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The Mediterranean Diet, fish oil supplements and Rheumatoid arthritis outcomes: evidence from clinical trials

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Abstract

The impact of dietary interventions such as specific types of diet or nutritional supplements in rheumatoid arthritis (RA) has been subject to increased attention in recent years. The recognition of the unmet need to better understand the effects of specific dietary interventions on disease outcomes in RA, along with the growing patient interest on lifestyle interventions beyond pharmacotherapy, have informed the undertaking of this narrative literature review. The benefits of the Mediterranean Diet (MD) have been shown in various studies, although only a limited number of trials focus specifically on RA. Based on the studies reviewed, the MD may provide benefits in reducing pain and swollen and tender joints in RA patients. There is more and better evidence that n-3 polyunsaturated fat (PUFA) supplementation has the potential to reduce inflammation and provide clinical benefit, possibly slowing progression to pharmacotherapy. Yet, many of these studies to date are limited in their methodology; this being partly a reflection of the complexity of the research questions being addressed. Consequently, the conclusions that can be robustly drawn from their results are restricted. With a focus on clinical trials on the MD and fish oil supplementation, this review critically appraises the evidence, discussing the findings of studies in the wider context of impact on RA outcomes, methodological challenges and practical points to consider as part of the routine care of RA patients.

Keywords: Mediterranean diet, fish oils, fatty acids, rheumatoid arthritis, patient-reported outcomes, DMARDs

Abbreviations

5-HETE 5-Hydroxyeicosatetraenoic acid

ALA alpha-linolenic acid

ACR20 American College of Rheumatology 20% improvement criteria

AID Anti-inflammatory Diet

AA arachidonic acid

CO corn oil

CRP C-reactive protein

COX-2 cycloxygenase-2

DAS28 Disease Activity Score-28

DMARD disease-modifying antirheumatic drug

DHA docosahexaenoic acid

DPA docosapentaenoic acid

EPA eicosapentaenoic acid

ESR erythrocyte sedimentation rate

EULAR European League Against Rheumatism

EVOO extra-virgin olive oil

FO fish oil

GLA gamma-linolenic acid

GS grip strength

HDFO high dose fish oil

IL interleukin

IU International Units

IV intravenous

JAK janus kinase

LTB4 Leukotriene B4

LTB5 Leukotriene B5

LA linoleic acid

LDFO low dose fish oil

MD Mediterranean Diet

NSAID non-steroidal anti-inflammatory drugs

OO olive oil

PUFA polyunsaturated fatty acids

RA Rheumatoid Arthritis

RF Rheumatoid factor

SFA saturated fat

SOFI Signals of Functional Impairment

SJC swollen joint count

TJC tender joint count

HAQ Health Assessment Questionnaire

TNF-a Tumor Necrosis Factor alpha

UP urinary pentosidine

VO Vegetable oil

VAS visual analogue pain

VAS Visual Analogue Scale

WD Western Diet ()

1. Introduction

Rheumatoid arthritis (RA) is a chronic, immune-driven inflammatory disease that continues to cause modest global disability [1]. Poorly controlled RA is associated with multiple clinical symptoms including fatigue, severe pain and functional disability, ultimately also 'end-stage' joint damage necessitating surgical intervention [2]. An increasing comorbidity burden, most importantly of cardiovascular disease has also been reported in RA, even at the early stages of disease with a negative impact on the achievement of treat-to-target goals [3]. Immunosuppression remains the cornerstone of treatment for RA and this is traditionally achieved through the use of conventional synthetic disease modifying anti rheumatic drugs (DMARDs), steroids and more targeted therapies including biologic DMARDs (e.g. Tumor Necrosis Factor (TNF)-α inhibitors) or small molecules (e.g. janus kinase [JAK] inhibitors). These treatments have made remission a possible treatment target in RA. Yet, there remains a substantial proportion of people who continue to suffer ongoing symptoms of disease, despite the use of effective pharmacotherapy.

It is thus perhaps not surprising that in an attempt to relieve their symptoms, patients often seek ('unorthodox') dietary 'therapies' as an adjuvant or even a replacement to their 'traditional' treatments; this is despite the reported outcomes being highly variable and the attribution of a proportion of their improvement to placebo effects [4]. Common dietary plans tried/used and reported in RA, include among many vegetarian or vegan diets, the Mediterranean diet (MD) or even various periods of fasting, while dietary supplements, especially n-3 polyunsaturated fatty acids (PUFA) or fish oils are commonly used. Whether these dietary interventions make a difference and

the extent of their effects in terms of the inflammatory burden and clinical symptoms, remains in part open to speculation and represents an unmet need. Having robust scientific evidence on which to base specific advice and recommendations as part of the routine clinical care of patients with RA is important, especially as it is an often-encountered question posed by patients (e.g. 'What can I eat / What supplements can I take to improve my symptoms/ Are there foods I should eat/not eat?'), albeit one that tends to be poorly addressed.

The increasing recognition of this unmet need to understand and appreciate the impact of dietary interventions on disease course in RA was well-reflected in the recent 17th Mediterranean Congress of RA and musculoskeletal diseases dedicated to nutrition and the environment [5]. It also stimulated this narrative review of literature presented here, which was based on a search for relevant papers on Medline and Embase via the OVID SP platform upto July 2017 using the following terms: Rheumatoid arthritis or arthritis, rheumatoid or inflammatory arthritis and Mediterranean diet or omega-3 supplements or fish oil supplements or fish oil infusions, restricting to clinical trials. This work was informed by increased patient interest and focused on dietary interventions such as the MD and n-3 PUFA fish oil supplementation that may be practically applied by patients and which could ultimately contribute to the development of Dietary Guidelines for people with RA.

2. The Mediterranean Diet

2.1 Key effects of the Mediterranean Diet on inflammation

The MD is characterized by an abundance of plant foods such as unrefined cereals, fruit, vegetables, legumes and extra-virgin olive oil (EVOO), a moderate consumption of poultry, dairy products and eggs and a low consumption of sweets and red meat [6]. As a rich source of antioxidants and anti-inflammatory nutrients, it seems to have a potential to modulate inflammatory pathways in RA [7;8] although the evidence from clinical trials is currently limited [9]. Central to the suppression of RA disease activity is the abundance of EVOO in the MD which contains not only oleic acid, an n-9 monounsaturated fatty acid (18:1, n-9), but also the phenolic compounds oleuropein, ligstroside and oleocanthal, and phenolic alcohols, such as hydroxytyrosol and tyrosol with potent anti-oxidant properties [8]. Ingestion of dietary EVOO [10] and EVOO-polyphenol extract [11] by collagen-induced RA mice has been shown to reduce joint edema and cartilage destruction; effects associated with reduced expression of inflammatory cytokines such as interleukin (IL)-1β, IL-6 and transduction signaling molecules [7;8]. Additionally, phenolic compounds both from olive oil but also from red wine such as resveratrol, inhibit cycloxygenase-2 (COX-2) protein expression and prostanoid and metalloproteinase production, important in angiogenesis, the key pathogenenic process in inflammatory chronic joint diseases [7]. Further to its antioxidant and anti-inflammatory properties, the MD is also rich in dietary fiber with beneficial effects on gut microbiota, promoting saccharolitic microbiota and favoring short-chain fatty acid production [12]. Gut microbiota regulate the T cell phenotype and T cell-mediated immunity and seem to have a role in RA development while gut dysbiosis contributes to the occurrence or development of a range of rheumatic diseases [13;14].

2.2 Clinical trial data

The effects of MD in RA patients have only been assessed in two clinical trials. McKellar et al [15] conducted a 6 month pilot study in 130 female patients with RA living in areas of social deprivation in Glasgow. The intervention group attended a 6-week cookery course with emphasis on a MD-type diet, while the control group received information on health eating only. At 6 months, the intervention resulted in a significant benefit in global assessment, pain score and early morning stiffness (EMS). Other RA outcomes assessed i.e. tender joint count (TJC), swollen joint count (SJC), Disease Activity Score 28 (DAS28), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) or IL-6 did not differ between groups. Although the authors concluded that the MD has modest benefits across a range of areas, the study had a number of limitations, in that random allocation to intervention or control was not feasible, statistical analysis was based on comparing the two groups at different time points instead of the changes from baseline, and the study included only females living in socially deprived areas and thus cannot be generalized to other populations. Additionally, most of the changes were in subjective rather than objective measures of disease and since the intervention group received such intense training, the possibility of placebo effect and the risk of bias remains high.

In another MD intervention study, Sköldstam et al [16] investigated the efficacy of a MD versus an ordinary Western diet (WD) for suppression of disease activity in 51 patients with RA in Sweden. A 3-month randomized controlled trial (RCT) was conducted where RA patients were randomly allocated to either a Cretan MD or a control WD. During the first 3 weeks, the diet group was served an MD from the hospital

canteen and a dietitian provided six lessons about MD food and cooking. Participants were supplied with monounsaturated oils and spreads, frozen vegetables and tea. The control group were served ordinary hospital food for the first 3 weeks and asked to return to their usual diets for the rest of the study period. Compliance was ascertained by a questionnaire and by dietary history interviews and validated by biological markers of food intake. At the end of the 12-week intervention, the MD showed improvements in RA outcomes such as DAS and HAQ scores, SJC, TJC, patients' global visual analogue scale (VAS), Pain VAS, CRP and thrombocyte count. There were also improvements in vitality and mental health, but no significant changes were seen in EMS, erythrocyte sedimentation rate (ESR), grip ability test (GAT) score or signals of functional impairment (SOFI) score. No improvements were seen in the control group. Although the study showed that adjusting to the MD can result in a reduction in inflammatory activity and an increase in physical function, the findings may not be generalized since it included mostly women, adjusted the MD to suit the Swedish subjects and had a short duration.

A key challenge and an important source of bias in studies that involve dietary manipulations, is the impossibility to 'blind' subjects to the diet being followed. On the other hand, studies involving supplementation, like the ones discussed below, are not generally limited by the issue of blinding.

3 Fish oil supplements

3.1 Key effects of n-3 PUFA on inflammation

In contrast the traditional diets such as the MD, the WD is usually characterized by deficiency in consumption of n-3 PUFA, especially the fish oils eicosapentanoic acid (EPA; 20:5 n-3), docosahexaenoic acid (DHA; 22:6, n-3), and increased consumption of n-6 PUFA such as linoleic acid (LA; 18:2 n-6) or arachidonic acid (AA; 20:4; n-6), derived mostly from vegetable oils such as sunflower and corn oil and animal sources. In fact, the vast roles of n-3 PUFAs as proinflammatory mediators has led to the recent recommendation of the Omega-3 Index (red blood cell EPA+DHA) to assess sufficiency of intake [17]. Dietary essential fatty acids are precursors of the inflammatory mediator prostaglandins (PGs) and leucotrienes (LTs) with n-6 and n-3 fatty acids having potent inflammatory and anti-inflammatory properties respectively. While the most potent inflammatory PGs originate from the n-6 AA, EPA competitively inhibits the production of PGs and LTs from AA by competing for the same enzymatic pathway while it also acts as the precursor of the less inflammatory series-3 PGs and series-5 LTs [18]. Dietary supplementation with n-3 PUFA has a number of anti-inflammatory actions as recently reviewed [19], with examples including reduction of the proinflammatory activities of AA, increase in the production of endocannabinoids having EPA or DHA in their structure and thus anti-inflammatory properties, reduction in the production of inflammatory cytokines such as IL-1β, IL-6 and TNF-α, reduction in the expression of adhesion molecules on immune cells and on endothelium, reduction in T-cell proliferation and the production of IL-2, as well as restoration of the homeostasis of tissues after inflammation through metabolites acting as specialized pro-resolving mediators.

In an attempt to study the anti-inflammatory actions of n-3 PUFA in RA outcomes, a range of studies using n-3 PUFA supplements provided mostly orally and in some studies intravenously (IV), varying in methodology, dosage, duration and outcomes examined, have been conducted as discussed in Sections 3.2-3.8.

3.2 Effects of low n-3 PUFA doses on RA outcomes

Studies using relatively low n-3 PUFA doses include Remans et al [20] where 55 RA patients were randomized to a liquid nutritional supplement providing 1.4 g EPA, 0.211 g DHA, 0.4 g DPA, 0.16 g ALA, 0.5 g GLA and 0.44 g LA and micronutrients, consumed for 4 months, or a placebo drink. Patients in the intervention group reported a significantly decreased consumption of NSAID at 3 and 6 months while physician's global assessment improved at 3 months. On the other hand, control patients reported an increased global arthritic activity at 6 months. However, other parameters such as ACR20 response criteria, SJC, TJC, CRP and ESR concentrations and HAQ score did not change. The study thus did not show any significant clinical benefit of daily nutrient supplementation with EPA, GLA and micronutrients. It did show some potential effect of fish oils on decreasing need for NSAID usage, however even here the findings were limited.

Sköldstram et al [21] conducted a 6-month double-blind RCT in 43 RA patients. The intervention consisted of 10 capsules/day containing 1 g fish oil, 18% EPA and 12% DHA while the control group received capsules made of maize, olive and peppermint oil. At the end of the intervention, both groups had a significant reduction in joint tenderness and increase in grip strength (GS) and platelet count while the placebo group had an

increase the ESR and a decline in global arthritic activity. Although use of NSAID significantly decreased in the intervention compared to the control group, patients' pain assessment using VAS, functional capacity and duration of EMS showed no change throughout the treatment in either of the groups. Thus, taken together studies using low doses show that FO supplementation may cause only a slight anti-inflammatory effect and have limited potential for lowering the NSAID intake in patients with RA.

3.3 Effects of higher n-3 PUFA doses on RA outcomes

Higher doses of n-3 PUFA supplements were used in other studies such as Cleland et al [22] who conducted a double-blind RCT in 46 patients with RA. The intervention consisted of 18 g fish oil/day providing 3.2g EPA and 2 g DHA with the control group receiving the same amount of olive oil. After three months of treatment there were significant improvements in TJC and GS in the fish oil treated group. The olive oil group also experienced significant improvements in EMS and GS. However there was no significant change in either group in SJC, the ARA functional class, or global assessment by patient and physician. Although the findings of this study suggest that higher n-3 PUFA supplementation could reduce some of the symptoms of RA, the study is limited in that there was a high drop-out rate and the inappropriate use of olive oil in the control group, which has itself anti-inflammatory properties [23].

Nielsen et al [24] also used a higher dose of n-3 at 3.6 g/day in a multicenter double blind RCT with the participation of 51 RA patients. The control group received six capsules/day each containing the equivalent amounts of a combination of fats typically present in a Danish diet. Unlike most other studies, compliance was assessed by

the increase of EPA in leucocyte fatty acids and shown to be significant in the intervention group. Joint tenderness improved in both groups but statistical significance was only achieved in the intervention group. No statistically significant findings were seen in the VAS pain score, GS, DAS or SJC. It is unclear why control patients also benefited from the study but this may be related to the fatty acids provided in the placebo arm of the study which themselves may have (unrecognized) anti-inflammatory actions.

Rajaei et al [25] in a better controlled 12-week double blind RCT of n-3 PUFA supplementation of 1.8 and 2.1 g EPA and DHA daily, evaluated the effects on disease activity and remission in 60 DMARD-treated RA patients. Placebo drugs consisted of starch thus overcoming the issue of possible confounding by use of other dietary fatty acids. Weight changes and reduction of analgesic drug consumption were also assessed. Significant improvements were seen in the n-3 PUFA treated group in EMS, severity of pain, physician's assessment, number of SJC, TJC and physical function. It was thus shown that n-3 PUFA supplementation may reduce the need for concomitant analgesic consumption without weight changes.

3.4 Comparison of n-3 PUFA doses on RA outcomes

Investigators have also tried to examine the effects of different amounts of n-3 supplements. To that effect, Geusens et al [26] randomly assigned RA patients to one of three regimens for 12 months: 2.6 g/day n-3, or 1.3 g/day n-3 plus 3 g olive oil, or 6 g olive oil used as placebo. A balanced diet was also advised. There were significant improvements in the patient's global evaluation and in the physician's assessment of pain only in those taking 2.6 g/day n-3 PUFA. Additionally, the proportions of patients who

improved and of those who were able to reduce their concomitant anti-rheumatic medications were significantly greater with the higher n-3 PUFA dose. There were no significant changes in the ESR, Rheumatoid Factor (RF), JSC or EMS. Although the study concluded that a higher dose of fish oil supplementation has significant clinical benefits to RA patients, and may ultimately reduce need for medication, it had a high drop-out rate of 30% and compliance was assessed only by capsule counting.

Kremer et al [27] also assessed the effects of two different doses of fish oil and one dosage of olive oil on clinical evaluations and immunologic variables in RA patients. Patients were randomized to either a low dose of n-3 PUFAs (27 mg/kg EPA and 18 mg/kg DHA; n=20), a high dose n-3 PUFAs (54 mg/kg EPA and 36 mg/kg DHA; n=17) or 6.8 g of oleic acid capsules (n=12). Over the study period, there were improvements in several RA clinical manifestations in both the low-dose and high-dose fish oil groups but also some in the olive oil group. Particularly, there were reductions in SJC, TJC and GS in both fish oil groups and improvement in patient and physician evaluation of pain only in the high-dose fish oil group. Interestingly patient evaluation of global arthritis activity improved only in the olive oil-supplemented group. There were also improvements in the physician's evaluation of global arthritis activity in the low fish oil and olive oil groups. Lastly, significant improvements in physician evaluation of global arthritis activity were seen in the high-dose fish oil group only, with a carryover improvement noted at 30 weeks when all patients were taking olive oil supplements. Neutrophil leukotriene B4 production decreased from baseline in both fish oil groups while macrophage IL-1 production decreased in all 3 groups. Thus although overall, ingestion of n-3 fatty acids led to beneficial effects on RA clinical parameters which were

sustained and more commonly observed after 18-24 weeks of treatment, the study is limited in that the olive oil group experienced a high number of withdrawals as a result of the increased disease activity in this group. Furthermore, as in previous studies e.g. [22;26], olive oil was again inappropriately used as placebo.

3.5 Combined dietary interventions and n-3 PUFA supplementation on RA disease outcomes

Some investigators attempted to combine dietary supplementation with changes in diet. For example, Kremer et al [28], in a highly-cited study published in the Lancet, assessed the effects of manipulation of dietary fatty acids, by combining dietary changes and supplementation, in a 12-week, double-blind RCT. The experimental diet was high in PUFA and low in saturated fat (SFA), with a daily supplement of 1.8 g of EPA (n=17) while the control diet had a lower PUFA:SFA ratio combined with a placebo supplement (n=20). At 12-weeks, both groups showed a significant decrease in the TJC, but the mean decrease was greater in the experimental than the control group. There were no differences between patients' and physicians' assessments of pain and overall condition in either group. At a follow-up evaluation 1-2 months after stopping the intervention, the status of the patients in the experimental group had deteriorated substantially while some improvements in the TJC and EMS were noted in the control group patients. Thus, overall the findings suggest that a higher PUFA intake might have some beneficial effects but these were not substantial.

Adam et al [29] conducted a double-blind crossover study aiming to examine fish oil (FO) supplementation in combination with a low AA diet in 62 individuals with RA.

One group was observed for 8 months on a WD and the other on an anti-inflammatory diet (AID) providing an AA intake of less than 90 mg/day. Patients in both groups were allocated to receive placebo (corn oil) or fish oil capsules (30 mg/kg body weight) for 3 months in with a 2-month washout period between treatments. In the AID group there was a reduction in SWJ and TJC during placebo treatment while fish oil led to a significant reduction in SJC and TJC only in the AID group. The patients' and physicians' global assessments of disease activity and the patients' assessments of pain improved in both groups but this was higher in the AID group. It was also possible to reduce the dose of NSAID in the AID group during FO. The study did not report differences in EMS or GS. Overall, the findings of this study suggest that there is synergism in a diet low in AA and high in FO, which in turn shows that EPA:AA ratio is crucial for consideration in a clinical advice.

A double blind cross-over RCT study by Dawczynki et al [30] measured the effect of fish oil-supplemented dairy products on the inflammation and the immunological and oxidative stress biomarkers, disease activity and serum lipids in 39 RA patients. Both groups received verum products or placebo for 3 months consecutively with a 2-month washout period. The patients received approximately 40g fat (from 200 g of 3.8% fat yoghurt and 30g of 50% fat cheese and 20-30 g butter), daily. The milk fat was partially replaced with fish, rapeseed and Dracocephalum ibericum oil, which are all high in EPA, DHA and ALA. The combination of n-3 PUFA came up to a daily intake of 2.4 g. Commercial dairy products with comparable, but non-n-3 fatty acid fat contents were used in the placebo group. Compliance to the intervention was measured through daily dietary diary entries. Acute-phase reactants and activity parameters such as CRP,

ESR, SJC, TJC, EMS and DAS28 score did not change significantly over the study period. There were also no effects on biomarkers of oxidative stress but long-term consumption of dairy products (2 x 12 weeks) diminished the excretion of hydroxypyridinium crosslinks, and favored the diastolic blood pressure leading the authors to comment that it acts against the cartilage and bone destruction in RA. Thus overall, there is limited evidence of a synergism between a low AA acid diet and n-3 supplementation used at medium dosage on RA outcomes.

3.6 n-3 PUFA supplements and possible effects on medication use

Studies have also investigated whether dietary supplementation with n-3 PUFAs would allow the discontinuation of medication or the slower progression to therapeutic interventions. To that effect, Kremer et al [31] investigated in double blind RCT whether n-3 supplementation would allow nonsteroidal anti-inflammatory drug (NSAID) discontinuation. 66 RA patients entered the study while taking diclofenac and were randomized to either 130 mg/kg/day of n-3 PUFA or 9 capsules corn oil per day. Placebo diclofenac was substituted at week 18 or 22 while fish oil supplements were continued for another 8 weeks. At 26 or 30 weeks, fish oil supplements were substituted by corn oil. In the group taking fish oil, there were significant decreases from baseline in the TJC, duration of EMS, physician's and patient's evaluation of global arthritis activity and physician's evaluation of pain. No clinical parameters improved in the corn oil group. When diclofenac was replaced by placebo, the fish oil group experienced significant worsening in patient's global evaluation, GS, physician's evaluation of pain and TJC. During this period, patients consuming corn oil showed significant worsening in both the

physician's and the patient's evaluation of global arthritis activity and in the patient's evaluation of pain, but not in the TJC. Interestingly, the decrease in the TJC remained significant 8 weeks after discontinuing diclofenac in the fish oil group. Although there was a significant decrease in IL-1β between baseline and weeks 18/22 in the fish oil group, the intervention did not result in inhibition of other assessed cytokines (IL-2, IL-6, IL-8 or TNF-α). In summary, the study showed some beneficial effects of fish oil supplementation in RA clinical parameters, but none of the improvements in the patients receiving fish oil achieved significance at the time of the maximum duration of diclofenac therapy compared with patients receiving corn oil. Whether this is due to beneficial immunologic effects of the placebo corn oil used, remains unknown. Moreover, the magnitude of the improvement observed with a very high fish oil dose reaching 9 g/day in a 70 kg person, was similar to that reported with lower doses (3-6 g/day) [27;28], leading the authors to conclude that further investigations with this high dose should not be recommended. Additionally, the study had a very high dropout rate; this being 26% dropout by week 22 and 56% by the end of the study.

Galarraga et al [32] conducted a 9-month dual-centre double-blind RCT to examine whether 2.2 g of n-3 EPA (taken as 10 g of cod liver oil) could help reduce daily NSAID requirement in 97 RA patients. At 12 weeks, patients were instructed to gradually reduce or if possible stop their NSAID intake. A higher percentage in the cod liver oil group compared to the control group were able to reduce their daily NSAID requirement by >30% at 9 months (39 vs 10%; p=0.002, intention-to-treat analysis). As per study's objective, this was indeed achieved without worsening the patients' condition since no differences were observed in clinical parameters or RA disease activity. Indeed

there was a modest but statistically significant improvement in the mean pain VAS from baseline in the cod liver oil group compared to the control group. Additionally, there were no differences in side-effects between the groups. The study thus provides evidence that n-3 PUFA can be used as NSAID-sparing agents, it is limited however in that there was a 40% dropout due to adverse events, patient's wishes or lack of efficacy.

Lastly, Proudman et al [33] in an eloquently designed double-blind RCT, examined the effects of fish oil supplements on use of DMARD using a treatment algorithm responsive to disease activity according to predefined rules, thus allowing the extent of DMARD use to be an outcome measure. 139 patients with recent onset RA and who were DMARD-naïve were randomized 2:1 to fish oil at high dose (5.5 g/day EPA + DHA) or low dose (0.4 g/day EPA + DHA) for 1 year. In the high dose group, failure of triple DMARD therapy was lower even when adjusted for smoking history, shared epitope and baseline anti-cyclic citrullinated peptide. The rate of first American College of Rheumatology (ARC) remission was significantly greater in the fish oil group but no differences between groups were noted in methotrexate dose, DAS28, the modified Health Assessment Questionnaire (mHAQ) scores or adverse events. The study showed that fish oil supplementation can provide benefits additional to those achieved by combination 'treat-to-target' DMARDs with similar methotrexate use, thus at least delaying progression to biological therapy. In a further analysis [34], it was shown that plasma phospholipid EPA (but not DHA) was related to time of remission, thus providing evidence that biomarkers of n-3 status can predict clinical outcomes in RA patients.

3.7 Intravenous n-3 PUFA administration

Of interest are studies that report on IV administration of n-3 FAs, suggesting good tolerability of the treatment and potentially greater efficiency than oral administration [35;36]. However, these studies are limited by their study design including the length of follow up, small numbers and high attrition rates thus decreasing the power of studies to detect 'true' effects of n-3 FAs. Furthermore, the study definitions of 'disease control' and 'efficiency' of the tested interventions can vary, with some studies referring to improvement in these parameters when subjective measures alone e.g. SJC and TJC, improve. For example, Bahadori et al [35]in a double-blind RCT of 0.2g of fish oil emulsion/kg (active) or 0.9% (placebo) IV infusion for 14 consecutive days, followed by 20 weeks of 0.05g of fish oil/kg (active) or paraffin wax (placebo) ingested orally as capsules, report on significantly lower SJC and TJC in n-3 FA group compared with placebo during and at the end of oral treatment; it should, however, be noted that this was the case for around 50% of the patients in total, completing the study. Interestingly, placebo treatment also led to a considerable reduction of SJCs and TJCs, which the authors concluded 'may be due to the placebo effect as well as the intensified physician's attention and care to both groups'. In the study by Leeb et al [36] although attrition rates were lower, IV administration of n 3-PUFA was only given for a week. In this study 2mL/kg (equal to 0.1-0.2 g fish oil/kg) IV fish oil emulsion was used for 7 consecutive days plus background therapy.

It is worth highlighting that none of the two studies demonstrated an improvement in objective measures of disease such as laboratory markers. Therefore, whereas these studies provide a rationale for potentiating serum omega-3 FA levels through use of infusion therapy of omega 3 FA, their study design, type and timing of outcome measures

studied raise crucial questions around the appropriateness of the studies in answering their respective research question. In addition, the cost and practicalities of IV administration of such therapies necessitate further cost-effectiveness studies on this topic, to justify their more widespread use.

3.8 Meta-analyses on n-3 PUFA supplementation

Since effects seen at low n-3 PUFA doses are generally not of clinical significance, using the right dosage is of paramount importance if any effects are to be seen. In particular, a meta-analysis of RCTs on fish oil supplements in RA reported a benefit for patient-assessed pain, EMS, number of painful and/or tender joints and NSAIDs consumption [37]. A further meta-analysis of 10 RCTs evaluating the effects of n-3 PUFAs at doses ≥2.7 g/day for a minimum of 3 months [38] on clinical outcomes in RA showed that n-3 PUFAs reduced NSAID consumption but TJC, SJC, EMS, physical function, showed a trend to improve but did not reach statistical significance. Since the conduction of these meta-analyses, further evidence as presented here has shown that n-3 supplementation at 2.2-4.0g/day could help reduce daily NSAID requirement and concomitant analgesic consumption [32], while 5.5 g/day of n-3 for 12 months can delay progression to biological therapy in DMARD-naïve patients [33].

4. What can we conclude from MD/Fish oil supplementation trials?

Tables 1 and 2 summarize the participant characteristics, interventions used and main findings of the studies presented. Based on the studies reviewed, the MD may provide benefits in reducing pain, SJC, TJC in RA patients. There is more and better evidence

that n-3 PUFA supplementation has the potential to reduce inflammation and provide clinical benefit in RA patients, although in many cases, only subjective, nevertheless, the importance of dosage, duration, potential side-effects and practicalities of intake need to be addressed. It should be noted that many of the presented studies have a number of methodological flaws. Several are based on only a small sample size and/or have a high dropout rate while being biased by reporting outcomes on the patients retained in the study rather than using an 'intention-to-treat' analysis. Additionally, the duration of the clinical trials, with some exceptions, is usually short to study important outcomes of disease making it challenging to disentangle the biological 'plausibility' of the potentially expected findings from administration of n-3 FAs and true (non-placebo) clinical effects. This becomes even more difficult in light of the fact that many studies used inappropriate 'placebo' treatments such as olive oil or corn oil capsules which as discussed have themselves, anti-inflammatory actions. Additionally, a number of studies reported on greater effects on the more subjective elements of disease such as SJC/TJC with less evidence on more objective features of active RA such as laboratory markers or radiographic progression. Whereas this may alone point towards the evidence being 'weak' in this aspect, the mere impact on those outcomes that are of greater relevance to the patients' themselves, including pain, EMS, fatigue, makes it all worthwhile. On the other hand, there is conflicting evidence from studies on the impact of n-3 FA on the acute phase response e.g. CRP concentration.

Nevertheless, despite the wide array of therapeutic options currently available for treating RA, some patients continue to report unmet clinical needs, including ongoing pain, impaired physical/mental function and fatigue [39]. This observation can be seen in

the case of people who appear to be in clinical remission, as defined by a composite and to a large extent subjective DAS that in some countries represents the main determinant of use of the more effective, albeit more expensive treatments such as the biologic DMARDs. This in part reflects discrepancies in the 'definitions' and the perception of 'remission' or 'treatment-success' by physicians compared to patients, an increasingly acknowledged issue [40;41]. What has become clearly apparent over time though is that the phenotype and disease course of RA has largely evolved over the past few decades [42], with fewer patients having the destructive, deforming form of the disease that once represented 'the norm'. This is largely attributed to the discovery of better and more effective drugs over time enabling tighter disease control.

However, even though the inflammatory burden of disease may be considerably improved, complete control of more subjective but highly important aspects of disease may continue to cause patient distress. As a consequence, overall patient perception of well-being appears to have decreased with regard to outcome measures considered important by patients themselves, as opposed to the ones traditionally used to guide clinical decision making, including pain, fatigue, physical function and quality of life [43]. This, for many patients, provides an important incentive for taking a more active role in their health and reaching out to alternative 'therapies' and non-pharmacological treatments to manage their symptoms.

5. What nutritional suggestions could be considered from the available evidence?

Over the years, there have been strong influences around nutrition, mediated by social media, but not always robustly supported by scientific evidence. The latter may reflect

the general lack of focus on nutrition in the literature on non-pharmacological interventions in inflammatory arthritis [44;45] where in contrast, interventions like exercise are recognized and reported. The MD is a non-restrictive, well-balanced diet, including all food groups and providing all nutrients in an easy-to-follow manner. Similarly, n-3 PUFA supplements in moderate amounts seem to play a role in alleviating important symptoms that matter to patients. Box 1 summarizes nutritional suggestions that could be considered from the available evidence**.**

Conclusions

Dietary interventions such as the MD and fish oil supplementation are important in RA but we advocate that they are used in conjunction (and not as a replacement) with other non-dietary interventions including appropriate pharmacotherapy where indicated. There remains considerable uncertainty around the therapeutic benefits of specific dietary manipulations and food supplementation such as fish oils in the setting of RA. Although the evidence is generally reassuring, at least for some aspects of disease, larger RCTs of good methodological quality are warranted. Addressing individual patient perceptions is important in guiding appropriate interventions, optimizing treatment outcomes, improving patient adherence and the sense of well-being. This may be particularly relevant for people with RA who fail to achieve and sustain optimal treatment targets despite effective use of pharmacotherapy. This work will be used to inform the research agenda for nutritional recommendations or points to consider for people with rheumatic and musculoskeletal diseases, RA included.

Box 1: Nutritional points to consider in RA regarding the MD and n-3 PUFA intake

POINTS TO CONSIDER
Mediterranean diet (MD)
The MD* to be recommended to RA patients for its benefits on disease manifestations, arthritic pain and function.
The MD to be recommended to RA patients for its benefits on comorbidities (cardio/neuro protection; anti-diabetic & anti-cancer and overall benefits on longevity).
n-3 polyunsaturated fatty acid (PUFA) supplements and dietary n-3 PUFA
Supplementation with n-3 PUFA in moderate amounts** for a period of at least 3 months to be recommended as an adjunct to treatment and in addition to the MD.
Consumption of 'fatty' fish*** 2/week to be recommended
Daily consumption of seeds^ and walnuts to be recommended.
**Adherence to the MD can be achieved by consuming wholegrain foods daily, consuming beans and legumes ≥2 times/week, consuming ≥2 fruit/day, ≥3 vegetables/day, using extra virgin olive oil as main fat, limiting red meat intake to ≤1/week and consuming poultry instead, consuming fish 1-2 times/week, consuming ≤4 eggs/week, limiting sweets to special occasions and if alcohol is consumed, consume 1 glass of red wine with meals* [6].

** n-3 PUFA at doses ≥2.7 g/day based on meta-analysis [38]

****Includes sardines, seabass, seabream, salmon, mackerel and trout, providing EPA and DHA.*

^*Includes flaxseeds and chia seeds providing ALA.*

Table 1: Participants' characteristics and intervention details

Study	Sample completing study - intervention and control (% drop out/	Age interv ention group mean +/- SD (range)	Proportion female in intervention group (%)	Intervention|Control diets	Intervention length (months)

	with draw al)				
McKellar et al, 2007 [15]	130 (0%)	58 (47 - 64) **	100	MD|Healthy diet advice	6
Sköldstam et al, 2003 [16]	51 (9%)	58 (33 - 73)	80	MD|WD	3
Remans et al, 2004 [20]	55 (17 %)	60 +/- 11	88	5g fat/d primarily: EPA (1400mg), DHA (211mg), DPA (40mg), ALA (16mg) GLA (500mg), LA (440mg)	4
Sköldstam et al, 1992	43 (7%)	58 (40 -	82	10 FO capsule/d|10 VO capsule/d 1 1 FO capsule = 1g FO 1 VO capsule = 1g maize, olive and peppermint oils	6

[21]		73)			
Clelan d et al, 1988 [22]	46 (23 %)	51	70	18g FO/d |18g OO/d	3
Nielse n et al, 1992 [24]	6 (11 %)	61 (33 - 78)	Not provided	3.6g of n-3 PUFA/d | 3.6g/d fat combination, typical in a Danish diet	3
Rajaei et al, 2015 [25]	49 (18 %)	42 +/- 7	82	1.8 g EPA + 2.1 g DHA/starch capsules	3
Geuse ns et al, 1994 [26]	60 (30 %)	LDFO: 57 +/- 2;	LDFO: 76 * H	LDFO: 3 FO + 3 OO capsules (1.3 g of n-3); HDFO: 6 FO capsules (2.6 g of n-3);| control: 6 OO capsules; FO capsule = 1g FO each OO capsule = 1g OO each	12

		H DF DF O: 59 +/- 2	O: 79 *		
Kremer et al, 1990 [27]	49 (23 %)	LDFO: 59 (32 - 81); HDFO: 58 (30 - 80)	67	LDFO: 27 mg/kg/d (9 mg EPA + 18 mg DHA/kg/d); HDFO: 54 mg/kg/d (18 mg EPA + 36 mg DHA /kg/d);| Control: 6.8g oleic acid/d	6
Krem	37	56	77	diet of PUFA: SFA ratio: 1.4:1 and1.8 g/d EPA |diet of	3

er et al, 1985 [28]	(29 %)		*	PUFA:SFA: 1:4 and 10 placebo capsules of paraffin wax/d	
Adam et al, 2003 [29]	62 (9%)	57 +/- 13	93	1g FO/kg/d | 1g CO/kg/d	3
Dawczynski et al, 2009 [30]	39 (13 %)	58 +/- 11	96	2.4g n−3 FA/d (from dairy products, where milk fat was partially replaced with fish + other oils) Control group had dairy products with comparable amount of non-n-3 FA fat.	3 intervention + 2 washout + 3 control
Kremer et al, 1995 [31]	49 (26 %) until week 18 or 22;	58	55	130 mg/kg/d n-3 FA week on months 0-6.5 months, substituted with 100% corn oil on months 6.5-7.5| Control: 9 capsules/d corn oil for 7.5 months	7.5 (+ 4.5 on diclofenac placebo + corn oil)

	29 (56 %) until week 26 or 30				
Galarraga et al, 2008 [32]	58 (40 %)	58	73	10 g FO (150 mg EPA, 70 mg DHA, 80 µg vitamin A, 0.5 µg vitamin D, 20 IU vitamin E) | air-filled placebo capsule	9
Proudman et al, 2015 [33]	122 (13 %)	56 +/- 16	71	5.5g/d FO | 0.4g/d FO	3.25
Bahadori et al, 2010 [35]	13 (46 %)	58 +/- 4	91	0.2g/kg IV fish oil emulsion (100 ml contains 6.56 g of n-3: 2.82 g EPA, 3.09 g DHA, 0.20 g ALA, 0.45 g of DPA) followed by 0.05g/g fish oil oral capsules | 0.9% OV saline infusion, followed by oral paraffin wax capsules	14 days IV + 20 weeks oral

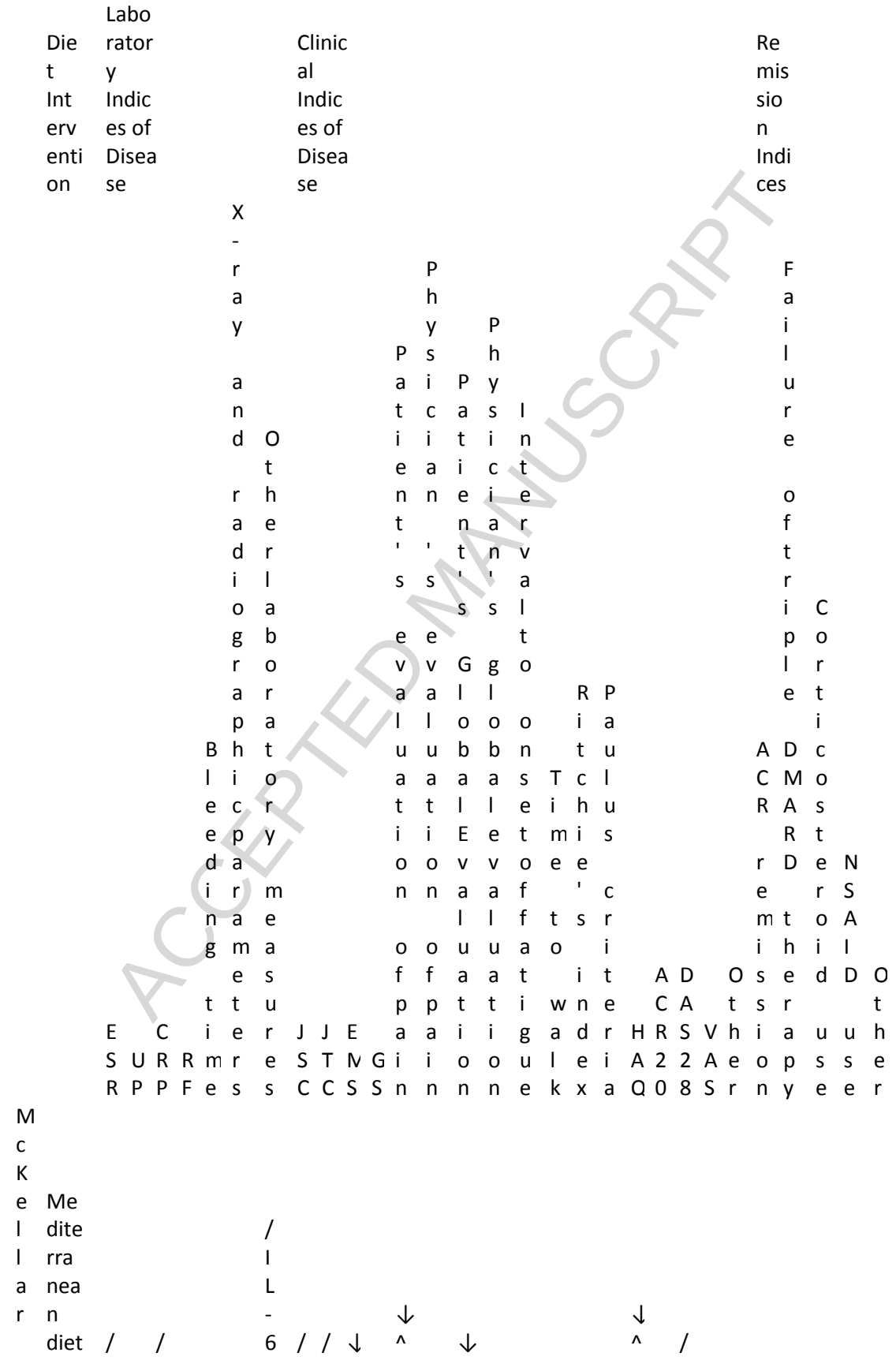
Leeb et al, 2006 [36]	30 (12 %)	60 [± 4.6]^	83 ^^	2 mL/kg IV fish oil emulsion (= 0.1-0.2 g fish oil/kg) (100 ml contains 6.56 g n-3 PUFA: 2.82 g EPA, 3.09 g DHA, 0.20 g ALA, 0.45 g of DPA) |no control group	7 days

Control group characteristics were not significantly different to intervention group characteristics, unless otherwise stated in text.

% based on baseline data of intervention groups only (not taking into account dropouts or withdrawals); **median;

^ showing median (95% CI) age for all participants completing study; ^^ % based on all participants completing study

alpha-linolenic acid (ALA), corn oil (CO), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), eicosapentaenoic acid (EPA), fish oil (FO), gamma-linolenic acid (GLA), linoleic acid (LA), low dose fish oil (LDFO), olive oil (OO), vegetable oil (VO)



McKellar

et al, 2007 [15]															
Sköldstam et al, 2003 [16]	Mediterranean diet	/	↓*	↓ thrombocyte count	↓	↓*	/	/	↓		↓*	↓	↓		/SOFI score
Remans et a	5g of fat, mainly made up of EPA	/	/		/	/			/	/			/	/	

l, 2004 [20]	(1400 mg), DHA (211mg), EPA (1400 mg), DPA (40 mg), ALA (16 mg) GLA (500mg), LA (440mg)									
Sköldstam et al, 19	Dietary fish oil supplementation	↑	/	↑ platelets	↓ *	↑ * (left hand only)	↑ *	/	↓ *	↓

92 [21]			
Cleland et al, 1988 [22]	Dietary fish oil supplementation		↓LTB4, ↓5-HETE, ↓LTB4+LTB5
Nielsen et al, 1992	Dietary fish oil supplementation	/ ↓*	/ ↓* / /

[24] Rajaei et al, 2015	Dietary fish oil supplementation	↓			↓	↓	↓		↓	↓	↓	↓		↓		
[25] Geusens et al, 1994	Dietary fish oil supplementation		↑					↑					↑			
[26]	- LDFO		*	/	/		/	*	/	/	/		*		/	/
	Die	/	/	/	/		/	↑	/	↓	↑		↑		↓	↓

	tary fish oil supplementation - HDFO												*	("NSAID or DMARD")	("NSAID or DMARD")
Kremer et al, 1990 [27]	Dietary fish oil supplementation - LDFO	/	/	/IL-1, /IL-2	↓*	↓*	↓*	/	/	/	↓*	/			
	Dietary fish oil supplementation	/	/	↓* IL-1, /IL-2	↓*	↓*	↓*	/	↓*	/	↓*	/			

	ntation - HDFO														
Kremer et al, 1985 [28]	Dietary fish oil supplementation	/*	↓*	/*	/*	/*	/*	↓*	↓*	/*	/*	↑*	↑*	↓^*	↓*
Adam et al, 2003 [29]	Dietary fish oil supplementation + WD	/*	↓*	↓*	↓*	/*	/*	↓↓	↓↓	/*	/*	↑↑	↑↑	↓*	↓*
	Dietary	/*	↓*	↓*	↓*	/*	/*	↓↓	↓↓	/*	/*	↑↑	↑↑	↓*	↓*

Dawczynski, 2009 [30]	fish oil supplementation + AID Milk fat was partially replaced with fish, rapeseed and Dracocephalum ibericum oil	/	↓*		/	/	/								/
Kremer et al,	Dietary fish oil supplementation - change from baseline to week 26/30 while on diclofenac palcebo			↑* TNF-α		↓*	/	/	/	/	/	↓*	/	/	

1995 [31]																		
	Dietary fish oil supplementation - change from week 18/22 to week 26/30	↓ * IL-1β	/	↓ *	/	/	/	/	↓ *	/	/	/						
Gallarraga et al, 2008 [32]	Dietary fish oil supplementation		/	/	/	/						/	/	↓				↓
Proudma	Dietary fish oil supplementation											/		/ EULAR	↓	↓	/	/	/ methotrexate

n et al, 2015 [33]									response	e
Bahadori et al, 2010 [35]	Intravenous fish oil infusion	/	/	↓	↓					
Leeb et al,	Intravenous fish oil infusion	/	/	↓*	↓*	↓*	↓*	↓*	/	

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Table 2: Results of reviewed studies, including laboratory and clinical parameters, as well as, parameters of remission.

↓	significant decrease
/	no significant result
↓↓/↑↑	Result was significantly stronger vs placebo as well as vs other intervention group as well as vs
*	only within group i.e. compared to baseline
^	mid-way assessment

≠ EMS longer in the control group, no change in the experimental group

5-Hydroxyeicosatetraenoic acid (5-HETE), American College of Rheumatology 20% improvement criteria (ACR20), Anti-inflammatory Diet (AID), alpha-linolenic acid

(ALA), corn oil (CO), C-reactive protein (CRP), Disease Activity Score-28 (DAS28), docosahexaenoic acid (DHA), disease-modifying antirheumatic drugs (DMARDs), docosapentaenoic acid (DPA), eicosapentaenoic acid (EPA), erythrocyte sedimentation rate (ESR), European League Against Rheumatism (EULAR), fish oil (FO), Health Assessment Questionnaire (HAQ), high dose fish oil (HDFO), low dose fish oil (LDFO), Leukotriene B4 (LTB4), Leukotriene B5 (LTB5), non-steroidal anti-inflammatory drugs (NSAID), olive oil (OO), Signals of Functional Impairment (SOFI), Tumour Necrosis Factor (TNF), Visual Analogue Scale (VAS), vegetable oil (VO), Western Diet (WD)

References

[1] Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, Williams B, Gabriel S, Lassere M, Johns N, Buchbinder R, Woolf A, March L: The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1316-1322.

[2] Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, Kiely P: Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Ann Rheum Dis 2016;75:2080-2086.

[3] Radner H, Yoshida K, Frits M, Iannaccone C, Shadick NA, Weinblatt M, Smolen JS, Solomon DH: The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2015;54:2076-2084.

[4] Darlington LG, Ramsey NW, Mansfield JR: Placebo-controlled, blind study of dietary manipulation therapy in rheumatoid arthritis. Lancet 1986;1:236-238.

[5] 17th Mediterranean Congress of Rheumatology: Effects of the diet and the climate in rheumatic and musculoskeletal diseases, Genoa, Italy, 12-14 April 2018: https://www mediterraneanrheuma com/.

[6] Naska A, Trichopoulou A: Back to the future: the Mediterranean diet paradigm. Nutr Metab Cardiovasc Dis 2014;24:216-219.

[7] Oliviero F, Spinella P, Fiocco U, Ramonda R, Sfriso P, Punzi L: How the Mediterranean diet and some of its components modulate inflammatory pathways in arthritis. Swiss Med Wkly 2015;145:w14190.

[8] Santangelo C, Vari R, Scazzocchio B, De SP, Giovannini C, D'Archivio M, Masella R: Anti-inflammatory Activity of Extra Virgin Olive Oil Polyphenols: Which Role in the Prevention and Treatment of Immune-Mediated Inflammatory Diseases? Endocr Metab Immune Disord Drug Targets 2018;18:36-50.

[9] Forsyth C, Kouvari M, D'Cunha NM, Georgousopoulou EN, Panagiotakos DB, Mellor DD, Kellett J, Naumovski N: The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies. Rheumatol Int 2018;38:737-747.

[10] Rosillo MA, Sanchez-Hidalgo M, Sanchez-Fidalgo S, Aparicio-Soto M, Villegas I, Alarcon-de-la-Lastra C: Dietary extra-virgin olive oil prevents inflammatory response and cartilage matrix degradation in murine collagen-induced arthritis. Eur J Nutr 2016;55:315-325.

[11] Rosillo MA, Alcaraz MJ, Sanchez-Hidalgo M, Fernandez-Bolanos JG, Alarcon-de-la-Lastra C, Ferrandiz ML: Anti-inflammatory and joint protective effects of extra-virgin olive-oil polyphenol extract in experimental arthritis. J Nutr Biochem 2014;25:1275-1281.

[12] Mitsou EK, Kakali A, Antonopoulou S, Mountzouris KC, Yannakoulia M, Panagiotakos DB, Kyriacou A: Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. Br J Nutr 2017;117:1645-1655.

[13] Maeda Y, Takeda K: Role of Gut Microbiota in Rheumatoid Arthritis. J Clin Med 2017;6.

[14] Zhong D, Wu C, Zeng X, Wang Q: The role of gut microbiota in the pathogenesis of rheumatic diseases. Clin Rheumatol 2018;37:25-34.

[15] McKellar G, Morrison E, McEntegart A, Hampson R, Tierney A, Mackle G, Scoular J, Scott JA, Capell HA: A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. Ann Rheum Dis 2007;66:1239-1243.

[16] Skoldstam L, Hagfors L, Johansson G: An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:208-214.

[17] Harris WS: The Omega-6:Omega-3 ratio: A critical appraisal and possible successor. Prostaglandins Leukot Essent Fatty Acids 2018;132:34-40.

[18] Simopoulos AP: The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood) 2008;233:674-688.

[19] Navarini L, Afeltra A, Gallo AG, Margiotta DPE: Polyunsaturated fatty acids: any role in rheumatoid arthritis? Lipids Health Dis 2017;16:197.

[20] Remans PH, Sont JK, Wagenaar LW, Wouters-Wesseling W, Zuijderduin WM, Jongma A, Breedveld FC, Van Laar JM: Nutrient supplementation with polyunsaturated fatty acids and micronutrients in rheumatoid arthritis: clinical and biochemical effects. Eur J Clin Nutr 2004;58:839-845.

[21] Skoldstam L, Borjesson O, Kjallman A, Seiving B, Akesson B: Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. Scand J Rheumatol 1992;21:178-185.

[22] Cleland LG, French JK, Betts WH, Murphy GA, Elliott MJ: Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. J Rheumatol 1988;15:1471-1475.

[23] Parkinson L, Cicerale S: The Health Benefiting Mechanisms of Virgin Olive Oil Phenolic Compounds. Molecules 2016;21.

[24] Nielsen GL, Faarvang KL, Thomsen BS, Teglbjaerg KL, Jensen LT, Hansen TM, Lervang HH, Schmidt EB, Dyerberg J, Ernst E: The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. Eur J Clin Invest 1992;22:687-691.

[25] Rajaei E, Mowla K, Ghorbani A, Bahadoram S, Bahadoram M, Dargahi-Malamir M: The Effect of Omega-3 Fatty Acids in Patients With Active Rheumatoid Arthritis Receiving DMARDs Therapy: Double-Blind Randomized Controlled Trial. Glob J Health Sci 2015;8:18-25.

[26] Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J: Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. A 12-month, double-blind, controlled study. Arthritis Rheum 1994;37:824-829.

[27] Kremer JM, Lawrence DA, Jubiz W, DiGiacomo R, Rynes R, Bartholomew LE, Sherman M: Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. Clinical and immunologic effects. Arthritis Rheum 1990;33:810-820.

[28] Kremer JM, Bigauoette J, Michalek AV, Timchalk MA, Lininger L, Rynes RI, Huyck C, Zieminski J, Bartholomew LE: Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. Lancet 1985;1:184-187.

[29] Adam O, Beringer C, Kless T, Lemmen C, Adam A, Wiseman M, Adam P, Klimmek R, Forth W: Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. Rheumatol Int 2003;23:27-36.

[30] Dawczynski C, Schubert R, Hein G, Muller A, Eidner T, Vogelsang H, Basu S, Jahreis G: Long-term moderate intervention with n-3 long-chain PUFA-supplemented dairy products: effects on pathophysiological biomarkers in patients with rheumatoid arthritis. Br J Nutr 2009;101:1517-1526.

[31] Kremer JM, Lawrence DA, Petrillo GF, Litts LL, Mullaly PM, Rynes RI, Stocker RP, Parhami N, Greenstein NS, Fuchs BR. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. Arthritis Rheum 1995;38:1107-1114.

[32] Galarraga B, Ho M, Youssef HM, Hill A, McMahon H, Hall C, Ogston S, Nuki G, Belch JJ: Cod liver oil (n-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. Rheumatology (Oxford) 2008;47:665-669.

[33] Proudman SM, James MJ, Spargo LD, Metcalf RG, Sullivan JM, Rischmueller M, Flabouris K, Wechalekar MD, Lee AT, Cleland LG: Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use.; 2015, pp 89-95.

[34] Proudman SM, Cleland LG, Metcalf RG, Sullivan TR, Spargo LD, James MJ: Plasma n-3 fatty acids and clinical outcomes in recent-onset rheumatoid arthritis. Br J Nutr 2015;114:885-890.

[35] Bahadori B, Uitz E, Thonhofer R, Trummer M, Pestemer-Lach I, McCarty M, Krejs GJ: omega-3 Fatty acids infusions as adjuvant therapy in rheumatoid arthritis. JPEN J Parenter Enteral Nutr 2010;34:151-155.

[36] Leeb BF, Sautner J, Andel I, Rintelen B: Intravenous application of omega-3 fatty acids in patients with active rheumatoid arthritis. The ORA-1 trial. An open pilot study. Lipids 2006;41:29-34.

[37] Goldberg RJ, Katz J: A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007;129:210-223.

[38] Lee YH, Bae SC, Song GG: Omega-3 polyunsaturated fatty acids and the treatment of rheumatoid arthritis: a meta-analysis. Arch Med Res 2012;43:356-362.

[39] Taylor PC, Alten R, Gomez-Reino JJ, Caporali R, Bertin P, Sullivan E, Wood R, Piercy J, Vasilescu R, Spurden D, Alvir J, Tarallo M: Clinical characteristics and patient-reported outcomes in patients with inadequately controlled rheumatoid arthritis despite ongoing treatment. RMD Open 2018;4:e000615.

[40] Nikiphorou E, Aletaha D, Bukhari M: Are we failing patients in our assessment of treatment failure? Rheumatology (Oxford) 2018.

[41] Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, Dixon WG, Hyrich KL, Askling J, Gossec L: Patient global assessment in

measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.

[42] Pincus T, Sokka T, Kautiainen H: Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. Arthritis Rheum 2005;52:1009-1019.

[43] Fautrel B, Alten R, Kirkham B, de lT, I, Durand F, Barry J, Holzkaemper T, Fakhouri W, Taylor PC: Call for action: how to improve use of patient-reported outcomes to guide clinical decision making in rheumatoid arthritis. Rheumatol Int 2018;38:935-947.

[44] Daien CI, Hua C, Combe B, Landewe R: Non-pharmacological and pharmacological interventions in patients with early arthritis: a systematic literature review informing the 2016 update of EULAR recommendations for the management of early arthritis. RMD Open 2017;3:e000404.

[45] Vliet Vlieland TP: Non-drug care for RA--is the era of evidence-based practice approaching? Rheumatology (Oxford) 2007;46:1397-1404.

Highlights

- Limited evidence that Mediterranean diet benefits pain, swollen and tender joints.
- Fish oil supplements may improve symptoms and progression of pharmacotherapy.
- Larger and methodologically-robust randomized controlled trials are necessary.
- Firm conclusions on impact/effect size of nutritional interventions cannot be drawn.