

Nutritional interventions and supplementation for rheumatoid arthritis patients: A systematic review for clinical application, Part 2: Supplementation

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease that is associated with local and systemic inflammation, resulting in chronic pain and physical function limitations that may negatively impact quality of life (QOL). Despite advances in pharmacological therapies, currently available treatment options may be associated with adverse events and come at a high price tag. As a result, research efforts have grown to focus on nutritional interventions to support pharmacological therapies, reduce inflammation (targeting biomarkers of disease activity) and improve QOL.

Objectives: In this systematic review, data was collected on the most recent non-pharmacological interventions used for RA management. The efficacy and potential practical applications of various nutritional interventions used in the RA management will be discussed. This review has been divided into three parts. In the second of our 3-part series we will discuss interventions involving supplementation and their clinical impact on patients with RA. The compounds discussed in this article include coenzyme q10 (CoQ10), fatty acids (n-3 PUFA and GLA), synbiotic/probiotics, and quercetin. For more information on the other contents of this systematic review you may refer to Part 1: Dieting and Part 3: Fruits and herbs.

Methods: A search of the literature was conducted to identify nutritional interventions in the progression and management of RA. Eligible study designs included meta-analyses, systematic reviews, randomized control trials (RCT), and prospective/retrospective studies. Exclusion criteria included non, *in vivo* human studies, n <40, cross-sectional studies, case-studies, and lack of access to available text.

Results: Initially, 334 articles were identified. After removing studies for lack of relevance, exclusion criteria and duplicates, 22 articles remained. The eligible articles were divided into five groups based on design: meta analyses, systematic reviews, RCTs, literature reviews, and prospective studies. The eligible articles were grouped together based on intervention type: diets, supplementation and the implementation of fruits and herbs. Ten articles were placed under the category of supplementation which includes three Meta analyses, one systematic review, four RCT and two literature reviews.

Conclusion: Nutritional interventions may be an effective method for reducing inflammation and symptoms associated with RA. In particular, the use of Omega-3 (n-3) polyunsaturated fatty acids (PUFA) demonstrated significant improvements in RA indices, in line with prior findings, and are considered safe and effective adjuvant therapies to utilize in clinical practice. Specific recommendations in this article for reduction of pain and medication management include dosage, ratio and duration. Coenzyme q10 and quercetin also demonstrated improvements in DAS-28 as well as TJC and displayed excellent safety profiles, but further research needs to be completed before recommendations as alternative therapy can be made. Despite this, these nutritional interventions are considered safe enough to incorporate into daily regimens with minimal risk. The use of synbiotic in clinical practice requires further research before recommendations can be made.

Keywords: Arthritis; Nutrition; Review; Rheumatoid Arthritis; Supplementation

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease that affects roughly 1% of the global population [1]. Although the exact pathogenesis remains unclear, manifestations of this disease have been well studied. Exacerbations result in an inflammatory process that causes joint swelling and cartilage erosion causing functional limitations. Additionally, this systemic inflammatory process increases the risk of cardiovascular disease, pulmonary disease and overall malignancy [1]. The standard management of these patients includes the utilization of pharmaceutical disease modifying agents such as Methotrexate (MTX), Hydroxychloroquine (HCQ), and Tumor Necrosis Factor Alpha (TNF- α) inhibitors. These medications are often expensive and can result in significant side effects [2]. MTX has been associated with risks of hepatotoxicity, nephrotoxicity and myelosuppression. Similar side effects have also been seen with the use of Leflunomide and Sulfasalazine. Other side effects from these medications include retinopathy (HCQ) and neutropenia (TNF- α) [2]. Factors of this disease include both genetics and environmental. Particularly, diet has been a topic of recent interest for its contribution to ongoing inflammatory processes, its impact on the gut microbiome and potential ability to relieve symptoms when combined with traditional pharmaceutical interventions [3].

In particular, previous studies have indicated that omega-3 supplementation may suppress production of inflammatory cytokines and reduce disease activity [4]. Several other compounds have also been shown to reduce inflammation including quercetin, coenzyme Q10 (CoQ10) and probiotics and may benefit RA patients. This article provides a systematic review of currently available data on the use of non-pharmaceutical interventions for RA management, which was published between 2017 and 2020. The objective is to provide clinicians information on the safety and effectiveness of non-pharmaceutical interventions in RA management to aid in their recommendations. These recommendations include whether these non-pharmaceutical approaches may be used in combination with or alternatively to pharmaceutical agents.

In this effort, standardized assessments have been developed to ascertain both subjective and objective clinical improvements in disease activity. The Disease Activity Score in 28 joints (DAS-28) has been used to monitor disease progression and assesses tender joint counts (TJC), swollen joint counts (SJC), erythrocyte sedimentation rate (ESR), and a global health rating [5]. The 36 item Short Form health survey (SF 36) is a subjective questionnaire utilized for gauging QOL [5]. The visual analog scale (VAS) is an instrument used to measure subjective pain ratings by selecting a value from 0 (no pain) to 100 (severe pain) [5]. The health assessment questionnaire (HAQ) is a tool utilized for self-report of functional status [6]. Additionally, the Ritchie score is a tool that is used to monitor disease severity. This score evaluates the tenderness of joint groups and scores them on a scale from zero to three [7]. These indices will be used because they emphasize the role of both pain and function and can provide clinicians a means of understanding the impact of these treatments on disease status.

Our original search included 22 articles which were then subsequently divided into three sections, Dieting, Supplementation and Fruits and herbs. In the second of our 3-part series we will discuss interventions involving supplementation and their clinical impact on patients with RA. The compounds discussed in this article

include coenzyme q10 (CoQ10), fatty acids (n-3 PUFA), synbiotics/probiotics, and quercetin. For more information on the other contents of this systematic review you may refer to Part 1: Dieting and Part 3: Fruits and herbs.

Methods

Search strategy

A computer assisted systematic literature review was performed using PubMed for research articles examining nutritional interventions in the progression and management of RA. The PubMed word search included “Rheumatoid Arthritis Nutrition”, filtering for articles published between 2017 and 2020. The reference lists of retrieved articles were also considered when found to be relevant and if they fit the search criteria but were not discovered through individual searches. Relevance of these articles were assessed through a hierarchical approach that evaluated first the title, followed by the abstract, and the full manuscript. For articles that were not freely available, access was gained using Nova Southeastern University (NSU) library resources.

Selection criteria

Studies were considered eligible if they discussed specific nutritional interventions evaluating the management or progression of active RA defined by criteria by the American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) [8]. Eligible study designs included meta-analyses, systematic reviews, randomized control trials (RCT), and prospective/retrospective studies. Exclusion criteria included non *in vivo* human studies, n <40, cross-sectional studies, case-studies, and lack of access to available text. A flow diagram (Figure 1) was developed using the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) 2009 outline [9].

Study characteristics

Based on study design studies were divided into five groups:

Meta analyses: 3

Systematic review: 2

Randomized control trials: 11

Literature reviews: 5

Prospective study: 1

Results

A total of 334 articles were identified from the initial electronic database search. Two hundred fifty-five articles were excluded based on lack of relevance found during title and abstract screening, and one duplicate was removed. Of the remaining 78 articles, 56 were excluded for the following reasons (based on exclusion criteria): Lack of *in vivo* human models, n <40, and lack of significant interventional study. A total of 22 articles remained for inclusion in this review.

Discussion

CoQ10

Effects of CoQ10 supplementation on matrix metalloproteinases and DAS-28 in patients with RA: A randomized, double-blind, placebo-controlled clinical trial:

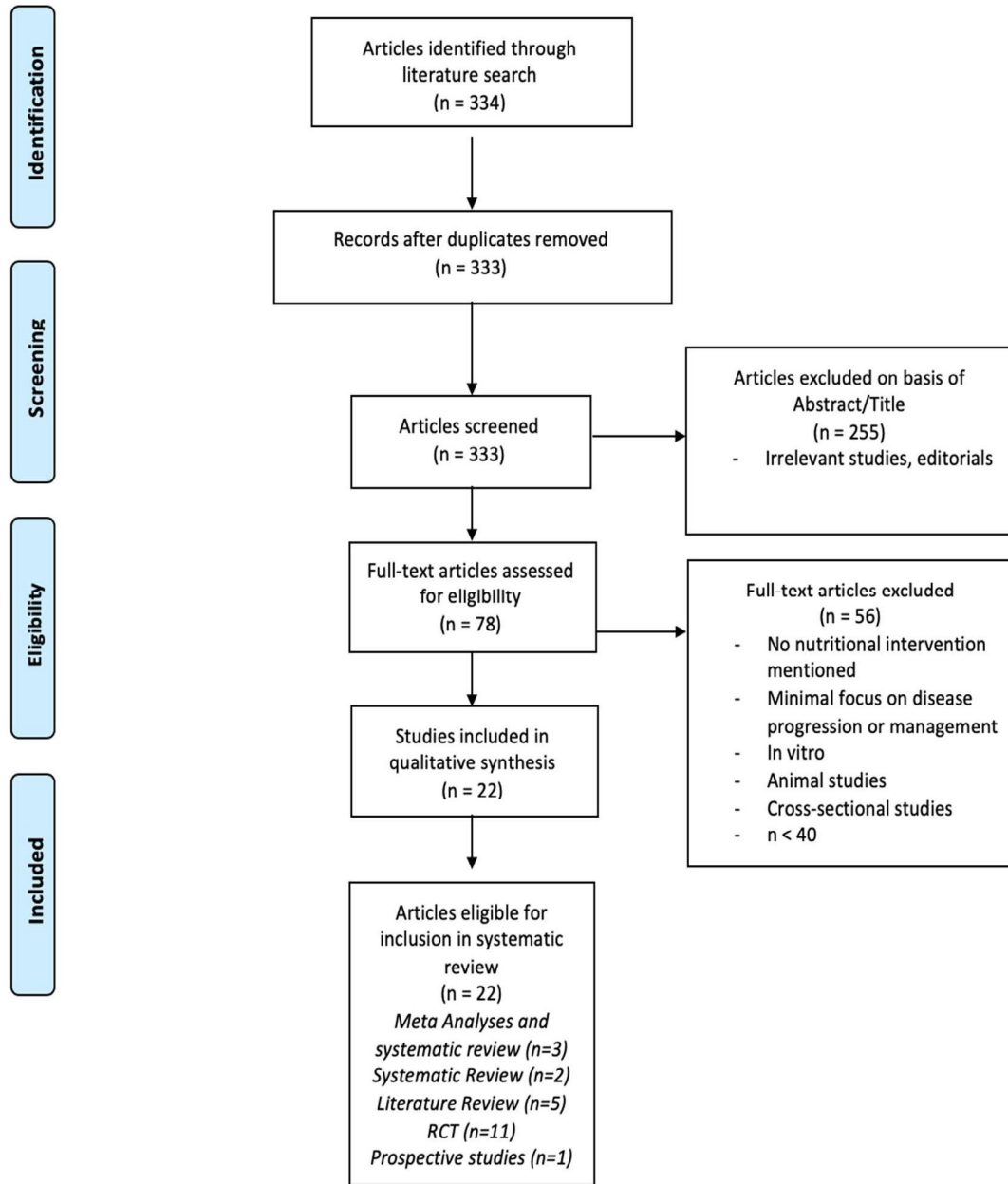


FIGURE 1: Selection process flow diagram.

Study	Publication Year	Subjects (n)	Intervention(s) - duration	Significant improvements
Effects of Coenzyme Q10 Supplementation on Matrix Metalloproteinases and DAS-28 in Patients with Rheumatoid Arthritis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial - Nachvack et al. [18]	2019	54	Coq10 Nachvack et al. [18] – 2 months	Compared to placebo: DAS-28 (p<0.001) ESR (p=0.001) Serum MMP-3 (p=0.027) SJC (p<0.001) TJC (p<0.001) VAS (p<0.001)
Managing Rheumatoid Arthritis with Dietary Interventions - Khanna et al. [56]	2017	1) 45 2) 46	Synbiotic/Probiotics 1. Mandel et al. [57] – 60 days 2. Veghef-Mehrabany et al. [58] – 8 weeks	Compared to placebo: 1) Pain Scale (p=0.046) 2) hs-CRP (p<0.01) DAS-28 (p<0.01) IL-6 and IL-12 (p<0.05) IL-10 (p<0.05). SJC (p=0.03) TNF-alpha (p<0.05) TJC (p=0.03) VAS decreased 43.96%
Clinical Benefits of n-3 PUFA and γ -Linolenic Acid in Patients With Rheumatoid Arthritis - Veselinovic et al. [20]	2017	1) 60 2) 56	GLA and N-3 PUFA 1. Veselinovic et al. [20]– 12 weeks 2. Zurier et al. [21] – 6 & 12 months 3. Cameron et al. [22]	Compared to placebo: DAS-28 1. Primrose + Fish oil/Fish oil (p ≤ 0.001) ESR 1) Primrose + Fish oil/Fish oil (p ≤ 0.001) HAQ 2. (p=0.027) SJC 2) (p=0.034) TJC 2) (p=0.006) VAS 1. Primrose + Fish oil/ Fish oil (p ≤ 0.001) 2. (p=0.004)

Marine Oil Supplements for Arthritis Pain: A Systematic Review and Meta-Analysis of Randomized Trials - Senftleber et al. [23]	2017	2751	Marine oil Senftleber et al. [23]	Inflammation reduction: (p=0.013) CRP avg. reduction of 1.7 mg/dl Pain reduction (p=0.007) VAS 8% improvement
The Mediterranean Diet, Fish Oil Supplements and Rheumatoid Arthritis Outcomes: Evidence From Clinical Trials - Petersson et al. [24]	2018	1) 46 2) 51 3) 60	N-3 PUFA 1. Cleland et al. [27] 2. Nielsen et al. [28] 3. Rajaei et al. [29]	N-3 PUFA 1. GS and TJC 2. TJC 3. EMS, SJC, TJC and VAS
Intake of ω -3 Polyunsaturated Fatty Acids in Patients With Rheumatoid Arthritis: A Systematic Review and Meta-Analysis - Gioxari et al. [37]	2018	1288	N-3 PUFA 1. Gioxari et al. [37] 2. Lee et al. [36] 3. Goldberg and Katz et al. [35]	1) EMS, ESR, GS, HAQ, Ritchie index, TJC, VAS and VAS 2) EMS (p=0.002), TJC (p=0.001) 3) EMS and TJC
Effect of ω -3 Polyunsaturated Fatty Acids on Arthritic Pain: A Systematic Review - Abdulrazaq et al. [40]	2017	1143	N-3 PUFA Abdulrazaq et al. [40]	VAS
The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women With Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial - Javadi et al. [49]	2017	50	Quercetin Javadi et al. [49] – 8 weeks	Compared to placebo: EMS (p=0.03) DAS-28 (p=0.04) HAQ (p=0.008) TJC (p=0.03) hs- TNFa (p=0.04)
Synbiotic Supplementation and the Effects on Clinical and Metabolic Responses in Patients With Rheumatoid Arthritis: A Randomised, Double-Blind, Placebo-Controlled Trial - Zamani et al. [59]	2017	54	Synbiotics/Probiotics Zamani et al. [59] – 8 weeks	Compared to placebo: hs-CRP (p=0.001) DAS-28 (p<0.001) NO levels (p=0.008) VAS (p<0.001)
The efficacy of probiotic supplementation in rheumatoid arthritis: a metaanalysis of randomized, controlled trials - Aqaeinezhad Rudbane et al. [63]	2018	153	Probiotics Aqaeinezhad Rudbane et al. [63]	DAS-28

Table 1: Summary of studies, interventions and significant outcomes.

CoQ10 is a lipid soluble antioxidant that plays a role in the oxidation-reduction process that occurs in cell membranes [10,11]. CoQ10 has been shown to serve as an antioxidant, primarily through effects on free radicals and suppression of TNF- α gene expression, as demonstrated in mouse models [12,13]. Additional animal models and *in vitro* research efforts have highlighted its anti-inflammatory effects, demonstrating clinical improvements in coronary artery disease (CAD), diabetes mellitus, and fibromyalgia [14-17]. In a placebo-controlled study, Nachvak et al. demonstrated significant improvements in DAS-28 score in participants receiving 100 mg/day of CoQ10 for two months as compared to placebo [18]. Results of analysis of covariance (ANCOVA) showed statistically significant differences between those who received CoQ10 and placebo in VAS score, SJC, and TJC. In addition, participants who received CoQ10 also experienced significant decreases in serum MMP-3 (a key enzyme in RA-related cartilage and bone destruction) as compared to placebo ($p=0.027$). One potential issue with this study was that changes in medication intake during the study period were considered as an exclusion criterion for analysis. Three participants were excluded from assessment due to medication change, which could have potentially altered the results. During the two-month study, there were no reported adverse events in either group. Based on these findings, we believe that supplementation with 100mg/d of CoQ10 for two months has the potential to result in significant clinical beneficial for patients with RA, with minimal risk for adverse events. Still, further studies may be needed to confirm the efficacy of this study.

Fatty acids

Clinical benefits of n-3 PUFA and γ -linolenic acid in patients

with RA: Fatty acids have been evaluated for use in clinical practice due to their anti-inflammatory effects. In particular, n-3 PUFA have been of interest to researchers, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Both EPA and DHA interfere with the conversion of arachidonic acid (AA) into pro-inflammatory compounds and have the ability to replace AA to alter cell membrane composition [19]. Other compounds including Gamma-Linolenic Acid (GLA) have similar anti-inflammatory properties and have been evaluated for their potential in serving as adjunct to pharmaceutical approaches in RA management [20]. In one study, Veselinovic et al. performed a double blind, randomized, controlled trial evaluating the effects of fish and primrose oils on clinical and laboratory markers among 60 female RA participants [20]. Participants were divided into three groups administered over 12 weeks: 1) fish oil (5 g; 1500 mg DHA and 1000 mg EPA), 2) fish oil (2 g; 600 mg DHA and 400 mg EPA) with primrose oil (2600 mg; 1898 mg LA and 234 mg GLA), or 3) no supplementation. The investigators included primrose oil to assess the synergistic effect of GLA in addition to n-3 PUFA (fish oil). Participants added one of the three regimens in addition to their normal treatment approach. They were considered eligible if their medication had been stable prior to and remained unchanged throughout the duration of the study. Primary outcomes for this study were alterations of n-3 PUFA in plasma phospholipids, obtained through venous sampling, which would indicate changes in eicosanoid generation with disease activity, serving as a secondary outcome. Clinical evaluation was performed utilizing the DAS-28, ESR, and VAS. Upon completion, significant decreases were seen in the DAS-28 for both the fish oil group as well as the primrose group ($p \leq 0.001$). Group three (no supplementation) also demonstrated

a downwards trend in DAS-28, although not significant ($p=0.053$). ESR decreased in all three groups, however, it was shown to be much lower in groups one and two ($p \leq 0.001$) than in group three ($p \leq 0.01$). VAS score and number of painful joints were significantly decreased in both experimental groups ($p \leq 0.001$). When evaluating the composition of the phospholipids in each of these groups, levels of GLA and AA were found to be higher in group two than in either one of the other groups. Additionally, the level of saturated fatty acids was found to be lower in both groups one and two. Ultimately, this study demonstrated the ability for fatty acid supplementation to improve clinical indices and as well as alter fatty acid composition. Therefore, fatty acid composition can serve as a reliable biomarker for fat intake and patient compliance when evaluating the efficacy of supplementation.

In their discussion, Veselinovic et al., references multiple studies which evaluated the application of GLA in RA patients and were included in this assessment. In a randomized, double blind study, 56 participants with RA were randomized to intake GLA (2.8 g/d of GLA) or placebo (sunflower seed oil) over a six-month. This was then followed by a single-blind trial in which all participants received GLA [21]. At six months, the GLA treatment group demonstrated improvements in SJC ($p=0.034$), TJC ($p=0.006$), duration of morning stiffness, VAS global assessment score, and assessment of pain ($p=0.004$) as well as improvements in HAQ score ($p=0.027$) as compared to placebo. At the end of the second six-month period, participants that were switched from placebo to GLA demonstrated improvements in disease activity with the previous GLA group continuing to show improvement as well. Fourteen of 22 participants in the GLA group demonstrated meaningful improvement, whereas the second group only demonstrated four of 19 participants with improvements. Clinical responses for these two groups were found to be statistically different ($p=0.015$). Fifteen months after the study was completed, most patients experienced exacerbations in RA disease activity as compared to the end of the study. Criticisms of this study include the use of sunflower oil as a placebo, which contained 35 percent oleic acid which may have had an impact on the placebo group's results. Adverse effects included belching (three participants) and diarrhea (four participants). The second study examined by Veselinovic was a meta-analysis performed by Cameron et al. [22] on the effect of herbal medicinal products in the treatment of arthritis. With respect to GLA, the analysis determined that doses of 1400 mg/day or higher alleviated rheumatic complaints, whereas lower doses were ineffective.

Marine oil supplements for arthritis pain: A systematic review and meta-analysis of randomized trials:

Senftleber et. al performed a systematic review and meta-analysis of randomized trials involving the effects of marine oil supplementation on arthritic symptoms [23]. The review included an analysis of 42 RCT. The primary outcome measure was pain, with inflammation and function serving as secondary outcomes. Thirty of the 42 trials included complete data on pain, which demonstrated statistically significant pain reduction ($p=0.007$) effects of marine oil (fish and mussels) and equated to an eight percent improvement in VAS. A significant amount of heterogeneity was detected that was only partly explained by type of diagnosis, supplementation type, and varying dosages. Post-hoc, meta-regression analysis explored the differences between the types of marine oil and pain. The investigators determined that only mussel oil demonstrated statistically beneficial effects. In terms of the secondary

outcomes, out of the 42, 23 and 25 trials were reported to have provided complete data on function and inflammation, respectively. The investigators determined that there was no statistically significant effect of marine oil on function ($p=0.953$), with moderate heterogeneity ($I^2=60\%$), indicating moderate agreement amongst studies. However, the effect of marine oil on inflammation was considered statistically significant ($p=0.013$) and corresponded to an average decrease of 1.7 mg/dl in CRP, with great heterogeneity ($I^2=70\%$). Adverse event analysis indicated no differences between those who received the interventions as compared to controls.

Overall, this meta-analysis suggests favorable effects of marine oils on pain in RA patients. Significant beneficial effects were seen with a EPA/DHA ratio >1.5 and determined there was an inverse dose-response relationship, suggesting less pain reduction at higher doses. The investigators believe this inverse relationship should be approached with caution and that it may be explained by a saturation dose-response-relationship where varying diets may differ in EPA and DHA amounts. Furthermore, the investigators also indicated that several studies included populations whose diets were already high in fish and others that indicated reductions of non-steroidal anti-inflammatory drugs (NSAID) doses, which may have made it more difficult to detect differences in pain. Although this review included various causes of arthritis, 33 of 42 trials were related to RA with at least 25 trials including ≥ 40 participants. With regards to dose, duration and ratio did not change when solely analyzing RA data. However, when only including RA patient's heterogeneity was found to be low ($I^2=32$ percent) thus indicating agreement on the effects of pain and inflammation in this population.

The Mediterranean diet (MD), fish oil supplements and RA outcomes: Evidence from clinical trials: In a review by Petersson et al., the investigators discussed clinical trials on the incorporation of a Mediterranean diet (MD) and various doses of fish oil supplementation [24]. The two MD studies are discussed in part 1 of this systematic review. Remans et al. [25] and Sköldstram et al. [26] performed low dose (LD) fish oil studies that included 55 and 43 RA patients, respectively. These patients were either given fish oil or placebo over a six-month period. Remans reported significant decreases in consumption of NSAIDs and improvements in physician's global assessment at three months and six months. However, there were no other clinical benefits. In the double blind, RCT by Sköldstram, the investigators noted significant reductions in joint tenderness and increases in grip strength (GS), at six months, while the placebo group demonstrated an increase in ESR and decreased global arthritic activity. Results of these studies indicate LD fish oil has limited benefit in improving clinical outcomes in RA patients.

High dose (HD), fish oil, double-blind RCT trials included those performed by Cleland et al. [27], Nielsen et al. [28], and Rajaei et al. [29]. These studies included 46, 51 and 60 RA patients, respectively. The daily doses used in these trials were 18 g (3.2 g EPA and 2 g DHA), 3.6 g, and 3.9 g (1.8 g EPA and 2.1 g DHA), respectively, which was compared to placebo. Cleland indicated that after three months of treatment, patients reported significant improvements in TJC and GS, with significant improvements in early morning stiffness (EMS) and GS in the placebo group (olive oil) as well. Although there was some improvement seen, this study was limited due to high dropout rates and the use of olive oil as a control. Nielsen's control group received capsules with a combination of fats typically present in a Danish diet. In this study, the intervention

group showed statistical improvement in joint tenderness but not in the VAS pain score, GS, DAS-28, or SJC. Rajaei used starch for a placebo and observed significant improvements in EMS, severity of pain, physician's assessment, number of SJC, TJC and physical function among the treatment group [29].

Dose comparison studies mentioned in Petersson's review were completed by Geusens et al. [30] and Kremer et al. [31]. Geusens conducted a 12-month study that included 90 RA patients and compared various doses of n-3 PUFA with placebo (olive oil). At the end of the study, significant improvements were observed in the patient's global evaluation and in the physician's assessment of pain only in the highest dose of n-3 PUFA (2.6 g/day). Participants who received higher doses demonstrated higher rates of medication reduction. This study was limited due to a 30 percent dropout rate, poor means of assessing compliance, and the inclusion of olive oil as placebo. Kremer's study included 49 RA patients and demonstrated significant improvements in SJC, TJC and GS using both high and low dose fish oil. Improvement in patient and physician evaluation of pain was only seen in the high-dose fish oil group. The investigators concluded that the ingestion of n-3 PUFA led to beneficial effects on clinical markers commonly seen and sustained after treatment of 18 to 24 weeks.

Additionally, Petersson's literature review discusses studies that attempted to determine the effects on lowering the need for medication in RA patients. In a double blind RCT by Kremer et al. [32], the investigators included 66 RA patients and found when replacing diclofenac with fish oil, participants experienced significant worsening of patient's global evaluation, GS, physician's evaluation of pain, and TJC. Meanwhile, Galarraga et al. [33] was able to demonstrate that over a nine-month period, patients consuming 2.2 g of EPA reduced their daily NSAID consumption by greater than 30 percent ($p=0.002$) as compared to controls. This study further demonstrates the potential for n-3 PUFA to reduce medication dosage, despite a 40 percent dropout rate. Proudman et al. [34] performed a double-blinded RCT with 139 RA patients and determined that the rate of failure of disease-modifying antirheumatic drugs (DMARD) therapy was lower in patients with a HD of fish oil at 5.5 g/day.

In addition, two referenced meta-analyses evaluating RCTs of fish oil supplementation resulted in conflicting findings. The first study found significant benefits on patient assessed pain, EMS, number of TJC, and NSAID consumption [35]. The other study evaluated 10 RCTs on the effects of n-3 PUFAs at doses ≥ 2.7 g/day for a minimum of three months and demonstrated improvements in clinical parameters were not determined to be significant, despite significantly reducing NSAID use [36].

Based on these studies, the investigators determined that n-3 PUFA supplementation led to beneficial effects on clinical parameters in RA patients. Although no statistical improvement was seen in one of the meta-analyses mentioned, previous research demonstrated clinical improvement was most commonly seen in those on n-3 PUFA for 18-24 weeks, thus indicating a potentially longer period of treatment time needed for statistical significance. From the results of their review, this investigator states that patients may receive benefits from supplementation with 2.2-4.0 g/day, which may assist in the reduction of daily NSAID use [33], whereas 5.5 g/day for 12 months may delay progression to biological therapy in DMARD-naïve patients [34].

Intake of ω -3 polyunsaturated fatty acids in patients with RA:

A systematic review and meta-analysis: Gioixari et al. performed a systematic review and meta-analysis in 2017 that evaluated on the use of n-3 PUFA in 1,288 RA patients in 20 RCT [37]. The analysis included the prerequisites of maintenance of drug therapy throughout the entirety of the study and a minimum duration of three months. This analysis confirms findings from previous studies and reviews including the 2012 meta-analysis by Lee et al. [33] that indicated the use of n-3 PUFA resulted in significantly improved EMS ($p=0.002$) and TJC ($p=0.001$). As mentioned in the reviews by Petersson [24] and Stamp et al. [38], the researchers concluded that beneficial effects of n-3 PUFA (2.7-4.0 g/day in addition to the adoption of a diet low in n-6 PUFA. In addition, Goldberg and Katz [35] found that use of n-3 PUFAs ≥ 2.7 g/day significantly improved EMS and TJC as compared to lower doses. Within the analysis, Gioixari included two sub-groups of n-3 PUFA doses for meta-regression analysis that indicated higher doses (≥ 3 g/d) were associated with significant improvements in physical global assessment and GS as compared to lower doses. Fourteen of the 20 RCT investigated the effects of n-3 PUFA supplementation on CRP levels, but no statistically significant changes were reported. One unique aspect of this review was the inclusion of the impact of n-3 PUFA supplementation on LTB₄ levels, which were shown to be significantly decreased when compared to placebo ($p<0.001$) thus confirming previous work performed by Jiang et al. [39].

Gioixari determined there was an overall high risk of bias in the studies reviewed due to insufficient reporting and poor study design, with discrepancies in reporting occurring in half of the trials. In addition, a large amount of heterogeneity was discovered, which was believed to be partially due to the use of varying laboratory tools, measurements, and types of n-3 PUFA used. Overall, the investigators determined that oral supplementation with n-3 PUFA resulted in significant improvements in markers of disease severity including EMS, TJC, ESR, pain scale, HAQ, GS, Ritchie articular index, and LTB₄.

Effect of ω -3 polyunsaturated fatty acids on arthritic pain: A systematic review: Abdulrazaq et al. performed a systematic review evaluating the effect of n-3 PUFA on arthritic pain and included studies through 2015 [40]. The review found that increased oral intake of EPA and DHA resulted in increased EPA and DHA levels in the membranes of inflammatory cells. AA is found in the cell membrane and is utilized by cells to synthesize pro-inflammatory mediators [41]. Increased cell membrane EPA and DHA content partially displaces AA and thus decreases its availability for prostaglandin synthesis thus decreasing synthesis of inflammatory prostaglandins. EPA is also a substrate for prostaglandin synthesis. However, it is synthesized into less potent and less inflammatory mediators such as prostaglandin E₃ (PGE₃) and leukotriene B₅ (LTB₅) [42].

This review was conducted using the 2009 PRISMA guidelines [9] and included 18 RCT published between 1985 and 2015. The review resulted in some varying results regarding the effectiveness of n-3 PUFA in reducing pain in RA patients. Ten of the 18 studies found beneficial effects on pain, while the others did not. Some of the limitations discussed included ineffective randomization, failure to state if and what type of blinding was implemented, in addition to other questionable methods further addressed in the article. In addition, the investigators indicated that inconsistent dosing across studies and the improper use of placebo could have led to the varying

results. The investigators emphasized the need for future studies to accurately determine compliance in order to ensure reliable studies. Many studies were found to implement less accurate methods such as capsule counting or participant questioning instead of more accurate methods such as blood cell fatty acid analysis. Overall, the author concluded that doses between three to six grams of n-3 PUFA per day significantly alleviated RA pain. This was determined by improvements in VAS, patient assessed pain, and physician assessed pain across multiple studies they reviewed.

Therapeutic potential of ω -3 polyunsaturated fatty acids in human autoimmune diseases: The 2019 review by Li et al., includes various articles above and is in line with the findings of this review [43].

Section summary: In evaluation of the most recent data regarding the use of fatty acids in RA patients, we found some varying evidence. Still, the following recommendations are a result of the consistencies across thousands of RA patients.

1. Majority of clinical benefits are observed in patients on supplementation for a minimum of 18 to 24 weeks [24]
2. In order to obtain clinical benefits >2.2 g/day of n-3 PUFA should be recommended [24]
3. To maximize benefits, EPA:DHA ratio should be >1.5 [23]
4. 2.2-4 g/day should be consumed for a reduction in NSAID use, with the greatest pain reduction seen at doses 3-6 g/day [42]
5. Patients naive to DMARD therapy may benefit from doses as high as 5.5-6 g/day for a period of over 12 months, which in some cases, has been shown to delay progression to DMARD therapy [24]. The rate of DMARD therapy failure has been seen to be lower in patients treated with 5.5 g/day of n-3 PUFA [24]
6. GLA doses up to 1400 mg/day have been shown to have synergistic effects on disease activity when used in combination with n-3 PUFA [22]

Quercetin

The effect of Quercetin on inflammatory factors and clinical symptoms in women with RA: A double-blind, RCT: Quercetin is an abundant bioflavonoid found in various fruits and vegetables, which is known for its antioxidant and anti-inflammatory properties [44-46]. Quercetin has been shown to suppress inflammatory cytokine secretion through the regulation of gene expression, particularly, impacting the transcription of NF- κ B [47,48]. Javadi et al. performed a randomized, double-blind, placebo-controlled clinical trial in which 50 women with RA were provided with either 500 mg/day of quercetin or placebo (lactose) for eight weeks [49]. At the beginning of the study, the investigators collected data including physician global assessment (PGA), TJC, SJC, and DAS-28 with ESR. Additionally, early morning stiffness (EMS) (pain in the morning and pain after activity), VAS, and HAQ scores were obtained. At the end of the study, Javadi reported a significant difference in hs-TNF alpha between the two groups ($p=0.04$), and in the quercetin group when compared to baseline ($p=0.03$). EMS was decreased in the quercetin group as compared to placebo ($p=0.03$, $p=0.05$ and $p=0.01$, respectively) and when compared to baseline

($p=0.01$, $p=0.004$ and $p=0.001$, respectively). The investigators found significant decreases in TJC ($p=0.03$), DAS-28, and HAQ score ($p=0.01$ for both) in the patients who received quercetin as compared to the start of the study and versus placebo ($p=0.04$ and 0.008 , respectively). The investigators concluded that quercetin supplementation had beneficial effects on clinical symptoms of several categories but saw no changes in ESR and SJC, potentially due to the short duration of the trial. Furthermore, the investigator's referenced a study that demonstrated greater benefits with quercetin in those under higher amounts of stress. For this reason, the investigators believe that improvements with quercetin use would be best seen in more severe cases and felt that the mild-mod severity of the patients in this study resulted in some limitations. No side effects were reported among those who received quercetin during the study.

This study demonstrated improvements in multiple RA clinical indices, providing supportive evidence for use in RA patient management. To date, only a few studies have been completed evaluating this compound (mostly animal and *in vitro* studies). A similar study to the one included in this review was completed by Bae, et al. in 2009 using quercetin and vitamin C that demonstrated similar outcomes [50]. The issue with this study is that it only evaluated 27 participants and did not meet our inclusion criteria for this review. Based on the data in this review and previous research efforts, there appears to be clear clinical benefits from the administration of 100 mg/d of quercetin over eight weeks to RA patients with mild-moderate disease severity. Still, further studies need to be completed to understand the risk of adverse events with long term use, efficacy in a larger patient population, and reproducibility.

Synbiotics/Probiotics

Managing RA With dietary interventions: With many new reports indicating alterations in the microbiome of patients suffering from various illnesses, research has begun to look at bacteria and synbiotics in relation to the onset and management of RA, fibromyalgia and various other illnesses [51-53]. Synbiotics are composed of both probiotics and prebiotics. Probiotics are live microorganisms that are administered to a host to confer health benefits [54], while prebiotics are non-digestible food products that serve to assist in the growth of helpful bacteria and their subsequent benefits [55].

Referenced in the article by Khanna et al. [56] was a double blinded, RCT conducted in 2010 that randomly assigned 45 patients with RA to be administered *Bacillus coagulans* GBI-30, 6086, or placebo once a day for 60 days in addition to their standard medications [57]. American College of Rheumatology (ACR) criteria, HAQ-DI, ESR, and CRP were collected at baseline, 30 days and 60 days. At the end of the study the treatment group was found to have statistically significant improvement in their pain scale ($p=0.046$) as compared to placebo. The patient pain assessment score, however, was not deemed significant ($p=0.052$). While the treatment group was found to have greater improvements in patient global assessment, self-assessed disability, reduction in CRP, and the ability to walk two miles ($P=0.072$), these findings were not statistically significant. Khanna additionally included a 2013 study by Veghef-Mehrabany where 46 female RA patients were given *Lactobacillus casei* 01 supplementation for eight weeks as compared to placebo [58]. The probiotic group was provided with capsules containing roughly 10(8) colony-forming units (CFU)/capsule while

the placebo group received maltodextrin. At the end of the study, disease activity scores were significantly decreased as compared to placebo ($p<0.01$). Levels of TNF-alpha, IL-6 and IL-12 ($p<0.05$) were also decreased, while IL-10 levels increased ($p<0.05$). TJC and SJC decreased significantly in the probiotic group ($p=0.02$ and $p=0.03$ respectively). VAS decreased by 43.96 percent as compared to 5.99 percent in the placebo group and decreases in serum hs-CRP levels were also seen in the probiotic group ($p<0.01$) [58]. From these results, it appears that the administration of *Bacillus coagulans* or *Lactobacillus casei* has the ability to significantly improve clinical indices, as well as inflammatory markers, in patients with RA as compared to placebo.

Synbiotic supplementation and the effects on clinical and metabolic responses in patients with RA: A randomized, double-blind, placebo-controlled trial: Zamani et al. performed a RCT evaluating RA patients receiving either synbiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* (2×10^9 colony forming units/g each plus 800mg inulin) or placebo [59]. Primary outcome measures included changes in inflammatory markers and DAS-28. Secondary outcome measures included changes in insulin metabolism, lipid concentrations, and biomarkers of oxidative stress. The study found that synbiotic supplementation over eight weeks among RA patients had beneficial effects on hs-CRP, DAS-28, VAS, nitric oxide, insulin levels, HOMA-IR, HOMA-B, and GSH levels. The intervention was not seen to alter any other glucose homeostasis parameters, lipid profiles, or biomarkers of oxidative stress. One limitation of the study was that compliance was not assessed using fecal testing of bacterial-load and short chain fatty acids. No adverse side effects were reported among participants in the synbiotic group.

The efficacy of probiotic supplementation in RA: A meta-analysis of RCT: Evidence suggests that the gut microbiome can influence the immune system [60]. Probiotics have been shown to attenuate inflammation and oxidative stress [61], two processes that are thought to play a role in RA [62]. To date, few studies have examined the role of probiotics on inflammation and oxidative stress present in RA. The goal of this meta-analysis was to analyze current literature to determine the effectiveness of probiotic supplementation in RA treatment [63].

The investigators analyzed studies obtained from Medline, Embase, the Cochrane Central Registry of Controlled Trials, and the Web of Science. Of the 240 studies initially identified, only four human RCT met the search criteria. The primary research aim was to examine probiotics' effect on inflammatory markers. Changes in DAS-28, SJC, TJC, HAQ, and oxidative stress were examined as secondary outcomes. All four studies observed reductions in CRP, but these results were borderline significant. Only two of the studies looked at ESR and no benefits were observed. One study observed a reduction in TNF α . Analysis revealed that all included studies did not observe significant changes in IL-1 β and IL 6 due to probiotic supplementation. While one study did find significant reductions in IL 10, two studies did not observe the same reduction. Of the studies that measured oxidative stress markers (Total Antioxidant Capacity (TAC) and Malondialdehyde (MDA)), no significant changes were observed with probiotic supplementation. Probiotic supplementation did significantly reduce DAS-28. One study found positive reductions in Tjc-28, but the overall impact was not significant.

There are many factors that can influence the effect of probiotics on the gut microbiome. These include duration, bacteria strain, and dosage. Probiotics are known to affect immune health, however for the treatment of RA, identifying a specific strain and dosage is necessary. The ability of probiotics to attenuate oxidative stress and inflammation make them an attractive alternative treatment, but this meta-analysis revealed that more research is needed to confirm efficacy. Limitations of this study include small sample size, limited number of studies that met search criteria, and lack of consistency in terms of biomarkers/indices of disease tested.

Section summary: With the exploration into the microbiome and its potential role in illnesses there appears to be growing evidence to support the utilization of synbiotics in the treatment of RA. In the studies by Mandel [57], Veghef-Mehrabany [58], and Zamani [59] significant changes were observed through the alteration of inflammatory biomarkers and improvements in clinical indices such as the DAS-28 and VAS. Each of these studies utilized different strains of bacteria as well as dosages thus demonstrating the variability found in these treatments. Furthermore, the meta-analysis by Aqaeinezhad Rudbane acknowledges that there is little data regarding optimal strains for specific diseases, doses, and the duration of time needed for these treatments to be efficacious [63]. Therefore, although there appears to be significant potential, at this time we cannot recommend these products further research is performed.

Conclusion

Overall, there are several nutritional interventions that have been shown to improve the clinical parameters in RA patients. These compounds can reduce medication doses and serve as adjuvant therapy to their current antiarthritic regimens. In this review, we discussed the most recent data from different types of nutritional support interventions in RA patients, with the goal of detecting clinical improvements that may serve as a tool for clinicians to confidently provide the most updated information to their patients. We made recommendations based on these findings for various compounds and diets that indicated sufficient data and safety profiles. Meanwhile, there were also other compounds that require further research before clear recommendations can be made, despite positive results. CoQ10 (100 mg/d) [10] and Quercetin (100 mg/d) [49] resulted in significant clinical improvements when compared to placebo. Both of these compounds had excellent safety profiles in addition to their clinical benefits but lacked the sufficient previous research for us to confidently make a clinical recommendation. Below is a brief summary table of the clinical improvements seen in these trials.

Other interventions with a more significant history of clinical trials included the use of n-3 PUFA. In providing these compounds to RA patients for pain reduction, the greatest improvements have been seen with 3-6 g/day with an EPA:DHA ratio of >1.5 at a minimum time period of 18 to 24 weeks [40,23,24]. For a goal of NSAID reduction, 2.2-4 g/day appears appropriate. Meanwhile, if

being used to slow the progression to DMARD therapy, doses at 5.5 to 5.6 g/day for a period of 12 months have been shown to be efficacious as well [24]. Many patients also benefit with concomitant use of GLA due to its synergistic effects with n-3 PUFA [20]. An intervention which lacked sufficient data for recommendation was the study on synbiotics [59]. There were several studies in addition to the meta-analysis by Aqaeinezhad Rudbane [63] that indicated great potential for probiotic compounds to be used in the management of RA. However, until more data identifying specific strains, dosages, and time frames for supplementation becomes available, we felt we could not recommend its application at this time.

We encourage researchers to utilize this review as a tool to guide further exploration of these interventions to be utilized in the treatment of various diseases. We also encourage clinicians to consider the evidence presented and use their judgement to implement it where patients are most likely to benefit.

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Conflict of interest

All the authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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	DAS-28	SJC/TJC	VAS	HAQ
CoQ10	✓	✓	✓	
Quercetin	✓	✓ (TJC)		✓

Table 2: Summary of clinical improvements; Significant improvements seen in Coenzyme q10 and Quercetin supplementation.

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