The Influence of Dietary Intervention in Connective Tissue Diseases: Evidence from Randomized Clinical Trials

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Abstract: The aim of this review is to identify and discuss randomized clinical trials conducted in patients with connective tissue diseases, including systemic lupus erythematosus, idiopathic inflammatory myopathies, vasculitis, Sjögren’s syndrome, and systemic sclerosis. Although limited, the results obtained with bioactive compounds, namely n-3 polyunsaturated and short-chain fatty acids, demonstrate that dietary intervention and nutritional counseling might have an important role as adjuvant therapy in patients with connective tissue diseases, particularly in the light of the comorbidities which characterize these conditions.

Keywords: dietary intervention; autoimmunity; inflammation; connective tissue diseases; systemic lupus erythematosus; idiopathic inflammatory myopathies; vasculitis; Sjögren’s syndrome; systemic sclerosis

1. Introduction

Nutritional status and dietary intake have long been recognized to affect health and disease. Increasing evidence shows how nutrient and non-nutrient (i.e., bioactive) compounds, which are being more frequently used according to a dietary lifestyle, are capable to modify disease risk factors, genetic and epigenetic pathways, inflammatory mediators and, therefore, clinical outcomes.

With respect to rheumatic diseases, much work has been conducted in an attempt to understand the pathogenic molecular mechanisms that can be affected by specific dietary substances. However, despite the encouraging experimental results, clinical studies evaluating their effect on disease activity or progression are still limited and mostly regard rheumatoid arthritis. The aim of this review is to identify and discuss randomized clinical trials (RCTs) conducted on autoimmune rheumatic diseases involving connective tissue.

2. Search Method

We searched for randomized clinical trials conducted on dietary intervention in patients with autoimmune connective tissue diseases, i.e., systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), vasculitis, Sjögren’s syndrome (SS), and systemic sclerosis (SSc), from inception to 2021. When no RCTs were available for a specific disease, the search was expanded to include clinical non-randomized studies. Databases included Medline, Embase, and the trial registry clinicaltrial.gov.
3. Evidence from Randomized Clinical Trials

3.1. Systemic Lupus Erythematosus

3.1.1. Omega-3 Polynsaturated Fatty Acids

Omega (n)-3 polynsaturated fatty acids are among the most studied of dietary interventions in SLE. The first RCTs conducted on these nutrients date back to the 1990s, when the beneficial clinical immunological and biochemical effect of fish oil was demonstrated in several animal disease models [1,2]. The epidemiological observation of a very low incidence of autoimmune and inflammatory disorders in Eskimo populations compared with matched European individuals, in addition to the association between higher intakes of the n-3 fatty acids (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) and lower risk of developing cardiovascular disease, pushed the research in this direction [3]. Since then, an impressive number of experimental and clinical studies have been conducted [4].

The first two RCTs have been performed in patients with active SLE over a period of six months (Table 1) [5,6]. In both studies, n-3 fatty acids were administered through MaxEPA capsules at 0.2 g/kg/die [5] or 20 g/die [6] according to a crossover design. While the first study showed a limited and short-lived clinical benefit, the second showed a significant benefit on patients’ clinical state. Interestingly, an increase in red blood cell EPA concentration was observed in patients receiving MaxEPA [6].

Table 1. Randomized clinical trials investigating the effect of diet and dietary supplementation in systemic lupus erythematosus.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial Type</th>
<th>Main Inclusion Criteria</th>
<th>Cases (N.)</th>
<th>Intervention/Die</th>
<th>Control</th>
<th>Intervention Period</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westberg, 1990 [5]</td>
<td>Randomized, double blind, crossover</td>
<td>Active disease</td>
<td>17</td>
<td>MaxEPA 0.2 g/kg</td>
<td>Olive oil</td>
<td>6 months</td>
<td>Clinical and laboratory parameters</td>
<td>Short-lived benefit</td>
</tr>
<tr>
<td>Walton, 1991 [6]</td>
<td>Randomized, double blind, crossover</td>
<td>Active disease</td>
<td>27</td>
<td>Low fat diet + 20 g MaxEPA</td>
<td>Olive oil</td>
<td>6 months</td>
<td>Clinical and laboratory parameters</td>
<td>Significant benefit</td>
</tr>
<tr>
<td>Clark, 1993 [7]</td>
<td>Randomized, double blind, placebo controlled, crossover</td>
<td>Stable active disease, with nephritis</td>
<td>26</td>
<td>Fish oil (2.7 g EPA, 1.7 g DHA)</td>
<td>Olive oil</td>
<td>12 months</td>
<td>Renal function, plasma lipids, SLEDAI, immunological markers</td>
<td>No significant changes in renal function or SLEDAI, and significant decrease in TG and VLDL levels</td>
</tr>
<tr>
<td>Clark, 2001 [8]</td>
<td>Randomized, double blind, non-placebo controlled, crossover</td>
<td>Hematuria, proteinuria</td>
<td>23 (23c + 23p)</td>
<td>Flaxseeds 30 g</td>
<td>No flaxseeds</td>
<td>24 months</td>
<td>Renal function, plasma lipids, Disease activity, Biochemical and immunological markers</td>
<td>Some renoprotective effects, poor adherence</td>
</tr>
<tr>
<td>Duffy, 2004 [9]</td>
<td>Randomized, double blind, placebo controlled, factorial</td>
<td>Stable active disease</td>
<td>52 (13c + 14p + 13c + 12p)</td>
<td>MaxEPA fish oil 3 g copper 3 mg</td>
<td>Double placebo (olive oil)</td>
<td>6 months</td>
<td>Disease activity, biochemical and immunological markers</td>
<td>Significant reduction in SLAM-R</td>
</tr>
<tr>
<td>Wright, 2008 [10]</td>
<td>Randomized, double blind, placebo controlled, parallel</td>
<td>SLE without comorbidities</td>
<td>60 (30c + 30p)</td>
<td>Fish oil (1.8 g EPA, 1.2 g DHA)</td>
<td>Olive oil capsules</td>
<td>6 months</td>
<td>Disease activity, endothelial functions</td>
<td>Significant reduction in SLAM-R, BILAG, and TG and significant increase in FMD and decrease in DSS Improvement in global disease assessment</td>
</tr>
<tr>
<td>Arriens, 2015 [11]</td>
<td>Randomized, single blind, placebo controlled</td>
<td>SLE with ACR criteria</td>
<td>50 (25c + 25p)</td>
<td>Fish oil (2.25 g EPA, 2.25 g DHA)</td>
<td>Olive oil capsules</td>
<td>6 months</td>
<td>Fatigue, QoL, disease activity, inflammatory biomarkers</td>
<td>Non-significant improvement in fatigue and decrease in ESR and IL-12</td>
</tr>
<tr>
<td>Borges, 2016 [12]</td>
<td>Randomized, parallel, pilot study</td>
<td>Female with SLE of disease duration &gt; 1 year</td>
<td>49 (22c + 27p)</td>
<td>n-3 fatty acids (540 mg EPA, 100 mg DHA), tablets</td>
<td>No intervention</td>
<td>3 months</td>
<td>Biochemical inflammatory and lipid markers</td>
<td>No benefit</td>
</tr>
</tbody>
</table>
Another crossover trial conducted in patients with SLE and nephritis [7] aimed at investigating the effect of EPA and DHA in renal function. No significant changes in clinical scores and renal function measures were observed in this study, including for proteinuria, glomerular filtration rate, urinary IgG, and serum creatine. However, supplementation with fish oil caused a reduction in values for a few lipid parameters, such as triglycerides and

### Table 1. Cont.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial Type</th>
<th>Main Inclusion Criteria</th>
<th>Cases (N.)</th>
<th>Intervention/Die Control</th>
<th>Intervention Period</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah, 2002 [13]</td>
<td>Randomized, controlled, double blind</td>
<td>Disease lasting 6 months, LDL ≥ 100 mg/dL</td>
<td>17 (8c + 7p)</td>
<td>NCEP Step II diet</td>
<td>No dietary advice</td>
<td>3 months</td>
<td>QoL, lipids Improvement in QoL and short benefit for lipids</td>
</tr>
<tr>
<td>Davies, 2012 [14]</td>
<td>Randomized, controlled, double blind</td>
<td>Mild and stable disease, treated with corticosteroids</td>
<td>23 (11c + 12p)</td>
<td>Low glycemic index diet</td>
<td>Calorie-restricted diet</td>
<td>6 weeks</td>
<td>Weight loss, CV risk markers, disease activity, sleep quality</td>
</tr>
<tr>
<td>Da Silva, 2018 [15]</td>
<td>Randomized, controlled, single blind</td>
<td>Juvenile SLE for at least 6 months</td>
<td>31 (15c + 16p)</td>
<td>Nutritional instruction</td>
<td>No dietary advises</td>
<td>9 months</td>
<td>Carbohydrates and fat intake, lipid and glucose metabolism biomarkers</td>
</tr>
<tr>
<td>Aranow, 2015 [16]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Stable, inactive disease with 25(OH)D &lt; 20 ng/ml</td>
<td>54 (17c + 18c + 19p)</td>
<td>Low-dose VitD3 (2000 IU) high-dose VitD3 (4000 IU)</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>IFN signature response No benefit</td>
</tr>
<tr>
<td>Andréoli, 2015 [17]</td>
<td>Randomized, double blind, crossover</td>
<td>Stable disease</td>
<td>34 (18c + 16c)</td>
<td>VitD3 50,000 IU/month</td>
<td>Cholecalciferol 25,000 IU/month</td>
<td>24 months</td>
<td>VitD levels, disease activity, bone metabolism markers No benefit</td>
</tr>
<tr>
<td>Kamen, 2015 [18]</td>
<td>Randomized, single blind, controlled, pilot study</td>
<td>VitD-deficient SLE subjects, inactive disease</td>
<td>9 (6c + 3p)</td>
<td>VitD3 5000 IU</td>
<td>VitD3 4000 IU</td>
<td>16 weeks</td>
<td>Endothelial function No significant increase in FMD</td>
</tr>
<tr>
<td>Lima, 2016 [19]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Juvenile-onset SLE</td>
<td>40 (20c + 20p)</td>
<td>VitD3, 5000 IU/week</td>
<td>Placebo tablets</td>
<td>6 months</td>
<td>Disease activity, fatigue Significant improvement in SLEDAI, ECLAM, and fatigue</td>
</tr>
<tr>
<td>Lima, 2018 [20]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Juvenile-onset SLE</td>
<td>40 (20c + 20p)</td>
<td>VitD3, 5000 IU/week</td>
<td>Placebo tablets</td>
<td>6 months</td>
<td>Bone microarchitecture parameters Significant improvement in trabecular number Modest reduction in lipid peroxidation</td>
</tr>
<tr>
<td>Tam, 2005 [21]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Stable disease</td>
<td>39 (20c + 19p)</td>
<td>Vitamins (500 mg VitE, 800 IU VitE)</td>
<td>Placebo</td>
<td>3 months</td>
<td>Markers of oxidative stress, endothelial function Significant decrease in proteinuria, hematuria and systolic blood pressure Significant improvement in SLEDAI Benefit on QoL</td>
</tr>
<tr>
<td>Khajehdehi, 2012 [22]</td>
<td>Randomized, placebo controlled</td>
<td>SLE with relapsing or refractory nephritis</td>
<td>24 (12c + 12p)</td>
<td>Turmeric 500 mg (221 mg curcumin), capsules</td>
<td>Starch capsules</td>
<td>3 months</td>
<td>Renal functions, hematological parameters</td>
</tr>
<tr>
<td>Shamsheh, 2017 [23]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Stable disease</td>
<td>31 (32c + 66p)</td>
<td>Green tea extract, 1000 mg, capsules</td>
<td>Starch, 1000 mg/day, capsules</td>
<td>3 months</td>
<td>Disease activity, QoL</td>
</tr>
<tr>
<td>Hayashi, 2014 [24]</td>
<td>Randomized, placebo controlled, crossover</td>
<td>Childhood-onset SLE with SLEDAI-2K ≥ 28</td>
<td>15 (7c + 8p)</td>
<td>Creatine monohydrate 0.1 g/kg, juice</td>
<td>Dextrose, juice</td>
<td>12 weeks + 8 washout</td>
<td>Muscle function Biochemical markers, QoL No benefit</td>
</tr>
</tbody>
</table>

ACR: American College of Rheumatology; BILAG: British Isles Lupus Assessment Group; CV: cardiovascular risk; DHA: docosahexaenoic acid; DSS: diastolic shear stress during reactive hyperemia; ECLAM: European Consensus Lupus Activity Measurement; EPA: eicosapentaenoic acid; ESR: erythrocyte sedimentation rate; FMD: flow-mediated dilation of the brachial artery; LDL: low-density lipoprotein; NCEP: National Cholesterol Education Program; QoL: quality of life; SLAM-R: Systemic Lupus Activity Measure, revised; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; TC: triglycerides; VLDL: very low-density lipoprotein.
VLDL levels. Despite the crossover design, a small sample size and the lack of validated measures of disease activity characterized and represent limitations of the mentioned studies. Furthermore, the choice of olive oil as a control has been supposed to represent a potential source of error due to its possible underestimated active effect [7].

Flaxseeds have been used in patients with documented hematuria and proteinuria to evaluate the effect of alpha-linolenic acid, the precursor of n-3 fatty acids, in renal function [8]. A two-year crossover non-placebo-controlled trial demonstrated that 30 g of flaxseeds administered daily induced a renoprotective effect in lupus but were difficult to tolerate in the long term, leading to poor adherence to the intervention and thus affecting the results of the study.

A larger cohort of patients has been included in another study evaluating the effect of 3 g/die of MaxEPA and 3 mg copper in patients with active disease [9]. This six-month trial that had a double placebo design showed a significant reduction in disease activity assessed by the SLAM-R (Systemic Lupus Activity Measure, revised) scoring system but no significant therapeutic benefit from copper supplementation. Contrary to the previous studies, this trial used a validated index for determining lupus activity considering different clinical and laboratory domains and is the first showing a potential beneficial role of n-3 fatty acids in SLE [9].

With the introduction of validated disease activity scores, other interventional trials on n-3 supplementation have been concluded. The benefit on disease activity has been confirmed in a placebo-controlled RCT conducted in 60 patients [10]. After a period of six months of fish oil administration, the patients showed a significant reduction in SLAM-R and BILAG indices and, importantly, an improvement in endothelial function as measured by vascular indices including flow-mediated dilation of the brachial artery and diastolic shear stress.

Using different concentrations of n-3 EPA and DHA, other authors did not find any significant benefit on disease activity and fatigue in a population of 50 patients with SLE [11]. However, they developed an improved version of the physician global disease assessment. Regarding inflammatory circulating markers, the supplementation with n-3 fatty acids showed no impact on serum concentrations of the cytokines IL-6 and IL-10, and adipokines leptin and adiponectin [12], whereas it exhibited a small effect on IL-13 [11].

3.1.2. Nutritional Counseling

Considering the higher prevalence of atherosclerotic cardiovascular disease in patients with SLE [25], some RCTs have been designed to examine the effect of nutritional intervention in patients’ lipid profiles [13–15].

The first of these studies applied dietary counseling based on the National Cholesterol Education Program (NCEPT) on patients with SLE to investigate lipid and lipoprotein levels [13]. Although highly accepted and effective in changing nutrient intakes and in improving the quality of life, the diet program induced only a modest effect on serum lipid, lipoprotein, and body weight after three months [13].

3.1.3. Low Carbohydrate Diet

Based on a similar concept, a low carbohydrate diet was assigned to a small cohort of patients with SLE to minimize the adverse effects of corticosteroids on glycemic control. This six-week study demonstrated the effectiveness of this diet in reducing weight comparably to a standard low-calorie diet, with both being safe and well-tolerated by the patients [14]. Notably, the patients showed a significant improvement in terms of the fatigue severity scale, suggesting an important role of diet in managing fatigue in SLE.

A population of adolescents with juvenile SLE were included in an RCT evaluating the effect of a nutritional intervention on cardiovascular risk-related lipid metabolism biomarkers and their variation over a period of nine months [15]. Compared with a control group that did not receive any dietary instruction, the nutritional intervention group of
adolescents showed a reduced carbohydrate, total fat, and calorie intake, with a significant improvement in their lipid marker profile.

3.1.4. Vitamin D and Other Vitamins

Another important nutrient with recognized immunomodulatory effects is vitamin D (VitD). Considered a booster of the immune system, VitD has been used in various RCT demonstrating contrasting results (Table 1). Different doses of VitD for periods of treatment ranging from three to six months were assessed in these studies. The daily supplementation of 2000 and 4000 IU showed no benefit on IFN signature response, evaluated through the analysis of IFNα-inducible genes, nor according to SELENA-SLEDAI disease activity index in clinically stable VitD-deficient patients with SLE [16]. Similarly, a crossover study on stable patients taking a monthly dosage of VitD according to an intensive (300,000 IU at baseline + 50,000 IU/month) and a standard (25,000 IU/month) regimen, showed no significant influence on SLEDAI disease activity index nor in complement levels and bone metabolism markers [17]. VitD-deficient patients with inactive SLE were also enrolled in a pilot study investigating the effect of 5000 IU/daily on endothelial function. Although the study was limited by a very small cohort of patients, no increase in flow-mediated dilation of the brachial artery was observed [18].

By contrast, two more recent placebo-controlled RCT carried out on juvenile-onset patients demonstrated that weekly administration of 50,000 IU VitD led to a significant improvement in SLEDAI and ECLAM indices along with reduced fatigue [19]. When looking at microarchitecture parameters, the treated adolescents showed a higher increase in the trabecular number at the tibia site compared to the placebo group after six months of VitD treatment. No difference was observed in volumetric bone mineral density in the two groups after supplementation [20]. The explanation for the different results achieved by the studies might lie in the different target populations, the inactive disease of some patients, the different doses and period treatment, and the difficulty to maintain sufficient VitD serum levels [17]. Given the safety of this nutrient, it will be important to identify those patients more likely to benefit from VitD supplementation.

Among other vitamins, vitamins C and E have been tested in patients with stable SLE disease to verify their antioxidant effects on oxidative stress markers and endothelial function, but only a modest reduction in lipid peroxidation was found after three months of therapy (Table 1) [21].

3.1.5. Plant Polyphenols

In the last few decades, great interest has been devoted to the anti-inflammatory and immunomodulatory properties of plant polyphenols. Their beneficial effects have been tested and demonstrated for several inflammatory, autoimmune, and degenerative diseases [26–29].

Regarding SLE, two different RCTs considered a three-month polyphenol supplementation. Restored renal function was the outcome of the first of these studies and was carried out in patients with relapsing or refractory nephritis taking 22 g/day curcumin. Compared to a control group taking a placebo, the treated group showed a significant decrease in proteinuria and hypertension, which represents an adverse prognostic sign in patients with lupus nephritis [22]. A second trial demonstrated that 1000 mg/day of green tea extract for three months lead to a significant improvement in the SLEDAI index and a benefit in quality of life in patients with stable disease compared to a placebo group consuming starch capsules as placebo [23].

Finally, a three-month study was designed to demonstrate the efficacy and safety of creatine in non-active childhood-onset SLE. The aim was to counteract adverse events associated with the treatment as well as the disease itself. A dose of 0.1 g/kg/die creatine supplementation did not show any influence on intramuscular phosphoryl creatine, muscle function, free fat mass, or quality of life [24].
3.2. Idiopathic Inflammatory Myopathies

Contrary to SLE, only a few RCT studies have examined the role of dietary intervention on the outcome of other connective tissue diseases.

Indeed, idiopathic inflammatory myopathies (IIM), which are characterized, among other features, by systemic and muscle inflammation with an increase in cytokine levels, might benefit from an anti-inflammatory diet or supplementation. Some clinical studies demonstrated, for instance, that vitamin E reduces levels of cell damage markers and the concentration of exercise-induced cytokines in hypoxia, suggesting a possible protective effect against hypoxia-induced inflammation [30]. Polyphenols were demonstrated to protect muscle inflammation and atrophy in a mouse model of chronic inflammation [31], while n-3 fatty acids were shown to prevent lipotoxicity and inflammation through the regulation of muscle lipid and glucose metabolism [32]. An association between dermatomyositis (DM) and celiac disease was documented in children [33] and adults [34], where a strict gluten-free diet can lead to disease resolution [34].

With respect to dietary interventional trials, three RCTs have been carried out in idiopathic inflammatory myopathies and are shown in Table 2. The first is the largest as it involved patients with both polymyositis (PM) and dermatomyositis (DM) that were assigned to receive a loading followed by a maintenance dose of creatine in combination with home exercise [35]. Compared to the placebo group (exercise alone), patients has improved muscle performance assessed as by a composite measure (Table 2) and endurance work after six months of treatment. The choice of creatine in IIM found its rationale in the reduced levels of intramuscular phosphocreatine in patients with IIM and increased creatine excretion, which was shown to be correlated with global disease damage in juvenile DM [36].

Table 2. Randomized clinical trials on the effect of diet in idiopathic inflammatory myopathies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Main Inclusion Criteria</th>
<th>Cases (N.)</th>
<th>Intervention</th>
<th>Control</th>
<th>Intervention Period</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung, 2007</td>
<td>Randomized, double blind, placebo controlled</td>
<td>PM or DM</td>
<td>37 (19c + 18p)</td>
<td>Creatine, 20 g/day for 8 days, 3 g/day plus exercise</td>
<td>Placebo plus exercise</td>
<td>6 months</td>
<td>Aggregate functional performance time, functional index</td>
<td>Significant improvement in muscle performance and functional index</td>
</tr>
<tr>
<td>Solis, 2015</td>
<td>Randomized, double blind, placebo controlled, crossover</td>
<td>Juvenile DM with stable medications</td>
<td>15</td>
<td>Creatine monohydrate, 0.1 g/kg/die</td>
<td>Dextrose</td>
<td>3 months</td>
<td>Muscle function, bone remodeling, and inflammatory markers</td>
<td>No effect on muscle function</td>
</tr>
<tr>
<td>Dover, 2021</td>
<td>Randomized, double blind, placebo controlled, multiple baseline design</td>
<td>Juvenile DM with stable medications</td>
<td>13</td>
<td>Creatine, 150 mg/kg/die, tablets</td>
<td>Placebo tablets</td>
<td>6 months</td>
<td>Muscle function and metabolism, fatigue, QoL</td>
<td>No clinical benefit, significant improvement in muscle metabolism</td>
</tr>
</tbody>
</table>

DM: dermatomyositis; PM: polymyositis.

Based on these findings, other two RCTs involving pediatric cohorts were designed to investigate the role of creatine in physical capacity and quality of life. Both studies included patients with juvenile DM that received creatine for either three or six months, but they failed to demonstrate significant clinical benefit [37,38].

3.3. Vasculitis

Only a proof-of-concept clinical study has addressed the possible influence of diet in vasculitis and concerns Behçet’s disease. In this disease, the depletion of some strains of
microorganisms in the gut microbiota is observed. Therefore, the decreased production of anti-inflammatory short-chain fatty acids (SCFA) was demonstrated [39]. These metabolites, including butyrate, acetate, and propionate, have been shown to possess positive immune-modulating activity by modifying the cytokine production profile of T helper cells, promoting intestinal epithelial barrier integrity, resolving intestinal inflammation, and regulating the acetylation of lysine residues, a covalent modification that affects proteins involved in a variety of signaling and metabolic processes [40].

As reported in Table 3, the effects of two butyrate-rich diets on blood redox status, fibrin degradation, and clinical modifications were assessed in patients with Behçet disease. After an intervention period of three months, both diets lead to a significant reduction in leukocyte ROS production and plasma lipid peroxidation and an increase in plasma total antioxidant capacity. Although disease activity significantly improved, the results were not associated with modified SCFA production, which presumably occurs after longer periods of nutritional intervention [41,42].

**Table 3.** Randomized clinical trials on dietary intervention in Behçet’s disease.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Main Inclusion Criteria</th>
<th>Cases (N.)</th>
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<th>Control</th>
<th>Intervention Period</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagliai, 2020 [41]</td>
<td>Randomized, open,</td>
<td>BD without any other</td>
<td>90</td>
<td>Lacto-ovo-vegetarian diet Mediterranean diet + butyrate</td>
<td>-</td>
<td>3 months</td>
<td>Gastrointestinal and systemic symptoms</td>
<td>Study protocol</td>
</tr>
<tr>
<td>Emmi, 2021 [42]</td>
<td>crossover</td>
<td>autoimmune disease</td>
<td></td>
<td>Butyrate (2.4 g/day) Lacto-ovo-vegetarian diet leading to increased butyrate production</td>
<td>-</td>
<td>3 months</td>
<td>Blood redox status, fibrin degradation, and clinical modifications</td>
<td>Significant improvement in redox status and reduction in disease activity</td>
</tr>
</tbody>
</table>

BD: Behçet’s disease.

### 3.4. Sjögren’s Syndrome

As a complex autoimmune condition with a wide range of disruptive symptoms, SS might benefit from a diet rich in immunomodulatory substances, including polyunsaturated fatty acids and bioactive compounds. An association between adherence to the Mediterranean diet and a lower likelihood of having primary SS has been observed [43]. In support of the role of nutrition in SS, it has been shown that a lifelong gluten-free diet reduced the infiltration of monocytes/macrophages and T cells in salivary glands in diabetic mice developing sialadenitis [44]. Although still partial, this evidence sustains the multifaceted relation between immunopathological features of different autoimmune diseases and the capacity of specific dietary compounds in modulating disease onset as well as expression in SS.

As shown in Table 4, randomized clinical trials are still scarce in SS. The deficiency of vitamin B6 in patients with SS and its association with altered T helper cells and IL-2 production has prompted some researchers to investigate the role of pyridoxine in IL-2 release from cultured T lymphocytes collected from SS and healthy subjects randomized to receive the vitamin or the placebo. Although no effect was evidenced at the end of the three-month study, the authors did not exclude the influence of pyridoxine at a different molecular level [45].
Table 4. Randomized clinical trials on dietary intervention in Sjögren’s syndrome.

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tovar, 2002 [45]</td>
<td>Randomized, double blind, placebo controlled, crossover</td>
<td>Primary SS</td>
<td>20c + 14 healthy subjects</td>
<td>Pyridoxine 25 mg Placebo</td>
<td>3 months</td>
<td>IL-2 production in cultured lymphocytes</td>
<td>No difference between patients and healthy controls</td>
<td></td>
</tr>
<tr>
<td>Singh, 2010 [46]</td>
<td>Randomized, double masked, placebo controlled</td>
<td>Primary or secondary SS</td>
<td>61 (38c + 23c)</td>
<td>n-3 fatty acids (450 mg EPA, 300 mg DHA) + VitE Wheat germ oil</td>
<td>3 months</td>
<td>Saliva secretion, inflammatory markers</td>
<td>Increased salivary production with no difference between groups</td>
<td></td>
</tr>
</tbody>
</table>

Another RCT investigated the role of n-3 fatty acids in improving SS symptoms, especially dry mouth and salivary secretion. Conducted in 61 patients over a three-month period, the study showed that n-3 supplementation may improve salivary secretion, but the effect was similar to that obtained with wheat germ oil also containing a certain amount of the n-3 precursor linolenic acid [46].

3.5. Systemic Sclerosis (SSc)

Very few studies have been conducted on the effect of dietary supplementation in SSc. Most of these were performed on the comorbidities related to this autoimmune condition. Gastrointestinal symptoms are a frequent comorbidity in SSc and represent one of the most important risk factors for malnutrition in the disease. It was shown that the combined assessment of nutritional parameters, including pre-albumin and disease activity, improves the evaluation of mortality risk in SSc [47]. Consequently, nutritional assessment and, more importantly, dietary intervention should be pursued in these patients.

Recently, SSc was found to be associated with altered intestinal microbiota, but the relationship between dysbiosis and the pathogenesis and features of the disease are not completely clear [48]. Starting from the above observations, probiotics have been tested for their known modulatory action on microbiota and immune system in patients with SSc and gastrointestinal involvement (Table 5). An 8-week RCT showed that probiotic supplementation did not have any effect in reducing gastrointestinal symptoms but led to a decrease in Th17 cell levels, indicating an immunomodulatory capacity of the probiotic strains used in the study [49]. Significant findings have been evidenced in another trial, where the efficacy of probiotics in systemic sclerosis-associated gastrointestinal disease was positively evaluated regarding gastrointestinal reflux. The SSc clinical outcomes were not, however, evaluated in that study [50].

A more dated study addressed the effect of fish oil supplementation on Raynaud’s phenomenon secondary to SSc [51]. While the ingestion of fish oil improved tolerance to cold exposure and delayed the onset of vasospasm in patients with the primary disorder, it showed no effect on Raynaud’s phenomenon secondary to SSc.
### Table 5. Randomized clinical trials on dietary intervention in systemic sclerosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Main Inclusion Criteria</th>
<th>Cases (N.)</th>
<th>Intervention/Daily</th>
<th>Control</th>
<th>Intervention Period</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marighela, 2019 [49]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Moderate-severe SSc with GI involvement</td>
<td>73 (37c + 36p)</td>
<td>Prebiotics (L. paracasei, L. rhamnosus, L. acidophilus, B. lactis) 10^9 CFU/each</td>
<td>Placebo 2 months</td>
<td>GI symptoms, Th levels</td>
<td>No benefit on GI symptoms, reduction in Th17 cell levels</td>
<td></td>
</tr>
<tr>
<td>Low, 2019 [50]</td>
<td>Randomized, double blind, placebo controlled parallel group</td>
<td>Primary or secondary SS</td>
<td>40 (19c + 21p)</td>
<td>Prebiotics (multistrain supplement *) 1800 billion CFU</td>
<td>Placebo 2 months</td>
<td>GI symptoms, HAQ-DI</td>
<td>Improvement in GI reflux</td>
<td></td>
</tr>
<tr>
<td>DiGiacomo, 1989 [51]</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Primary or secondary Raynaud’s phenomenon</td>
<td>32 (16c + 16p)</td>
<td>Fish oil 3.96 g EPA, 2.64 g DHA</td>
<td>Olive oil 4 months</td>
<td>Onset of vasoospasm, digital systolic pressure, and arterial flow</td>
<td>Improvement in primary but not secondary Raynaud</td>
<td></td>
</tr>
</tbody>
</table>

CFU: colony-forming units; GI: gastrointestinal; HAQ-DI: Health Assessment Questionnaire Disability Index; Th: T helper. * L. paracasei DSM 24733; L. plantarum DSM 24730; L. acidophilus DSM 24735; and L. delbrueckii subsp. bulgaricus DSM 24734; B. longum DSM 24736; B. breve DSM 24732; and B. infantis DSM 24737; S. thermophilus DSM 24731.

### 4. Discussion

Connective tissue diseases encompass different complex disorders with an autoimmune background and a broad variety of clinical manifestations. Besides the involvement of connective tissue, these diseases share features, such as fatigue, and comorbidities mainly affecting the cardiovascular system.

Although anti-inflammatory dietary habits have long been recognized to influence these comorbidities, it is not clear how much diet or dietary supplementation might affect the clinical course of patients with connective tissue diseases.

As outlined in this review, most of the RCTs were conducted in SLE and often show varying results. Certainly, some benefit on disease activity indices were obtained using n-3 fatty acids and VitD, even if the different dosages and intervention period make it difficult to compare the various studies [9–11].

Fatigue, which is a common feature in connective tissue disorders, seems to be affected by healthy nutritional intervention and VitD [14,20]. Creatine supplementation showed some benefit on muscle performance and metabolism in IIM [35,38] while interesting results for Behçet disease were achieved with a butyrate-enriched diet [42].

Promising data regarding both renal function and disease activity in SLE were obtained for the use of polyphenols. Although the evidence is still limited, the wide range of favorable effects of these compounds already been demonstrated in many chronic diseases support their use as adjuvant therapy in SLE patients.

Finally, although most dietary supplements do not require a medical prescription and supervision, it is always recommended that a doctor be consulted for specific nutritional indications and contraindications.

### 5. Conclusions

The results from RCTs conducted on connective tissue diseases are still too limited to draw firm conclusions on the clinical benefit of dietary intervention under these conditions. Notwithstanding, the results are encouraging and deserve to be explored upon in depth and with larger cohorts of patients.

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