

Mediterranean diet and rheumatic diseases

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Dietary habits have long been known to have a critical role on human health and diseases. Recently, growing evidence has emerged on the impact of dietary factors in shaping the pathogenesis and progression of several chronic conditions, including rheumatic diseases.

Food-derived molecules have been shown to act as epigenetic modifiers, affecting immune response and the so-called *mosaic of autoimmunity* through differential interactions with the gastrointestinal epithelial barrier, the mucosal immune system and intestinal microbial flora.¹

It is therefore not surprising that nutritional intervention has now been part of a broader multidisciplinary approach to several chronic diseases, becoming of central concern for both patients and clinicians.

Regarding rheumatic diseases, this approach is supported by the evidence of a dietary-based inflammatory phenotype, which has derived from a progressive *westernization of diet*. In fact, modern western diets, characterized by high consumption of refined carbohydrates, added sugars and salty foods, could progressively induce a pro-inflammatory state and therefore autoimmune diseases.^{2,3} It has in fact been shown that visceral adiposity drives naïve myeloid

cells into M1 pro-inflammatory macrophages and that high concentration of sodium chloride induces differentiation of Th17 cells and overproduction of inflammatory cytokines.²

The aim of nutritional intervention in the course of rheumatic diseases is instead to provide a dietary regimen centered on a high anti-inflammatory and antioxidant profile of nutrients.² To this purpose, different dietary approaches have been investigated, mainly focusing on rheumatoid arthritis (RA), as the prototypical chronic inflammatory disease.⁴

Among the proposed dietary approaches, the Mediterranean diet (MedDiet) is the best-balanced and most complete diet and the only one to support substantial health benefits for rheumatic diseases.²

Originating in the rural areas of the upper Mediterranean basin, MedDiet is characterized by a large variety of nutrients reflecting the eating habits and geographical resources of those territories. It consists in an abundant intake of antioxidant and anti-inflammatory compounds - derived from extra-virgin olive oil (EVOO), vegetables, fresh fruits, nuts, whole grains, fish and from a small number of dairy products and from red wine - and an appropriate lipid profile with low intake of saturated fats and optimal ratio of n-6 to n-3 polyunsaturated fatty acids (PUFAs).²

There is accumulating evidence that MedDiet, beyond its preventive role on general health, could also be beneficial for most rheumatic diseases, offering effective integrative treatments to a pharmacological approach.²

A recent systematic review has confirmed the beneficial effect of MedDiet in reducing pain and increasing physical function in RA patients.⁵

More specifically, a large number of experimental and observational studies have focused on the properties of each bioactive compounds provided by MedDiet, reporting their positive effects on rheumatic diseases progression.⁶

Dietary antioxidants, highly contained in red fruits, vegetables, nuts and cocoa, are a heterogeneous group of bioactive compounds with a strong anti-inflammatory function and analgesic effect.⁶ Interestingly, these nutrients have been recently reported to reduce pain and inflammation in experimental models and in human clinical studies of arthritis. Specifically, resveratrol, which is found in high concentrations in grapes and red wine, has been reported to potentially inhibit nuclear factor kB (NF-kB) activity, preventing inflammation in RA *in vitro* models.⁶

Anti-inflammatory properties are mostly attributed to spices, traditionally an integral part of MedDiet. These contain components such as curcumin and capsaicin, which exert a regulatory effect on oxidative stress and inflammation.^{1,2}

Curcumin has been used in Ayurvedic medicine for centuries for its properties in treating various inflammatory conditions, including psoriasis and arthritis.¹ More recently, *in vitro* studies have reported its efficacy in suppressing inflammatory cascade by blocking NF-kB and cyclooxygenase 2 pathways and, specifically, in

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down-regulating interleukin (IL)-1- and IL-6-driven immune response in RA synoviocytes.¹ Beneficial properties of curcumin have even been reported in lupus nephritis and colitis mice models, these latter supporting its potential regulatory action on gut microbiota composition.²

Capsaicin, which is strongly present in chili pepper, exerts multiple pharmacological effects, including modulation of neuroimmune inflammatory response through the upregulation through anti-inflammatory M2 macrophages upregulation and autoreactive T cells blockage, as well as mitigation of neurogenic pain at topical level.^{1,2}

Interesting results have recently emerged with regard to tea, which is not purely of Mediterranean origin but is now integrated into the culture and dietary habits of this geographical area. Epigallocatechin 3-gallate, the most abundant polyphenol in tea, has in fact been reported to exert positive effect in modulating inflammation and preventing cartilage damage in RA *in vitro* models, by interfering with the NF- κ B pathway and reducing matrix metalloproteinases (MMPs) production.⁶

As previously mentioned, MedDiet provides a balanced and appropriate lipid intake, particularly rich in Omega-3 PUFAs, which have been shown to interact with a multitude of processes such as leukocyte chemotaxis, production of cytokines, oxygen free radicals and several redox-sensitive transcription factors, as well as gut microbiota regulation.² Interestingly, a recent meta-analysis of 20 randomized controlled trials confirmed a positive action from oral intake of Omega-3 PUFAs on RA disease activity related markers, with a notable reduction of leukotriene B4, as well as an additional improvement in lipid profile.⁷

The beneficial effects of EVOO, which is one of the cornerstones of MedDiet, have traditionally been related to its balanced lipid composition, mainly consisting of high concentration of monounsaturated fatty acids (MUFAs) and PUFAs.² In several mice models, EVOO supplementation has been associated with general improvement of inflammation, through reduction of M1 macrophages, pro-inflammatory cytokines and MMPs levels and inhibition of NF- κ B and Janus kinase signaling pathways.⁶ Additionally, a large recent study has suggested high intake of MUFAs as a key factor in predicting clinical remission in RA.⁶

Finally, overall evidence seems to support a favorable role of MedDiet-derived nutrients in the regulation of gut microbiota, which

is now considered as a major driver in rheumatic diseases progression, contributing to its anti-inflammatory and tolerogenic state.⁸

Globally, MedDiet has been shown to exert beneficial effects on rheumatic diseases progression, contributing to a tolerogenic and anti-inflammatory phenotype both at intestinal and systemic level.

Further research on this field may better elucidate potential immunomodulatory properties of both microbial and dietary metabolites, unraveling their multifaceted interactions, to be exploited as novel therapeutic targets.

References

1. Dahan S, Segal Y, Shoenfeld Y. Dietary factors in rheumatic autoimmune diseases: A recipe for therapy? *Nat Rev Rheumatol* 2017;13:348-58.
2. Cutolo M, Nikiphorou E. Don't neglect nutrition in rheumatoid arthritis! *RMD Open* 2018;4:e000591.
3. Zinöcker M, Lindseth I. The Western diet-microbiome-host interaction and its role in metabolic disease. *Nutrients* 2018; 10:e365.
4. Hu Y, Sparks JA, Malspeis S, et al. Long-term dietary quality and risk of developing rheumatoid arthritis in women. *Ann Rheum Dis* 2017;76:1357-64.
5. Forsyth C, Kouvari M, D'Cunha NM, et al. The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies. *Rheumatol Int* 2018;38:737-47.
6. Paolino S, Pacini G, Patanè M, et al. Interactions between microbiota, diet/nutrients and immune/inflammatory response in rheumatic diseases: focus on rheumatoid arthritis. *Reumatologia* 2019;57:151-7.
7. Gioxari A, Kaliora AC, Marantidou F, Panagiotakos DP. Intake of ω -3 polyunsaturated fatty acids in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Nutrition* 2018;45:114-24.e4.
8. Abdollahi-Roodsaz S, Abramson SB, Scher JU. The metabolic role of the gut microbiota in health and rheumatic disease: mechanisms and interventions. *Nat Rev Rheumatol* 2016;12: 446-55.