-style-type: none"> <li>• Improved blood lipids (increased HDL)</li> <li>• Suppressed immune responses</li> <li>• Increased whole blood monocyte COX 1</li> <li>• Decreased lipopolysaccharide stimulated COX 2</li> </ul> <p>→ Long term consumption of dairy products was found to prevent elevated cartilage and bone resorption in RA patients</p> <p>→ The combination of dairy products and n-3 LC-PUFA did not improve disease activity however it did show evidence of cardio-protective effects.</p> <p>→ Prescribed medication for arthritis was maintained throughout the study</p> <p>→ Statistically significant improvement (<math>P &lt; 0.05</math>) in the fish oil and fish oil plus olive oil groups compared to the placebo in:</p> <ul style="list-style-type: none"> <li>• joint pain intensity</li> <li>• right and left handgrip strength after 12 and 24 wk</li> <li>• duration of morning stiffness</li> <li>• onset of fatigue</li> <li>• Ritchie's articular index for pain joints after 24 wk</li> <li>• ability to bend down to pick up clothing from the floor</li> <li>• getting in and out of a car after 24 wk.</li> </ul> <p>→ Fish oil PLUS olive oil showed additional improvements in:</p> <ul style="list-style-type: none"> <li>• duration of morning stiffness after 12 wk</li> <li>• patient global assessment after 12 and 24 wk</li> <li>• ability to turn faucets on and off after 24 wk</li> <li>• rheumatoid factor after 24 wk</li> <li>• a significant improvement in patient global assessment</li> </ul> <p>→ Patients on the anti-inflammatory diet compared to the western diet found:</p> <ul style="list-style-type: none"> <li>• a reduction in the numbers of tender and swollen joints by 14% during placebo treatment.</li> <li>• with fish oil supplementation, a significant reduction in the numbers of tender (28% versus 11%) and swollen (34% versus 22%) joints (<math>P &lt; 0.01</math>) was found.</li> </ul>
DBRCCT <sup>67</sup> [45 RA]	3 months with a 2 month washout phase. Group 1: oil infused dairy products (fish, rapeseed, <i>Dracolephalum ibericum</i> oil = 2.4 g EFA) Group 2: placebo (dairy products)	
BRCT <sup>68</sup> [34 RA]	24 week duration—three groups: Group 1: received placebo (soy oil). Group 2: received fish oil omega-3 fatty acids (3 g/d). Group 3: received fish oil omega-3 fatty acids (3 g/d) and 9.6 mL of olive oil.	
DBRCCT <sup>69</sup> [60 RA]	8 months on a normal western diet or an anti-inflammatory diet = arachidonic acid <90 mg/day. Placebo or fish oil capsules (30 mg/kg body weight) for 3 months with a 2-month washout period.	

(Continued)

Table 1 (Continued)

Dietary recommendation	Study type [no patients]	Duration	Results
Probiotics	DBRCT <sup>79</sup> [29 RA]	<i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14 or placebo for 3 months.	→ An anti-inflammatory diet with fish oil supplementation given in the 6–8 months of the trial, resulted in: <ul style="list-style-type: none"> <li>• higher enrichment of eicosapentaenoic acid in erythrocyte lipids (244% vs 217%)</li> <li>• lower formation of leukotriene B(4) (34% versus 8%, <math>P &gt; 0.01</math>), 11-dehydro-thromboxane B(2) (15% versus 10%, <math>P &lt; 0.05</math>), and prostaglandin metabolites (21% versus 16%, <math>P &lt; 0.003</math>)</li> </ul> → Although probiotics did not clinically improve RA as measured by the ACR20, it is interesting that there was functional improvement seen within the probiotic group compared to placebo.
	DBRCT <sup>80</sup> [45 RA]	<i>Bacillus coagulans</i> GBI-30, 6086 or placebo for 60 days.	→ This pilot study suggest that adjunctive treatment with <i>Bacillus coagulans</i> GBI-30, 6086 LAB probiotic appeared to be a safe and effective for patients suffering from RA.
	DBRCT <sup>81</sup> [21 RA]	<i>Lactobacillus rhamnosus</i> GG (LGG) or placebo for 12 months.	→ Although there were no statistical significant differences in the activity of RA, more subjects in the LGG group reported subjective well-being.

**Abbreviations:** DBRCT, Double Blind Randomized Controlled Trial; SBRCT, Single Blinded Randomized Controlled Trial; RCT: Randomized Controlled Trial; ESR, Erythrocyte sedimentation rate; CRP, C-Reactive Protein.

number of tender joints, Ritchie's articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, erythrocyte sedimentation rate (ESR), C-reactive protein, white blood cell count, and a health assessment questionnaire score. In the control group, only the pain score improved significantly. The benefits in the diet group were still present after 1 year, and evaluation of the whole course showed significant advantages for the diet group in all measured indices. It was further reported that improvements observed through the dietary manipulation could be sustained after 2 years.<sup>14</sup> This dietary regimen may be a useful adjunct to conventional medical treatment for reducing pain in RA.

Research on fasting and vegan diets for RA remains variable, however, with an earlier study assessing a fasting/vegan eating plan ( $n = 26$ ) showing no significant differences at the end of the diet plan.<sup>15</sup> Another clinical study investigating a vegan dietary intervention ( $n = 66$ ) reported that dietary modification may be of clinical benefit for certain RA patients. The authors stated that this benefit may be related to a reduction in immunoreactivity to food antigens in the GIT that can be eliminated by the change in dietary consumption.<sup>16</sup> A subsequent study ( $n = 42$ ) that tested the effects of an uncooked vegan diet rich in lactobacilli in RA patients reported that the uncooked vegan diet decreased subjective symptoms of RA compared to the control group. Moreover, it was reported that large doses of live lactobacilli consumed daily may also have positive effects on objective measures of RA.<sup>17</sup> Nevertheless, additional randomized long-term studies are needed to confirm efficacy by improved methodologically convincing data.<sup>12</sup>

## The Mediterranean diet

The Mediterranean diet reflects a dietary pattern that is largely characteristic of an anti-inflammatory diet.<sup>18–22</sup> Typically, the diet comprises abundant plant foods (including fruits, vegetables, wholegrain cereals, beans, nuts, and seeds); minimally processed, seasonally fresh and locally grown foods; fish and poultry; and olive oil as the main source of lipid, with dairy products, red meat, and wine in low to moderate amounts. Thus, the diet is rich in long-chain  $n-3$  polyunsaturated fatty acids (PUFAs) and oleic acid ( $n-9$  monounsaturated), phytochemicals, and unrefined carbohydrates. The Mediterranean diet has been linked with a significant reduction in all-cause morbidity and mortality,<sup>23</sup> and therefore there is a propensity towards a plausible clinical improvement in RA inflammatory symptoms (that may promote the disablement process). A small number of studies have demonstrated efficacy (Table 1); however, a systematic review reported



that the effects of dietary manipulation, including vegetarian, Mediterranean, elemental, and elimination diets, on RA still remain uncertain.<sup>24</sup>

## Exclusion diet

An early double-blinded, placebo-controlled study that employed an exclusion diet in 53 RA patients demonstrated clinical improvement in joint pain and stiffness, ESR, and fibrinogen levels.<sup>25</sup> All patients underwent a washout period from all previous therapy and then followed an exclusion phase for 1 week, in which only foods that were nonallergenic (foods that were unlikely to be ill tolerated) were allowed. Foods were then reintroduced one at a time to assess which foods caused symptoms. Foods that provoked an allergic reaction were then excluded from the diet. Darlington et al<sup>25</sup> found that cereal foods induced the most reactions, with corn and wheat producing symptoms in over 50% of the patients. Cereal foods comprised four of the top seven symptom-inducing foods, with other foods such as pork, dairy, eggs, certain fruits, peanuts, lamb, coffee, and soy also causing intolerance and an exacerbation of RA symptoms in patients.<sup>26,27</sup> The study concluded that it was possible to hypothesize that improvement included reduced food intolerance, reduced GIT permeability, and that the RA patients benefited from the observed weight loss and from a reduced intake of substrates for prostaglandin production. There is some evidence supporting dietary elimination therapy for RA,<sup>28–31</sup> although inconsistencies have been noted and reported.<sup>32,33</sup> Notwithstanding the contentious reporting, a small study that directly eliminated allergens from the diet provides a further insight that food intolerance may significantly influence the clinical activity of RA. This study enrolled 94 patients diagnosed with RA.<sup>34</sup> The study postulated that there may be a subgroup of patients with RA in whom food intolerance influences the activity of rheumatoid factor seropositive RA and that there is a need for further serious consideration. This study further illustrates the notion that the GIT may have a significant role in influencing the progression of RA.

## Elemental diet

Two clinical studies that investigated an elemental diet in 47 and 30 patients diagnosed with RA demonstrated partial efficacy (Table 1).<sup>35,36</sup> The improvements were transient, however. Elemental diet (E028) is a hypoallergenic, protein-free artificial diet consisting of essential amino acids, glucose, trace elements, and vitamins. The elemental diet is taken as an oral drink or administered via a nasogastric tube; however, due

to poor tolerance it should only be considered as a temporary therapy.<sup>36</sup> A small pilot trial ( $n = 30$ ) investigated an elemental diet to oral prednisolone in a comparative study and reported that an elemental diet, when complied with for over 2 weeks, provided a clinical improvement in patients with active RA.<sup>37</sup> This pilot study supported the hypothesis that RA may be a reaction to food antigens and that the disease process starts within the GIT. A further small pilot trial<sup>38</sup> ( $n = 17$ ) demonstrated that some RA patients may respond to the elimination of offending food items. However, the results do not encourage treatment with an elemental diet in unselected RA patients.

Research investigating the role that food antigens may have in promoting RA presents a complex inflammatory picture. Studies have reported that the production of cross-reactive antibodies is significantly increased in the GIT of many RA patients.<sup>39</sup> Ingested food-related problems might reflect an adverse additive effect of multiple modest hypersensitivity reactions that are mediated by immune complexes that then may promote autoimmune reactions in the joints via a GIT joint axis. A recent review provides an insight into RA as a complex, polygenic, autoimmune disorder where genes have a role, but that environmental factors are required for disease manifestation.<sup>40</sup> Furthermore, it suggested that disease pathogenesis may require a significant interplay with the GIT microbiome.

## Dietary foods

Investigations of dietary elements considered to reduce the risk of RA have indicated that foods high in olive oil, omega-3-rich fish, fruit, vegetables, and beta-cryptoxanthins (found in red fruit and vegetables) have been reported to have a protective role for RA.<sup>21,41</sup> A review of clinical trials on red meat, coffee, and alcohol consumption demonstrated contentious results, and no firm conclusions could be made as to their influence on RA.<sup>21</sup> However, a further study of diet and risk indicated that although consumption of high-fat fish ( $\geq 8$  g of fat/100 g fish) appeared to provide a reduced risk, medium-fat fish (3–7 g/100 g fish) was associated with an increased risk of RA.<sup>41</sup> A prospective study suggested that cauliflower, broccoli, and other cruciferous vegetables and fruit were protective of RA.<sup>42</sup> However, a further study indicated that fruit, coffee, olive oil, and meat intake showed no association with RA risk reduction, nor did intake of the vitamins A, E, C, D, and the minerals zinc, selenium, or iron.<sup>43</sup> Additionally, a review of studies into the relationship between obesity and RA suggests that obesity may lead to less changes on radiography and better survival rates, although this needs to be confirmed.<sup>44</sup>

A dietary intervention study with 109 patients diagnosed with RA demonstrated significant improvement in

the duration of morning stiffness, number of swollen joints, pain status, and reduced cost of medicine, in spite of doctors' global assessment, laboratory data, X-ray, and daily activities remaining unaltered.<sup>45</sup> A further study with 50 patients<sup>46</sup> diagnosed with RA reported that an experimental diet that was high in unsaturated fats, low in saturated fats with hypoallergenic foods versus a controlled well-balanced diet improved four RA-associated variables (Ritchie's index, tender and swollen joints, and ESR) reaching statistical difference by multivariate analysis. When the data were adjusted for weight variations, the number of tender joints ( $P=0.014$ ) and ESR ( $P=0.025$ ) remained statistically significant. Hence, the study concluded that dietary manipulation, either by modifying food supplements or by reducing weight, may provide some clinical benefit.

## Omega-3 polyunsaturated fatty acids from fish and supplements

Early descriptive observations demonstrated that populations such as the Greenland Eskimos, a group consuming a high-fat diet rich in omega-3 PUFAs containing high levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were afforded protection from cardiovascular disease.<sup>47,48</sup> Similarly, the Japanese population, reported to consume a diet relatively high in fish, presented lower rates of acute myocardial infarction and atherosclerosis.<sup>49,50</sup> Hence, a clinical picture is presented that shows that EPA and DHA can significantly and favorably influence downregulation of proinflammatory profiles by reregulating the inflammatory response.

Omega-6 (*n*-6) and omega-3 (*n*-3) PUFAs are precursors of potent lipid mediators, termed eicosanoids, which play an important role in the regulation of inflammation. Eicosanoids derived from *n*-6 PUFAs (eg, arachidonic acid) have proinflammatory and immune-active functions, whereas eicosanoids derived from *n*-3 PUFAs (eg, EPA and DHA) have anti-inflammatory properties, traditionally attributed to their ability to inhibit the formation of *n*-6 PUFA-derived eicosanoids. While the typical Western diet has a high ratio of *n*-6 PUFAs compared with *n*-3 PUFAs, research has shown that by increasing the ratio of *n*-3 to *n*-6 fatty acids in the diet, and consequently favoring the production of EPA, or by increasing the dietary intake of EPA and DHA through the consumption of fatty fish or fish-oil supplements, reductions may be achieved in the incidence of many chronic diseases such as cardiovascular disease, inflammatory bowel disease, cancer, and RA that involves inflammatory processes.<sup>47</sup>

A meta-analysis covering 17 randomized controlled clinical trials (Table 1) demonstrated that *n*-3 fatty acid

supplementation may be an effective adjunctive treatment for RA.<sup>51</sup> The study showed a significant beneficial effect on RA pain, morning stiffness, number of painful and/or tender joints, and nonsteroidal anti-inflammatory drug (NSAID) consumption.

Several studies have reported that *n*-3 PUFAs have been demonstrated to exhibit immunomodulatory effects by changing the profiles of the eicosanoids produced and decreasing the levels of proinflammatory cytokines, via both lipid-mediator-related and non-lipid-mediator-related mechanisms.<sup>52,53</sup> The content of marine *n*-3 fatty acids varies greatly according to the species of fish, the total fat content of the fish, and their geographical origin.<sup>54</sup>

Deepwater fish that have been described as oily (eg, tuna, salmon, mackerel, herring, and sardines) from cold climates have the highest content of EPA and DHA, since lipids are stored in the fish's flesh, whereas lean fish that store lipids in the liver (eg, cod) contain less EPA and DHA. One portion of cod provides approximately 0.3 g of EPA and DHA, compared to one portion of salmon, which provides approximately 1.5 g of EPA and DHA, and one portion of mackerel, which provides approximately 3 g.<sup>55</sup> The EPA and DHA obtained from the flesh of oily fish or from the livers of lean fish is rich in *n*-3s, and one fish-oil capsule from these sources consists of approximately 30% of these fatty acids. Hence, supplementation with a typical 1-g fish-oil capsule provides approximately 300 mg of EPA and DHA, which is equivalent to the consumption of one portion of cod. However, it should also be noted that it has been reported that the intake of *n*-3 fatty acids in the absence of oily fish or from a fish-oil supplement is likely to be <100 mg/day.<sup>56,57</sup> Consuming a daily supplement of *n*-3 fatty acids (standard fish-oil capsule per day) can increase *n*-3 levels fivefold (or more) in the absence of any other fish intake.<sup>58</sup>

Increased consumption of fatty fish or fish-oil supplements containing *n*-3 PUFAs increases the amount of these fatty acids and their metabolites in human immune cells and consequently changes the production of important mediators and regulators of inflammation and immune responses towards an anti-inflammatory profile. Since excessive intake of *n*-6 PUFAs, which is characteristic of Western diets, could potentiate inflammatory processes and consequently predispose to, or exacerbate, inflammatory diseases, increasing intake of fatty acids that elicit anti-inflammatory effects, such as *n*-3 PUFAs, could decrease the risk of many chronic diseases like arthritis and improve health. Based on the published health effects of *n*-3 PUFAs, recommendations

have been made to increase dietary intake of these fatty acids, achieved by increasing consumption of oily fish or by consuming fish-oil supplements.<sup>59</sup>

An early clinical trial with patients (n = 66) taking dietary supplements of fish oil reported that the patients exhibited improvements in clinical parameters of disease activity from baseline.<sup>60</sup> These included the number of tender joints, and these improvements were associated with significant decreases in levels of interleukin-1 beta from baseline. Some patients who took fish oils were also able to discontinue NSAIDs without experiencing a disease flare. A recent clinical trial that investigated cod liver oil supplementation versus placebo in RA (2.2 g EPA per 10 g cod liver oil) reported that cod liver oil supplements containing *n*-3 fatty acids demonstrated NSAID-sparing effects in RA patients.<sup>61</sup> Numerous other clinical studies reported in a meta-analysis<sup>51</sup> and listed in Table 1 further support the role that fish fats may have on improving disease outcome in patients diagnosed with RA.<sup>62–69</sup>

## Gastrointestinal influences in RA

Two of this group of researchers have previously reviewed the nutritional supplement and herbal medicine scientific/medical literature for osteoarthritis and RA<sup>70</sup> and it will not be repeated here. Suffice to add that importantly, we have focused on the GIT and briefly on probiotics and prebiotics in this review. The commensal (normal microflora, indigenous microbiota) GIT microbiome and functional foods such as probiotics and prebiotics may have a useful role as pharmacobiotics in RA.

## Gastrointestinal complaints in RA patients

Gastrointestinal symptoms are reportedly common among patients with rheumatic disorders, and medications alone are not responsible for the high prevalence, suggesting that the underlying chronic rheumatic condition predisposes the patient to GIT symptoms.<sup>71–73</sup> Prescribed medications used for the treatment of rheumatic disorders, including NSAIDs, steroids, and disease-modifying drugs, have been associated with numerous adverse GIT events.<sup>72,73</sup> In particular, dyspepsia, abnormal bowel habits (hard/loose stool), and abdominal bloating have been reported by RA and osteoarthritis patients. Interestingly, such symptoms are also reported by patients with irritable bowel syndrome, in which they have been associated with an altered profile of intestinal microbiota and unbalanced fecal organic acid levels.<sup>71,72</sup>

## Enteric microbiota in RA patients

Different dietary profiles such as higher fat intake and lower fiber intake have recently been shown to be correlated with particular bacterial groups.<sup>74</sup> Enterotypes appeared to be determined by long-term diet. Namely, the *Bacteroides* enterotype was positively associated with animal protein and saturated-fat intake, whereas the *Prevotella* enterotype was associated with predominantly plant-based nutrition with high carbohydrates and low meat and dairy consumption. Such studies may have important implications when considering dietary manipulation for RA. Furthermore, the association between the intestinal microbiome and disease activity may have implications for how diets can affect RA.

A recent study has investigated the fecal microbiota in early RA.<sup>6</sup> This study showed that RA patients had significantly less bifidobacteria and bacteria of the *Bacteroides-Porphyromonas-Prevotella* group, *Bacteroides fragilis* subgroup, and *Eubacterium rectale-Clostridium coccooides* group, indicating that intestinal microbes participate in the etiopathogenesis of RA. The aim of the work was to study colonic microbial biocenosis and colonizing ability of opportunistic bacteria in 32 patients with RA and 30 healthy subjects. RA was associated with significant modification of the intestinal flora. A decrease in lactobacteria and significant increases of enterococci, clostridia, and colibacteria were reported in RA patients showing reduced enzymatic activity, and an increase in opportunistic species. Also, symbiotic relationships between microorganisms were altered. The fraction of bifidobacteria, bacteroids, and lacto-positive colibacteria were reduced, while the abundance of opportunistic enterobacteria and staphylococci were increased. Opportunistic Enterobacteriaceae species were present in urine and nasal mucosa, suggesting their translocation from the intestines. Consistent with these observations, it has been further reported that changes in intestinal microflora and colonization by opportunistic bacteria enhance the risk of development of comorbid conditions in patients with RA.<sup>7</sup>

## Dietary-induced changes in fecal microflora in RA patients

Clinical studies that have investigated a vegetarian diet<sup>75</sup> or a form of uncooked vegan diet rich in lactobacilli<sup>76</sup> have shown that these diets can change the fecal microbiota profile in RA patients. Changes in the fecal flora were associated with improvement in RA activity. Hence, could there be a role for probiotics as a pharmacobiotic?<sup>77</sup>

The past six decades have seen a significant increase in the prevalence of autoimmune diseases.<sup>78</sup> Hence, an autoimmune

disease such as RA has forced a refocusing of research on the role the GIT and the microbiota may have on inducing autoimmune diseases. This was the catalyst that led to the formulation of the hygiene hypothesis. This hypothesis provides a biologically plausible explanation for the trend that implicates diminished exposure in early childhood to those normal infections that boost immune defenses. This deficit subsequently enhances the risk, for later life, of GIT inflammatory problems that disrupt normal/regulated GIT inflammatory responses and increases the susceptibility to developing autoimmune diseases.<sup>78</sup>

### Probiotic supplementation in RA patients

A recent randomized double-blind clinical study has examined the effects of probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 capsules administered orally to RA patients.<sup>79</sup> The study demonstrated that there was functional improvement seen within the probiotic group compared to placebo. In a further small clinical study,<sup>80</sup> participants who received *Bacillus coagulans* GBI-30, 6086 experienced borderline statistically significant improvement in the Patient Pain Assessment score and statistically significant improvement in Pain Scale versus placebo. Moreover, compared with placebo, *B. coagulans* GBI-30, 6086 treatment resulted in greater improvement in patient global assessment and self-assessed disability; reduction in C-reactive protein; as well as the ability to walk 2 miles, reach, and participate in daily activities. In an additional double-blinded study, it was reported that *Lactobacillus* LGG was not better than placebo in the activity of RA.<sup>81</sup>

### Prebiotics

Prebiotics are nondigestible food ingredients that are of benefit to the host by selectively promoting the growth and activity of a limited number of bacteria in the GIT. While probiotics provide bacteria to the GIT, prebiotics provide a food source for the growth of bacteria already in the gut. The predominant use of prebiotics is to potentiate the beneficial actions of bacteria in the GIT.<sup>10</sup>

### Synbiotics

Synbiotics are functional foods that contain both a probiotic and prebiotic component.<sup>10</sup> The rationale for such combination products is that together the formulation enhances the survival of probiotic bacteria in transit through the proximal GIT and improves commensal bacteria interactions with the probiotic in the large bowel, such as a stimulating effect on the growth of the endogenous flora.<sup>82</sup> This effect may rescue the

GIT from a continued dysregulated inflammatory response that may increase the risk of developing an autoimmune disease such as RA.

## Discussion

Musculoskeletal diseases can be incapacitating and detrimental to quality of life. Although effective pharmacologic treatments are available, the continuing high burden of disease and lost productivity affirms the need for further innovation. Diet, nutrition, and weight loss have shown promise in alleviating some of the disease burden of RA.<sup>83</sup>

Although the evidence presented from clinical trials for diets and foods is not robust, dietary advice does have a place in rheumatology as part of an integrative approach for the patient diagnosed with RA. The clinical trials presented in this review do demonstrate that a subset of patients will benefit from following a vegetarian, vegan, or Mediterranean-style diet, or by eliminating certain foods from their diet. There are observed similarities between the Mediterranean and the Paleolithic diets. Furthermore, a recent review has argued that Paleolithic diets are increasingly acknowledged as templates for healthy diets, partly because very low age-adjusted rates of cardiovascular disease and other nutrition-related disorders have been observed among contemporary hunter-gatherers.<sup>85</sup> Moreover, it has been reported that there are no obvious risks with avoiding dairy products, margarine, oils, refined sugar, and cereal grains, which provide 70% or more of the dietary intake in northern European populations.<sup>85</sup> The importance of diet for human health may, amongst other things, be due to the influence of different nutrients on the health and integrity of the intestinal microbial flora.<sup>14</sup> The intestinal microbial flora are crucial for the provision of important cues that assist the GIT innate immune system achieve full maturation.<sup>77</sup> Dietary interventions have been assumed to have modulating effects on GIT permeability and integrity with clinical relevance to RA.<sup>15</sup> Hence, it is plausible that dietary interventions that can unfavorably uncouple the GIT microbiome and innate immune system interchange may enhance the lifetime risk of developing RA.

The ever-increasing importance of the GIT microbiome in maintaining a regulated inflammatory response locally and systemically has grown further since the advent of the hygiene hypothesis.<sup>86</sup> A recent review has outlined the historical clues that suggest a possible role for the microbiota in the pathogenesis of RA.<sup>40</sup> A plausible hypothesis is that intestinal dysbiosis could lead, in a genetically predisposed individual, to a disruption in immune tolerance, followed by systemic immune disequilibrium that ultimately favors



proinflammatory responses locally within the GIT. This then further escalates systemic reactions, resulting in peripheral tissue damage of the joints. Hence, the role of commensal bacteria and importantly of probiotic species in RA is a paradigm shift toward their implementation as pharmacobiotics.<sup>77</sup>

In order to ensure the induction of tolerance and protective immunity, discriminative responses are required to the commensal bacteria that make up the GIT microbiome in respective comparisons with pathogens.<sup>86</sup> Namely, segmented filamentous bacteria can promote the differentiation of T-helper 17 cells, while certain *Bifidobacterium*, *Lactobacillus*, and *Clostridium* species can promote T<sub>reg</sub> development.<sup>87,88</sup> Hence, as postulated by the hygiene hypothesis, it may therefore seem most advantageous to maintain the GIT microbiome through dietary interventions that would promote GIT microbiome tolerance to environmental antigens.

There are no studies that have investigated the efficacy of either a prebiotic or synbiotic functional food in RA. However, a recent review does provide an insight into the biological plausibility of these functional foods assisting with the management of RA. Inflammation is a stereotypical physiological response to infections and tissue injury, as reported by Calder and colleagues.<sup>81</sup>

Furthermore, and importantly, an integrative approach that includes prudent nutritional practices (based on a Mediterranean-style diet that closely resembles a Paleolithic diet) with multistrain probiotics that synergistically down-regulate proinflammatory responses may be a useful long-term management strategy for patients diagnosed with RA.<sup>84</sup> Functional foods such as probiotics and prebiotics promoting gut-barrier function and anti-inflammatory responses may provide useful adjuncts as dietary therapies.

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