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Focus on Dietary Pattern: Would this be the Answer to the Rising Prevalence of Autoimmune Diseases? Results of a Systematic Review

Eduarda Luckemeyer Banolas[1], Mikaela Rita Schroeder Zeni[1], Catarina Vellinho Busnello[1], Mariana Graeff Bins Ely[1], Marilia Oberto da Silva Gobbo[1], Janine Alessi[2,3*]

Abstract

Considering the different mechanisms by which lifestyle habits may influence autoimmunity, dietary patterns emerge as potential mediators of this effect. This study aimed to synthesize the results of experimental studies evaluating the effect of different dietary interventions on the clinical presentation and inflammatory markers of autoimmune diseases with joint involvement, generating important insights for dietary recommendations to patients and future studies to come. A systematic literature review was performed (MEDLINE, Embase and Cochrane Library), using a prespecified search strategy. Inclusion criteria were randomized clinical trials with adults diagnosed with autoimmune diseases with joint involvement, and evaluated any dietary intervention compared to usual diet or western diet. The studies included were fully evaluated for data extraction and, subsequently, were combined based on the type of diet used in the intervention. A total of 12 studies were included in this review. Clinical trials with a Mediterranean diet demonstrated improvement in health-related quality of life and suppression of the activity of the disease in patients with rheumatoid arthritis. Vegan or lactovegetarian diets have shown to promote changes in fatty acid patterns in patients with rheumatoid arthritis and improve their symptoms, especially with a strict diet (vegan, rich in lactobacilli, uncooked). Vegan diet and raw diet had a positive influence on symptoms in patients with rheumatoid arthritis and with fibromyalgia. Finally, fasting was associated with decrease in IL-6 serum levels in patients with rheumatologic diseases, and both fasting and ketogenic diets increase serum dehydroepiandrosterone concentrations.

Keywords: Rheumatoid arthritis; Mediterranean diet; Lactovegetarian diet; Vegan diet; Raw diet; Inflammatory diseases

Introduction

Autoimmune diseases are the focus of raising attention as their prevalence increases and new pathophysiological mechanisms have been progressively better understood. These diseases, which are characterized by failures of the immune system to discern between foreign and host antigens, may result in different clinical manifestations, making patients vulnerable to the appearance of serious symptoms that may compromise, in addition to their health, their quality of life [1,2]. Increasingly prevalent, it is estimated that autoimmune diseases affect around 3 to 5% of the population [3,4]. Nevertheless, it is still unknown whether the increase in the number of new cases is related to changes in recognition and diagnosis, or if they are true temporal changes in incidence [5]. Changes in the epidemiology of autoimmune diseases have

Affiliation:

[1]School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Brazil

[2]Post-graduate Program in Medical Science, Pontifícia Universidade Católica do Rio Grande do Sul, Brazil

[3]Endocrinology Division, Hospital São Lucas – Pontifícia Universidade Católica do Rio Grande do Sul, Brazil

***Corresponding author:**
Janine Alessi, Pontifícia Universidade Católica do Rio Grande do Sul, Brazil, Avenida Ipiranga, 6690, Partenon, 90619-900 - Porto Alegre, RS, Brazil

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traditionally been associated with changes in habits in the general population, although the causal relationship is not yet clear. Some possible explanations have been suggested. First, the "Western lifestyle", which is marked by smoking, high caloric and alcohol intake, brings a variety of risk factors for the development of autoimmune diseases [6]. Second, the hypothesis that changes in hygiene habits, also called the "hygienic hypothesis", would be responsible for a reduction in the incidence of infections and recognition of antigens and, therefore, would be associated with a higher incidence of immune-mediated diseases [7]. Finally, changes in the gut microbiota are potential collaborators in this process, considering that they are associated with numerous mechanisms of dysregulation of the immune system [8]. Considering the different mechanisms by which lifestyle habits may influence autoimmunity, dietary patterns emerge as potential mediators of this effect. Dietary characteristics directly affect the incidence of risk factors for autoimmune diseases, such as obesity and diet induced proinflammatory state [9]. Furthermore, current evidence suggests that, from dietary changes, it is possible to interfere in the quality of the gut microbiota, preventing the unregulated activation of inflammatory and immunological pathways [10]. The effects of dietary patterns on the incidence and natural history of patients with autoimmune diseases are not fully understood and are traditionally studied in a fragmented way, and there is a lack of studies synthesizing the quality evidence available so far. The aim of this study was to synthesize the results of experimental studies evaluating the effect of different dietary interventions on the clinical presentation and inflammatory markers of autoimmune diseases with joint involvement, generating important insights for dietary recommendations to patients and future studies to come.

Methods

Search strategy

The systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11] and was registered at the International Prospective Register of Systematic Reviews (PROSPERO) platform (No CRD42021251725). We searched MEDLINE (1946 to Jun, 2021), Embase (1974 to Jun, 2021) and Cochrane Library (1992 to Jun, 2021), using a search strategy with the terms 'rheumatoid arthritis' OR 'lupus erythematosus systemic' OR 'sjögren disease' OR 'ankylosing spondylitis' OR 'psoriatic arthritis' OR 'reactive arthritis' OR 'rheumatic') AND ('diet' OR 'dietary' OR 'food' OR 'fasting') AND 'randomized controlled trial', including spelling variations. This search strategy was predetermined, and was not limited by language. Non-English language papers were translated using Google Translate (Google, Mountain View, CA, USA). Two independent researchers (ELB and MZ) did the different stages of the systematic review and another researcher (JA) acted as the third reviewer in cases where the two main researchers could not reach an agreement. We screened search results first by title and abstract and then by full text. We eliminated abstracts in the initial screen if they were not experimental and did not investigate the dietary pattern effect in autoimmune diseases. We also excluded studies that did not report original data. Abstracts meeting these criteria were eligible for full-text review. Afterwards, the studies that met the eligibility criteria were selected for data extraction.

Selection criteria and data extraction

To be included in the systematic review, we selected studies which were randomized clinical trials, included patients aged 18 years or older diagnosed with autoimmune diseases with joint damage (such as rheumatoid arthritis, lupus erythematosus systemic, seronegative spondyloarthropathies or Sjogren disease), and evaluated some dietary intervention *vs* usual diet or western diet. Studies involving patients diagnosed with diabetes mellitus type 1 or 2, celiac disease, Crohn's Disease, ulcerative colitis, pregnant women and patients with cancer, will be excluded.

A second team (ELB, MZ, MGBE, MG and CVB) was responsible for data extraction. An electronic data abstraction form was used to record patient and study characteristics, including main author, year, sample size, inclusion and exclusion criteria, intervention comparisons and outcomes. To assess the quality of studies, we used a revised version of the Cochrane Collaboration-endorsed risk-of-bias tool for randomized trials (RoB 2) [12].

Data analysis

According to the initial design, the studies included in the systematic review were fully evaluated for data extraction. We combined studies based on the type of diet used in the intervention and on the base-disease used as inclusion criteria in the original study. However, considering the small number of works published on the subject, it was not possible to gather sufficient meta-analyzable data. Thus, the results were presented descriptively throughout the manuscript, according to the type of diet used in the intervention group.

Results and Discussion

Mediterranean Diet

The Mediterranean diet has been widely studied and reported in the scientific world as a promising diet in the prevention of systemic inflammatory processes, given the longer life expectancy and lower incidence of certain comorbidities in countries that culturally adopt this diet. As rheumatoid arthritis is a pathology that essentially involves the activation of numerous inflammatory mechanisms, it is hypothesized that a Mediterranean diet could contribute to the reduction of disease activity and the quality of life of patients with rheumatoid arthritis. García-Morales JM

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et al., conducted a randomized clinical trial with 144 female patients with rheumatoid arthritis in Mexico City [13]. These participants had low disease activity (functional class I-III) and were using conventional disease-modifying antirheumatic drugs (DMARDs). The study aimed to evaluate the effect of diet and exercise on the quality of life of these individuals (HRQoL) after 6 months of intervention, defined by the change in the global score of the 36-item Short Form Health Survey (SF-36 score). The study found that, in the Mediterranean diet + dynamic exercise program (PED) group, the physical function scores and the global score increased significantly, demonstrating a 15-point increase in this score ($p = 0.01$). Furthermore, in the Mediterranean diet + PED group, the physical activity, vitality, mental health and social function scores improved significantly [13]. In conclusion, the García-Morales study demonstrated that a combined intervention, including a Mediterranean diet and dynamic exercise program, improved health-related quality of life in patients with rheumatoid arthritis. The Mediterranean diet intervention alone showed improvement in several domains of the SF-36 score, such as physical function, body pain, global score, physical and mental components, but without significant differences compared to the other groups [13]. Similarly, Sköldstam L. *et al*., sought to establish whether a Mediterranean diet based on Cretan particularities (rich in fruits, vegetables, cereals, vegetables, fish, olive oil and moderate wine consumption) could have a disease activity-suppressing effect in patients with rheumatoid arthritis compared to a usual Western diet [14]. For this study, 51 patients from Sweden, were randomized to receive a Mediterranean diet *vs* control group for 3 months. A total of four outcomes were assessed: (1) Disease activity (DAS28); (2) physical function [Health Assessment Questionnaire (HAQ)]; (3) health-related quality of life [Short Form-36 Health Survey (SF-36)]; (4) Daily dose use of non steroidal inflammatory drugs (NSAIDs) (14). The Sköldstam L study found that, at the end of the 12 weeks of the trial, DAS28 showed a reduction, with a drop of 0.56 ($p<0.001$), HAQ decreased by 0.15 ($p=0.020$) and the SF36 score increased in two domains. Only the use of NSAIDs remained unchanged. Moreover, while patients in the control group maintained constant weight and plasma cholesterol during the study, individuals in group Mediterranean diet lost 3 kilograms ($p<0.001$) and also had a decrease in plasma cholesterol after 3 weeks ($p<0.001$), which remained after 6 weeks ($p<0.001$) and 12 weeks ($p=0.008$). Considering these results, this randomized clinical trial demonstrated that the Crete mediterranean diet possibly suppress the activity of rheumatoid arthritis and health-related quality of life parameters [14].

Diet without animal protein and/or with strictly raw food

It is speculated that a vegetarian diet could have positive results in alleviating the symptoms of patients with rheumatologic diseases. One of the theories that might explain the association proposed is the alteration of the intestinal microbiota [15]. Choosing foods rich in lactobacilli and fiber, without the presence of animal products or refined foods, the intestinal flora tends to reconstitute itself and it could contribute to the regression of inflammatory activity [15]. In addition, fruits and vegetables are known to contain significant amounts of both vitamin C and vitamin E, and certain vegetables also contain carotenoids and flavonoids [16]. These compounds have antioxidant action. Moreover, arachidonic acid is a precursor of inflammatory activity, which is produced from the endogenous conversion of linoleic acid. In this sense, knowing that vegan diets contain more linoleic acid, some studies proposes that these diets might decrease the level of pro-inflammatory molecules in the body [16]. Haugen MA *et al*. perfomed a clinical trial including 44 participants with rheumatoid arthritis, aiming to analyze the impact of a vegetarian diet for 1 year on disease activity [16]. The outcomes of the study were plasma fatty acid levels, concentration of lipid peroxidation products measured as reaction to thiobarbituric acid substances (TBARS), number of swollen joints, Stanford Index Health Assessment Questionnaire (SIHAQ), pain level on visual scale, and patient global assessment. The study found that participants who followed a vegan diet showed an important reduction in dihomo-y-linolenic acid and arachidonic acid ($P < 0.0001$ and $P < 0.01$), but with an increase after the introduction of a lactovegetarian diet. On the other hand, eicosapentaenoic acid decreases both after a vegan and lactovegetarian diet ($P < 0.0001$ and $P < 0.01$). The TBARS concentration showed an important reduction in the diet group when compared to the control group ($p=0.03$). Despite the association found, authors state that the improvement in disease symptoms cannot be explained solely by this change in fatty acid levels [16]. Another study, conducted by Nenonen MT *et al*., compared the effect of a vegan raw diet rich in lactobacilli with an omnivorous diet (usual in the control group) in patients diagnosed with rheumatoid arthritis chronic and active [17]. Overall, 43 participants were included in the study, with a follow up of 3 months. The main outcomes assessed were disease activity (DAS28), gastrointestinal symptoms (visual scale 0-10), C-reactive protein, number of swollen joints, number of painful joints, pain level on visual scale, SIHAQ, and erythrocyte sedimentation rate. This study found a subjective improvement in rheumatoid arthritis symptoms in the intervention group ($P=0.03$), with a worsening when returning to an omnivorous diet ($P<0.01$). Most of the control group did not notice any difference in disease. There was no difference in the disease activity parameters. Therefore, the study concluded that patients with active rheumatoid arthritis may improve their symptoms with a strict diet (vegan, rich in lactobacilli, uncooked). However, the study did not show

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significant results in the objective parameters of disease activity, such as C-reactive protein, erythrocyte sedimentation rate and number of sore joints [17]. Hanninen KK *et al.* also evaluated health parameters and consumption of a raw vegan diet [living food (LF)], in comparison with an omnivorous diet [18]. In this study, individuals with fibromyalgia (n=33) and with rheumatoid arthritis (n=42) were randomly divided between LF and omnivorous diet (control). In this study, subjective symptoms were assessed through standardized questionnaires, rheumatoid arthritis activity through the relative activity index (RAI) and biochemical parameters, serum carotenoids, daily urinary lignans and compounds. Furthermore, the assessment of daily changes, such as feelings of effectiveness, energy, mood, tiredness and number of hours slept [18]. Regarding biochemical parameters, the Hanninen KK study found a significant increase in serum vitamin C levels, proportion of vitamin E cholesterol and carotenoids (such as beta and alpha carotenes, lycopene and lutein). Moreover, the study observed that individuals who consumed raw vegan foods showed a significant improvement in subjective symptoms, and this outcome worsened when they returned to their omnivorous diet. Finally, an improvement in the symptoms of patients with fibromyalgia was evidenced when using the LF diet, with positive results in relation to joint stiffness (p=0.001), pain (by visual analogue scale) - (p=0.003) and health in general [18]. Hare DC *et al*. also conducted a clinical trial with patients with chronic rheumatism to assess which cases would respond to a specific diet [19]. A total of 12 patients with muscular rheumatism, osteoarthritis or rheumatoid arthritis were included, being submitted to a raw food diet. During the Hare DC study, 8 patients noted a subjective clinical improvement at the end of 1-4 weeks. This improvement was mainly due to the decrease in pain, swelling and stiffness, which is also noticeable in cinematographic recordings. There was no relief from joint pain resulting from bone disease. The blood count remained unchanged with the diet [19].

Low cholesterol diet

Epidemiological studies indicate that the mortality rate from atherosclerosis in patients with systemic lupus erythematosus is 9 times higher than in healthy patients [20]. Furthermore, in general, 53% of patients with systemic lupus erythematosus have 3 or more risk factors for developing cardiovascular disease, such as hypertension, obesity and dyslipidemia. Thus, prevention strategies, such as a diet with low cholesterol levels, emerges as a possible intervention factor in the management of systemic lupus erythematosus [20]. In view of this knowledge, Shah M, *et al*. performed a randomized clinical trial with 17 patients with systemic lupus erythematosus and low density lipoprotein (LDL) cholesterol level ≥ 100 mg /dl (20). This study aimed to determine the cholesterol-lowering effect of a 12 weeks diet on lipid and lipoprotein levels, body weight, nutrient intake and quality of life in these patients. The Shah M study found that, at 6 and 12 weeks of follow up, there was a greater reduction in the total cholesterol (TC), VLDL, and triglycerides (TG) in the diet group. The TC:HDL ratio increased at 6 weeks and decreased at 12 weeks in the intervention group and decreased at 6 and 12 weeks in the control group. Only for high density lipoprotein (HDL) there was a significant treatment interaction effect for time (p=0.004). However, after repeated measures analysis of variance within the intervention group, there was a significant drop in TC at 6 and 12 weeks, LDL at 6 weeks and body weight at 12 weeks (p = 0.01 to 0.0002) . Regarding quality of life, there was a reported increase of 15-17% in the intervention group and a reduction of 4-6% in the control group. The treatment-by-time interaction effect was significant (p=0.005) [20]. Therefore, this study concluded that a diet program with a reduction in cholesterol levels was quite effective in changing the diet and quality of life of patients with systemic lupus erythematosus [20].

Fasting and ketogenesis

Evidence indicates that adrenal androgens (AA) seem to be related to the pathophysiology of rheumatoid arthritis, since decreased plasma levels of AA, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) have been observed in women with premenopausal onset of rheumatoid arthritis [21]. In this sense, it is noteworthy that DHEAS has an inverse relationship with the serum levels of interleukin 6 (IL-6), which plays an important role in the development of inflammatory conditions [21]. One of the mechanisms that increases the concentration of DHEAS in serum is fasting. In view of this knowledge, a clinical trial, performed by Fraser DA *et al*., sought to investigate how fasting affects the serum levels of IL-6 and DHEAS in patients with rheumatoid arthritis [21]. For this study, 10 patients adhered to a 7-day fast. Furthermore, as a comparison, the ketogenic diet was used, whose effect promotes adaptations in the body similar to those that occur during fasting. Clinical, hormonal and laboratory parameters were analyzed on the first, seventh and twenty-first day of the study.

The Fraser DA study found that, on day 7 of fasting, the serum levels of IL-6 had a reduction of 37% ($p<0.05$), being lower than the initial and final (day 21) values, and there were changes significant in erythrocyte sedimentation rate (ESR) ($p<0.01$), C-reactive protein ($p<0.05$) and sensitive joint count ($p<0.05$). On either fasting or ketogenic diet, serum DHEAS levels increased around 34% ($p<0.05$) on day 7. This study concluded that only fasting decreases serum IL-6 levels, while both interventions (fasting and ketogenic diet) increase serum DHEAS concentrations [21].

Other dietary interventions

A study conducted by Podas T *et al.* in the United Kingdom compared the effect of prednisolone administration and adherence to an experimental diet in the management

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of patients with acute rheumatoid arthritis [22]. Patients underwent the intervention for 2 weeks, during which time the diet included na "elemental liquid diet E028" and contained 86 Kcal and 2.5 g of protein for every 100 ml of solution administered. In this study, the use of an elemental diet was shown to be as effective as the use of 15 mg/day of prednisolone in improving clinical parameters of rheumatoid arthritis, except for joint edema. This study points out that dietary interventions may be beneficial in the treatment of rheumatologic diseases [22]. In another study, performed by Beri D *et al.*, a total of 27 patients with rheumatoid arthritis who had never received any DMARDs were included and submitted to 5 steps of diets including new types of foods. The outcomes were laboratory parameters, morning stiffness duration, joint pain scale, joint index and global assessment of patients [23]. After the introduction of an isocaloric diet (consisting of fruits, vegetables, sugar and refined oil), 58.8% of participants showed a clinical improvement, ranging from 25 to 54% improvement in erythrocyte sedimentation rate compared to their baseline. When was introduced vegetables in the diet, 41% of participants showed clinical and erythrocyte sedimentation rate improvement of approximately 45%. With the introduction of wheat and derivatives, 6 patients deteriorated clinically. The introduction of non-vegetarian proteins, was accompanied by clinical worsening in the 2 patients [23]. The results of the Beri D study showed that a high proportion of patients improved on dietary manipulations, and that there was marked individual variation in response to the elimination of different dietary items. The study also highlighted the practical difficulty involved in instituting dietary treatment as a major mode of treatment in rheumatoid arthritis as the follow up was difficult and the dropout rate was high. Finally, Panush RS *et al*. conducted a randomized clinical trial with 30 individuals (with rheumatoid arthritis, in which they evaluated the influence of an experimental diet on clinical, laboratory, immunological and radiological aspects of the disease [24]. The diet consisted in a reduction in the consumption of meat (except fish and fowl) and the absence of consumption of fruits, herbs, spices, dairy products, alcoholic beverages, aditives. After 10 weeks, this study found that 5 participants from the experimental diet group and 6 from the placebo diet showed improvements in aspects of their disease, not showing a significant difference in outcomes when comparing the two groups. Thus, it was concluded that the intervention of an exclusion of certain types of foods, in this study, did not show a benefit in patients with rheumatoid arthritis [24].

Limitations

This systematic review has some limitations. First, the small number of randomized clinical trials on each dietary pattern included made it impossible to perform a meta-analysis of the data. Second, the studies carried out to date have included a small number of participants, and possibly compromised the power of the individual analyses performed. Third, a large number of clinical trials were conducted and published in the 1990s and lack recent studies carried out under current socio-environmental conditions. Fourth, the associations found between clinical, laboratory and behavioral parameters and dietary styles are not necessarily causal, and more complex studies in the pathophysiology of rheumatologic diseases are needed to understand the interrelationships of these findings in all their dimensions. Finally, it is not possible to differentiate what is an effect directly associated with a specific dietary pattern and what is the result of the reduction of some specific micro or macronutrient, which needs more specific studies for its evaluation.

Conclusion

This systematic review summarized the results of randomized clinical trials published to date on the impact of dietary patterns on clinical symptoms, laboratory changes, and psychosocial aspects of patients with autoimmune diseases with joint involvement. Among the diets assessed, studies with a Mediterranean diet demonstrated improvement in health-related quality of life and suppression of the activity of the disease in patients with rheumatoid arthritis. Vegan or lactovegetarian diets have shown to promote changes in fatty acid patterns in patients with rheumatoid arthritis and improve their symptoms, especially with a strict diet (vegan, rich in lactobacilli, uncooked). Vegan diet and raw diet had a positive influence on symptoms in patients with rheumatoid arthritis and with fibromyalgia. Finally, fasting was associated with decrease in IL-6 serum levels in patients with rheumatologic diseases, and both fasting and ketogenic diets increase serum dehydroepiandrosterone concentrations. The results of this study fill a gap in current knowledge about the impact of diet on autoimmune diseases and constitute the basis for further studies about the potential benefits of dietary patterns in the clinical history of these diseases. Thus, it is possible that dietary patterns are a complementary strategy, in addition to the traditional treatment, for the rising prevalence of autoimmune diseases.

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ELB is the guarantor of this study and, as such, has full access to all the data and takes responsibility for the integrity and accuracy of the data.

Authors' Contributions

ELB: Conceptualization, Methodology, Data curation, Writing- Original draft preparation. MZ: Conceptualization, Methodology, Data curation, Writing- Original draft preparation. CVB: Methodology, Writing- Original draft preparation. MGBE: Methodology, Writing- Original draft preparation. MOSG: Methodology, Writing- Original draft preparation. J.A: Conceptualization, Supervision, Writing-Reviewing and Editing.

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Consent for publication

All authors have reviewed the final version of the manuscript and agree with the publication of the results presented.

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Ethics approval and consent to participate

The study was registered on the PROSPERO platform before study procedures began and based on guidelines for reporting systematic reviews. The consent form does not apply.

Availability of data and materials

The data collected for the study will be available upon justified request to the email address of the main researcher and with a signed data access agreement.

Conflict of interest disclosure

No potential conflict of interest was reported by the authors.

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SUPPLEMENTARY FILES

Supplemental Table 1: Description of clinical trials included in the systematic review.

First author, Year	Inclusion criteria	Intervention group	Outcomes of the study	No	Main results
Sköldstam L, 2003	-Rheumatoid arthritis (the 1987 American College of Rheumatology criteria); -disease duration ≥2 years; -clinically stable and under adequate control;	Mediterranean diet	-DAS28; - Health Assessment Questionnaire; - Physical function index; - SF36 Health Survey; -health survey of quality of life; -daily consumption of NSAID;	56	- MD group showed a decrease in DAS28 of 0.56 (p<0.001), in HAQ of 0.15 (p=0.020), and in two dimensions of the SF-36 Health Survey: an increase in "vitality" of 11.3 (p=0.018) and a decrease in "compared with one year earlier" of 0.6 (p=0.016).
Margaretha AH, 1994	- Rheumatoid arthritis (American Rheumatism Association criteria)	Vegetarian diet (vegano or lactovegetarian diet)	-Fatty acids in the plasma; -No of swollen joints, - HAQ; - Pain score on a visual analogue scale - Patients global assessment - ESR	27	-The concentrations of the fatty acids were significantly reduced after 3.5 months with a vegan diet (P < 0,0001 and e P < 0,01 respectively), but the concentration increased to baseline values with a lactovegetarian diet. -The alterations of the fatty acid profiles in plasma phospholipids as a result of a vegan and a lactovegetarian diet were extensive in patients with rheumatoid arthritis.
Nenonen MT, 1998	-Chronic and active rheumatoid arthritis (American Rheumatism Association criteria criteria); - Steinbrocker's functional class II–III;	Uncooked vegan diet, rich in lactobacilli	-Subjective experiences; - Gastrointestinal functions on the 0–10 visual scale - CRP and ESR - Changes in the disease activity: - No number of swollen and tender joints, number of tender joints; - HAQ - DAS28	43	-Subjective relief of the symptoms of the rheumatoid arthritis was achieved with a radical dietary manipulation (uncooked extreme, lactobacilli rich vegan diet, 'living food') P<0.03, but a return to an omnivorous diet aggravated symptoms. - Decrease in the disease activity with lactobacilli-rich and chlorophyll-rich drinks, increase in fibre intake, and no need for gold, methotrexate or steroid medication (R2=0.48, P=0.02). - No significant effects on other disease markers;
García-Morales JM, 2020	- Women older than 18 years, with a confirmed diagnosis of rheumatoid arthritis (American College of Rheumatology 2010 classification criteria); - Functional class I–III;	Mediterranean diet; DEP; DEP + MD	-DAS28 -Perception of pain: visual analog scale (0–10). -CRP and ESR; -HAQ -SF 36 Health Survey	144	-The combination of MD + DEP improved the quality of life in rheumatoid arthritis patients with low disease activity receiving DMARDs -TheMD intervention alone exerted improvements in several dimensions of the SF-36 score (i.e., physical function, body pain, global score, physical and mental components), but without reaching a significant difference compared with the other groups. -Patients who were included in the MD + DEP and DEP groups showed 15 points of increase in health-related quality of life global punctuation (p = 0.01).

Citation: Eduarda Luckemeyer Banolas,Mikaela Zeni, Catarina Vellinho Busnello, Mariana Graeff Bins Ely, Marilia Oberto da Silva Gobbo, Janine Alessi. Focus on Dietary Pattern: Would this be the Answer to the Rising Prevalence of Autoimmune Diseases? Results of a Systematic Review. Journal of Food Science and Nutrition Research. 6 (2023): 40-50.

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Hanninen O, 2000	- Fibromyalgic subjects, - Rheumatoid arthritis	Living food diet Omnivorous;	-Subjective symptoms. -Activity of rheumatoid arthritis. -Joint stiffnes at morning and pain at rest in fibromyalgic subjects. -Serum carotenoids, -Antioxidant and lignan levels, -Daily urinary lignans and related compounds.	115	LF users, compared to omnivorous controls, showed high amounts of quercetin, kaempherol and myricetin in their diet; serum vitamin C levels and vitamin E cholesterol ratio had a statistically significant increase; significantly higher amounts of various carotenoids; the serum levels of beta and alfa carotenes as well as those of lycopene and lutein were several folds higher in long term users of the living food. The rheumatoid patients reported significant subjective alleviation of their symptoms. In the fibromyalgic subjects, their joint stiffness at morning (P=0.001), their pain at rest (P=0.003) as well as their general health improved.
Hare DC, 1936	-Rheumatoid arthritis; Or - Osteoarthritis which have led to deformity of the joints and osteophytic outgrowths;	Raw diet	- Perception of pain and symptoms; - ESR and heamoglobin; - Weight records.	12	Eight patients felt better within from one to four weeks, of the other four patients, two improved up to five or six weeks and then had relapses, and two found no relief at all. The improvement noted in each case was a decrease of pain, stiffness and swelling. The conditions which were not relieved were the pain arising in joints with active disease of bone and the symptoms due to toxemia. All the patients lost weight during the first week on the diet.
Panush RS, 1983	Rheumatoid arthritis stage I-III, who were on stable medication regimens;	Experimental diet (little meat except fish and occasional fowl, no fruit, no herbs or spices, no dairy products, no alcoholic beverages, no aditives)	-Patients' and examiner's global assessments; - Duration of morning stiffness, joint count, swelling of joints, bilateral grip streght, time to walk 50 feet; -Hand films, complete blood count and differential count; - Urinalysis, - Dhemistry profile; - Rheumatoid factor, -Antinuclear antibody test, C3, C4, and ESR	30	There were no clinically important differences among rheumatologic, laboratory, immunologic, radiologic, or nutritional findings between patients on experimental and placebo diets. This study failed to provide evidence of objective overall clinical benefit of this diet as followed by a group of patients with longstanding, progressive, active rheumatoid arthritis.
Shah M, 2002	- Systemic lupus erythematosus for at least 6 months - have an LDL cholesterol level ≥ 100 mg/dl	National Cholesterol Education Program Step 2 diet: 30% or less calories from fat (7% from saturated fat, 13% from monounsaturated fat, and 10% from polyunsaturated fat), and < 200 mg of cholesterol per day;	-TC, LDL, HDL, TG; - TC:HDL ratio; - Body weight; - nutrient intakes (percentage total calories from fat, SFA, MUFA and PUFA); - QOL;	17	- -The treatment by time interaction was significant for all the dietary variables (p = 0.0003 to 0.02). QOL was reported to improve by 15–17% in the diet group and decrease by 4–6% in the control group, and the treatment by time interaction was significant (p = 0.05). -The treatment by time interaction was significant for HDL cholesterol (p = 0.04). -A significant reduction was seen in the diet group for total cholesterol at 6 and 12 weeks, LDL and HDL cholesterol at 6 weeks, and body weight at 12 weeks (p = 0.0002 to 0.01).

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Beri D, 1988	Rheumatoid arthritis who had not received any DMARDs drugs previously	Diet I: isocaloric diet consisting of fruit, vegetables, sugar, and refined oil. Diet II: diet I + all pulses. Diet IIIA: diet I + wheat and wheat products. Diet IIIB: diet I + rice and rice products. Additions of milk and milk products (diet IV) and non-vegetarian food (diet V).	- Morning stiffness - Joint pain score - Articular index: Ritchie's method. - Patients' global assessment; - Hemoglobin, total leucocyte estimation; -ESR -Latex fixation titre;	27	- 71% of the participants showed significant clinical improvement (responsive), and four didn't show benefit from the first and second diets. - Responsive patients and diet I: patients showed a mean percentage improvement in the clinical variables varying from 25% to 54%, comparing with their baseline levels, and the improvement in their ESR was 33%. - Responsive patients and diet II: it led to deterioration in the condition of three patients; one showed a rapid flare of symptoms. The resting two patients had aggravation of their disease, especially with one pulse. The other seven patients had clinical improvement and a mean percentage improvement of 45% in their ESR. - Responsive patients and diet III (A and B): it led to deterioration in the status of the remaining six patients; four of them worsened with the cereals and two with rice and rice products. Only four patients joined diet IV; two deteriorated, and two improved. Two patients entered diet V, and both worsened. - Five patients (9%) presented weight loss (there was no difference between good and poor responders' weight loss).
Abou-Raya A, 2014	Adults with a body max index ≥ 30, who satisfied the classification of psoriatic arthritis criteria.	Diet only, exercise only, and diet plus exercise groups	- PASI; - DAS28; - HAQ; - DBI - Fatigue numeric rating scale. - Glucose, lipid profile, ESR, CRP; - TNF alpha, IL-6, IL-17; - BMI - ACR20 - systemic inflammation markers, -PGA	55	- In the intervention groups, the mean reduction in body weight was 15.0% (12 months); in the control group it was 2% (p=0.001). - Diet plus exercise group showed a significant improvement in ACR20, PASI, DAS28, BDI, fatigue, PGA. Further, there was significant reductions in serum levels of IL-6, TNF-alpha, CRP and IL-17 compared to controls. - Exercise group showed significant reductions in systemic inflammatory markers and significant improvement in ACR20 and response. - Linear correlation between mean percent of body weight loss and PASI score reduction (r=0.587; p=0.002). - There was evidence that lifestyle modification supports traditional pharmacological approach in the treatment of obese PsA patient.

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Fraser DA, 2000	Rheumatoid arthritis (American Colege of Reumatology criteria)	**Fasting:** 7 day supervised sub-total fast <50 g carbohydrate/day, total energy < 865 kJ (205kcal)/day. **Ketogenic diet:** 7 days providing between 2000 and 2500kcal (8.4-10.5 MJ) per day, including 0.8g protein/kg body weight per day and < 40g carbohydrate/ day.	- IL-6; - DHEAS and cortisol; - Kketone body - b-HB	23	- Significant changes at day 7 of fasting: decrease in the concentration of serum IL-6, improvements in ESR, CRP and tender joint count. - No changes in disease activity variables during ketogenic diet study at any time-point. - DHEAS concentrations were increased (by 34%) at day 7 comparing to baseline after fasting and ketogenic diet. - Cortisol increased significantly at day 7 of the ketogenic diet. - Significant increases in b-HB at day 7 (in both groups). - Statistically significant correlations: *IL-6 and tender joint count at baseline ($\tau = 0.57$, $p < 0.03$) *IL-6 and CRP at day 7 ($\tau = 0.55$, $p < 0.03$) in the fasting patients * IL-6 and ESR ($\tau = 0.47$, $p < 0.05$), CRP ($\tau = 0.47$, $p < 0.05$) and tender joint count ($\tau = 0.55$, $p < 0.02$) at day 21 in the ketogenic diet patients. * IL-6 concentrations correlated with cortisol at baseline ($\tau = 0.63$, $p < 0.02$) and day 21 in the fasting patients ($\tau = 0.54$, $p < 0.03$). * DHEAS and ESR at day 21 ($\tau = 0.49$, $p < 0.05$) in the fasting study.

No: number; MD: Mediterranean diet; DMARDS: The disease modifying antirheumatic drugs;NSAID: non-steroidal anti-inflammatory drug; DAS 28: Disease Activity Score Calculator for Rheumatoid Arthritis; SF36 Health Survey: Short Form 36-item Health Survey; HAQ: Stanford Health Assessment Questionnaire Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DEP: dynamic exercise program; LF: living food diet; TC: Total Cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglyceride; SFA: saturated fat; MUFA: monounsaturated fat; PUFA polyunsaturated fat; QOL: Quality of life; PASI: psoriasis area and severity index; BDI: Beck's Depression Inventory; TNF-alpha: tumour necrosis factor alpha; IL-6: interleukin- 6; IL-17: interleukin-17; ACR20: American College of Rheumatology 20 criteria; PGA: patient global assessment; PsA: psoriatic arthritis criteria. DHEAS: dehydroepiandrosterone; B-HB:beta-hydroxybutyrate;