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Review

# Nutrients, foods and dietary patterns in the management of autoimmune rheumatic diseases

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SUMMARY

*Background:* Rheumatic disease (RD) represents a broad spectrum of systemic conditions characterized by inflammation and pain in muscles or joints with a significant burden on quality of life. Increasing evidence suggests that diet could play a modulatory role in RD by influencing cardiovascular diseases (CVD) risk factors frequently present in these patients as well as inflammation and antioxidant defence.

*Objectives:* This review aims to summarize the available evidence on the effect of nutrients, foods and dietary patterns on the most common autoimmune inflammatory RD including rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus and systemic sclerosis.

*Results:* We documented that MUFAs and PUFAs seem to have positive effects in modulating the inflammatory process. Regarding the dietary interventions, low-calorie diets, Mediterranean diet and fasting appear to be effective in reducing the symptoms of the most common RD. Positive results were also obtained in some cases with gluten-free, low-fat, vegan, elimination or anti-inflammatory diets.

*Conclusion:* Although further and specific studies are needed, the fact that people obtained an improvement in clinical outcomes

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after almost all these dietary patterns suggests that a healthy diet could play a pivotal role in the RD management.



## 1. Introduction

Rheumatic diseases (RD) represent a broad spectrum of systemic conditions characterized by inflammation and pain in muscles or joints with a significant burden on quality of life. Rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus and systemic sclerosis are among the most common autoimmune RD. The RD aetiology and pathogenesis are highly complex and characterized by auto-reactive immune responses that cause immune-mediated organ damage, which, in turn, is associated with increased morbidity and mortality [1]. It has been estimated that one third of the mortality associated with autoimmune diseases is due to cardiovascular diseases (CVD). Indeed, a complex interaction between traditional and disease-specific traits leads to a premature atherosclerotic process in RD patients [2].

In this scenario, increasing evidence suggests that diet could play an important modulatory role in RD by influencing the traditional CVD risk factors frequently present in these patients – i.e., obesity, insulin resistance, dyslipidaemia, or diabetes mellitus – as well as inflammation and antioxidant defense [3]. Recent evidence suggests that gut microbiota (GM) could be involved in the RD pathogenesis, thus suggesting that a diet that could influence the GM might influence disease activity [4]. Furthermore, diet is able to influence the pharmacological treatment efficacy so it is gaining interest among healthcare providers.

Even if nutritional care appears promising, current nutritional information in the RD management is extremely scarce and varies according to the different diseases. A recent survey by Pham and colleagues [5] revealed that only a small percentage of people diagnosed with RD received nutritional advice and that most of them were rather dissatisfied with information and service provided. RD patients frequently ask their doctors about which diets to follow, and even in the absence of advice, most of them are undertaking different dietary choices since its own experience.

It is therefore clear that the question of whether diet plays a role in the progression of rheumatic diseases is a crucial issue for many patients and healthcare providers. Thus, the aim of our review is to summarize the current available evidence regarding the ideal dietary approach for the management of the most common RD to decrease the counteracting inflammation and the symptomatology, in order to improve the life quality of patients.

## 2. Nutrients, foods, dietary patterns and rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic chronic immune-mediated inflammatory disease characterized by joint swelling and tenderness, bone and cartilage damage, and production of autoantibodies such as anti-citrullinated protein and rheumatoid factor. RA is the most common of inflammatory arthritis, affecting about 1% of the global population with profound impact on patients' quality of life, causing severe disability [6]. Extra-articular manifestations affecting internal organs occur frequently and lead premature mortality, mainly due to an increased atherosclerosis leading to cardiovascular events that are independent of traditional risk factors and are associated with systemic inflammation [7]. Joint inflammation and synovial hyperplasia are caused by the influx of activated inflammatory cells, abnormal activation of fibroblast-like synoviocytes, and induction of angiogenesis thus inhibiting several apoptotic pathways. Moreover, several proinflammatory cytokines (e.g. TNF-α, IL-1, IL-6, IL-17, and IL-12p70) play a pivotal role in RA pathogenesis. Although the disease etiology remains unknown, an increased risk for developing RA has been associated with HLA-DRB1 alleles. As with many autoimmune illnesses, the risk is major in the women with a female-male ratio of 3:1. Several triggering

factors that could lead to the onset or promote progression of RA have been identified including infections, smoking, pollution, diet, oral hygiene, periodontitis, and imbalance in the gastrointestinal microbiota. Although numerous new drugs, particularly biologic agents, are now available for RA treatment, morbidity and mortality remain high [6].

The RA is certainly the most studied RD; detailed studies in humans on the relationship between nutrients or food intake and disease progression in RA patients are still lacking (Fig. 1 and Table 1). Most

| Nutrients | RA | SS | SLE | SSc |
|---|---|---|---|---|
| Carbohydrates | x | x | - | x |
| Dietary fiber | x | x | + | - |
| MUFAs | + | x | x | x |
| PUFAs | x | x | + | x |
| Proteins | x | x | - | x |
| Vit. B6 | x | x | + | x |
| Vit. C | x | x | x | = |
| **Foods** | **RA** | **SS** | **SLE** | **SSc** |
| Alcohol | = | x | x | x |
| Cereals | = | x | = | x |
| Dairy products | = | x | = | x |
| Fish | = | x | = | x |
| Fruit | + | x | = | x |
| Legumes | = | x | = | x |
| Meat | = | x | = | x |
| Vegetables | + | x | = | x |
| **Dietary patterns** | **RA** | **SS** | **SLE** | **SSc** |
| Anti-inflammatory diet | + | x | x | x |
| Elimination diet | + | + | x | x |
| Fasting | + | x | + | x |
| Gluten-free diet | + | x | x | + |
| Individualizedbalanced diet | x | x | x | = |
| Liquid diet | x | + | x | x |
| Low-calorie diet | + | x | + | x |
| Low-fat diet | + | = | + | x |
| Low-FODMAPs diet | x | x | x | + |
| Low-glycaemic index diet | x | x | + | x |
| Low-sodium diet | + | x | x | x |
| Medical nutrition therapy | x | x | x | + |
| Mediterranean diet | + | x | + | + |
| Vegan diet | + | x | x | x |

RA: rheumatoid arthritis; SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; SSc: systemic sclerosis.

+ positive effects; - negative effects; = no effects or inconclusive results; x no available studies

**Fig. 1.** Summary of the evidence about the effect of nutrients, foods and dietary patterns on RD.

**Table 1**
Nutrients, foods, dietary patterns and rheumatoid arthritis

| Author, year | Country | Type of study | Population, n | Age, yrs | Sex | Duration | Nutrient/food/dietary pattern | Outcomes | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Matsumoto *et al.*, 2018 [8] | Japan | Case-control | 208 RA patients; 205 healthy controls | 61 (51–70) RA; 60 (50–67) controls | 84% F | NA | MUFA, SFA, alcohol, pulses, seafood, grains, tubers and roots, fruits, vegetables, meat, milk and dairy products | DAS28-ESR, MHAQ | DAS28-ESR inversely correlated with MUFA/SFA intake |
| Tedeschi *et al.*, 2017 [9] | US | Cross-sectional | 217 RA patients | 65 (53–71) | 83% F | NA | Milk, cheese, red meat, tomato, eggplant, white potatoes, bell or hot peppers, diet soft drinks, beer, fish, spinach, blueberries, strawberries, chocolate, red wine, soft drinks with sugar, coffee, tea | RADAI, MHAQ, DAS28-CRP, CDAI | Blueberries and spinach were the foods most often reported to improve RA symptoms, while soda with sugar and desserts were most often reported to worsen RA symptoms |
| Crilly *et al.*, 2012 [10] | UK | Cross-sectional | 114 RA patients | 54 ± 6.6 | 81% F | NA | Fruits, vegetables | PWA | Daily vegetable consumption, but not daily fruit consumption, was independently associated with more favourable arterial function in patients with RA |
| Lu *et al.*, 2014 [11] | US | Cohort | 662 RA patients | 54.6 ± 14.3 | 83% F | 7 years | Alcohol | DAS28-CRP3, MHAQ | Moderate alcohol consumption was associated with a better functional status in RA |
| Bergman *et al.*, 2013 [12] | Sweden | Cross-sectional | 1,238 RA patients | 65 ± 13 | 70% F | NA | Alcohol | HRQL, DAS28 | There was an association between alcohol consumption and both lower self-reported disease activity and higher HRQL in female, but not in male, RA patients |
| Kjeldsen-Kragh *et al.*, 1991 [13] | Norway | RCT | 53 RA patients | 53 (26–63) | 89% F | 1 year | Fasting followed by vegetarian diet | Pain, morning stiffness, functional ability, MHAQ, joint count, grip strength, haemoglobin, ESR, platelet count, WBC, CRP, albumin | Diet group showed a significant improvement in number of tender joints, swollen joints, pain score, morning stiffness, grip strength, ESR, CRP, WBC, and MHAQ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mc Dougall *et al.*, 2002 [16] | US | Dietary intervention trial | 24 RA patients | 56 ± 11 | 92% F | 4 weeks | Hypocaloric low-fat vegan diet | CRP, rheumatoid factor, ESR, body weight, joint count, pain, ability function, morning stiffness | Patients with moderate-to-severe RA experienced significant reductions in RA symptoms, body weight, CRP and rheumatoid factor |
| Elkan *et al.*, 2008 [17] | Sweden | RCT | 66 RA patients | 49.9 (46.6–53.3) | 93% F | 1 year | Gluten-free vegan diet | DAS28, HAQ, CRP, albumin, cholesterol, triglycerides, HDL, LDL, oxLDL, anti-PCs | A gluten-free vegan diet in RA induces atheroprotective and anti-inflammatory changes, including decreased LDL and oxLDL levels and raised anti-PC IgM and IgA levels |
| Panush *et al.*, 1983 [19] | US | RCT | 26 RA patients | 53.6 | 46% F | 10 weeks | Diet free of additives, preservatives, fruit, red meat, herbs, and dairy products | Pain, morning stiffness, joint count, grip strength, CBC, rheumatoid factor, antinuclear antibodies, C3, C4, stool occult blood tests ESR | No clinically important differences among rheumatologic, laboratory, immunologic, radiologic, or nutritional findings between patients on experimental and placebo diets |
| Darlington *et al.*, 1986 [20] | UK | RCT | 53 RA patients | NA | 81% F | 6 weeks | Elimination diet with the exclusion of food which often cause intolerance | Pain, morning stiffness, joint count, grip strength, physical function, haemoglobin, absolute eosinophil count, platelet count, ESR, antinuclear antibodies, rheumatoid factor, C3, cryoglobulins, fibrinogen | Elimination diet in RA patients led to a significant improvement during periods of dietary therapy compared with periods of placebo treatment, particularly among “good responders” |
| Van De Laar *et al.*, 1992 [21] | Netherland | RCT | 94 RA patients | 58 | 70% F | 4 weeks | Elimination diet with the exclusion of allergens | Morning stiffness, joint count, grip strength, physical function, haemoglobin, % eosinophils, ESR, leucocytes, thrombocytes, body weight | Comparison between baseline and subsequent periods showed only subjective improvements. No differences were seen between the clinical effects of the tested diet |

(*continued on next page*)

**Table 1** (*continued*)

| Author, year | Country | Type of study | Population, n | Age, yrs | Sex | Duration | Nutrient/food/dietary pattern | Outcomes | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Sarzi-Puttini *et al.*, 2000 [22] | Italy | RCT | 50 RA patients | 49.6 (32-64 | 78% F | 6 months | Elimination diet with the exclusion of allergens, high in unsaturated fats, low in saturated fats | Morning stiffness, joint count, pain, HAQ, BMI, body weight, CBC, rheumatoid factor, urinalysis, CRP, C3, C4, immunoglobulins, ESR, cholesterol, HDL, triglycerides | The elimination diet did better for all the variables considered but only four variables (Ritchie's index, tender and swollen joints, and ESR) reached a statistical difference by multivariate analysis |
| Scrivo *et al.*, 2017 [23] | Italy | RCT | 14 RA patients | 58.5 (50–67) | 93% F | 3 weeks | Low-sodium diet | Th17, Treg, cytokines | A trend toward a reduction in the frequencies of Th17 cells, TGFβ and IL-9 over the low-sodium diet regimen was observed, while Treg cells exhibited the opposite trend |
| Vadell *et al.*, 2020 [24] | Sweden | RCT | 50 RA patients | 61 ± 12 | 77% F | 10 weeks | Anti-inflammatory diet | DAS28-ESR, DAS28-CRP | DAS28-ESR significantly decreased during the intervention period, while no significant differences in the components were observed |
| McKellar *et al.*, 2007 [25] | UK | RCT | 130 RA patients | 58 (47–64) | 100% F | 6 months | Mediterranean diet | joint count, pain, morning stiffness, DAS28, HAQ, ESR, CRP, IL-6 | Significant benefit in pain score, morning stiffness and HAQ was shown in the intervention group |

anti-PCs: natural atheroprotective antibodies against phosphorylcholine; CBC: Complete Blood Count; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 Joints; DAS28-CRP: Disease Activity Score in 28 Joints and C-reactive protein; DAS28-ESR: disease activity scores in 28 joints and erythrocyte sedimentation rates; ESR: erythrocyte sedimentation rates; HRQL: health related quality of life; MHAQ: modified Health Assessment Questionnaire; MUFA: mono-unsaturated fatty acids; oxLDL: blood lipids oxidized low-density lipoprotein; PWA: pulse wave analysis; RADAI: RA Disease Activity Index; RCT: Randomized Controlled Trial; SFA: saturated fatty acids; Th17: T helper 17 cells; Treg: regulatory T cells; WBC: white blood cell.

of the studies investigating the effects on RA of fat intake – especially omega-3 and omega-6 – use dietary supplements. However, one study reported that MUFAs, as part of a Mediterranean diet, were associated with disease severity in RA since high MUFAs intake resulted to be an independent predictor of remission, and the ratio of daily consumption of MUFAs to saturated fatty acids was inversely associated with disease severity [8]. In a survey by Tedeschi *et al.*, 24% of patients reported a diet influence on RA symptomatology; 15% reported positive effects of some foods, especially spinach or berries, while 19% observed negative effects of sweets and sugary drinks [9]. In addition, daily vegetable consumption resulted to be significantly associated with more favorable arterial function in RA patients [10]. Finally, there are contrasting data regarding the effect of alcohol on RA disease activity, with some studies pointing that alcohol consumption leads to worsening of inflammation, disease activity or radiographic damage [11] and some others reporting decrease in self-reported tender joint count and pain in drinkers with respect to non-drinkers [12].

To date, several studies on RA progression and different dietary patterns have been performed (Fig. 1 and Table 1). Fasting followed by a vegetarian diet may be useful in the RA treatment by reducing inflammation and pain [13] as confirmed by Muller and colleagues that reviewed all the available evidence on fasting and disease progression in RA [14], even if long-term effects on RA symptoms are still controversial [15]. A 4-week hypocaloric very low-fat vegan diet led to a reduction of body weight and RA symptoms in 24 RA patients [16]. In addition, 1-year gluten-free, vegan diet rich in whole cereals was associated with a significant reduction of oxidized LDL levels, anti-beta-lactoglobulin and anti-gliadin antibodies levels, as well as a reduction of disease severity [17,18]. Other studies intervened with allergen-free diets by eliminating certain foods that commonly cause allergies such as eggs, wheat, dairy products, and spice, finding improvements in specific patient subgroups, but no significant differences were found overall between the intervention and control groups [19–22]. Low-sodium diet seems to have some anti-inflammatory potential, indeed, a decrease in TGFβ, IL-9 and Th17 cell after a 3-week low-sodium diet and their increase after 2 weeks of normal-sodium diet was observed, whereas an opposite trend was observed for Treg cells [23]. Furthermore, a low-inflammatory diet rich in omega-3 fatty acids, dietary fiber and probiotics compared to a typical Swedish diet high in saturated fats showed a mild symptomatic improvement in RA patients, but no significant changes in disease activity were observed [24]. Finally, a paper by McKellar and colleagues examined the effects of Mediterranean diet in patients with RA, concluding that it has beneficial effects in people living with RA in reducing pain and improving physical function [25], as also confirmed by a recent systematic review [26].

## 3. Nutrients, foods, dietary patterns and Sjogren's syndrome

Sjogren's syndrome (SS) is one of the most common autoimmune disease, typically associated with the production of antinuclear autoantibodies (including an-ti-Ro60, anti-Ro52/SSA and anti-La/SS) and characterized by lymphocytic infiltration. SS affects the exocrine glands, mainly the lacrimal and salivary glands, as well as extra-glandular epithelial tissues [27]. Principal symptoms associated with SS include frequent dryness of eyes (xeropthalmia) and mouth (xerostomia), however in most cases (50–70% of patients) these symptoms are also associated with severe extra-glandular manifestations (e.g., arthritis, vasculitis, bronchiectasis, nephritis, autonomic nervous system dysfunction and peripheral neuropathy). The prognosis is mainly conditioned by the extra-glandular involvement. Unfortunately, SS is oftentimes misdiagnosed and undertreated, and although it is considered a benign condition, patients have an in-creased risk to develop lymphoma. SS may occur in any age, but primarily affects middle-aged women, with a 9:1 female: male ratio and a prevalence ranging from 0.04 to 0.17%. Its pathogenesis is thought to be a multistep process, triggered by an environ-mental factor, most likely viral, in genetically predisposed individuals [28].

Regarding dietary habits, a study on 24 SS women evidenced a lower intake of omega-3 fatty acids and vitamin C, and a greater intake of calcium with respect to healthy control [29]. To date, evidence on dietary patterns, foods, or nutrients' intake in patients with SS is extremely scarce (Fig. 1 and Table 2). A letter by Peen *et al.* [30] showed the efficacy of a 4-week period of liquid diet on salivary and lacrimal flow in 23 SS patients. A case report on 5 SS children (5 months–8 years) reported no effects on SS symptoms after a low-fat diet supplemented with medium-chain fatty acids [31]. Finally, a case report on a 42-year-old woman with SS and premature ovarian failure showed a reversal of her premature ovarian failure and

**Table 2**
Nutrients, foods, dietary patterns and Sjögren's syndrome

| Author, year | Country | Type of study | Population, n | Age, yrs | Sex | Duration | Nutrient/food/dietary pattern | Outcomes | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Peen *et al.*, 2008 [30] | Norway | RCT | 23 SS patients | 56.6 (34–73) | 91% F | 4 weeks | Liquid diet | UWSC, Schirmer I test, CRP, ESR, fatigue, joint pain | UWSC and the sum of Schirmer I (both eyes) increased significantly even in the pSS patients with no lacrimal flow at the start of the study |
| Maaswinkel-Mooij *et al.*, 1994 [31] | Netherland | Case series | 5 SS patients | 5 months -8 years | NA | NA | Low-fat diet supplemented with medium-chain fatty acids | Plasma octadecanol levels, skin lesions, neurologic symptoms | Plasma octadecanol levels remained unchanged, and skin lesions and neurologic symptoms did not abate |
| Feuerstein *et al.*, 2010 [32] | US | Case report | 1 SS patient | 42 | 100% F | 4 months | Elimination diet with the exclusion of gluten, refined sugars, beef, dairy products, eggs, nightshade vegetables, and citrus | FSH, ESR, rheumatological symptoms | Elimination diet led to a drop in FSH and ESR. Menses resumed and rheumatological symptoms significantly improved |

CRP: C-reactive protein; ESR: erythrocyte sedimentation rates; FSH: follicle-stimulating hormone; UWSC: unstimulated whole salivary collection.

restoration of normal menses using an elimination diet with the exclusion of gluten, refined sugars, beef, dairy products, eggs, nightshade vegetables, and citrus fruit for 4 months [32].

## 4. Nutrients, foods, dietary patterns and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a severe, chronic autoimmune disease of unknown etiology that can affect virtually any organ, leading to significant morbidity and mortality. It is characterized by immune-dysregulation with the production of autoantibodies (anti-nuclear, anti-double-stranded DNA and anti-Smith), immune complex formation and deposition in tissues resulting in local and systemic inflammation [33]. The SLE pathogenesis remains unclear, however, it is widely considered as multi-factorial with a combination of genetic susceptibilities, environmental factors (such as infections, UV exposure, stress, pollution, or diet) and epigenetic modifications that may impact the disease in terms of triggering or altering its course. SLE is most prevalent in females of childbearing age, with a female: male ratio of 9:1. Estimated incidence rate is 1–25 per 100,000 people in Europe, with a prevalence of about 0.04%. Clinical features vary widely, overlap with other illnesses, and are often initially subtle. They range from mild skin and joint involvement to life-threatening manifestations in the kidney, lung, components of the blood, central nervous system, and heart. SLE may be associated with the presence of lupus anti-coagulant and antiphospholipid antibodies leading to a severe thrombophilic state, increasing the risk for thrombosis, or disseminated intravascular coagulation. Gastrointestinal manifestations are frequent in SLE patients and may be caused either by the disease itself or by the highly aggressive treatments [34].

Very few studies examined the effect of nutrients or single foods on SLE progression (Fig. 1 and Table 3). One observational study investigated the association between dietary habits and disease severity, blood lipids and atherosclerosis showing that lower omega-3 intakes and higher carbohydrate intakes among SLE patients appeared to be related with increased disease severity, adverse serum lipids and plaque presence [35]. Regarding dietary proteins, Milovanov and colleagues [36] reported that a protein-restricted diet (0.6 g/kg/die) had a beneficial effect on nutritional status and glomerular filtration rate in SLE patients with chronic kidney disease. Furthermore, excessive protein intake has been linked to bone mineral loss in patients with juvenile SLE [37]. Finally, a study on 279 SLE women investigating the association between dietary intake of vitamin B6 and B12, folate, and dietary fiber and the risk of active disease and atherosclerotic events, showed an inverse association between vitamin B6 and dietary fiber intake and occurrence of active disease in SLE [38].

More than half of the SLE patients present three or more CVD risk factors and obesity, dyslipidaemia and diabetes are certainly the most common [3]. Davies and colleagues [39] compared a hypoglycemic diet with a calorie-restricted diet and observed a statistically significant reduction in weight and perceived fatigue after both interventions, while no changes in disease activity, total cholesterol, HDL-cholesterol, LDL-cholesterol, and glycaemia were observed. Shah *et al.* [40] investigated the effectiveness of a low-fat diet to lose weight and cholesterol levels in a restricted group of SLE patients, showing an increase in quality of life as well as a significant decrease in weight and total cholesterol but no changes in LDL-cholesterol, HDL-cholesterol, and triglyceride levels were observed. Only one study explored the effects of the Mediterranean diet in 280 SLE patients, revealing that subjects with higher adherence to this dietary pattern reported lower disease severity and disease damage scores, lower BMI and fat mass and fewer CVD risk factors [41]. In addition, higher consumption of fish, vegetables, fruits and olive oil, and lower consumption of red meat and meat products and sugars resulted to be associated with lower disease activity and damage [41]. In addition, another study assessed the effects of the Ramadan fasting in a cohort of SLE patients reporting, after 24 days of fasting, a significant reduction in total cholesterol and a significant increase of anti-dsDNA antibodies that remained stable and significant after 3 months [42]. However, no changes in disease activity and patients' quality of life were observed [42]. Finally, a study highlighted the importance of personalized nutrition counselling which resulted to be effective in initiating dietary changes in SLE patients [43].

## 5. Nutrients, foods, dietary patterns and systemic sclerosis

Systemic sclerosis (SSc) is a rare and complex connective tissue disorder with high mortality rate. It is characterized by widespread fibrosis, early micro-vasculopathy, and immune-system dysregulation

**Table 3**
Nutrients, foods, dietary patterns and systemic lupus erythematosus

| Author, year | Country | Type of study | Population, n | Age, yrs | Sex | Duration | Nutrient/food/dietary pattern | Outcomes | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Elkan *et al.*, 2012 [35] | Sweden | Case-control | 114 SLE patients; 122 controls | 47.9 (45.5 −50.4) SLE; 49.1 (46.8 −51.4) controls | 88% F | NA | Dietary fiber, carbohydrate, protein, total fat, SFA, MUFA, PUFA, Omega-3, Omega-6 | SLAM, SLEDAI, SLICC, CRP, ESR, blood lipids, lipoproteins, carotid plaque, fatty acid content | The higher intake of carbohydrate, lower fibre intake and lower intake of omega-3 and omega-6 in SLE patients appear to be associated with worse disease activity, adverse serum lipids and plaque presence |
| Milovanov *et al.*, 2009 [36] | Russia | RCT | 33 SLE patients | NA | NA | 24–48 months | Low-protein diet | Renal function | Protein-restricted diet had a beneficial effect on nutritional status and glomerular filtration rate in SLE patients with chronic kidney disease |
| Caetano *et al.*, 2009 [37] | Brazil | Cross-sectional | NA | 16.5 | NA | NA | Carbohydrate, protein, total fat | Disease activity | Excessive protein intake has been linked to bone mineral loss in patients with juvenile SLE |
| Minami *et al.*, 2011 [38] | Japan | Cohort | 412 SLE patients | 40 ± 13 | 100% F | 46 months | Vitamin B6, vitamin B12, folate, dietary fiber | LACC, SLICC, atherosclerotic vascular events | Inverse association between vitamin B6 and dietary fiber intake and the risk of active disease |
| Davies *et al.*, 2012 [39] | UK | RCT | 23 SLE patients | 44 ± 12 | 100% F | 6 weeks | Low glycaemic index diet, Calorie-restricted diet | Body weight, BILAG, SLEDAI, ECLAM, SLICC, FSS, PSQI, cholesterol, LDL, HDL, glycaemia, triglyceride, lipoprotein A, homocysteine, fibrinogen, hsCRP, uric acid, ketones | A statistically significant reduction in weight and perceived fatigue after both interventions, while no changes in disease activity, total cholesterol, HDL, LDL and glycaemia were observed. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Shah *et al.*, 2002 [40] | US | RCT | 17 SLE patients | 44.1 ± 9.3 | 100% F | 12 weeks | Low-fat diet | Blood lipids, lipoproteins, body weight, quality of life | An increase in quality of life as well as a significant decrease in weight and total cholesterol but no changes in LDL, HDL, and triglyceride levels were observed. |
| Pocovi-Gerardino *et al.*, 2021 [41] | Spain | Cross-sectional | 280 SLE patients | 46.9 ± 12.9 | 90,4% F | NA | Mediterranean diet | CRP, homocysteine, SLEDAI, SLICC, lipid profile, body weight, C3, C4, homocysteine | Greater adherence to the Mediterranean diet was significantly associated with better anthropometric profiles, fewer cardiovascular disease risk factors, and lower disease activity and damage accrual scores |
| Goharifar *et al.*, 2015 [42] | Iran | Case-control | 40 SLE patients (21 cases; 19 controls) | 39.7 ± 13.4 SLE; 40.2 ± 11.2 controls | 100% F | 12 weeks | Ramadan fasting | SLEDAI, lipid profile, quality of life, C3, C4, anti-ds DNA, CBC, ESR, BMI | Ramadan fasting led to a significant reduction in total cholesterol and a significant increase of anti-dsDNA antibodies, while no changes in disease activity and patients' quality of life were observed |

BILAG: British Isles Lupus Assessment Group; BMI: Body Mass Index; CBC: Complete Blood Count; CRP: C-reactive protein; ECLAM: European Community Lupus Activity Measure; ESR: erythrocyte sedimentation rates; FSS: Fatigue Severity Scale; HDL: High-density Lipoprotein; hsCRP: high sensitivity C-reactive protein; LACC: Lupus Activity Criteria Count; LDL: Low-density Lipoprotein; MUFA: Mono-unsaturated Fatty Acids; PSQI: Pittsburgh Sleep Quality Index; PUFA: Poli-unsaturated Fatty Acids; SFA: Saturated fatty Acids; SLAM: Systemic Lupus Activity Measure; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics.

**Table 4**
Nutrients, foods, dietary patterns and systemic sclerosis

| Author, year | Country | Type of study | Population, n | Age, yrs | Sex | Duration | Nutrient/food/ dietary pattern | Outcomes | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Gough *et al.*, 1998 [49] | UK | Case series | 4 SSc | 46–71 | 100% F | NA | Dietary fiber | Gastrointestinal symptoms | High-fiber diet seems to exacerbate gastrointestinal symptoms in SSc |
| Lazarus *et al.*, 1970 [50] | US | Dietary intervention trial | 11 SSc patients | NA | NA | NA | Low-vitamin C diet | Collagen sysntesis, scleroderma lesions | Low-vitamin C diet did not impair collagen synthesis and consequently did not improve the lesions of SSc |
| Marie *et al.*, 2015 [51] | France | Dietary intervention trial | 80 SSc patients | 52.5 (22–79) | 82.5% F | 4 weeks | Low-FODMAPs diet | Digestive symptoms, BMI, ESR, CRP, albumin, prealbumin, ferritin, folic acid, vitamin B12, magnesium, zinc, selenium, 25OHvitamin D | Low-FODMAPs diet resulted in a marked decrease of gastrointestinal clinical manifestations in SSc patients with fructose malabsorption |
| Marie *et al.*, 2016 [52] | France | Dietary intervention trial | 99 SSc patients | 53.5 (21–79) | 82% F | 4 weeks | Lactose-free diet | Digestive symptoms, BMI, ESR, CRP, albumin, prealbumin, ferritin, folic acid, vitamin B12, magnesium, zinc, selenium, 25OHvitamin D | In SSc patients with symptomatic lactose malabsorption, digestive symptoms were lower after initiation of lactose-free diet |
| Ortiz-Santamaria *et al.*, 2014 [53] | Spain | RCT | 9 SSc patients | 62.6 ± 11.7 | 89% F | 1 year | Individualized balanced diet | Body weight, BMI, quality of life | No significant improvements in body weight, food intake, nutritional biochemical parameters, and quality of life were observed after individualized balanced diet intervention |
| Doerfler *et al.*, 2017 [54] | US | Dietary intervention trial | 18 SSc | 51.3 ± 11.0 | 89% F | 6 week | Medical nutrition therapy | Body weight, BMI, body composition, sarcopenia | Individually tailored medical nutrition therapy improved symptom burden and sarcopenia in patients with SSc involving the gastro-intestinal tract. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Guillen-Del Castillo *et al.*, 2013 [55] | UK | Dietary intervention trial | 4 SSc | NA | NA | NA | Gluten-free diet | Gastrointestinal symptoms | After gluten-free diet all SSc-CD patients had an improvement of small bowel symptoms. |
| Luchetti *et al.*, 2016 [56] | Italy | Case-control | 38 SSc; 25 controls | NA | NA | 24 weeks | Mediterranean diet | I-FABP, LPS, CD14, clinical symptoms | Mediterranean diet significantly improves the clinical symptoms and the gastro-intestinal damage (I-FABP), thus reducing microbial translocation (LPS) and immune system activation (CD14) |

BMI: Body Mass Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rates; I-FABP: intestinal-type fatty acid-binding protein; LPS: lipopolysaccharide.

with production of autoantibodies (anti-nuclear, and the more specific anti-centromere and anti-ScL-70). The distinguishing SSc hallmark is represented by a progressive fibrosis of skin and internal organ owing to a maladaptive repair process characterized by excessive production of collagen and other components [44]. The SSc aetiology remains quite obscure, and the pathogenesis may encompass multiple genetic and environmental factors such as infections, drugs, diet, and lifestyle. The disease onset is earlier in women than in men, generally occurring between 40 and 50 years of age, with a male to female ratio of 3–4:1. SSc is an unpredictable disease that may have different clinical features at onset as well as a heterogeneous course with time [45]. The early disease diagnosis is very problematic in the oligosymptomatic phase because initial symptoms, such as Raynaud's phenomenon and puffy fingers, are not specific signs. Consequently, delays in diagnosis may lead to progression of the disease up to the point that important organ damage and SSc-related vasculopathy complications (i.e., interstitial lung disease and pulmonary arterial hypertension) ensue [46].

Since oesophageal dysmotility and abnormalities of intestinal function are important manifestations in SSc, several dietary guidelines for the SSc management have been published to date, even if evidence on dietary patterns, food or nutrients' intake in these patients is extremely unusual [47] as reported in Fig. 1 and Table 4. A study performed thirty years ago evaluated the dietary habits of 30 SSc patients finding a lower intake of dietary fiber, fruit, and vegetables with respect to healthy controls [48]. Few years later Gough and colleagues [49] – based on a small case series – suggested that a high-fiber diet may exacerbate gastrointestinal symptoms in SSc. Another study explored the effect of a vitamin C-deficient diet on 11 SSc patients to determine whether lack of this substance would impair collagen synthesis and consequently improve the lesions of SSc, but none of the signs or SSc symptoms improved in any of the patients [50]. In two subsequent works, Marie *et al.* hypothesized that fructose and lactose malabsorption – reported in 40% and 44% of the patients, respectively – may play a critical role in the onset of gastrointestinal symptoms in these patients, showing that low-fructose diet resulted in a marked decrease of gastrointestinal clinical manifestations in SSc patients with fructose malabsorption [51,52].

To date there are only two small RCTs testing the effect of different dietary patterns in the SSc management. The first one investigated the effect of a one-year individualized balanced diet intervention on 9 SSc patients at risk for malnutrition, finding no significant improvements in body weight, food intake, nutritional biochemical parameters, and quality of life of these patients [53]. The second one investigated the effect of a 6-week medical nutrition therapy (MNT) intervention on 18 SSc subjects with gastrointestinal involvement and unintentional weight loss, reporting an improvement in the symptom burden and in the sarcopenia, defined as appendicular lean height (ALH) [54]. Finally, two abstracts (which have never been published as complete papers) showed an improvement in gastrointestinal symptoms in 4 subjects with SSc and coeliac disease by following a gluten-free diet and in 38 SSc subjects after a 6-month intervention with Mediterranean diet [55,56].

## 6. Conclusions

Emerging data suggest that diet plays a crucial role in the treatment of RD, through management of inflammation, nutritional status, and oxidative stress. Considering that a specific diet can be a helpful support for patients suffering from RD, we have summarized and discussed all the available evidence on the effect of nutrients, foods, and dietary patterns on the most common RD, including rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus and systemic sclerosis.

Although only few studies on single food or food components are available in the literature, dietary fats seem to have a pivotal role in the RD progression. Saturated fats showed a negative effect on disease progression – probably due to their pro-inflammatory effects – while omega-3 and MUFAs seem to have a positive effect in modulating the inflammatory process. The role of dietary fiber remains controversial with some evidence suggesting a positive effect on inflammation and disease severity and some others reporting a worsening of gastrointestinal symptoms – especially in some predisposed subjects with gastrointestinal dysfunction – due to the increase of fermentable substrates. Regarding the dietary interventions, low-calorie diets, Mediterranean diet and fasting appear to be effective in reducing the symptomatology of the most common RD. Indeed, most of the included studies showed a significant improvement in chronic pain, inflammation, and gastrointestinal symptoms. Furthermore,

weight loss in most of the included RD (except for SSc, in which patients are at high risk for malnutrition) seems to be associated with both reduced inflammation and improved quality of life, thus suggesting that body weight could have a functional repercussion in these patients. Positive results were also obtained in some cases with gluten-free diets, low-fat diets, vegan, elimination or anti-inflammatory diets. As reported in our previous study [57], all these diets are generally regarded as healthy dietary models, rich in plant foods and antioxidants and poor in animal products and saturated fats, so the fact that people reported an improvement in clinical outcomes after almost all these dietary patterns, suggests that a healthy diet could play a pivotal role in the RD management.

However, it is important to note that most of the investigated diets were hypocaloric diets, so we cannot exclude that the beneficial effects could be exclusively due to the weight loss, that is directly linked to a reduced inflammatory state. In addition, in many cases, elimination diets have led to positive results because subjects with some food intolerances were considered. In these patients, we expect an improvement, but this doesn't mean that these benefits are valid and extendable to the entire population with no food intolerances. Furthermore, these results should be interpreted with caution since the available studies have several biases that limit the robustness of the findings. First, the limited sample size with no possibility of blinding could affect the results. Secondly, outcomes are often analysed without considering possible confounding factors such as drugs' treatments. In addition, different methods to collect dietary data are frequently used, with most of them reporting several bias i.e. recall bias. Finally, a follow-up is almost never carried out to determine whether the positive effects are maintained over time or are only transient.

In conclusion, although nutritional therapy could be a promising way to approach RD, further research should be conducted to understand the specific mechanisms that interconnect the regulation of immunity, inflammation, oxidative stress, and nutrition in order to reduce clinical symptoms and ameliorate the quality of life of the patients with autoimmune RD.

## Author Contributions

G.P., B.C. and S.B.R. wrote the article. A.A., S.G. and F.S. participated in the critical revision and final approval. All authors have read and agreed to the published version of the manuscript.

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## Conflicts of interest

The authors declare no conflict of interest.

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