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Review

Mediterranean diet and rheumatoid arthritis

Running title: Diet and rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease in which persistent synovial inflammation leads to pain, fatigue, functional impairment, and progressive joint damage, with substantial extra-articular morbidity and excess cardiovascular risk. While treat-to-target pharmacotherapy remains essential, dietary patterns may complement care by influencing inflammation, oxidative stress, immunometabolism, adiposity, and the gut microbiome.

The Mediterranean Diet (MD), including extra virgin olive oil as the main fat and high vegetable and fruit intake has strong cardiometabolic benefits and is biologically plausible in RA. MD may modulate cytokines, reduce oxidative stress and support microbial resilience and short-chain fatty acid production.

Human evidence is most consistent for modest improvements in pain and physical function in established RA, whereas effects on composite disease activity and prevention of incident RA remain uncertain. Currently, MD is best viewed as a safe adjunct to standard therapy.

Keywords- Autoimmunity; Olive oil; Mediterranean diet; Quality of life

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I. INTRODUCTION

Rheumatoid arthritis (RA) constitutes a chronic inflammatory disease that affects primarily the joints, often leading to permanent deformities and disability [1]. RA can extend beyond the musculoskeletal system and diminish patients' quality of life, particularly when inflammation is not controlled early and consistently [2]. Therapeutic progress over the last two decades, specifically treat to target strategies, conventional disease modifying antirheumatic drugs (DMARDs), biologics and newer targeted agents, have changed the prognosis for many patients [3]. Yet, the concept of "best care" still rarely means medication alone.

RA emerges from an interplay between genetic susceptibility and modifiable exposures, namely smoking, body composition, physical activity, stress infections and diet [4-6]. The reality remains that patients visiting a rheumatology practice, often inquire about specific dietary modifications that may alter the disease's course. The conversation has shifted from "Is diet the cure?" to whether dietary patterns can reduce inflammatory load, improve symptoms and strengthen long term health alongside evidence-based pharmacotherapy. This aligns with general lifestyle guidance in rheumatic diseases, which emphasizes weight control, cardiometabolic risk reduction and balanced diet as part of a comprehensive management.

Mediterranean diet (MD) is a dietary pattern that includes high intake of vegetables, fruits, legumes, nuts as well as minimally processed grains and fish. The above is combined with a modest consumption of dairy and meat,

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while olive oil plays a central role as the principal fat [7, 8]. Habitual movement is often embedded in the traditional lifestyle framing, which matters since adiposity and inactivity are known to amplify inflammation independent of diet composition.

It is known that RA is expressed in a milder form in South Europe, compared to North Europe [5]. These differences have been attributed to many factors, such as immunogenetic background and environmental factors [9]. However, there is limited data available regarding the impact of MD in RA, in comparison with other diseases such as cardiovascular events, diabetes mellitus and dementia where the influence of MD in reducing mortality is well documented.

The purpose of this review is to highlight evidence on the importance of nutrition to the onset and progression of RA in an attempt for a more holistic approach.

II. MEDITERRANEAN DIET AND RA: MECHANISTIC RATIONALE

A. FATTY ACIDS

A core Mediterranean Diet feature is replacing saturated fats with monounsaturated fats (olive oil) and increasing omega-3 intake through fish and seafood. Omega-3 polyunsaturated fatty acids (EPA/DHA) can shift eicosanoid biology toward less inflammatory signaling, with downstream effects on cytokines central to RA pathophysiology, such as IL-1β, TNF-a and IL-6 [10]. A recent umbrella review demonstrates the consistent positive effects of omega-3 fatty acids in disease activity and inflammatory markers in RA [11]. Furthermore, in early RA fish oil was associated with benefits additional to those achieved by treat to target DMARDs, after adjustment for smoking history, shared epitope and baseline anti-cyclic citrullinated peptide (anti-CCP) antibodies. Specifically, a randomized controlled trial (RCT) demonstrated that the rate of first American College of Rheumatology (ACR) remission was significantly greater in patients who received fish oil and failure of triple DMARD therapy was lower [12].

B. POLYPHENOLS AND OXIDATIVE STRESS

MD is rich in polyphenols and antioxidants from extra virgin olive oil (EVOO), vegetables, fruits and cocoa. Polyphenols have been repeatedly associated with reduced oxidative stress in various clinical and experimental contexts. Majeed et al. reported that pineapple juice in rats suffering from arthritis exhibits mild anti-inflammatory effects [13]. In a similar manner, custard apple juice seems to reduce oxidant status, catalase, and glutathione peroxidase levels in rats suffering from RA [14].

Cocoa flavanols also exhibit immunomodulatory and antioxidant properties in experimental models. The phenolics from cocoa also modify the glycemic response and the lipid profile, decreasing platelet function and inflammation along with diastolic and systolic arterial pressures, which, taken together, may reduce the risk of cardiovascular mortality. [15]. Cocoa polyphenols additionally modulate intestinal inflammation via various transcription factors expression, leading to decreases in proinflammatory cytokines [15]. A recent systematic review demonstrated that dietary polyphenols may improve Disease Activity Score-28 (DAS28) in patients with RA, reduce C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and improve oxidative stress [16].

C. GUT MICROBIOTA

MD can alter the composition of gut microbiota, which is central to immune regulation. Greater adherence to MD has been linked to a more favorable microbiome profile, including lower abundance of proinflammatory species such as Prevotella copri [17]. These diet-driven shifts in the microbiome may help explain the reductions in RA disease activity reported among patients following a MD [18]. Beyond microbiome changes, MD may influence immune function through epigenetic mechanisms and by supporting the integrity of the gastrointestinal epithelial barrier and mucosal immune system. Bioactive compounds commonly consumed in this dietary pattern, including curcumin and capsaicin from spices, have been shown to reduce oxidative stress and inflammation by inhibiting NF-κB and cyclooxygenase-2 signaling pathways [19]. Although direct causal pathways in RA remain under active investigation, microbiome-centered models offer a coherent framework linking MD adherence with systemic inflammatory load.

D. ADIPOSITY

Body composition and metabolic context are clinically important modifiers of RA. Higher BMI is repeatedly associated with higher disease activity, greater pain, worse functional outcomes, and reduced likelihood of remission in multiple cohorts and meta-analyses [20-23]. Mechanistically, adipose tissue acts as an endocrine/immune organ that can amplify inflammation and recruit inflammatory leukocytes; models suggest obesity can worsen joint inflammation through chemokine signaling and myeloid cell activation [23]. Beyond adiposity itself, emerging work highlights metabolic dysregulation within immune cells: lipid-dependent signaling pathways in RA T cells may favor pathogenic Th1/Th17 differentiation, supporting synovitis [24]. Glucose metabolism is also implicated; altered routing of glucose metabolism in RA T

cells has been proposed to support hyperproliferation and inflammatory phenotypes [25].

MD is not inherently calorie-restrictive, but it is often associated with improved diet quality, lower energy density, and better glycemic or lipid profiles. These features can facilitate weight management and reduce cardiometabolic risk, which in turn may improve inflammatory milieu and clinical responsiveness. In parallel, fasting and caloric restriction have been reported to improve inflammatory markers and composite scores in RA in some studies, potentially through microbiome and metabolic shifts, but adherence and feasibility remain challenges for long-term implementation [26]. Compared with restrictive strategies, MD offers a more sustainable pattern for many patients.

III. HUMAN EVIDENCE

Geographic variation in RA severity and prevalence has long been observed, with suggestions that environmental and lifestyle factors, including diet, may contribute [9]. However, when the MD hypothesis is tested prospectively, results have been cautious rather than definitive. A large cohort analysis using an MD adherence score (MEDI-LITE) reported that higher adherence was associated with lower risk of developing RA [27]. Another study reported that the Cteran MD demonstrated a reduction in disease activity, improved physical function and vitality [18].

Evidence is more encouraging for symptom outcomes in established RA. A systematic review of human prospective studies concluded that MD interventions were associated with improvements in pain and physical function in RA, while effects on composite disease activity scores were less consistently demonstrated and prevention evidence was limited [7].

Table 1. Prospective studies on RA and MD

Study	Country	Design	Sample	Tool	Effect size
Hu, 2015 [27]	USA	Cohort	NHS: N=83,245; 30–55; F only. NHS II: N=91,393; 25–42; F only	aMED	RA: HR 0.98 (0.80–1.20); Seropositive: HR 1.10 (0.85–1.42); Seronegative: HR 0.80 (0.57–1.13)
Sund-strom, 2015 [28]	Sweden	Case-control	Cases: N=386; age: 30–61; sex: 271/115. Controls: N=1886; age: 30–61; sex:1323/563	MDS	RA: OR 0.94 (0.68–1.29); RF+: OR 0.89 (0.63–1.27); anti-CCP+: OR 0.93 (0.64–1.36)

Table 1 abbreviations: anti-CCP, anti-cyclic citrullinated peptide; aMed, alternate Mediterranean diet score; HR, hazard ratio; F, Female; MD, Mediterranean diet; MDS, Mediterranean diet score; NHS, Nurses' Health Study; OR, odds ratio; RA, Rheumatoid arthritis; RF, rheumatoid factor

Table 2. Clinical trials on RA and MD

Study	Country	Design	Sample	Intervention	Main results
McKellar, 2007 [29]	Scotland	UCT	MD: N=75; age 47–64 Control: N=55; age 45–61	6 week MD, + weekly cookery course + written materials	Pain and physical function improved;global VAS and morning stiffness improved
Sköldstam, 2003 [18]	Sweden	RCT	Cases: N=386; age: 30–61; sex: 271/115. Controls: N=1886; age: 30–61; sex:1323/563	12-week modified Cretan MD (oil-focused). Phase 1 (3 wks inpatient): Phase 2 (9 wks outpatient): printed guidance/recipes + supplied foods (incl. oils) + dietitian	Swelling, physical function, CRP and QoL. DAS28 reduction at week 12 ($p<0.001$)

Table 2 abbreviations:CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; MD, Mediterranean diet; RCT, randomized controlled trial; UCT, Unrandomized clinical trial; VAS, visual analogue scale; QoL, quality of life; wks, weeks

IV. DISCUSSION

Two practical interpretation points emerge: First, MD appears most consistently beneficial for outcomes that matter to patients such as pain, function and vitality rather than acting as a stand-alone disease modifying therapy. Second, dietary trials in RA are structurally difficult: blinding is limited, adherence is variable, interventions often include education and behavioral components, while medications can obscure incremental effects. hese realities do not negate MD's utility; they emphasize that MD should be framed as an adjunctive strategy that supports symptom control, metabolic health, and comorbidity prevention alongside treat-to-target pharmacotherapy.

From a clinical standpoint, MD should be presented as a safe, sustainable adjunct to treat-to-target therapy. Its most dependable value may be indirect: improving cardiometabolic health, supporting weight management, and reducing exposures (added sugars, ultra-processed foods, excessive red/processed meat) that are plausibly linked to inflammatory activation and poorer RA outcomes.

Future research priorities include adequately powered randomized trials with standardized MD definitions and objective adherence measures, longer follow-up, and integration of microbiome/metabolomic profiling to identify responders and mechanistic mediators. Until such data mature, a MD framework centered on EVOO, plant foods, regular fish, and minimal added sugars represents a scientifically grounded, patient-acceptable strategy to complement pharmacologic control of RA and improve long-term health trajectories.

V. CONCLUSION

The Mediterranean diet appears to offer modest improvements in pain and physical function in established RA and is a safe, sustainable adjunct to standard treat-to-target therapy.

AUTHOR CONTRIBUTIONS

All authors participated in manuscript preparation. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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