Management of Rheumatoid Arthritis

Subjects: Health Care Sciences & Services

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Rheumatoid Arthritis (RA) is a chronic autoimmune condition characterized by symptoms of inflammation and pain in the joints. RA is estimated to have a worldwide prevalence of 0.5–1%, with a predominance in females.

dietary interventions rheumatoid arthritis omega-3 supplements

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects almost 0.5–1% of the population globally [1]. RA is the most prevalent form of inflammatory polyarthritis and is three times more common in women compared to men [2]. RA occurs when the immune system mistakes the body's cells for external invaders and releases inflammatory substances that attack the lining of the joints. Symptoms of RA may include pain, joint stiffness, swelling, fatigue and weakness [3]. RA affects nearly all organs in the body leading to comorbid conditions [4] such as cardiovascular diseases, gastrointestinal disorders, infections, osteoporosis and depression [5]. The prevalence of comorbid conditions reported in different studies varies between 40 and 66% [6][7]. Treatment for RA involves lifelong pharmacological adherence to delay the advancement of the disease, control symptoms and maintain the person's ability to function [8]. The most commonly prescribed medications include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) to decrease joint pain, swelling, and inflammation [9].

The pathogenesis of RA remains unclear; genetic predisposition represents a great percentage of risk while the remainder is thought to be connected to modifiable factors such as tobacco smoking, diet and exercise [10]. Diet is a major modifiable determinant of chronic conditions with a large body of evidence showing that modifications to improve diet quality are directly associated with health benefits [11]. Diet is an area of interest for people living with RA as a way of improving symptoms [12]. However, the effect of various dietary interventions in RA remains controversial and inconclusive within existing literature. Despite the number of trials that have explored different diet and nutrient supplementation approaches, specific dietary recommendations and evidence-based dietary guidelines for this population are lacking. A recent systematic review concluded that the evidence for the effects of diets and dietary supplements on the Disease Activity Score in 28 joints (DAS28) in people with RA is insufficient and conclusions may not be drawn [13]. Similarly, another review evaluating the effects of diets, dietary supplements, and fasting in RA established that the effectiveness of and need for diets and dietary supplements in RA remains unclear as the responses to diets and supplements vary from one person to another [14]. Conclusions from the two recently published systematic reviews are in line with findings from a Cochrane review published in 2009 on the effectiveness and safety of dietary interventions in RA [15].

Omega-3 polyunsaturated fatty acids (PUFAs) include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which are mainly derived from oily fish and fish oil supplements and alpha-linoleic acid (ALA) derived from plant sources [16]. The effect of marine omega-3 PUFAs on the functional responses of cell types involved in inflammation has been researched for many years [17]. Omega-3 PUFAs regulate signaling pathways of anti-oxidants and alter inflammatory pathways by competing with omega-6 PUFAs which are transformed to pro-inflammatory eicosanoids [18]. Omega-3 PUFAs are the most studied supplements in RA with several clinical trials conducted among adults over the years [19][20]. A recently published systematic review [21] concluded that supplementation with omega-3 PUFAs led to substantial improvements in the duration of early morning stiffness (EMS), pain levels, erythrocyte sedimentation rate (ESR), physical function, grip strength, joint tenderness and levels of leukotriene B4 (LTB4). Given the evidence relating inflammation to disease progression, omega-3 PUFAs play a significant role through modulation of the inflammatory processes and pathways.

2. Study Selection

A total of 3370 articles were retrieved from the database searches, 2921 articles remained after duplicates were removed of which 327 full-text articles were assessed for eligibility. In total, twenty studies met the inclusion criteria and were included in this systematic review. The search strategy and selection process are reported as per the PRISMA flowchart [22] and presented in **Figure 1**. Additionally, the reference lists of searched articles were screened to identify any potential studies; however, no further articles were retrieved. Of the 20 studies included, 18 were randomized controlled trials (RCTs) and two were non-randomized controlled trials (NRCTs) [23][24]. A summary of the included studies' characteristics is shown in **Table 1**.

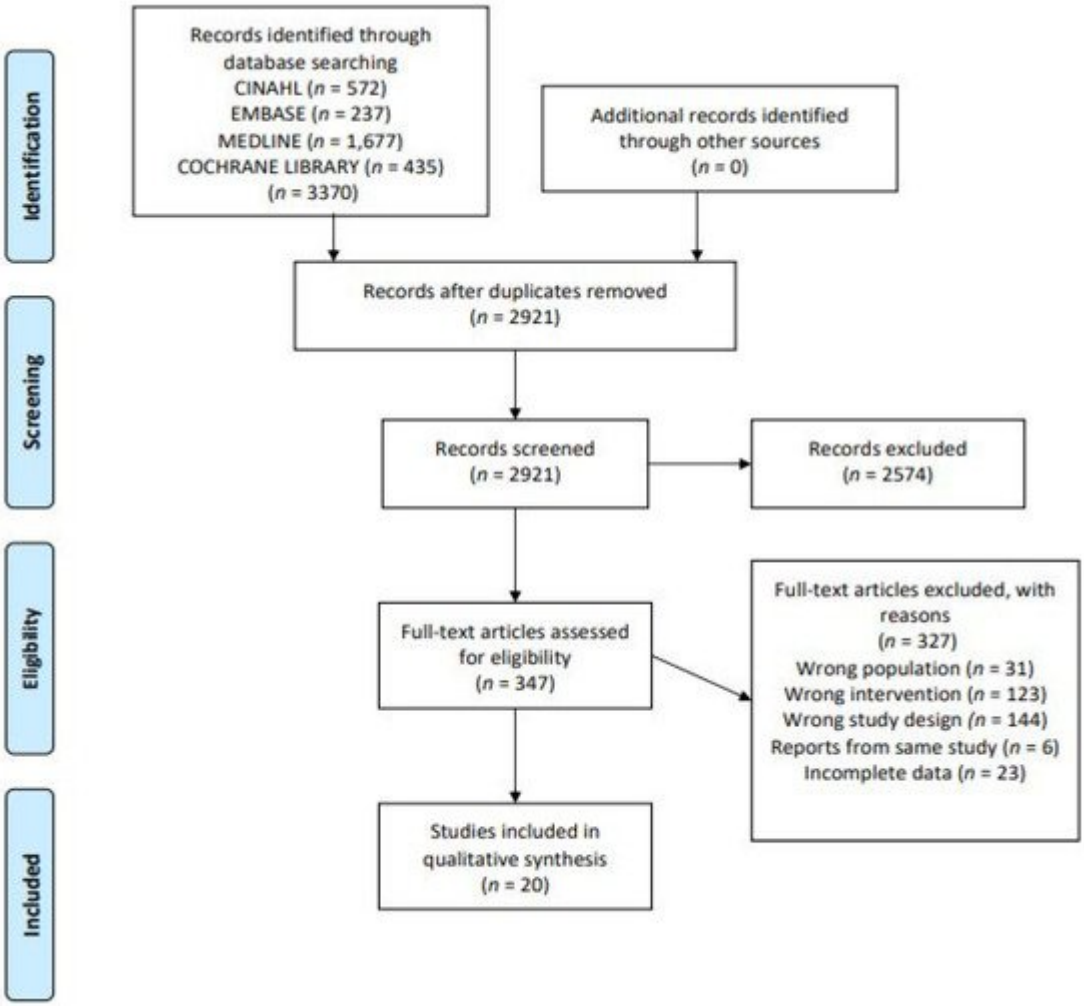

Figure 1. PRISMA flow diagram of study selection.

Table 1. Summary of study characteristics for included studies.

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
Skoldstam et al. (1979) [25]	Sweden	RCT	*n* = 26 Mean age: 53 yrs Sex: 73% f	7–10 days fasting followed by 9-week lactovegetarian diet	Habitual diet	10 weeks	Pain, EMS, dose of NSAIDs	NSD	
Panush et al. (1983) [26]	US	RCT	*n* = 33 Mean age: 55 yrs Sex: 34.6% f	Diet free of additives, preservatives, fruit, red meat, herbs, and dairy products	Placebo diet	10 weeks	EMS, number of tender and swollen joints, grip strength, patient and examiner assessment, walk	NSD	

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
							time, ESR, RF, Hct/C3/C4		
Darlington et al. (1986) [27]	UK	RCT	*n* = 45 Mean age: not reported Sex: 89% f	Elimination diet Week 1: tolerated foods followed by reintroduction of foods that are unlikely to cause intolerance followed by habitual diet	Habitual diet	6 weeks	Pain, EMS, grip strength, number of painful joints	NSD	Inadequate reporting
Magaro et al. (1988) [28]	Italy	RCT	*n* = 12 Mean age: Group A: 37 yrs Group B: 36 yrs Sex: 100% f	Group B: Diet high in PUFAs (P:S ratio 5:0) + fish oil supplement (1.6 g EPA/d and 1.1 g DHA/d)	Group A: Diet high in saturated fatty acids (P:S ratio 1:33)	4 weeks	DAS28, neutrophil chemiluminescence, Ritchie's index, EMS, grip strength	Significant improvements in Group B: Ritchie's inde X(17.2 (3.38) to 10.6 (3.48)); (p < 001), EMS (33 (7.34) to 22 (8.45)) mins; (p < 001); Grip strength (116 (13–26) to 136 (12–88)) mmHg; (p < 001)	Significant differences in: Ritchie's index (Group B: 10.6 (3.48) vs. Group A: 21–4 (3.2); (p < 0.005) EMS (Group B: 22 (8.45) vs. Group A:36 (10.17) minutes; (p < 0.01) Grip strength (Group B:136 (12–88) vs. Group A: 104 (21–58) mmHg; (p < 0.01)
Kjeldsen-Kragh et al. (1991) [29]	Norway	RCT	*n* = 53 Mean age: 4.5 years Sex: 85% f	7–10 days: fasting followed by 3·5 months: gluten-free vegan diet followed by 9 months: vegetarian diet	Habitual diet	13 months	Grip strength, Ritchie index, EMS, Global assessment, Number of tender and swollen joints, pain HAQ, ESR, CRP, white blood cells/platelet count	Significant improvements in the intervention group for: Grip strength (p < 0.0005), Ritchie Index (p < 0.0004), EMS (p < 0.0002); Number of	Significant improvement in the intervention group as compared with control for: Grip strength (p < 0.02), Ritchie index

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
								tender joints ($p < 0.0002$), Number of swollen joints ($p < 0.04$), Pain (VAS) ($p < 0.0001$ for intervention group and $p < 0.02$ for control), HAQ ($p < 0.0001$), ESR ($p < 0.002$), CRP ($p < 0.005$) White blood cells/platelet count decreased significantly in the intervention group ($p < 0.0010$) and in the control group ($p < 0.006$)	($p < 0.0004$), EMS ($p < 0.0001$), Global assessment ($p < 0.0001$), Number of tender joints ($p < 0.0001$), Number of swollen joints ($p < 0.02$), pain ($p < 0.02$), HAQ ($p < 0.0001$), ESR ($p < 0.001$), CRP ($p < 0.0001$)
Van de Laar and van der Korst (1992) [30]	Netherlands	RCT	$n = 94$ Mean age: 58 yrs Sex: 70% f	Allergen free diet	Allergen restricted diet	12 weeks	EMS, number of tender and swollen joints, Ritchie's index, grip strength, global assessment, ESR, CRP, walking time	Significant decrease in body weight in the allergen free diet group ($p = 0.016$)	NSD
Haugen et al. (1994) [23]	Norway	NRCT	$n = 17$ Mean age: 50 yrs Sex: 80% f	Elemental diet (E028)	Soup that included: milk, meat, fish, shellfish, orange, pineapples, tomatoes, peas and flour of wheat and corn	3 weeks	Ritchie's index, number of tender and swollen joints, grip strength, EMS, pain, ESR, CRP, hemoglobin, albumin and erythrocyte count, global assessment	Number of tender joints decreased significantly in the intervention group ($p = 0.04$) ESR and thrombocyte count improved in the control group ($p = 0.03$) and ($p = 0.02$), respectively	NSD

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
Kavanagh et al. (1995) [31]	UK	RCT	*n* = 47 Mean age: 45.6 yrs Sex: 78.7% f	E028 followed by reintroduction of food	Habitual diet with E028	4 weeks	ESR, CRP, Ritchie's index, thermographic score, grip strength, functional score	Significant improvements in the intervention group for: Ritchie's index (12.6 ± 6.8 to 10.4 ± 7.2) (p = 0.006), Grip strength (140.2 ± 96 to 155.9 ± 98.3 mmHg) (p = 0.008)	NSD
Hansen et al. (1996) [32]	Denmark	RCT	*n* = 109 Mean age:57 yrs Sex: 74.6% f	Graastener diet: 20–30% fat, 1.5 g/kg BW protein, 800 g fresh fish per week	Habitual diet	4 months	Number of tender and swollen joints, pain, HAQ, Global assessment, acute phase reactant, X-ray, EMS	Authors state: 'Significant improvement in the duration of morning stiffness, number of swollen joints, pain status'	NSD
Nenonen et al. (1998) [33]	Finland	RCT	*n* = 43 Mean age:53 yrs Sex: 83% f	Uncooked vegan diet	Habitual diet	3 months	Pain, number of swollen joints, number of tender joints, EMS, HAQ, Ritchie's index, CRP, ESR	NSD	
Holst-Jensen et al. (1998) [34]	Denmark	RCT	*n* = 30 Mean age: 49.5 yrs Sex: 80% f	Commerical liquid elemental diet (top upTM Standard, Ferrosan Ltd., Denmark)	Habitual diet	4 months	EMS, HAQ, number of swollen joints, pain, Ritchie's index, global assessment, ESR	EMS decreased significantly in the control group (3.5 to 2.5 min) (p < 0.05) Ritchie's inde Xdecreased significantly in the control group (12.5 to 10) (p < 0.05)	Significant reductions in the intervention group as compared with control for: Number of tender joints (7 vs. 9) (p = 0.006), ESR (40 vs. 47 mm/h) (p = 0.018)

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
Fraser et al. (2000) [24]	Norway	NRCT	*n* = 23 Fasting group: Mean age: 49 yrs, Sex: 90% f Ketogenic group: Mean age:44 yrs, Sex: 92% f	7-day ketogenic diet	7-day fast	1 week	IL-6, DHEAS	IL-6 decreased significantly after fasting for 7 days (35.5 to 22.5 pg/mL) ($p < 0.05$) DHEAS increased significantly after fasting for 7 days (3.28 to 4.40 mmol/L) ($p < 0.01$) and after a 7-day ketogenic diet group (2.42 to 3.23 mmol/L) ($p < 0.01$)	Not reported
Sarzi-Puttini et al. (2000) [35]	Italy	RCT	*n* = 50 Mean age:50 yrs Sex: 78% f	Diet free from: wheat meal, eggs, milk, strawberries and acid fruit, tomato, chocolate, crustacean, dried fruit Lean cuts of red meat allowed	Diet containing common allergenic foods	24 weeks	EMS, HAQ, number of tender and swollen joints, pain, Ritchie's index	Number of tender and swollen joints decreased significantly in the intervention group (9.5 ± 4.1 to 7.1 ± 3.2) ($p = 0.031$) and (6.4 ± 3.1 to 5.1 ± 2.3) ($p = 0.002$), respectively Ritchie's inde Xdecreased significantly in the intervention group (13.2 ± 4.4 to 9.2 ± 3.8) ($p = 0.002$)	Not reported
Hafstrom et al. (2001) [36]	Sweden	RCT	*n* = 66 Mean age: 50 yrs Sex: not reported	Gluten free vegan diet	Well-balanced non-vegan diet	12 months	IgG, IgA, radiographic progression	IgG anti-gliadin decreased significantly in the vegan diet group (5 to 2) ($p = 0.0183$) IgA anti-gliadin decreased	NSD

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
								significantly in the non-vegan diet group (14.5 to 12.5) (p = 0.0201) Modified Larsen score, number of erosions and the joint count improved significantly in both groups	
Skoldstam et al. (2003) [37]	Sweden	RCT	n = 56 Mean age: 58.5 yrs Sex: = 82% f	Cretan Mediterranean diet (MD)	Habitual diet (HD)	12 weeks	DAS 28, HAQ, SF-36, dose of NSAIDs	DAS28 decreased significantly in MD group (4.4 to 3.9) (p < 0.001) HAQ decreased significantly in MD group (0.7 to 0.6) (p = 0.02) Improvement in vitality (+11.3) (p = 0.018) and overall health compared to one year earlier (−0.6) (p = 0.016) in the SF- 36 in MD group	Significant improvements in MD group as compared to control group for: DAS28 (3.9 for MD vs. 4.3 for control) (p = 0.047) HAQ: (0.6 for MD vs. 0.8 for control) (p = 0.012)

[31][39] [35] [23][24][29] [32][34] [27] [33] [30] [25][36][37][40] [26] [38][42]

Adam et al. [43] [38] Germany RCT Double-blind crossover [44] 68 Mean age: 57.4 ± 12.8 yrs Sex: 93.3% f Anti-inflammatory diet (AID) Patients in both diet groups were assigned to receive either placebo or fish oil capsules (30 mg/kg body weight) Western diet (WD) 6 months Global assessment, pain, grip strength, EMS, HAQ, Number of tender and swollen joints, blood cells, cytokines, eicosanoids, dose of Corticosteroids, CRP, LBT4, TNF-α CRP decreased significantly for individuals in both WD and AID groups who are on methotrexate when fish oil was supplemented (2.03 ± 1.8 mg/dL vs. 1.69 ± 1.5 mg/dL) (p The number of tender and swollen improved significantly in the AID group as compared to WD group (28% vs. 11%) and (34% vs. 22%) (p < 0.01),

[37] [39]

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diet [33][36][40][42]. Two studies intervened with fasting for 7–10 days followed by one year vegetarian diet for the remainder of the study period [25][29]. Three studies intervened with an elemental diet provided in the form of an easily digestible liquid formula [23][31][34] and another four studies intervened with allergen-free diets by eliminating certain foods that commonly cause allergies such as wheat, eggs, dairy products and spice [26][27][30][35] Two studies intervened with an anti-inflammatory diet rich in omega-3 PUFAs [38][41]. One study compared a ketogenic diet to 7-day fasting [24], one study compared a diet high in polyunsaturated fatty acids (PUFAs) to a diet high in saturated fatty acids [28] and one study compared an energy adjusted diet to habitual diet [32]. Only two studies included omega-3 PUFAs supplementation with the dietary intervention. One study was a double-blind crossover study whereby participants in both study groups were assigned to receive either placebo or fish oil capsules (30 mg/kg body weight) [38] and the latter included a diet high in PUFAs and complemented with omega-3 supplements providing 1.6 g EPA and 1.1 g DHA per day [28].

5. Risk of Bias within Studies

Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
								< 0.05) Number of tender joints improved significantly in AID group when fish oil was supplemented in months 5,6,7,8 (37% improvement) (p < 0.001) LTB4 decreased significantly in AID group when fish oil was supplemented for 3 months (p = 0.009) Dose of corticosteroid decreased significantly in both WD and AID groups after 3 months of fish oil supplementation (p = 0.027 for WD group, p = 0.022 for AID group) TNF-α decreased significantly in both WD and AID groups when fish oil was supplemented for months 6,7, 8 (p = 0.004)	respectively Patients' and physicians' global assessment of disease activity and patients' assessments of pain improved significantly more in the AID group as compared to WD group (p < 0.05)
McKellar et al. (2007) [39]	Scotland	RCT	n = 130 Mean age: 54 yrs Sex: 100% f	Mediterranean diet (MD)	Healthy diet	5 months	Number of tender and swollen joints, patient global assessment, pain,	Not reported	Significant improvements in the intervention group as

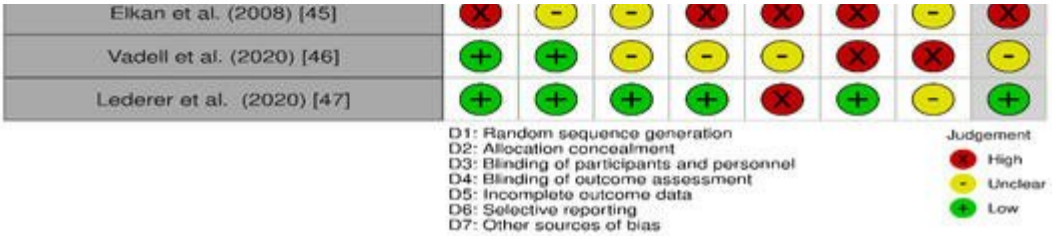

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

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Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
							EMS, DAS28, HAQ, ESR, CRP, IL-6		compared with the control group for: patient global assessment (p = 0.002), pain (p = 0.049) and EMS (p = 0.041)
Elkan et al. (2008) [40]	Sweden	RCT	n = 58 Vegan group: Mean age: 49.9 yrs, 93.3% f Non-vegan group Mean age:50.8 yrs, 85.6% f	Gluten- free vegan diet	Well-balanced non-vegan diet	12 months	oxLDL, anti-PCs	OxLDL decreased Significantly in the vegan diet group (54.7 to 48.6) (p = 0.09)	Anti-PC IgM was significantly higher in vegan group (F = 8.0, p = 0.0006)
Vadell et al. (2020) [41]	Sweden	RCT	n = 50 Mean age: 61 ± 12 yrs Sex: 77% f	Diet rich in anti-inflammatory foods	Habitual diet	10 weeks	DAS28-ESR	DAS28-ESR decreased significantly in the intervention group (3.39 to 3.05) (p = 0.012)	NSD
Lederer et al. (2020) [42]	Germany	RCT	n = 53 Mean age: 31 yrs Sex: 63% f	Vegan diet (VD)	Meat rich diet	5 weeks	Sialylated antibodies, percentage of regulatory T-cells, IL-10	Significant improvement in: Sialylated antibodies in VD (0.8 ± 0.4 to 1.4 ± 1.4) (p = 0.023) and in the meat rich group (0.9 ± 0.5 to 1.6 ± 1.2) (p = 0.010) T-cells in VD group (6.0 ± 1.7% to 7.1 ± 1.9%) (p < 0.001) and in meat rich	NSD

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Author (Year)	Country	Study Design	Participants' Characteristics	Intervention	Comparator	Duration	Primary Outcome Measures	Results (Post-Intervention Changes)	
								Within Group	Between Groups
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								group (6.3 ± 2.2% to 7.7 ± 2.4%) (p < 0.001)	

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