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DEBATE

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Nutrition in RMDs: is it really food for thought? Focus on rheumatoid arthritis

Alessia Alunno^{1*} , Elena Nikiphorou^{2,3}, Elena Philippou⁴, Claire Daien⁵, Dieter Wiek^{6,7}, Marios Kouloumas⁸ and Maurizio Cutolo⁹

Abstract

Background: The relationship between food and health is known since the antiquity and in the field of rheumatic and musculoskeletal diseases (RMDs), mainly rheumatoid arthritis (RA), a large number of studies has been published over the last 50 years encompassing different aspects of nutrition. This led to postulate a role of nutrients for both primary prevention of RMDs in the general population and secondary prevention of disease flares and complications in patients with an established RMD.

Main body of abstract: We aimed to summarise and critically discuss current evidence on the role of different nutrients and dietary regimens in RMDs with a focus on RA. Over the last years, some seminal papers proved that some compounds, such as salt, can directly modulate the immune system and large epidemiological studies have been linking dietary patterns with the risk to develop RMDs. However, physicians' knowledge about the role of diet in disease prevention and treatment is often poor and ultimately diet is rarely perceived as a companion of pharmacological treatment.

Conclusions: Based on the currently available evidence, we are not (yet?) in the phase of putting diet on the same level as pharmacological treatment in RMDs and in particular, RA, but future studies will likely shed additional light on this controversial topic and at least might suggest a value as dietary prevention of risk factors.

Keywords: Rheumatoid arthritis, Mediterranean diet, Immune system

Background

The relationship between food and health is known since the antiquity, with the extensively used quote from Hippocrates "Let the food be thy medicine" being the most evident proof. However, as often highlighted, the physicians' knowledge on diet-disease associations is poor and therefore the potential use of diet as a companion of pharmacological treatment often neglected [1]. This is particularly true in the field of rheumatic and musculoskeletal diseases (RMDs) in particular arthritis, since the increase of published papers on this topic does not seem to result in a parallel increase of awareness nor of dietary counselling in general and rheumatology practice. A simple search on "nutrition AND rheumatic diseases" in PubMed results in over one thousands of hits with the oldest paper, on clinical aspects of nutrition in

rheumatic fever, dating back in the late 1940s. Interestingly, of these publications, nearly 900 pertain to rheumatoid arthritis (RA). The concept of nutrition in RMDs goes far beyond the control of weight and encompasses many different aspects. RMDs result from the action of different environmental factors on genetically predisposed individuals, with food being by definition an environmental factor to which every human being is daily exposed. However, it is up to the person how to mix and match the nutrients and if to complement it with voluptuary habits such as alcohol and coffee drinking. This highlights the huge potential to modulate dietary habits for preventive purposes not only in patients with an established RMD as secondary prevention [2] but also in the general population to reduce the risk of RMD development.

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Main body of the article

'Feeding' RA prevention while 'starving' autoimmunity and inflammation

Overall, a 'western' type diet might increase the risk of RMDs both directly through increasing inflammation [3] and indirectly through increasing insulin resistance, obesity and associated co-morbidities [4]. On the other hand, as demonstrated by Hu and colleagues in women, a higher adherence to the 2010 Alternative Healthy Eating Index (AHEI-2010) is associated with reduced risk in RA [5]. The AHEI-2010 includes a variety of food/nutrients and defines fruits, vegetables, whole grains, nuts, long-chain n-3 polyunsaturated fatty acids (LC-PUFAs), and moderate alcohol consumption as healthy items, while sugar-sweetened beverages, red/processed meat, trans fat and sodium intake are classified as unhealthy components. While a high consumption of red meat, meat products and overall proteins has been associated with an increased risk of inflammatory polyarthritis [6, 7], the consistent intake of fish, which provides LC-PUFAs displaying anti-inflammatory properties, was linked to decreased risk to develop rheumatoid arthritis (RA) [8] (Table 1). The risk of developing RA is also inversely correlated with olive oil or cooked vegetable consumption [12] and directly correlated with sodium (salt), the latter in a dose-dependent manner [9]. Possible mechanisms include the antioxidant properties of fruit and vegetables, natural tocopherols contained in olive oil acting as radical scavengers, and the pro-inflammatory action of salt. As far as salt is concerned, two recent studies provided the mechanistic link between sodium and autoimmunity by the identification of a salt-sensitive kinase and salt-responsive gut commensals which are involved in the differentiation of pathogenic T helper 17 cells [14, 15]. A reduction in salt intake by RMD patients would thus result in both direct and indirect benefits on the cardiovascular system. In fact, both the immune response and chronic inflammation ultimately participate also in endothelial dysfunction. Other nutrients, such as polyphenols, curcumin or citric acid also display antioxidant properties, while in contrast, saturated fatty acids promote oxidative stress [16]. Other research evidence

suggests that sugar-sweetened drinks are associated with an increased risk of seropositive RA [10] and in support of this, consumption of ≥ 5 times/week of high-fructose corn-syrup sweetened soft drinks, fruit drinks and apple juice has been associated with arthritis in young US adults [17]. This may be linked to the fact that consumption of excess free fructose (defined as fructose to glucose ratio $> 1:1$) contributes to fructose reactivity in the gastrointestinal tract and intestinal in situ formation of advanced glycation end products, which once absorbed, travel beyond the intestinal boundaries to other tissues and promote inflammation [17]. As far as alcoholic drinks are concerned, surprisingly consumption of 3–5 standard drinks/week has been associated with 22–31% reduced risk of developing RA compared to non-alcoholic drinks [13]. One item not included in the AHEI 2010 but deserving attention due to its widespread use, is coffee. A recent meta-analysis found that consumption of ≥ 4 cups coffee per day increases risk of seropositive, but not seronegative RA [11]. However, these results should be interpreted with caution since they are in striking contrast with data from in vitro studies demonstrating that caffeine owns anti-inflammatory properties via protein kinase A activation, including reduced production of autoantibodies [18]. Diet, in addition, is one of the main drivers of gut microbiota composition which in turn is closely related to the immune system. An altered microbiota, namely 'dysbiosis' can induce gut permeability and pro-inflammatory cells which could favour the development of autoimmunity [19]. The western diet, deprived in dietary fibre further favours dysbiosis and therefore the triggering of pro-inflammatory cells [20].

Is diet a possible concomitant DMARD in RA?

The level of evidence in clinical studies on diet manipulation in patients with RMDs is low, since good-quality trials are difficult to conduct. Restrictive-diet studies often lack appropriate control groups since it is not possible to have a placebo group and since the placebo effect of diet changes is expected to be important, any firm conclusion cannot be drawn. This is the case for two open studies on gluten and vegan free diets, which suggest a slight improvement of disease activity [21, 22]. However, some data are suggesting that a gluten-free diet increases cardiovascular risk factors [23] and might increase cardiovascular events [24]. This is a major point as patients with RMDs already have an increased risk of cardiovascular events [25]. No pre-clinic or clinical study is available examining a lactose-free diet. However, a lactose-free diet favors calcium deficiency which can promote osteoporosis in patients that are already at increased risk [26]. Many open studies have assessed the impact of fasting on RA activity. The fasting protocols strongly vary between studies and a beneficial effect on pain, morning stiffness and inflammation has been

Table 1 Nutrients associated with higher or lower risk to develop rheumatoid arthritis (RA)

Evidence	Food/Drink	Ref
↑ risk to develop RA	-red meat/meat products	[6, 7]
	-salt	[9]
	-sugar-sweetened drinks	[10]
	-coffee (≥ 4 cups/day)	[11]
↓ risk to develop RA	-fish	[8]
	-olive oil	[12]
	-cooked vegetables	[9]
	-alcoholic drinks (3–5 drinks/week)	[13]

observed, however, this effect is transient, as inflammation relapse with food resumption [27, 28]. Open studies suggested a small but significant effect of the Mediterranean diet on pain and global assessment [29]. Stronger evidence shows that the Mediterranean diet decreases cardiovascular events and cardiovascular mortality [30]. This is of particular relevance due to the well-established increased cardiovascular risk in rheumatic diseases [31]. The Mediterranean diet is enriched in fiber, olive oil, a source of mono-unsaturated fatty acid and in fish, an important source of dietary n-3 PUFA. The effect of n-3 PUFA supplements on RA activity has been assessed in several placebo-controlled studies. A very recent meta-analysis of randomized controlled trials assessing the effect of n-3 PUFA supplementation showed a slight but significant decrease of pain, tender joints, health assessment questionnaire and erythrocyte sedimentation rate [32]. Consistent with those results, a randomized controlled trial showed that the consumption of 10 ml per day of fish oil doubles the chance of achieving ACR remission in patients with early RA treated with a combination of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) [33]. Interim data from the total management of risk factors in rheumatoid arthritis patients to lower morbidity and mortality (TOMORROW) study revealed that daily consumption of monounsaturated to saturated fatty acids (MUFA/SFA) as part of a Mediterranean diet is inversely correlated with disease activity while high MUFA intake is an independent predictor of remission in the RA [34]. On the contrary, probiotic use in RA showed controversial results, which could be explained by the use of different bacterial strains [35]. A recent randomized placebo-controlled trial showed that the association of *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* probiotics with fiber supplement could significantly decrease disease activity [36].

What can we learn from existing evidence?

Since people do not consume individual foods but diets, the pursuit of RMD/arthritis prevention in the general population and RMD control in patients is ultimately a matter of dietary patterns. Adherence to the Mediterranean diet is generally recommended, with a plant-based regimen abundant in wholegrains, legumes, five or more fruit and vegetables per day, preferably seasonal. Daily consumption of extra-virgin olive oil, 1–2/week consumption of fatty fish (sardines, salmon, seabream, seabass and trout), weekly consumption of other types of fish and poultry and limited consumption of red meat to 1–2 per month encompasses all the current available evidence. It is also recommended to avoid or reduce consumption of sugar-sweetened drinks and salt, limit coffee consumption to 3 cups a day, and if alcohol is

consumed, drink in moderation and with meals. This latter concept also fits with the general recommendation to reduce, ideally avoid, alcohol consumption by people receiving potentially hepatotoxic DMARDs [37]. Restrictive diets should not be recommended to patients with arthritis, as no evidence supports benefits and data suggests risk. Modulation of microbiota through specific multistrain probiotics and fibers might be a promising strategy but to date only low quality evidence is available. Finally, food and drink intake should be balanced with requirements by controlling portion sizes and engaging in daily physical activity aiming to maintain a normal body weight, as recently underscored also by EULAR recommendations on physical activity in RMDs [38], is imperative.

Conclusions

In conclusion, the currently available evidence disputes, at least in part, Hippocrates' notion that food should be a medicine by definition. We are not (yet?) in the phase of putting diet on the same level as pharmacological treatment in RMDs and in particular arthritis, but we are confident that future studies will shed additional light on this controversial topic and at least might suggest a value as dietary prevention of risk factors. However, although Greeks and Romans were the first populations following the Mediterranean diet, Hippocrates recognised himself that the definition of food as medicine should be performed with caution, and anticipating centuries of research, eventually concluded: "if we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have the safest way to health." The Romans added a wise sentence: "*Est modus in rebus*" that doctors should always suggest to their patients and to themselves regarding the pleasures of the table!

Abbreviations

AHEI-2010: 2010 Alternative Healthy Eating Index; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; LC-PUFAs: Long-chain n-3 polyunsaturated fatty acids; MUFA/SFA: Monounsaturated to saturated fatty acids; RA: Rheumatoid arthritis; RMDs: Rheumatic and musculoskeletal diseases; TOMORROW: Total management of risk factors in rheumatoid arthritis patients to lower morbidity and mortality

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AA and MC conceived the idea of this article. AA, EN, EP and CD produced a draft which was then critically reviewed by DW, MK and MC. The final draft was approved by all co-authors.

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