

Effects of Mediterranean diet on the treatment of rheumatoid arthritis

Maximiliano Porras^{a,b}, Gabriel Rada^{b,c}, Josefina Durán^{b,d,*}

^a Facultad de Medicina, Universidad Católica del Norte, Coquimbo, Chile

^b Proyecto Epistemonikos, Santiago, Chile

^c Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

^d Departamento de Inmunología y Reumatología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

*Corresponding author jgduran@uc.cl

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Abstract

Introduction

It has been suggested that environmental and lifestyle factors might contribute to the severity and progression of inflammation in rheumatoid arthritis. An intervention generating high interest due to its supposed anti-inflammatory properties is the Mediterranean diet.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified seven systematic reviews including four primary studies, of which only one corresponded to a randomized trial. We concluded Mediterranean diet may make little or no difference in pain or disease activity and may slightly increase weight in rheumatoid arthritis patients, but the certainty of the evidence is low. On the other hand, it was not possible to clearly establish whether Mediterranean diet has any effect on functionality, morning stiffness or quality of life as the certainty of the existing evidence has been assessed as very low.

Problem

Rheumatoid arthritis is a chronic autoimmune disease whose etiology is not fully known. There are important variations in its frequency, which cannot only be attributed to genetic or racial factors, so it has been suggested that environmental factors, such as tobacco use and diet might contribute to both the development and the severity of the disease¹.

Moreover, the Mediterranean diet has beneficial effects in the prevention and treatment of various health conditions, which are mediated by various mechanisms, such as increasing antioxidant levels, modifying intestinal flora, promoting an anti-inflammatory lipid profile (omega 3: omega 6 ratio) and possibly decreasing inflammation in other ways². Its anti-inflammatory properties have generated a particular interest in its use as part of the treatment of rheumatoid arthritis, however, if this really translates into a relevant clinical effect is a matter of controversy.

Key messages

- The Mediterranean diet may make little or no difference in pain and disease activity for patients with rheumatoid arthritis (low certainty evidence).
- We are uncertain whether Mediterranean diet improves functionality, morning stiffness and quality of life in rheumatoid arthritis as the certainty of the evidence has been assessed as very low.
- Mediterranean diet may slightly increase weight among rheumatoid arthritis patients (low certainty evidence).

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and re-analyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found seven systematic reviews ¹⁻⁷ which included four primary studies, reported in six references ⁸⁻¹³ of which only one was a randomized trial ⁸ . The information provided by the observational studies did not increase the level of certainty of the evidence, nor did add new relevant information. Therefore the table presented and the summary is based on the only randomized trial.
What types of patients were included*	The trial was conducted in Sweden ⁸ and included 51 patients, mostly women (82.3%), with rheumatoid arthritis diagnosed by criteria ACR 1987, with at least two years from diagnosis and controlled disease according to the clinician criteria at randomization. The trial excluded patients who already had a vegetarian or Mediterranean diet, with high doses of corticosteroids, or recent adjustments in therapy.
What types of interventions were included*	The trial⁸ evaluated a Mediterranean diet high in oils for 12 weeks in the intervention group, compared to Western diet in the control group. The intervention was conducted in two stages with three weeks of education and diet in the hospital, followed by nine weeks of strict clinical follow-up where the food included in the diet was provided.
What types of outcomes were measured	The trial⁸ evaluated multiple outcomes, which were grouped by the systematic reviews as follows: • Pain (visual analogue scale, VAS) • Functionality (Health Assessment Questionnaire, HAQ) • Morning stiffness (minutes) • Activity Score (Disease Activity Score, DAS 28)

	• Vitality (SF-36) • Weight (kg) at week 12 of the intervention. • Inflammatory parameters (C reactive protein, CRP)
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* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information on the effects of the Mediterranean diet in rheumatoid arthritis is based on one randomized trial [8] that included 51 patients for the outcomes pain, disease activity, functionality, morning stiffness, quality of life and weight.

The summary of findings is as follows:

- Mediterranean diet may make little or no difference to pain in rheumatoid arthritis (low certainty of the evidence).
- Mediterranean diet may make little or no difference to disease activity in rheumatoid arthritis (low certainty of the evidence).
- We are uncertain whether Mediterranean diet improves functionality in rheumatoid arthritis as the certainty of the evidence has been assessed as very low.
- We are uncertain whether Mediterranean diet improves morning stiffness in rheumatoid arthritis as the certainty of the evidence has been assessed as very low.
- We are uncertain whether Mediterranean diet improves quality of life in rheumatoid arthritis as the certainty of the evidence has been assessed as very low.
- Mediterranean diet may slightly increase weight in rheumatoid arthritis (certainty of low evidence).

Mediterranean diet for rheumatoid arthritis				
Patients	Adults with rheumatoid arthritis			
Intervention	Mediterranean diet			
Comparison	Western diet			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT Mediterranean diet	WITH Mediterranean diet		
Pain VAS scale 0-100 mm	34 mm	20 mm	--	⊕⊕○○ ^{1,2} Low
	MD: 14 less (Margin of error: 4.37 to 23.63 less)			
Disease Activity DAS28**	A reduction of 0.56 points was reported in the Mediterranean diet group, which was reported as statistically significant [8].		--	⊕⊕○○ ^{1,2} Low
Functionality HAQ***	0.8 points	0.6 points	--	⊕○○○ ^{1,2} Very low
	MD: 0.2 less (Margin of error: 0.48 less to 0.08 more)			
Morning stiffness	70 minutes	44 minutes	--	⊕○○○ ^{1,2} Very low
	MD: 26 less (Margin of error: 58.08 less to 6.08 more)			
Quality of life vitality SF-36****	4.2 points	11.3 points	--	⊕○○○ ^{1,2} Very low
	MD: 7.1 more (Margin of error: 3.1 less to 17.3 more)			
Weight	72.6 kg	75.9 kg	--	⊕⊕○○ ^{1,2} Low
	MD: 3.3 more (Margin of error: 3.97 less to 10.57 more)			
Margin of error: 95% confidence interval (CI). MD: Mean difference. GRADE: Evidence grades of the GRADE Working Group (see later). *Means WITHOUT Mediterranean diet are based on the means of the control group in the trial. Means WITH Mediterranean diet (and their margin of error) are calculated from the relative effect (and its margin of error). ** The DAS28 is an instrument that measures activity in rheumatoid arthritis. Its calculation includes the number of painful joints (PJ), number of inflamed joints (IJ), global health of the patient measured with a visual analogue scale (VAS) and inflammatory parameters (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)). This is calculated with the following formula: $DAS28 = 0.56 * \sqrt{(PJ)} + 0.28 * \sqrt{(IJ)} + 0.70 * \ln (ESR / CRP) + 0.014 * SG$. The minimally clinically important difference (MCID) for this scale is 1.2. *** HAQ is an instrument that measures functional disability with a range between 0 (no limitation) and 3 (being unable to perform all of the activity types). The minimally clinically important difference (MCID) for this scale is 0.22. **** SF-36 is a generic instrument that measures quality of life and has 8 dimensions. The vitality dimension is only presented because in the other dimensions (physical functioning, physical role, body pain, social function, emotional role, mental health and general health) there were no significant changes. ¹ The certainty of the evidence was downgraded in one level due to imprecision, since decisions at both ends of the confidence interval would vary. For the outcomes functionality, morning stiffness, quality of life and weight, two levels were downgraded since the decisions would vary substantially at each end of the confidence interval. ² The certainty of the evidence was downgraded in one level for risk of bias, since the trial had a high risk related to blinding of participants and personnel. In the case of weight, we decided not to decrease the certainty of the evidence since the absence of bias would reinforce the conclusion.				

Follow the link to access the interactive version of this table ([Interactive Summary of Findings – iSoF](#))

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕○○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

These results are applicable to patients with rheumatoid arthritis with controlled disease. The population with uncontrolled (active) disease was explicitly excluded from the trial and it is reasonable, from the clinical point of view, to expect a different effect in these cases.

About the outcomes included in this summary

The outcomes selected are those considered critical for decision-making by the authors of this summary, among those reported in the analyzed trial. In the case of having had information about other relevant outcomes such as ACR 20 or ACR 70 these would have been incorporated as well.

It is important to emphasize that although the effect observed in some outcomes is statistically significant in favor of the Mediterranean diet, the magnitude of the benefit does not exceed the thresholds usually defined to consider the effect clinically relevant. It is not possible to establish whether the Mediterranean diet really has a small but existing effect, or if it is only a spurious finding derived from the methodological limitations of the trial.

Balance between benefits and risks, and certainty of the evidence

This is an intervention where the benefits on symptoms and progression of rheumatoid arthritis are uncertain in some outcomes and not clinically relevant in others.

Although the adverse effects of the intervention are minimal, which translates into treatment withdrawal rates due to adverse effects that were not different from the control group [7], it is important to note that a higher final weight was reported.

Resource considerations

This intervention has costs associated to both food and the necessary processes to get people to incorporate it efficiently into their lives. For example, in the trial analyzed, a first stage of intensive education was carried out in an in-hospital setting, followed by an out-of-hospital follow-up managed by the health team, including the appropriate food

for the study participants. The total cost of implementing an intervention with these characteristics depends to a large extent on whether there are nutritional programs that are responsible for training dietary changes or food provision for patients.

None of the identified studies reported a formal cost or cost-benefit analysis.

What would patients and their doctors think about this intervention

When faced with the evidence presented in this summary, most patients and treating physicians should lean against its use.

However, people might be inclined in favor of its use, since there is a positive perception regarding the possible benefits that the Mediterranean diet has on other diseases that are not related to rheumatoid arthritis symptoms and progression (cardiovascular effects, cancer, dementia, among others).

Differences between this summary and other sources

The results of this summary are in general in agreement with the reviews analyzed, in terms of the limitations of existing evidence and the associated uncertainty.

Although the conclusions presented by the authors of the trial are concordant with this summary, they are in general more optimistic on interpreting the results, based on the effect on some surrogate outcomes, such as plasma markers of inflammation⁸.

In the main clinical guidelines, such as the American College of Rheumatology 2015¹⁴ and the European League Against Rheumatism 2016¹⁵, the Mediterranean diet is not mentioned.

Could this evidence change in the future?

The conclusions of this summary are likely to change when new evidence is available, due to the existing uncertainty.

Two relevant randomized trials were identified in the International Clinical Trials Registry Platform of the World Health Organization^{16,17}, but their results have not yet been published. These could shed new light on this debate.

	Sköldstam L 2003	McKellar G 2007	Hagfors L 2003	Michalsen A 2005	Hagfors L 2005	Abendroth A 2010
González Cernad... 2014						
Hagen KB 2009						
Forsyth C 2018						
Bloomfield HE 2016						
Serra-Majem L 2006						

An evidence matrix is a table that compares systematic reviews that answer the same question. Rows represent systematic reviews, and columns show primary studies. The boxes in green correspond to studies included in the respective revisions. The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version**: [Mediterranean diet for rheumatoid arthritis](http://dx.doi.org/10.5867/medwave.2014.06.5997).

Referencias

- 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 May;38(5):737-747. | CrossRef | PubMed |
- Hagen KB, Byfuglien MG, Falzon L, Olsen SU, Smedslund G. Dietary interventions for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2009 Jan 21;(1):CD006400. | CrossRef | PubMed |
- Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2016 Oct 4;165(7):491-500. | CrossRef | PubMed |
- Cramp F, Hewlett S, Almeida C, Kirwan JR, Choy EH, Chalder T, Pollock J, Christensen R. Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2013 Aug 23;(8):CD008322. | CrossRef | PubMed |
- González Cernadas L, Rodríguez-Romero B, Carballo-Costa L. [Importance of nutritional treatment in the inflammatory process of rheumatoid arthritis patients; a review]. *Nutr Hosp*. 2014 Feb 1;29(2):237-45. | CrossRef | PubMed |
- Serra-Majem L, Roman B, Estruch R. Scientific evidence of interventions using the Mediterranean diet: a systematic review. *Nutr Rev*. 2006 Feb;64(2 Pt 2):S27-47. | PubMed |
- Smedslund G, Byfuglien MG, Olsen SU, Hagen KB. Effectiveness and safety of dietary interventions for rheumatoid arthritis: a systematic review of randomized controlled trials. *J Am Diet Assoc*. 2010 May;110(5):727-35. | CrossRef | PubMed |
- Hagfors L, Nilsson I, Sköldstam L, Johansson G. Fat intake and composition of fatty acids in serum phospholipids in a randomized, controlled, Mediterranean dietary intervention study on patients with rheumatoid arthritis. *Nutr Metab (Lond)*. 2005 Oct 10;2:26. | PubMed | PMC |
- Sköldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003 Mar;62(3):208-14. | PubMed | PMC |
- Hagfors L, Leanderson P, Sköldstam L, Andersson J, Johansson G. Antioxidant intake, plasma antioxidants and oxidative stress in a randomized, controlled, parallel, Mediterranean dietary intervention study on patients with rheumatoid arthritis. *Nutr J*. 2003 Jul 30;2:5. | PubMed | PMC |
- Abendroth A, Michalsen A, Lütke R, Rüffer A, Musial F, Dobos GJ, Langhorst J. Changes of Intestinal Microflora in Patients with Rheumatoid Arthritis during Fasting or a Mediterranean Diet. *Forsch Komplementmed*. 2010;17(6):307-13. | CrossRef | PubMed |

Notes

The upper portion of the matrix of evidence will display a warning of “new evidence” if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (<http://dx.doi.org/10.5867/medwave.2014.06.5997>)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

12. Michalsen A, Riegert M, Lüdtker R, Bäcker M, Langhorst J, Schwickert M, Dobos GJ. Mediterranean diet or extended fasting's influence on changing the intestinal microflora, immunoglobulin A secretion and clinical outcome in patients with rheumatoid arthritis and fibromyalgia: an observational study. *BMC Complement Altern Med*. 2005 Dec 22;5:22. | PubMed | PMC |
13. McKellar G, Morrison E, McEntegart A, Hampson R, Tierney A, Mackle G, Scouler 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 Sep;66(9):1239-43. | PubMed | PMC |
14. Singh, J. A., et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis & rheumatology*, 68(1), 1-26. | CrossRef | PubMed |
15. Smolen, J. S., et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Annals of the rheumatic diseases*, 76(6), 960-977. | CrossRef | PubMed |
16. Castillo Martínez, L. Exercise and Mediterranean Diet on Body Composition, Disease Activity and Inflammatory Markers in Rheumatoid Arthritis. *clinicaltrials.gov*. 2014. | Link |
17. Harokopio University. Lifestyle Interventions Based on the Mediterranean Diet for Patients With Rheumatoid Arthritis. *clinicaltrials.gov*. 2009. | Link |

Correspondence to

Centro Evidencia UC
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago
Chile



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