Review

The effects of different dietary patterns in rheumatic diseases: a still unresolved question

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ABSTRACT

Genetic and environmental factors are well recognised pivotal players in the pathogenesis of inflammatory and systemic autoimmune rheumatic diseases. In recent years, increasing research focused on the effects of diet and of dietary components in enhancing the inflammatory response in genetically predisposed individuals. Accumulating evidence suggests that nutrition might be implicated in the risk of autoimmune disease, in particular rheumatoid arthritis (RA), through the pro- or anti-inflammatory effects of certain foods or micro and macronutrients. However, literature evidence is quite inconsistent due to methodologic limits suggesting the urgent need of different studies to establish solid evidence-based recommendations and guidelines. The review aims to highlight current evidence concerning the effects of diet and of specific dietary patterns on disease activity and functional status of patients with rheumatic diseases with focus on specific dietary patterns such as the Mediterranean diet and some types of elimination diets. In this setting, a close collaboration between rheumatologists and dietitians is highly needed to improve disease management and to support patients in a well-balanced diet according to individual needs.

Introduction

In recent years, the relationship between diet and systemic rheumatic diseases gained considerable attention, resulting in several publications. Indeed, it is well established that, in genetically susceptible individuals, environmental factors and exogenous triggers may induce a pathological and aberrant immune system activation that contribute to development of systemic autoimmune diseases. Among environmental factors, different studies suggest that dietary habits, the type of diet and the modification of intestinal microbiota induced by different food ingestion may result in induction, re-activation or worsening of these diseases (1). However, as many of these studies are cross-sectional, it is often difficult to establish whether the described association is causal or not (2).

Moreover, is difficult to assess how single dietary component- such as omega-3 fatty acids, antioxidant vitamins, minerals- can influence rheumatic disease development and their activity and course. However, over the last twenty years, the analysis of dietary patterns, such as the Mediterranean diet (MD), vegetarian diet (VD), gluten free diet and fasting, has provided a valuable complementary strategy to also investigate the effects of single-nutrient or single-food assumption on rheumatic diseases (3). Indeed, over the past decade, continuous shifts in diet and in lifestyle habits have occurred and food availability has extremely increased with the consequence that, nowadays, people do not eat isolated nutrients or food, but meals consist in a variety of different components and in a combination of nutrients. Moreover, several factors, including the heterogeneity of the disease, the geographical setting, the duration of the disease and its severity, may influence dietary patterns and lifestyle habits (3). However, the benefits of many of these dietary patterns have been questioned and the effects of different diets on the course and outcome of rheumatic diseases are still highly debated. Thus, the aim of this review is to analyse how the different dietary patterns, rather than the single nutrients or food, can impact

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the course and activity of rheumatic diseases and to evaluate if they exert a protective or detrimental effect.

Rheumatic diseases and anti-inflammatory effects of diet

Preventing adverse lifestyle factors could potentially reduce the incidence and burden of systemic autoimmune diseases and eventually reduce associated comorbidities (4). Indeed, the chronic nature of these conditions, along with their unpredictable progression and potentially disabling course, negatively impacts the quality of life of these patients (5, 6). Moreover, at diagnosis, patients often ask for specific dietary advice or to modify their dietary habits (7). Although several studies report that some food items could improve or worsen disease symptoms, these statements are often based on small population studies, resulting in significant discrepancies and inconclusive results. However, some dietary macronutrients and several antioxidants and sources of bioactive antioxidative compounds may have a positive effect on disease activity and systemic inflammation, although high quality studies are needed (8-10).

Carbohydrates

Carbohydrates are fundamental macronutrients in the vast majority of diets and their influence on systemic inflammation has been widely investigated in the general population, with conflicting results. Ma *et al*. examined the association between dietary fibre intake and markers of systemic inflammation, including serum C-reactive protein (CRP), interleukin (IL)-6 and tumour necrosis factorα receptor 2 (TNFα-R2), in a cohort of 1958 post-menopausal women from United States (11). Authors demonstrated that higher intake of total fibre, both soluble and insoluble, was associated with lower plasma concentrations of IL-6 and TNF-α-R2, without modifying CRP levels (11). In this setting, as IL-6 regulate CRP production, it may be hypothesised that a high-fibre diet may firstly induce IL-6 and TNF-α-R2 and, indirectly, regulate CRP levels (11). On the other hand, different studies reported a significant inverse relationship between higher fibre diet intake and plasmatic CRP levels (12-14). Differences in race or ethnicity may lead to differences in factors that affect both fibre consumption and CRP concentration. In this setting, a cross-sectional and longitudinal study including a predominantly white cohort found a strong effect of fibre consumption on CRP levels in comparison to studies enrolling African-American and Mexican-American participants (13). Moreover, these findings remained significant after adjustment for other concomitant factors which may hamper fibre intake, as age, BMI, smoking habit and infections. Moreover, fibres may decrease lipid oxidation maintaining a healthy intestinal environment (12, 15).

In summary, although further larger longitudinal studies are needed to confirm these findings, it is plausible that carbohydrate intake may be protective for systemic inflammation.

Proteins

Dietary protein assumption is essential for production of hormones and enzymes, as well as for cell repair and fluid balance and the Recommended Daily Intake of protein is 0.8-1.2 g/kg body weight per day. In recent years, the association between dietary protein intake and inflammation has been investigated, particularly focusing on the distinction between animal- and plant-based dietary proteins.

As far as meat is concerned, results from systematic reviews suggest that a high consumption of red meat and high protein intake may be risk factors for rheumatoid arthritis (RA) development, with a significant reverse association between fish consumption and risk of RA (16, 17). However, several concomitant environmental factors, such as smoke, alcohol and sodium intake, may interfere with the analysis of diet protein effects on systemic inflammation (18, 19).

Surely, the pro-inflammatory effect of a meat-rich diet (as, for example, the Western diet) may be partly related to higher risk of obesity, with consequent reduction in adiponectine production and increase in leptin and in inflammatory markers, type 2 diabetes mellitus and, of consequence, cardiovascular disease (20, 21).

Similarly, there is no consensus on the anti-inflammatory properties of fish consumption. A study identified that consuming fish 1-7 times/week guarantee long-term protection against RA onset, with an odds ratio of 0.8 (95% IC= 0.6-1.0) for both women and men, after adjustment for age, residential area, sex and smoking (22). Similar results were seen for subjects consuming oily fish 1-3 times a month (22). However, this was not confirmed by other studies which found no significant association between fish consumption and the risk of developing RA (18, 23, 24). Indeed, the protective effect of fish and oily fish may be due to their high content of long-chain omega-3 poly-unsaturated fatty acids (LC-PUFAs), which have strong anti-inflammatory properties. Thus, difficulty in assessing real intake of these components, as well as dietary habits related to ethnic diversity, may explain such discrepancy.

Fats

Numerous studies have reported the pro-inflammatory effects of trans-fatty acids due to an increase of plasmatic inflammatory cytokines (IL-1, TNF-α) and inflammatory mediators, as CRP; on the contrary, omega-3 PUFAs have been demonstrated to be negatively associated with IL-6, matrix metallopeptidases3 (MMP3) and CRP plasmatic levels (10, 15).

Several mechanisms have been proposed to explain anti-inflammatory properties of omega-3 fatty acids. Firstly, eicosanoids synthesized from omega-3 and their metabolites (resolvins, protectins, maresins) compete with those produced from omega-6, which exert pro-inflammatory effects (25, 26). Secondly, omega-3 fatty acids may modulate cytokine secretion. In this setting, some studies demonstrated a reduction of CD4+ T cell concentration and consequent production of interferon-γ (IFN-γ) and IL-17 with oil supplementation (22, 27). Finally, omega-3-fatty-acids act as precursors in the production of PGF2A eicosanoids, whose action inhibit the arachi-

donic acid pro-inflammatory pathway and inflammatory cytokine release, as IL-1B, TNF-α and IL-6 (27–29).
A prospective study conducted by Di Giuseppe *et al*. analysed the association between dietary PUFAs and incidence of RA observing an inverse association between PUFAs intake and RA risk (30). In particular, a long term consistent intake (PUFA >0.21 g/day) was associated with a statistically significant decrease in risk of RA (30). Similarly, even if with lower strength, in a nested case-control study, PUFAs and monounsaturated fatty acids (MUFAs) were considered protective, while saturated fats were associated with a higher risk of arthritis (17).
In conclusion, unsaturated fatty acids seem to have anti-inflammatory properties which may be beneficial for the management of systemic inflammatory diseases, including rheumatic and musculoskeletal conditions.

Alcohol
As for the other categories, there are no homogeneous data related to alcohol consumption, although many studies agree on its anti-inflammatory effect and its role as a protective factor for RA development.
A national case-study observed that a positive history of alcohol consumption was inversely related to the risk of seropositive RA development, suggesting possible protective effect of alcohol (31). Moreover, a prospective study demonstrated that alcohol may affect levels of inflammatory cytokines, as IL-6 and TNFR2, with a cumulative effect of long-term moderate alcohol exposure (32). These beneficial effects may be mediated by downregulation of leukocyte migration and up-regulation of testosterone production which inhibit NF-kB activation and consequent cytokines/chemokine production (33). However, no studies have quantified the amount of alcohol that may exert an anti-inflammatory effect, due to lack of consensus in a standardised definition of low, moderate and heavy alcohol consumption (34, 35).
Despite different studies demonstrated a protective effect of moderate alcohol intake on the development of different RMDs, it is not possible to drive definite evidence due to several study limits and confounding factors, as concomitant smoking. Moreover, it is not advisable to encourage patients to increase their alcohol intake due to the several negative effects.

Diet patterns
Mediterranean diet
The definition of the Mediterranean diet (MD) was first given in 1960s by Keys who defined it as a low saturated fat and high vegetable oil diet (36). During the subsequent years, several definitions have been proposed, all emphasising that the diet is essentially based on some key elements, as high intake of extra virgin olive oil, vegetables, fruits, cereals, nuts, pulses, moderate intake of fish, meat, dairy products, alcohol and low intake of eggs and sweets. The weekly frequency of their assumption is illustrated by the diet pyramid (36). In this diet, comprehensive of MUFAs, PUFAs, SFAs, an amount of carbohydrate intake at 42.8±3.3 grams/day, proteins equal to 14.9±2.3 grams/day and fibres equal to 31.3±9.2 grams/day are recommended. Other elements include vitamin C, folate and potassium (36).
In last years, studies focused on the effects of MD on the development of RMDs, in particular RA, and its influence on disease activity, highlighting that high adherence to the MD may potentially reduce inflammation and RMD symptoms (23). Additionally, the protective role of the MD against cardiovascular disease, type 2 diabetes, obesity and other metabolic diseases is well established (37-39). Indeed, considering the higher risk of cardiovascular disease in these patients, adherence to MD may be important, as also demonstrated in patients with Sjögren's syndrome. Carubbi *et al*. pointed out that the introduction of a regular MD, with particular attention to fish consumption, was associated with lower prevalence of hypertension and was inversely related to disease activity, as measured by ESSDAI and ClinESSDAI (40). In fact, levels of IL-6 and CPR, molecules involved both in the pathogenesis and inflammatory burden of RMDs and atherosclerotic plaque formation, are reduced in patients regularly following the MD (23, 41, 42).
Due to this implication, it is possible that reduction of fat accumulation and body weight by the adoption of MD and of physical activity might induce a reduction of systemic inflammation and, of consequence, control the activity of RMDs, as demonstrated in the MADEIRA trial (43).
Limited evidence from clinical trial investigated the effects of the MD on disease activity (44). Moreover, the dietary inflammatory index (DII) score, a quantitative measure of the inflammatory potential of daily food and nutrient intake, is significantly higher in RA patients in comparison to control subjects (44), although not associated with disease activity, reflecting the importance of other concomitant factors besides diet in determining RA disease activity. Moreover, MD may improve some patient reported outcomes, as Pain Score, Patient Global Assessment and Function (42). This suggests that potential benefits derived by assumption of MD are related to its multiple effects. Firstly, it is a well-balanced diet without strictly restrictions resulting in high levels of adherence and few side effects, thus providing an ideal condition to evaluate its long-term effects, which may not always be feasible with other types of diets that require more restrictive rules (41, 46). Moreover, the beneficial effects of the MD on cardiovascular disease have been largely studied as well as its efficacy in promoting weight loss (9, 43, 47). Weight loss has been associated to higher confidence and self-esteem, both responsible of improvements in functional status in these patients.
Interestingly, a dietary pattern analysis examined five categories representing different dietary behaviours: antioxidant vitamins and fibre (predominantly carbohydrates), starch-rich (predominantly proteins), vegetables unsaturated fatty acids (VUFA), animal unsaturated fatty acids (AUFA) and animal products (high in cholesterol and saturated fatty acids). The study demonstrated a significant decrease in disease activity and in CRP levels among patients with

higher consumption of VUFA, AUFA and animal products (3). Among all analysed DPs, VUFA and AUFA exerted the most significant effect on disease activity. Moreover, the VUFA DP was mainly characterised by higher consumption of nuts, olives and olive oil, typical elements of the MD (3).

In conclusion, there is no clear evidence of a protective effect of MD on RA development or decreasing disease activity. However, dietary intervention may contribute to establishing an anti-inflammatory status which, combined with other factors, could improve patient quality life. Surely, important limits of these studies are the small sample sizes and the inability to assess the possibility of the placebo effect.

Restriction diets

Following the evidence that single nutrients, as VUFA and carbohydrates which are predominant in MD, may improve systemic inflammation in patients with RMDs, many studies tried to elaborate an anti-inflammatory diet based on assumption of food described as protective against systemic inflammation combined with restriction in daily calories intake. Vadell *et al*. investigated the effects of a restriction diet in a controlled crossover trial involving 50 RA patients randomised to an intervention diet or to control group (8). The proposed intervention diet contained foods rich in n-3 fatty acids, fibre, antioxidants and probiotics. Although initial analyses showed significant differences in DAS28-PCR between intervention and control group, the results were not confirmed after adjustment for variables. Moreover, the small sample and the low disease activity at inclusion hamper the interpretation of the study. It is possible that high consumption of these components may lead to a reduction in oxidative stress biomarkers and to an increase in antioxidant defences (48). Another possibility may be associated with the effect of MUFAs in decreasing pro-inflammatory cytokines, as CRP, TNF-α, IFN-γ, IL-6, and inhibiting NF-ϰ signalling (49). Dietary restrictions include different dietary patterns, ranging from vegetarian to hypocaloric, ketogenic, fasting and gluten free. Studies on these diets are less conclusive due to small size of intervention group and scarce patient compliance.

Hypocaloric diet

The main beneficial effect of hypocaloric diet might be associated with weight loss, as described for to the MD. In fact, as recently demonstrated by a 12 week controlled trial study, obese RA patients assigned to a hypocaloric diet (1000-1500kcal/day consisting in 3-4 meal replacements/day and one meal of 500 calories) showed significant weight loss in comparison to the control group (47) . Additionally, reduction in disease activity, PCR levels, clinimetric and ultrasonographic measures were observed (47). Similar results were reported by Klinberg *et al*. in an interventional study involving obese patient affected by Psoriatic Arthritis (PsA) (50). In these patients, a very low energy diet (VLED) containing 640 kcal/day for a short term period was associated with significant weight loss and significant positive effects on disease activity, both at articular and cutaneous levels (50). However, it is impossible to determine how much weight loss may have contributed to these improvements, particularly in the latter study, as the underlying mechanism remains unclear. Moreover, small population size and limited duration of dietary regimen should be taken into account. Additionally, it has to be considered that CRP is a non-specific biomarker of systemic inflammation whose serological levels may vary with a wide range of conditions (51, 52).

Ketogenic diet

The ketogenic diet (KD) is a high fat, moderate protein and very low carbohydrate diet aiming to shift body metabolism towards the use of ketone bodies. Originally, this diet was proposed as an alternative to fasting which, before the introduction of anti-epileptic drugs, was considered the method of choice to treat epilepsy (53). In consideration of the impossibility of maintaining fasting for long period, in 1921 Dr. Wilder proposed the KD as a more suitable method to induce a metabolic state similar to fasting (53).

In recent years, the KD have gained interest for its application in weight loss, cancer treatment protocols, Alzheimer's disease and in reducing systemic inflammation (54, 55).

The KD acts controlling circulating levels of ketone bodies by control of ketogenesis and ketolysis. The entirely process is under control of insulin and glucagon which, in favour of reduced levels of insulin, induce increase of glucagon which, in turn, increases gluconeogenesis. This metabolic shift occurs due to restricted carbohydrate consumptions, leading to the utilisation of ketones and fatty acids as primary energy (54).

Physiological effects of KD are substantially three: (I) insulin reduction, (II) glucagon increase, (III) synthesis of β-hydroxybutyrate (BHB), acetoacetate and acetone. These effects contribute to weight loss, which is crucial for reducing systemic inflammation, as well as for reducing articular load, key factors in patients with RMDs. Several mechanisms have been proposed to explain the potential anti-inflammatory properties of the KD. Firstly, it may reduce eicosanoid formation by reducing generation of reactive oxygen species (ROS) (56). This leads to less activation of phospholipase A2, sited in immune cells' membranes, and reduced oxidation of arachidonic acid (AA), responsible of decrease of eicosanoid formation. Moreover, through increase of adenosine, ketogenic diet may have anti-inflammatory properties which alleviate pain (57). Recently, it has been proposed that BHB, the main ketone body, may induce the reduction of IL-17 (58), a pivotal cytokine involved in the pathogenesis of ankylosing spondylitis (AS) and PsA (59).

For these reasons, the KD has been investigated for its potential beneficial effects in patients with AS and PsA. A recent randomised controlled trial by Lambadiari *et al*. have demonstrated reduction of activity scores (PASI and DAPSA) in patients affected by Psoriasis or PsA following the introduction of a 22-week KD. Furthermore, a significant reduction of IL-6, IL-17, IL-22 and IL-23 was observed in the

KD group (60). Although promising in PsA patients have been demonstrated, no studies evaluated the effects of KD in patients with AS and RA. Further research and large-scale studies are needed to understand the potential benefits and applications of the KD in RMDs.

Fasting

Fasting consists in eating no more than minimal amounts of food and calories for a period ranging from 12 hours to 3 weeks. Fasting differs from caloric restriction, a dietary regime which consider reducing calorie intake by 20%-40% while maintaining meal frequency (61). In ancient Greece fasting was considered beneficial for improvement of cognitive function (62).

Intermittent fasting (IF) is a dietary pattern that consist in alternating period of fasting and eating. The most common type of IF, practiced by Muslims during Ramadan, entails fasting for 12 hours and eating for 12 hours. Other types of IF have been recently proposed, as periodic fasting (PF), involving two or more consecutive days of fasting done periodically, time-restricted eating (following the rule 16/8 or 14/10) and the 5:2 diet (63, 64). Studies on fasting suggest its potential role in delaying aging and preventing diseases with minimal side effects. Animal models have demonstrated that fasting regimes may improve outcomes of different diseases, such as cancer, myocardial infarction, diabetes, stroke, autoimmune diseases (61). Moreover, fasting has positive effects in weight loss, whose efficacy has been compared with hypocaloric regimens (65).

Regarding RA, several studies have evaluated possible effects of fasting in changing the course of the disease. A controlled trial conducted in 1991 investigated the benefits of a 7-10 day subtotal fast followed by a gluten-free vegan diet and, lastly, a lactovegetarian diet, observing symptoms improvement during the initial period of fast but relapse upon food reintroduction (66).

The last decades have seen a growing number of reports that examined the potential effect of Ramadan IF on chronic musculoskeletal disorders. Despite differences between studies in daily fasting duration and dietary norms and the low number of patients included, results showed that the majority of RA or spondyloarthritis (SpA) patients which fasted during Ramadan experienced improvement of disease activity measures and of articular pain (67). A frame of 3 months may be the recommended interval between fasting periods to maintain the positive effects of IF on RA activity (68). Surely, differences in energy intake can affect weight loss, influencing the reduction of systemic inflammation and differences in disease activity observed in these studies (67). Indeed, as with other dietary interventions, energy intake variations in different types of IF need further evaluation. While during Muslim Ramadan patients do not have to adhere to a selective diet, in other countries it is common reducing food consumption (69). In conclusion, as fasting has been demonstrated part of therapeutic strategies for epilepsy, it is possible that in future further researches might suggest IF as a potential non-pharmacological intervention for improving the course of chronic diseases.

Gluten-free

Gluten, composed of two proteins, gliadin and glutenin, is present in many grains, including wheat and rye and can activate an aberrant immune response in certain individuals. Gluten-free diets are commonly prescribed for patients with celiac disease or non-celiac gluten intolerance, although in recent years this dietary regime has gained popularity among non-celiac people.

The positive effects of a gluten-free diet on weight are attributed to lower accumulation of lipid due to their mobilisation and oxidation in adipose tissue. Additionally, gluten-free diet improves insulin sensitivity by increasing expression of PPAR-γ, insulin-receptor, GLUT-4 and adiponectin. Moreover, after gluten exclusion, it has been suggested a reduction in TNF-α production, which might contribute to improve insulin sensitivity.

As far as RMDs are concerned, the potential role of gluten-free diet in the prevention of autoimmune diseases or improvement of their clinical manifestations is a largely debated unmet need, as very few studies specifically considered the effects of a gluten-free diet in these patients (70, 71). While it is generally recommended to substitute refined grains with whole grain due to their association with higher levels of inflammatory markers, no definitive evidence supports complete gluten elimination in these patients (70-72).

Whether a gluten-free diet can alter the course of RA in non-celiac patients remains uncertain, as studies often involve gluten-free vegan diets rather than focusing solely on gluten deprivation (73, 70). To our knowledge, no studies have investigated the effects of gluten-free diet in patients affected by other RMDs. Despite potential benefits of gluten-free diets on weight loss, it is not possible conclude whether gluten exclusion might have a role in non-pharmacological treatment of RA and other types of RMDs.

Discussion

In recent years the relationship between diet and systemic RMDs has gained significant attention, with numerous studies exploring the impact of dietary habits on disease development and progression. While it is well-established that environmental factors, including diet, can influence immune system activation and contribute to the onset of systemic autoimmune diseases in genetically susceptible individuals, the exact causal mechanisms remain unknown.

Different dietary patterns, such as the MD, vegetarian diet, gluten-free diet and fasting, have been investigated for their potential effects on the course of RMDs. However, literature evidence shows significant discrepancies and inconclusive findings, partly due to the complexity of analysing specific dietary regimes. Additionally, factors like disease heterogeneity, geographical differences, socioeconomic status, disease severity and its duration can influence dietary patterns and lifestyle habits, further complicating the interpretation of results. Indeed, diets have been developed in different historical and cultural frameworks and for different groups of patients, thus hampering

the evaluation of their effects in different clinical setting, also due to the progressive reduction of patient adherence to more restrictive dietary patterns.

Studies examining macronutrients like carbohydrates, proteins, fats and alcohol have provided insights into their potential impact on systemic inflammation. For example, high fibre intake has been associated with lower levels of inflammatory markers, while the effects of proteins and fats remain debated, with some evidence suggesting pro-inflammatory properties. Alcohol consumption, although showing some anti-inflammatory effects, lacks consensus due to various confounding factors and classification issues.

Some dietary patterns, like the MD, have revealed promising results in reducing inflammation and improving symptoms in RMDs, probably through their anti-inflammatory and cardiovascular protective effects (74). However, the evidence of their direct impact on disease development and activity remains inconclusive, highlighting the need for further research, particularly in larger populations. Restriction diets, including hypocaloric, ketogenic and fasting diets, have also been explored for their potential therapeutic benefits. While some studies suggest positive effects on disease activity and inflammation, particularly in diseases like PsA, the evidence is highly limited due to small sample sizes and short follow-up. In general, it is plausible that the initial beneficial effects of such dietary regimes may be related to the consistent weight loss, with consequent improvement of disease activity, patient quality of life and functional status (75). Moreover, additional challenges are the limited evidence from the employment of inflammatory markers, beyond CRP levels, to evaluate the effects of dietary regimes.

In conclusion, while dietary interventions hold promise as adjunctive therapies for rheumatic diseases, more rigorous research is needed to elucidate their mechanisms of action and therapeutic potential fully. Future studies should focus on larger, well-designed trials including different populations and based on long-term, validated outcomes in order to provide definitive evidence for dietary recommendations in patients with RMDs.

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