Dietary interventions for reduced disease activity in patients with rheumatoid arthritis: a critical review

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune condition in which an inflammatory response causes permanent damage to the cartilage and bone of affected joints, and is often associated with additional systemic complications. The pathogenesis of RA is not fully understood, and standard treatment requires trial and error of pharmacological interventions that may have serious side effects. Evidence suggests that dietary interventions, when added to standard pharmacotherapies, may effectively mitigate disease progression and symptoms of RA. The aim of the current review was to evaluate existing research on dietary interventions for treatment of RA symptoms to determine which diet therapies may be effective for improving symptoms and inflammatory markers of disease activity. Relevant studies were identified within PubMed, and inclusion and exclusion criteria were established *a priori*. Included studies incorporated an experimental design, a diet therapy component, and human participants with an existing diagnosis of RA. Studies not available in the English language or as full text, were excluded. The initial search yielded 110 records, and after evaluation of inclusion and exclusion criteria and topic relevance, results of nineteen studies were synthesized for interpretation. Included study interventions varied by duration, participants, objective, and prescribed diet. Assessments of disease activity were categorized as subjective, semi-objective, or objective markers of symptoms and inflammation. The prescribed diets included a period of fasting followed by a plant-based diet, vegan diets, Mediterranean diets, and three other dietary interventions that were hypothesized to have anti-inflammatory effects in patients with RA. A reduction in overall disease activity was observed in all nineteen of the included studies. However, statistical significance was more prevalent for semi-objective measurements of disease activity than more subjective and objective measures. Overall, the current review suggests that

plant-based dietary interventions may be effective for reducing subjective measures of disease activity in patients with rheumatoid arthritis. Additional high-quality and longer-term interventions are needed to identify which dietary components and additional dietary interventions may be beneficial for reducing objective inflammatory markers of disease activity, when added to pharmacological therapy in patients with RA.

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Acknowledgements

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Introduction

Rheumatoid arthritis (RA) is the most common type of autoimmune arthritis, affecting as many as 1.3 million Americans [1]. Risk factors include age, gender, history of smoking, and family history of disease. RA can manifest in childhood, but peak development is between 30 and 50 years of age[2,3]. Familial clustering and monozygotic twin studies indicate that genetic factors may account for up to 50 percent of disease risk[2]. The pathogenesis of RA is not fully understood, but it is suspected that the disease process involves a complex interaction between genetic factors and environmental triggers[3].

Autoimmune conditions are characterized by the inability of the immune system to differentiate between healthy cells and antigens, which results in an attack by the immune system on healthy tissues[3]. In RA, the synovium is the primary tissue targeted by the negative autoimmune reaction[3]. The synovium is flooded with inflammatory cells, new blood vessels are formed, and hypertrophy leads to degradation of the cartilage and bone in affected joints[4]. Ultimately, RA leads to physical disability, systemic complications, and increases the risk of early death[3].

Due to prolonged inflammation of the synovial tissue, deterioration of bone in the affected joints becomes evident within the first year of diagnosis in 80% of patients[3]. Therefore, early intervention and treatment is key to preventing long-term damage[3]. Unfortunately, there is no definitive diagnosis for RA and the disease can be mistaken for other autoimmune conditions or viruses[1,2]. Typically, the presentation of RA includes pain and stiffness of multiple joints, and morning stiffness that lasts longer than one hour. The primary joints affected in the early stages of the disease include the wrists, proximal interphalangeal joints, and the metacarpophalangeal

joints[2]. Additionally, low-grade fever, fatigue, and weight-loss are common systemic symptoms that may indicate disease activity[2].

Upon the onset of symptoms, a complete blood count (CBC) is typically obtained to determine the presence of RA specific antibodies and to assess for renal and hepatic function[1,2]. Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are present in 50–80% of RA patients; however, these inflammatory markers are not exclusive to rheumatoid arthritis. Erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) have been added to the American College of Rheumatology and European League Against Rheumatism diagnostic criteria because elevated levels are indicative of inflammation[2]. ESR and CRP can help to establish a diagnosis of RA and can be monitored routinely to assess overall disease activity. Additionally, radiographs of hands and feet may be obtained to determine the presence of periarticular erosion[2]. A combination of symptoms and the process of elimination ultimately leads to an RA diagnosis.

Rheumatoid arthritis is most recognized for its destruction and deformity of joints; however, it also has several serious comorbidities and systemic complications. RA patients are susceptible to extra-articular complications that may include Raynaud's phenomenon, pericarditis, and systemic vasculitis[5]. There is also a higher incidence of cardiovascular disease (CVD) among RA patients than in healthy adults, which leads to increased risk for myocardial infarction, stroke, and heart failure[3]. Cognitive decline, liver disorders, fibrotic or inflammatory lung diseases, and several other debilitating conditions are common in patients with RA[3]. The development of additional health conditions may be correlated with the severity and length of the disease process[5]. Therefore, early intervention is fundamental to preventing complications, as well as preserving the quality of life.

Over the past several decades, there have been substantial improvements in pharmacological therapies for rheumatoid arthritis; however, there is currently no cure. The effectiveness of traditional treatments varies from person to person and often requires trial and error of multiple medications[2]. The goal of treatment is to induce remission, but it is currently only attainable in 10–50% of patients with RA, and is dependent upon both the definition of remission, and the intensity of the interventions[2]. Standard therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), biologic agents, and Janus kinase (JAK) inhibitors[1]. Each medication has its own list of side effects and is not taken without risk. Moderate to severe RA may require administration of biologic agents or JAK inhibitors, which reduce inflammation and joint damage by suppressing the immune system[1]. While these drugs may effectively manage symptoms, suppression of the immune response also leaves patients susceptible to infection, which can have debilitating and life-threatening consequences[2].

In addition to standard physician-prescribed treatments, the Arthritis Foundation recommends lifestyle-based therapies. Daily movement and activity are encouraged to prevent stiff joints; however, rest should balance activity[6]. Low-impact exercises, such as swimming and aerobics, may prevent further joint damage[1]. Stress reduction and relaxation therapies promote mental wellness and may reduce triggers of symptom flares. The Arthritis Foundation also recommends a balanced diet for healthy weight management and suggests consideration for supplementation of curcumin/turmeric and omega-3 fatty acids[6]. Neither the Arthritis Foundation, nor the American College for Rheumatology provides additional RA-specific nutrition information, and neither recommends specific anti-inflammatory dietary patterns[1,6].

Inflammation can be a double-edged sword[7]. While it acts as a mechanism of defense against microbial infiltration and promotes the healing of injured tissues, excess inflammation can damage organ systems, and leads to the development of chronic diseases, such as RA[7]. In addition to the presence of microbes and physical injury, the inflammatory response can be triggered by dietary components that can be anti- or pro-inflammatory in nature. For example, increased consumption of omega-3 eicosapentaenoic acid (EPA) can inhibit the pro-inflammatory action of omega-6 arachidonic acid (AA). Therefore, the intracellular ratio between AA and EPA and is a reliable marker of inflammation and often becomes elevated years before C-reactive protein (CRP)[8]. Carbohydrate consumption is thought to be an important dietary factor in the inflammatory process, primarily due to the role of insulin in carbohydrate uptake. Foods that do not elicit a large secretion of insulin in response to consumption reduce the conversion of linoleic acid (LA) to AA, which reduces the amount of AA available for use in pro-inflammatory eicosanoids. Therefore, these foods are considered anti-inflammatory[8].

Modern dietary trends are constantly changing, and often seem to be recycled after a period of time has passed. Several popular diets that are thought to be anti-inflammatory include the Mediterranean diet (MD), various plant-based diets, and intermittent fasting or time-restricted feeding[2,9]. Common components of the MD include plenty of fruits, vegetables, and whole grains, limited meat consumption, and frequent intake of fish and olive oil. Research suggests that the MD may be a beneficial for patients with RA because it is low in AA, rich in omega-3s, and incorporates many low glycemic index foods[10]. Plant-based diets, such as vegan and vegetarian diets, are also rich in low glycemic index foods and low in AA. Because of their capacity to reduce the production of proinflammatory eicosanoids and decrease the inflammatory potential of excess insulin secretion, research suggests these dietary interventions may be

beneficial for patients with RA[11]. Intermittent fasting has been utilized for centuries in religious practices and has been reported to aid in weight loss[9]. Research has demonstrated the potential of intermittent fasting to reduce blood pressure and prevent the progression of type II diabetes[9]. A diet that includes periods of fasting could potentially be beneficial for patients with RA, because fasting may also reduce the action of pro-inflammatory cytokines and immune cells and reduce circulating glucose levels[9]. RA patients may benefit from one or a combination of these anti-inflammatory diets; however, research is required to determine their effectiveness for reducing the severity of RA symptoms. Therefore, the objective of this critical review was to evaluate the existing research on dietary interventions for treatment of RA symptoms to determine which diet therapies may be effective for improving symptoms and inflammatory markers of disease activity.

Methodology

Relevant studies for inclusion were obtained through searches conducted within PubMed. Search terms included “Arthritis, Rheumatoid” [Mesh] AND “Diet Therapy” [Mesh]. One hundred records were identified in this initial step. The following filters were applied to limit articles to the highest quality studies: “clinical trials” and “randomized controlled trials”. Filter application reduced results to forty-six articles.

Criteria for inclusion and exclusion were established *a priori*. The titles and abstracts of each record were screened for eligibility. Systematic and critical reviews, meta-analyses, non-English articles, journal entries published as commentary on existing research, objectives which did not align with the aim of current research, and articles that were not available as full text were excluded. In addition to the experimental design, the inclusion of a diet therapy component, and human participants with an existing diagnosis of rheumatoid arthritis, were required criteria. No restrictions were applied regarding age of participants, duration of trial, number of participants, or type of dietary intervention. Thirty-one articles remained following the initial review of inclusion and exclusion criteria. Upon examination of full-text articles, two were review articles, and ten had experimental objectives that did not align with the aim of the current research. Nineteen articles met all criteria and were available for review.

While the *a priori* intent was to limit sources to clinical trials and randomized controlled trials, several additional study types were ultimately included: a case-control study, two prospective cohort studies, and a double-blind crossover study. These sources were not automatically removed by the applied search filters. Upon review of the full-text articles, other than experimental design, content aligned with inclusion criteria and supported the current research objective. All sources included in the current critical review sought to assess the effect

of dietary interventions on clinical and laboratory inflammatory markers in patients with rheumatoid arthritis.

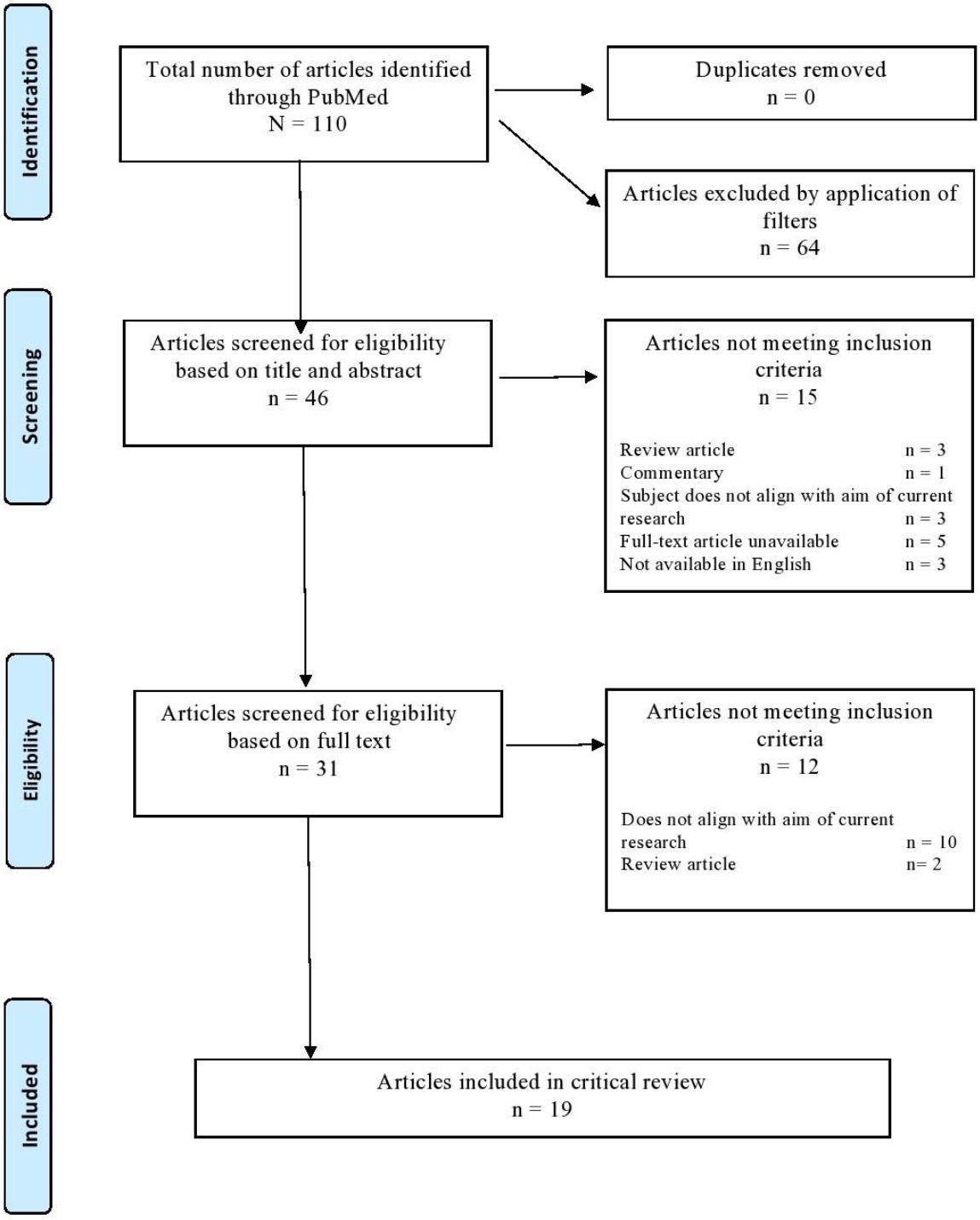

Figure 1. A Flowchart of the Research Methodology for the Critical Review

Results

Search criteria yielded 110 results. After review for inclusion and exclusion criteria, as well as topic relevance, 19 articles remained. A flow chart has been included in the Methods section of this review to portray the process through which studies were selected for inclusion. The key components of the 19 articles included in this critical review are summarized in Table 1.

Table 1. Key Components of the 19 Articles Included in the Critical Review

Study	Type	Objective/Aim	N, N_E, N_C, inclusion criteria	Duration	Dietary Intervention	Assessment	Results/Conclusion
Abendroth et al., 2010 [10]	Prospective, observational non-randomized clinical trial	Evaluate the effects of fasting followed by MD and MD on SCFA profiles and clinical outcomes in RA	• N = 50 • N_E = 22 • N_C = 28 • Inpatients from the Internal and Integrative Medicine Department in Essen, Germany • Diagnosis of RA per ACR criteria • No medication alterations permitted during	20 months	Experimental: 7-day fasting period followed by MD Control: MD All participants: 1–2 portions of meat per week; no caffeinated or alcoholic beverages	• DAS-28 • ESR • VAS for pain • CRP & serum cholesterol • Stool samples collected at baseline and at the end of the intervention • HAQ • SF-36	No correlation was been identified between dietary changes of SCFA in intestinal microflora and disease activity; however, decreased disease activity was observed in both groups Fasting and/or MD is effective at improving pain, disease activity, and overall health in patients with RA
Adam et al., 2002 [11]	Double-blind crossover study	Investigate the effect of vegetarian diet w/ or w/o fish oil supplementation on clinical effects and laboratory values in patients with RA	• N=68 • N_E = 34 • N_C = 34 • Diagnosis of RA per ACR criteria • ≥6 tender joints • ≥ 3 swollen joints • ESR of ≥28 mm/h OR serum CRP level of <0.6 mg/dl OR morning stiffness for ≥ 30 min. • < 10 mg/d NSAID or corticosteroids for ≥ 4 weeks and throughout study • DMARDs for ≥ 8 weeks and throughout study	Dietary intervention: 8 months Crossover design for placebo/fish oil spanning 3 months each with 2-month period between treatments	Experimental: AID- modified lactovegetarian, arachidonic acid intake ≤ 90 mg/day Control: WD All participants: fish oil or placebo supplements	• Assessment of disease activity • Pain • Bilateral grip strength • Morning stiffness • Laboratory values: ESR, cytokines, eicosanoids, fatty acids	Clinical improvements were observed in patients who followed the AID diet; however, improvements were more substantial when supplemented with fish oil rather than placebo EPA:AA ratio may be correlated to effectiveness

Elkan et al., 2008 [12]	Randomized controlled trial	Investigate impact of vegan diet on oxLDL and anti-PCs in patients with RA	• N = 66 • N_E = 38 • N_C = 28 • Diagnosis of RA per ACR criteria • Ages 20–69 years • Disease duration of 2–10 years • No previous dietary intervention • Active disease defined as ≥ 2 criteria: morning stiffness of ≥1 hour, ESR of ≥ 30 mm, and/or ≥ 6 swollen/tender joints • Medication alterations permitted during trial	1 year	Experimental: vegan, gluten-free diet with 1-day low-energy fasting followed by gluten-free vegan diet for 1 year Control: well-balanced, non-vegan diet	• BMI • DAS-28 • Stanford HAQ • oxLDL and anti-PCs in blood samples assessed at baseline, after 3 months, and after 1 year	Vegan diet decreased LDL and oxLDL levels and increased anti-PCs Vegan diet may be atheroprotective and anti-inflammatory in RA patients
Hafstrom et al., 2001 [13]	Randomized controlled trial	Determine whether a gluten-free vegan diet can improve clinical symptoms of RA as measured by the ACR20, assess impact on radiological joint damage, and assess immune reactions linked to clinical improvements	• N=66 • N_E =38 • N_C =28 • Diagnosis of RA per ACR criteria • Ages 20–69 years • Disease duration of 2-10 years • No previous dietary intervention • No history of food sensitivity or food allergy • Active disease • Stable doses of NSAIDs, glucocorticosteroids, and DMARDs	1 year	Experimental: gluten-free, vegan diet Control: non-vegan, well-balanced	• ACR20 response criteria • Antibodies v. food-related antigens: IgG and IgA v. gliadin and β-lactoglobulin • Radiographic assessment of hands, wrists, and feet at baseline, 6 months, and 12 months	Vegan diet may have positive effects on RA symptoms due to reduction of food antigens Vegan diet may produce a positive immune response No differences were observed in radiographs
Haugen et al., 1994	Prospective, single-blind,	Determine whether change	• N=53; M=8, F=45 • N_E =27	1 year	Experimental: 7–10 day fast	• Assessments performed at	No significant differences were

[14]	controlled clinical trial	in fatty acid profile is associated with decreased disease activity in RA patients when following a vegetarian diet	• N_C =26 • Diagnosis of RA per ARA criteria • Active disease defined by 3 out of 4 of the following criteria: ≥ 3 swollen joints, ≥ 6 tender joints, morning stiffness ≥ 45 min, ESR ≥ 28 in the 1st hr. • Stable dose of slow-acting antirheumatic drugs (SAARDs), cytostatic drugs, or NSAIDS for ≥ 3 months • Corticosteroid dose ≤ 7.5 mg/day and stable for ≥ 4 weeks		with "new" food reintroduced every 2nd day; strict gluten-free, vegan diet for 3–5 months; lactovegetarian diet for remainder of study; supplementary vitamin D Control: continue normal diet with no dietary instructions for patients with normal lab values	baseline, 1 month, 4 months, and termination of study • Blood analysis of plasma phospholipid acids and ESR • number of swollen joints • Stanford HAQ • VAS for pain • number of tender joints • global assessment	observed in fatty acid concentrations in patients who responded to diet and patients who did not Vegetarian diet leads to decreased disease activity in RA patients
Iwashige et al., 2004 [15]	Clinical trial	Assess effects of caloric restriction and fasting on urine pentosidine levels in patients with RA and determine whether it is associated with reduced disease activity	• N_E =10, F • N_C = 15, F • Experimental: diagnosis of RA per ARA criteria, ages 48–77 • Control: healthy patients, ages 43–80 • Medication alterations permitted during trial in accordance with symptom improvement	54 days	Caloric restriction from days 0–10, 14–24, 31–43 & 49–54 Fasting conducted from days 11–13, 25–30, & 44–48 Calorie restricted: 1085 kcal	• Blood serum and urine samples collected on days 0, 25, and 54 • LI • Measurement of urinary pentosidine	Calorie-restricted diet demonstrates reduced disease activity and also reduced urinary pentosidine in patients with RA
Kjeldsen-Kragh et al., 1991 [16]	Prospective, randomized, single-blind controlled trial	Evaluate effectiveness of 7–10 day fast followed by	• N= 53; F= 45, M = 8 • N_E= 27 • N_C = 26	13 months	Experimental: 7–10 day fast, individually adjusted gluten-	• Clinical examination conducted at baseline, 4	An individually adjusted diet reduces disease activity in patients with RA

		individually adjusted vegetarian diet as a supplemental treatment for patients with RA	• Classic or definite RA diagnosis in class II or III • Active disease • ¾ of the following criteria: ≥ 3 swollen joints, ≥ 6 tender joints, morning stiffness ≥ 45 min, ESR ≥ 28 in the 1st hr. • Stable dose of slow-acting antirheumatic drugs (SAARDs), cytostatic drugs, or NSAIDS for ≥ 3 months • Corticosteroid dose ≤ 7.5 mg/day and stable for ≥ 4 weeks		free; vegan diet for 3–5 months; lactovegetarian diet for remainder of trial Control: ordinary diet with no interventions	weeks, and every 3 months • VAS for pain • Duration of morning stiffness assessed daily • HAQ • Radiographs of hand, wrist, and forefoot taken at baseline and upon completion • Lab values: ESR, hemoglobin, CRP, serum albumin	Allergens or food intolerances may be involved in the pathogenesis of RA
Kjeldsen-Kragh et al., 1994 [17]	Prospective cohort study utilizing patients from a 1993 controlled trial	Determine whether fasting followed by individually adjusted vegetarian diet remains effective at suppressing disease activity in patients with RA one year after completion of original trial	• N= 45 • Divided into responders vs. non-responders • Medication alterations permitted after conclusion of initial trial	1993 trial: 1 year Current study: 1 year after termination of 1993 trial	Experimental: individually adjusted vegetarian diet Control: omnivorous diet Note: At 2-year follow-up, ½ of diet responders had continued to follow individually adjusted vegetarian diet	• Number of swollen joints • Stanford HAQ • VAS for pain • Number of tender joints • Global assessment • ESR	An individually adjusted vegetarian diet remained effective at reducing disease activity two years after initial implementation Subjective and objective clinical variables were indicative of sustained reduction in disease activity
Kjeldsen-Kragh et al., 1995	Clinical trial	Compare serum antibody activity against food	• N_E= 27 • N_C = 30	1 year	Experimental: 7–10 day fast, individually	• Antibody measurement in both	Disease activity did not appear to correlate with fluctuations in

[18]		antigens with disease activity in patients with RA Compare anti-food antibody activity in healthy patients to RA patients	• Experimental: diagnosis of RA • Control: healthy individuals with no history of allergy • No specifications regarding medication alterations during trial		adjusted gluten-free; vegan diet for 3–5 months; lactovegetarian diet for remainder of trial	experimental and control: IgA, IgG, IgM, IgE • Clinical examination in experimental group: Stoke disease activity index	food antigens, IgG, IgA, or IgM antibody activity The study did not assess overall benefit of diet in reduction of disease activity
Kjeldsen-Kragh et al., 1995 [19]	Randomized, single-blind controlled trial	Examine the impact of fasting and vegetarian diet on biochemical and immunological variables in patients with RA	• N=57 • N_E=27 • N_C =26 • Diagnosis of classic or definite rheumatoid arthritis • No specifications regarding medication alterations during trial	1 year	Experimental: 7–10 days fasted, gluten-free vegan diet for 3 months, lactovegetarian diet for remainder of study Control: omnivorous diet	• Blood samples collected at 1, 4, 7, 10 and 13 months • Number of swollen joints • Stanford HAQ • VAS for pain • Number of tender joints • Global assessment • ESR	Significant decreases in leukocyte count, IgM, RF, C3 and C4 were observed in vegetarian patients with clinical improvements Evidence suggests dietary intervention can reduce disease activity in RA patients
Kjeldsen-Kragh et al., 1995 [20]	Controlled clinical trial	Identify an association between proteus antibodies and disease activity in patients with RA when treated with fasting and vegetarian diet	• N=53 F= 45, M = 8 • N_E=27 • N_C ==26 • Classic or definite RA diagnosis in class II or III • Active disease • ¾ of the following criteria: ≥ 3 swollen joints, ≥ 6 tender joints, morning stiffness ≥ 45 min, ESR ≥ 28 in the 1st hr.	1 year	Experimental diet: First 7–10 days fasted; 3–5 months gluten-free, vegan diet; lactovegetarian diet for remainder of study Control diet: normal omnivorous diet	• Number of swollen joints • Functional disability • Pain score • Number of tender joints • Global assessment • ESR • Observed at baseline, 1, 4, 7, 10, and 13 months	Vegetarian diet significantly decreased anti-proteus titer in patients who experienced improvements in disease activity Evidence suggests antibodies may be involved in pathogenesis of RA

			• Stable dose of slow-acting antirheumatic drugs (SAARDs), cytostatic drugs, or NSAIDS for ≥ 3 months • Corticosteroid dose ≤ 7.5 mg/day and stable for ≥ 4 weeks				
Kjeldsen-Kragh et al., 1996 [21]	Clinical trial	Identify a correlation between IgG and clinical changes in RA patients when prescribed a 7–10 day fast followed by 3.5 months of vegetarian diet	• N=26 • Classic or definite RA diagnosis in class II or III • Active disease • ¾ of the following criteria: ≥ 3 swollen joints, ≥ 6 tender joints, morning stiffness ≥ 45 min, ESR ≥ 28 in the 1st hr. • Stable dose of slow-acting antirheumatic drugs (SAARDs), cytostatic drugs, or NSAIDS for ≥ 3 months Corticosteroid dose ≤ 7.5 mg/day and stable for ≥ 4 weeks	7–10 days, followed by 3.5 months	Fasting period of 7–10 days; gluten-free vegan diet for 3.5 months	• number of swollen joints • Stanford HAQ • VAS for pain • Number of tender joints • Global assessment • ESR • Improvement defined by ≥20% improvement	Results do not suggest that glycosylation of IgG plays an important role in RA Clinical and laboratory values improved during fasted state and improvements were sustained throughout vegan diet
McDougall et al., 2002 [22]	Single-blind dietary intervention study	Determine the impact of a low-fat vegan diet on patients with RA.	• N=24, 92% female • moderate to severe RA • ages 27–80 • Stable dose of medications 4 weeks prior to study	4 weeks	Low-fat, vegan diet No animal products or added fats/oils of any kind	• Evaluations conducted before and after 4-week period • Joint swelling and joint	Significant reduction in RA symptoms is associated with low-fat, vegan diet

			• No vegan or dairy-free diet prior to study • No other significant diseases i.e. diabetes			tenderness score • VAS for pain • Functionality • Severity of morning stiffness • Duration of morning stiffness • Body weight • Lab values: ESR, CRP and RA factor • Intake assessed by 4-day food list & food monitoring checklist	
Nenonen et al., 1998 [23]	Randomized controlled trial	Investigate the effects of an uncooked vegan diet, rich in lactobacilli, on RA and identify potential therapeutic components of the diet to assess in further studies	• N=43 • Chronic and active RA per ARA criteria • Steinbrocker's functional class II-III • ≥ 3 swollen joints or ≥ 5 tender joints • ESR > 20 mm/h or CRP > 10 mg/l • Medication alterations permitted during trial	2–3 months	Experimental: uncooked "living food" vegan diet, rich in lactobacilli Control: omnivorous diet	• 7-day dietary records collected before, during, and after the intervention • ESR • Number of swollen joints • Number of tender joints • VAS for pain • HAQ • Global patient estimate • Increase or decrease of ≥ 20% considered significant	"Living food" diet rich in lactobacilli may improve subjective symptoms in patients with RA; no changes were observed in objective measures of disease activity

Peltonen et al., 1994 [24]	Prospective, single-blind, randomized controlled trial	Determine the role of fecal flora in improvements of RA patients treated with dietary modifications	• N=53; F=45, M=8 • Stable dose of DMARDS or cytostatic drugs for ≥ 3 months • N_E = 27 • N_C = 26	13 months	Experimental: 7–10 day fast, vegan diet for 3.5 months, lactovegetarian diet for remaining 9 months; individually adjusted based on foods associated with inflammation Control: omnivorous diet	• Examinations performed at baseline, 4 weeks, and every 3 months thereafter • VAS for pain • Stanford HAQ • Number of tender joints • Number of swollen joints • Collection of stool samples	Significant differences in fecal flora were observed between the HI and LI groups Clinical improvements in RA may be associated with intestinal bacteria
Peltonen et al., 1997 [25]	Randomized controlled trial	Determine an association between changes in fecal flora and decreased disease activity in patients with RA when following an uncooked, vegan diet high in lactobacilli	• N=43 • Diagnosed with RA per ARA criteria • Functional class II-III • ≥ 3 swollen joints or ≥ 5 tender joints • Elevated ESR > 20 mm/h CRP > 10 mg/l • Medication alterations permitted after first month of trial	1 month	Experimental: "living food" diet classified as uncooked vegan diet rich in lactobacilli Control: normal omnivorous diet	• Dietary records collected for 1 week prior to intervention and after 1 month • Pain scale • HAQ • Number of swollen joints • Subjective evaluation of improvement and ESR • Blood and stool samples collected prior to intervention and at 1 month	Vegan diet was associated with changes in fecal flora in patients with RA Changes in fecal flora are associated with decreased disease activity in patients with RA
Sarzi-Puttini et al., 2000 [26]	Double-blind, randomized controlled trial	Examine the effects of two different diet regimens on	• N= 50 • Definite or classical rheumatoid arthritis per ACR criteria	24 weeks	Experimental: includes common hypoallergenic	• Evaluations at entry, biweekly for 4 weeks, monthly for	Patients reported satisfaction with dietary intervention despite lack of

		disease activity in patients with RA	• Ages 25–70 • Function class I or II • Stable dose of DMARDs ≥12 weeks prior to study • Presence of 4/5 of following criteria: ≥ 5 painful joints, ≥ 3 swollen joints, pain score ≥ 4 on VAS, morning stiffness ≥ 45 min, ESR ≥ 30 mm/h, informed written consent		foods; deprived of allergenic foods, canned foods, or "transformed" foods Control: well-balanced diet All participants: maintain or pursue ideal body weight; 1400–2000 kcal/day 1:1 ratio of unsaturated to saturated fats in control and 2:1 ratio in experimental	remaining study • Duration of morning stiffness • Number or tender/swollen joints • Ritchie's index • Pain scale • Global assessment • HAQ administered at entry, after 12 weeks, and after 24 weeks • BMI • Laboratory values: CBC, differential, rheumatoid factor, CRP, ESR, lipid panel, urinalysis	statistical significance observed in measures of disease activity Perceived benefits may have been attributed to modification of food supplements or weight reduction
Skoldstam et al., 1979 [27]	Randomized controlled trial	Determine the effects of fasting and lactovegetarian diets in patients with RA	• N=26 • Diagnosis of RA per ARA criteria • Functional class I and II • No major medications changes prior to examination • N_E=16 • N_C =10	7–10 days followed by 9 weeks	Experimental: 7–10 day fast followed by 9 weeks of lactovegetarian diet Control: normal diet	• Evaluations at baseline, the day after fasting, and at the end of the vegetarian diet • VAS and graphic rating scale every 3 weeks for pain and stiffness	Temporary improvements observed during fasting Lactovegetarian diet does not appear to be beneficial in RA patients

						• Vernon finger-joint comparator • Grip strength and hand measurements • "clinical 6 joint score" to assess pain, tenderness, and swelling • Functional assessment • T & B lymphocytes	
Skoldstam et al., 2003 [28]	Single center, randomized, parallel study	Compare a MD versus a WD in suppression of disease activity in patients with RA	• N=56 • N_E=29 • N_C =27 • 2–6 patients per test group • Diagnosis of RA per ACR criteria • Disease duration >2 years • No changes to DMRADS for ≥ 3 months, corticosteroids for ≥ 4 weeks, or NSAIDS for ≥ 10 days prior to trial • No doses of prednisolone greater than 12.5 mg • Baseline DAS28 score > 2.0	3-month periods occurring between Sept. 1998 and Nov. 2000	Control: normal food Experimental: Cretan Mediterranean diet	• Clinical assessments performed at baseline, end of the 3rd week, midpoint, and completion of the study • DAS-28 • HAQ • GAT • Quality of life assessed via Short Form-36 Health Survey • Daily dose of NSAIDs • Lab values: ESR, CRP, thrombocyte count	Reduced inflammation, increased physical function, and improved lab values were associated with implementation of Mediterranean diet in RA patients
ACR indicates American College of Rheumatology; AID, anti-inflammatory diet; anti-PCs, atheroprotective antibodies against phosphorylcholine; ARA, American Rheumatism Association; CRP, C-reactive protein; DAS-28, disease activity score-28; DMARD, disease modifying anti-rheumatic agent; ESR, erythrocyte sedimentation rate; F, female; GAT, grip ability test; HAQ, health assessment questionnaire; LI, Lansbury Index; M, male; MD, Mediterranean diet; MUFA, mono-unsaturated fatty acids; N, total number of participants; N_C, number of participants in control group; N_E, number of participants in							

experimental group; NSAID, nonsteroidal anti-inflammatory drug; oxLDL, oxidized low-density lipoprotein; RA, rheumatoid arthritis; SCFA, short-chain fatty acids; SF-36; short form 36 health survey; VAS, visual analogue scale; WD, western diet

The duration of each dietary intervention varied by study; however, for the purpose of analysis, they have been broadly classified as interventions that were less than six months, six months to one year, and greater than one year. Nine (45%) interventions were completed in less than six months, seven (35%) were completed between six months and one year, and four (20%) extended beyond one year.

Participants in all studies were over the age of 18 years, and a majority were female. No consistency in the average age of participants was observed. The number of participants ranged from 24 to 413, with an average of 66 participants per trial. Eight studies (40%) included fewer than 50 participants, 11 studies (55%) included between 50–100 participants, and one study (5%) included more than 100 participants. All studies required a pre-existing diagnosis of RA. Six studies (30%) required diagnosis that was consistent with standards set by the American College of Rheumatology, four (20%) aligned with diagnostic standards determined by the American Rheumatism Association, and one study (5%) recruited participants through newspaper ads and letters to rheumatologists. The remaining eight studies (40%) assessed a group of outpatients from the Department of Oslo Sanitetsforening Rheumatism Hospital in Norway, originally described by Kjedlsen-Kragh et al., 1991[16].

Dietary interventions implemented in the 19 included studies were varied; however, they have been grouped into four general categories: a period of fasting followed by a plant-based diet, vegan diet, Mediterranean diet, and other dietary interventions.

Period of fasting followed by plant-based diet:

Of the 19 articles included in this review, ten (50%) incorporated a 7–10 day period of fasting followed by a plant-based dietary intervention. Eight (40%) of the nineteen studies were

based on results from the 13-month trial conducted by Kjeldsen-Kragh in 1991[16]. All eight of those studies examined different outcomes from the trial. The intervention began with a 7–10 day period of fasting in which caloric intake was restricted to 800–1260 kJ/day (190–300 kcal). The period of fasting only allowed consumption of herbal teas, garlic, vegetable broth, potato and parsley broth, and juice extracts from carrots, beets, and celery. Fruit juices were not permitted[16]. After the period of fasting, participants followed an individually adjusted, gluten-free, vegan diet for 3.5 months. "New foods" were introduced to the diet every 2nd day. If participants began to experience an increase in pain, swelling, or stiffness, the new food was removed for a minimum of seven days. If symptoms were exacerbated upon reintroduction of the food, it was eliminated from the diet for the remainder of the study[16]. No refined sugar, strong spices, alcohol, coffee, or tea were permitted during this period[16]. For the remainder of the study, participants could reintroduce milk products and gluten on the precipice that foods were omitted if symptoms increased[16]. Kjeldsen-Kragh et al., 1994 conducted a prospective cohort study to determine whether the individually adjusted vegetarian diet remained effective for suppressing symptoms of RA a year after completion of the original trial[17].

Skoldstam et al., 1979 used a similar dietary intervention to the trial described above. Participants followed a 7–10 day fast with a caloric limit of 800 kJ/day (190 kcal)[27]. Patients were permitted three liters of fruit and vegetable juice per day. After the period of fasting, participants followed a lactovegetarian diet for nine weeks. No animal or fish proteins, alcohol, or tobacco, were permitted. Yogurt was acceptable, but participants were discouraged from consuming milk or cream, and were encouraged to restrict salt, sugar, and white flour intake. Small amounts of grain products were permitted outside of breakfast[27].

The study conducted by Abendroth and colleagues has been included here as well as in the Mediterranean diet category, as it incorporates multiple dietary interventions. In this study, the experimental group followed a 7–10 day fast, followed by a Mediterranean diet (MD); the control group also followed a MD[10]. The duration of the study was 20 months. Participants were inpatients of the Internal and Integrative Medicine Department in Essen, Germany. The experimental group began a pre-fast on the third day of admission. They were provided 3350 kJ (800 kcal) of pure rice and vegetables. From the fourth day to the tenth day, participants were restricted to a maximum caloric intake of 1255 kJ/day (300 kcals). The period of fasting permitted tea (no green or black teas), 200 mL of fruit juice, and light vegetable soup. The two days following the period of fasting were low in calories and incorporated stepwise reintroduction of foods[10]. The details of the MD are described in a later section.

The objectives of the studies included in this grouping were heterogeneous, and some were more quantifiable than others. Kjeldsen-Kragh et al., 1991[16], Kjeldsen-Kragh et al., 1994[17], and Skoldstam et al., 1979[27] sought to assess the effectiveness of the overall dietary intervention for suppressing disease activity in patients with RA. Disease activity is defined by measurements of symptoms and disease progression. Table 2 categorizes measurements of disease activity as subjective, semi-objective, and objective variables, and is applicable to all nineteen studies included in this review.

Table 2. Subjective, Semi-Objective, and Objectives Measurements of Disease Activity in Patients with RA

Measures of Disease Activity		
Subjective	**Semi-Objective**	**Objective**
VAS	LI	Fecal flora
HAQ	DAS-28	Anti-proteus titer

SF-36 Global assessment	GAT ACR20 Ritchie articular index Number of swollen joints Number of tender joints Duration of morning stiffness	Anti-PCs Lipid profile (oxLDL, LDL, HDL, etc.) Antibodies (IgM, IgG, IgA, etc.) CBC values (ESR, CRP, RF WBC, hemoglobin, platelet count, serum albumin, etc.)
ACR20 indicates American College of Rheumatology 20%, anti-PCs; atheroprotective antibodies against phosphorylcholine; CRP, C-reactive protein; DAS-28, disease activity score-28; ESR, erythrocyte sedimentation rate; GAT, grip ability test; HAQ, health assessment questionnaire; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LI, Lansbury Index; oxLDL, oxidized low-density lipoprotein; RF, rheumatoid factor; SF-36; short form 36 health survey, VAS, visual analogue scale; WBC, white blood count		

The remaining seven studies that incorporated a period of fasting followed by a plant-based diet sought to identify correlations between quantifiable variables and disease activity in patients with RA. These variables included immunological and biochemical lab values[19], serum antibodies[18,21], proteus antibodies[20], and fecal flora[25]. Reduced disease activity was observed in all 10 of the studies that incorporated a period of fasting followed by a plant-based diet. Table 3 is a depiction of assessed variables that reflected reduced disease activity in RA patients who participated in a fast followed by a plant-based diet.

Table 3. Observations of Reduced Disease Activity for a Period of Fasting Followed by a Plant-based Dietary Intervention

Study	Subjective	Semi-Objective	Objective
Abendroth et al., 2010 [10]	•	•	
Haugen et al., 1994 [14]		•	
Kjeldsen-Kragh et al., 1991 [16]	•	•	•
Kjeldsen-Kragh et al., 1994 [17]	•	•	•

Kjeldsen-Kragh et al., 1995 [18]		•	
Kjeldsen-Kragh et al., 1995 [19]		•	•
Kjeldsen-Kragh et al., 1995 [20]		•	•
Kjeldsen-Kragh et al., 1996 [21]		•	
Peltonen et al., 1994 [24]		•	•
Skoldstam et al., [28] 1979	•	•	•
• indicates statistical significance for reduced disease activity			

Vegan diet:

A vegan diet was independently utilized in five (25%) of the nineteen studies. The studies published by Hafstrom et al., 2001 and Elkan et al., 2008 were based on the 2001 Hafstrom et al. trial; however, each study focused on a separate outcome[12,13]. Participants were randomly assigned to an experimental gluten-free, vegan diet, or an omnivorous control diet. The experimental diet began with one a one-day low-energy fast consisting of vegetable broth and berry juice[13]. The participants then immediately began the gluten-free, vegan diet, which was followed for the next year. Energy was restricted to 10% protein, 60% carbohydrates, and 30% fat. Less than 10% of fats could come from saturated fats. The diet included vegetables, root vegetables, nuts, fruits, buckwheat, millet, corn, rice, and sunflower seeds. Calcium was derived from sesame milk[13]. The control diet contained a variety of foods from all food groups, and energy intake was limited to 10–15% protein, 55–60% carbohydrates, and 30% fat. Participants were encouraged to consume five or more servings of fruits and vegetables per day, as well as increased intake of starches and complex carbohydrates[13].

Both Peltonen et al., 1997 and Neonen et al.,1998 were based on the 1997 Peltonen et al. trial; however, the studies examined separate outcomes[23,25]. Participants were recruited from the Rheumatic Outpatient Clinic at Kivela Hospital in Finland. Participants were randomly assigned

to an experimental uncooked, vegan diet rich in lactobacilli or an omnivorous control diet. Participants of the experimental group received the "living food" components of their diet from a specialized kitchen that weighed and pre-packaged the foods. The diet did not contain animal products, refined products, or added sat. Foods could be soaked, sprouted, fermented, blended, or dehydrated[25]. The control group prepared their food at home.

McDougall et al., 2002 conducted a single-blind dietary intervention study that implemented a 4-week low-fat vegan diet[22]. Participants received weekly education regarding dietary practices. Less than 10% of energy consumption was derived from fats. No animal products or added fats or oils were permitted. Dietary components included common starches, such as beans, pasta, potatoes, and rice, and fresh or fresh-frozen fruits and vegetables. Dehydrated cereals, soups, and main entrees supplemented daily meals. Participants were encouraged to eat as much and as often as they liked[22].

Two of the studies in this group investigated lipid profiles[12], antibodies[12], and fecal flora[26] and their relationships to disease activity. The remaining three studies sought to identify the effects of a vegan diet on overall disease activity. In all five studies, reduced disease activity was observed following the period of the experimental diet. Table 4 is a depiction of assessed variables that reflected reduced disease activity in RA patients who participated in vegan diets.

Table 4. Observations of Reduced Disease Activity for a Vegan Dietary Intervention

Study	Subjective	Semi-Objective	Objective
Elkan et al., 2008 [12]	•	•	•
Hafstrom et al., 2001 [13]		•	•
McDougall et al., 2002 [22]	•	•	•
Nenonen et al., 1998 [23]	•	•	
Peltonen et al., 1997 [25]		•	•

• indicates statistical significance for reduced disease activity

Mediterranean diet:

The MD was used in two (10%) studies. Abendroth et al., 2010, which was mentioned in an earlier section, compared a Mediterranean control diet to a 7-day fast followed by a MD[10]. The MD component of the intervention was the same for both the control and the experimental groups. Caloric intake was restricted to 2,000 kcal/day. Participants were allotted 1–2 portions of meat per week. No alcohol or caffeine was permitted. Additional dietary components included seven portions of fruits and vegetables per day, high intake of whole-grain bread, pasta, and rice, two portions of fish per week, and olive oil and canola oil, exclusively[10].

Skoldstam et al., 2003 compared an experimental MD to a Western control diet (WD)[28]. Fifty-six Swedish RA patients participated in the study for increments of three months. Test groups consisted of 2–6 participants, who were randomly assigned to the MD or a standard WD generally consumed by Swedish individuals. Food was provided for both groups for the first three weeks of the intervention. Participants of the MD group could use olive oil and canola oil, but were encouraged to reduce consumption of milk, fermented milk, and dairy products. There were no recommendations regarding alcohol consumption; however, participants were encouraged to drink green or black tea for polyphenolic content. MD participants received lessons from a dietitian and written instructions/recipes to facilitate meal preparation[28]. Control participants returned to their normal diets after the first three weeks of the intervention[28].

The objective of Abendroth et al., 2010 was to evaluate the effect of a MD versus a period of fasting followed by a MD, on lipid profiles and clinical outcomes in patients with RA[10]. There were no significant differences in the outcomes of either dietary approach; however, reduced disease activity was observed in both interventions[10]. Skoldstam et al., 2003 sought to compare a MD to a Swedish WD for suppression of RA symptoms and disease progression[28].

Outcomes demonstrated improvements in symptoms and perceived quality of life in participants who followed the MD diet, but not the WD diet[28]. The results of both studies suggest a MD diet may be beneficial at reducing the overall disease activity in patients with RA. Table 5 is a depiction of assessed variables that reflected reduced disease activity in RA patients who participated in Mediterranean diets.

Table 5. Observations of Reduced Disease Activity for a Mediterranean Dietary Intervention

Study	Subjective	Semi-Objective	Objective
Abendroth et al., 2010 [10]	•	•	
Skoldstam et al., 2003 [28]	•	•	•
• indicates statistical significance for reduced disease activity			

Other dietary interventions:

The three remaining studies were grouped into a separate category as they utilized "other" dietary interventions. In an 8-month double-blind crossover study, Adam et al., 2002 compared an experimental modified lactovegetarian, anti-inflammatory diet (AID) to a control WD[11]. Participants in both groups received supplements with dosages based on body weight, either a placebo or fish oil. Interventions were three months in duration, each with a 2-month washout period between treatments. Participants in the AID intervention were required to reduce arachidonic acid (AA) intake by limiting meat consumption to a maximum of two servings of 120g per week. Fats and oils were derived from plants, and consumption of dairy products was reduced relative to intake prior to participation in the trial[11]. Participants in the control group continued their typical dietary habits, often consuming meat or produce more than twice a week[11].

Ten RA outpatients of the Kouda Clinic in Osaka, Japan participated in the 54-day trial conducted by Igwashige et al[15]. Participants followed a calorie-restricted diet from days 0–10, 14–24, 31–43, and 49–54. During these periods, energy intake was limited to 2085 kcal/day. For breakfast, participants were supplied 250g of fresh vegetables. Lunch and dinner consisted of 80g of brown rice porridge, 5g of kelp powder, 200g of tofu, and 10g of sesame paste. Diets were supplemented with 2.5g of non-refined salt[11]. From days 11–13, 25–30, and 44–48, participants followed a period of fasting. On these days, caloric intake was limited to 720 kcal/day, and only vegetable soup was provided[11].

In the Sarzi-Puttini et al., 2000 study, fifty RA patients were randomized to an experimental hypoallergenic diet or a calorie-restricted control diet foods[26]. Both diets were designed to maintain or lead to ideal weight and limited energy intake to 1400–2000 kcal/day. The experimental diet contained foods that are typically considered to have a low risk for allergic reactions following consumption: rice, cornmeal, cornbread, hydrolyzed milk, fresh pineapple, and cooked apples. The diet was void of wheat, eggs, milk, strawberries, acidic fruit, tomato, chocolate, shellfish, and dried fruit. Only lean cuts of meat were permitted with restrictions of consumption no more than three times per week[26]. Both diets incorporated olive oil. The control diet included a 1:1 ratio of unsaturated fatty acids to saturated fatty acids, while the experimental diet included a 2:1 ratio[11].

Both Adam et al. 2002 and the Igwashige et al. 2004 sought to determine whether fluctuations in objective biochemical variables, such as levels of cytokines and urine pentosidine, following dietary interventions correlated with reduced disease activity[11, 15]. The Sarzi-Puttini et al. 2000 study investigated the effect of the dietary intervention on both clinical and laboratory markers of disease activity. Reduced disease activity was observed following all three dietary

interventions. Table 6 is a depiction of assessed variables that reflected reduced disease activity in RA patients who participated in trials with "other" dietary interventions.

Table 6. Observations of Reduced Disease Activity for Other Dietary Interventions

Study	Subjective	Semi-Objective	Objective
Adam et al., 2002 [11]	•	•	•
Iwashige et al., 2004 [15]		•	•
Sarzi-Puttini et al., 2000 [27]		•	•
• indicates statistical significance for reduced disease activity			

Discussion

The objective of this critical review was to evaluate the existing research on dietary interventions for treatment of RA symptoms to determine which diet therapies may be effective for improving symptoms and inflammatory markers of disease activity. Nineteen studies were included and varied by duration, number of participants, and dietary intervention. For analysis, the studies were separated by type of dietary intervention. These interventions included a period of fasting followed by plant-based diet, vegan diet, Mediterranean diet, and other dietary interventions. The objectives of the studies were heterogeneous, and some variables were more objective/quantitative than others. Overall, a reduction of some combination of symptoms and inflammatory markers of disease activity was observed in RA patients within all studies.

Semi-objective measurements of disease activity were the most frequent type of outcome showing statistical significance for reduced disease activity across all dietary interventions. This is most likely due to the use of DAS-28, ACR20, and study-specific disease indices that were frequently used to assess overall disease activity. A composite score of several objective and semi-objective variables was combined to create a disease index; therefore, variables were assessed as a semi-objective collective, rather than by individual components of disease activity.

Determining the clinical significance of the assessment variables is difficult for several reasons. There is no definitive diagnosis for RA, and an established diagnosis is based on criteria that are constantly changing and evolving[1]. Current diagnostic standards, as established by the American College of Rheumatology in 2010, require that a patient with suspected rheumatoid arthritis, score ≥ 6 out of 10 on the criteria index for classification of disease[29]. A score is assigned based on review of symptom duration, joint evaluation, one serologic antibody test for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), and an acute-phase

response measurement of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). A patient may, however, receive 6 points on the criteria index for the number of involved joints and duration of symptoms, and therefore, the requirement for serologic or acute-phase response testing is no longer essential for diagnosis[29]. Additionally, biochemical (objective) variables of disease activity, such as ESR, are not specific to any one disease, and may be influenced by several factors, including pregnancy, aging, and red blood count abnormalities[30]. For these reasons, the assessment variables utilized to establish reduced disease activity may not accurately reflect notable improvements in symptoms or disease progression in patients with rheumatoid arthritis. Additionally, patient-specific variables may better demonstrate reduced disease activity than observing each variable, or classification of variables, as a collective for the sample population. For example, a statistically significant reduction in ESR simply implies that a reduction of ESR was observed. It does not, however, suggest a significant reduction in inflammatory activity, nor is it necessarily associated with subjective or semi-objective improvements of disease activity, such as reduced number of tender or swollen joints or improved overall quality of life.

Aside from reduced disease activity, several other findings were notable. Some studies examined the role of fatty acids or lipid profiles in disease activity. One study concluded that the ratio of eicosapentaenoic acid (EPA) to arachidonic acid (AA) might be associated with a reduction of disease activity in patients with RA when following an anti-inflammatory diet[11]. Further, Elkan and colleagues observed decreases in total cholesterol, LDL, and the ratio of LDL to HDL throughout the vegan diet group, but decreased oxLDL was only observed in participants of the vegan diet whose reduced disease activity classified them as a diet responders[12]. These findings suggest that fatty acid consumption and metabolism may be associated with disease

activity; however, Haugen and colleagues did not observe changes in fatty acid concentrations in patients who responded positively to a period of fasting followed by a plant-based diet[14]. It cannot be concluded that weight loss and decreased BMI secondary to dietary interventions, are not explanatory for changes in lipid profiles and decreased disease activity; therefore, further research is necessary to identify the role of fatty acids in the pathogenesis of RA.

Findings to support the role of immunological and biochemical markers in disease activity were inconsistent. These markers included objective variables, such as IgM and anti-proteus titers, which could be indicative of inflammation but are not often used to confirm active disease in patients with RA. Hafstrom and colleagues found that a vegan diet may have a positive effect on immune response[13]. Results from additional plant-based dietary interventions identified an increase in antibodies, decrease in IgM, RF, and leukocyte count, a decrease in anti-proteus titer, and changes in fecal flora [12,13,19,20,27,28]. All of these results were identified in patients who also experienced reduced disease activity, according to the assessed variables[12,13,19,20,27,28]. Caloric restriction also produced positive results for disease activity and reduced levels of urine pentosidine[15]. Contrastingly, two studies that analyzed data from the 1991 trial conducted by Kjeldsen-Kragh and colleagues, identified no significant positive correlations between immunological variables and reduced disease activity in patients with RA[16,18,21]. While the research has identified some correlations between dietary interventions and alterations in objective immunological and biochemical variables, there is not sufficient evidence to confirm their role in disease activity. Thus, further experimentation is necessary.

Given the lack of current research, further examination of additional dietary interventions is necessary to determine the therapeutic potential for reducing symptoms and disease progression in patients with RA. For example, a study which was excluded from this review due

to observational rather than experimental design, identified monounsaturated fatty acids and polyunsaturated fatty acids as components of the Mediterranean diet, which may play a direct role in reduced disease activity in patients with RA[31]. Research suggests that increased consumption of omega-3 fatty acids derived from fish or plant sources results in the production of eicosanoids that have fewer inflammatory properties and may inhibit the synthesis of pro-inflammatory cytokines[32]. A Mediterranean diet is not only rich in omega-3 fatty acids, but it is also abundant in fruits, vegetables, and whole grains, which have been associated with lower levels of CRP and increased intake of anti-inflammatory antioxidants[32].

In addition to a Mediterranean diet, research suggests that a dietary pattern with an intake of balanced macronutrient ratios may be important for the regulation of inflammation[8]. Excess carbohydrate consumption is associated with excess secretion of insulin, which promotes the conversion of EPA to AA, and fosters the production of inflammatory eicosanoids[8]. Conversely, consumption of too few carbohydrates can initiate ketosis, thereby leading to increased cortisol levels[33]. Excess caloric intake has been shown to be associated with hypothalamic inflammation and increased appetite[34]. Regulation of inflammation is dependent upon a delicate balance between total calorie consumption and proportions of macronutrient intake[8]. Future research should investigate other dietary interventions that show promise for reducing inflammation, as anti-inflammatory diets for the treatment of symptoms and disease progression in patients with RA may extend beyond the dietary interventions that have been explored in the current review.

With any study, there are limitations that need to be considered when interpreting results. In the current review, while nineteen studies were included, twelve studies assessed outcomes from the same data samples. Therefore, only ten separate trials were available to review based on the study question and the inclusion and exclusion criteria. There is a strong potential for bias

given the reoccurrence of data samples. Additionally, the incorporation of multiple dietary interventions within a single trial, for example, the transition from a period of fasting to a gluten-free, vegan diet to a lactovegetarian diet, increases the difficulty of ascertaining which components of an intervention may be beneficial for reducing symptoms and disease progression in patients with RA. Future research should evaluate each component of the dietary intervention separately using a randomized controlled trial methodology. In addition, there is a need to extend the duration of the dietary interventions to determine the longer-term effects of diet therapy on RA disease activity.

Despite the aforementioned limitations, the current review has several strengths. The overall study question is novel, and the identified dietary strategies have the potential to be beneficial for RA patients as well as patients with other autoimmune disorders. Given the inclusion and exclusion criteria, only the highest quality available evidence regarding the promise of dietary therapies for mitigation of disease activity in patients with RA, was reviewed. The critical approach that was taken to synthesize the results of the included studies allowed for an in-depth analysis of the dietary interventions that have been used for therapy in patients with RA and the types of observed outcomes.

In conclusion, there is limited high-quality research regarding diet therapies for the treatment of symptoms and disease progression in patients with RA. Given the promise of the dietary interventions conducted thus far, further research is necessary to determine the effectiveness of diet therapies, when paired with standard pharmacological interventions, for the reduction of symptoms and disease progression in patients with RA.

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