Clinical Nutrition 40 (2021) 661–689

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Narrative Review

Ideal food pyramid for patients with rheumatoid arthritis: A narrative review

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ARTICLE INFO

Article history:
Received 2 July 2020
Accepted 21 August 2020

Keywords:
Rheumatoid arthritis
Nutrients
Food
Inflammation
Body composition
Antioxidants

SUMMARY

Emerging literature suggests that diet plays an important modulatory role in rheumatoid arthritis (RA) because diet is an environmental factor that affects inflammation, antigen presentation, antioxidant defense mechanisms and gut microbiota. Patients with RA frequently ask their doctors about which diets to follow, and even in the absence of advice from their physicians, many patients are undertaking various dietary interventions.

Given this background, the aim of this review is to evaluate the evidence to date regarding the ideal dietary approach for management of RA in order to reduce the counteracting inflammation, and to construct a food pyramid for patients with RA. The pyramid shows that carbohydrates should be consumed every day (3 portions of whole grains, preferably gluten free), together with fruits and vegetables (5 portions; among which fruit, berries and citrus fruit are to be preferred, and among the vegetables, green leafy ones.), light yogurt (125 ml), skim milk (200 ml), 1 glass (125 ml) of wine and extra virgin olive oil; weekly, fish (3 portions), white meat (3 portions), legumes (2 portions) eggs (2 portions), seasoned cheeses (2 portions), and red or processed meats (once a week). At the top of the pyramid, there are two pennants: one green means that subjects with RA need some personalized supplementation (vitamin D and omega 3) and one red means that there are some foods that are banned (salt and sugar). The food pyramid allows patients to easily figure out what to eat.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease, characterized by synovial hyperplasia, production of autoantibodies, destruction of cartilage and bone, and malformation and destruction of multiple joints [1]. The pathogenesis of RA is complicated and involves both genetic and external factors [2]. Similar to other autoimmune diseases, RA involves an aberrant pathway of T cell activation in both the initial and progression phases of the disease [3]. However, it has become clear that pathogenesis of RA cannot simply be explained in terms of a classical antigen-driven expansion of effector T cells, but that disease progression involves a more complex autoimmune response. It is largely accepted that RA is closely associated with CD4+ T effector cells (both Th-1, 2, 17) which can be detected in RA synovial joints [4].

Moreover, patients with RA have a premature immune aging phenotype including accumulation of CD4+ CD28− T cells, telomeric shortening in hematopoietic stem cells, proliferation defects of naïve CD4 T cells, premature loss of naïve CD4 T cells telomeres, loss of telomerase in T cells, and impaired DNA damage repair due to ATM insufficiency [5].

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https://doi.org/10.1016/j.clnu.2020.08.020

In the development of novel therapeutics for autoimmune disorders, targeting T cell metabolism by dietary interventions provides an alternative way to control T cell fate and function [6].

In fact, the metabolic and nutritional status of the organism as a whole also has a critical role in regulating immunity. One of the most fundamental cellular requirements is the ability to access sufficient and appropriate nutrients to support essential cellular functions. As cells are stimulated to grow, proliferate, or die, their metabolic requirements change, and it is important that cellular metabolism matches these demands. Although immune cells spend a significant amount of time in the blood, where nutrients are generally abundant, the manner in which these cells uptake and utilize nutrients remains of fundamental importance. The regulation of nutrient uptake and utilization is critically important for the control of immune cell number and function. Furthermore, the pathways that control immune cell function and metabolism are intimately linked. These associations and newly-found coordination between the immune system and classical metabolic tissues now provide new opportunities to impact immune function in both healthy and diseased states [7]. So, dietary and lifestyle factors contribute to RA [8].

Moreover, there are significant implications of diet in RA comorbidities [9,10].

In fact, RA comorbidities (obesity, diabetes, insulin resistance) can benefit from a correct diet.

RA is significantly associated with subclinical atherosclerosis and the risk of cardiovascular disease [11], with a 50% higher risk of cardiovascular mortality in RA patients than in the general population [12].

Obesity represents an important and growing comorbidity also for RA in the onset phase and is a determining factor for insulin resistance, and for circulating proinflammatory cytokines [13]. Furthermore, the metabolic syndrome is associated with a high risk of RA [14] and the fact that is already present in early diagnosed RA [15] underlines the its role as a risk factor and further underlines the importance of diet and optimal glycemic and lipid control.

There is evidence of a strong association between RA and diabetes, although not likely mediated by inflammation [16].

A double relationship between diabetes and RA has been reported: a high prevalence of type 2 diabetes in patients with RA and RA as a risk factor for developing type 2 diabetes. Ruscitti and colleagues studied in a Italian cohort of RA patients, the prevalence of type 2 diabetes and impaired fasting glucose (IFG), and compared it with age and gender controls, showing that RA was significantly associated with abnormal metabolism of the glucose both in relation to traditional CV risk factors (eg metabolic syndrome) and in relation to specific characteristics of RA such as CRP levels, duration of the disease and extent of joint damage [17].

Regrettably, patients with RA have unsatisfactory dietary quality, and poorer diet than healthy controls [18,19]. Poor dietary quality is associated with longer lasting morning stiffness [18] and more functional disabilities [19].

Salminen et al. reported that 33–75% patients believe that food plays an important role in their symptom severity and approximately 50% will have tried dietary changes in an attempt to improve their symptoms [20]. So, patients with RA clearly understand that dietary intake impacts the disease [21].

Given this background, the aim of this review is to evaluate the evidence to date regarding the ideal dietary approach for the management of RA in order to reduce oxidative stress, counteract inflammation and alteration in immune system, and to construct a food pyramid for patients with RA.

2. Materials and methods

This narrative review was performed following the steps of Egger et al. [22]: 1. Configuration of a working group: three operators skilled in clinical nutrition (one acting as a methodological operator and two participating as clinical operators). 2. Formulation of the revision question on the basis of considerations made in the abstract: “the state of the art on management of dietary approach in RA.” 3. Identification of relevant studies: a research strategy was planned on PubMed [Public MedLine run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bethesda (USA)] as follows: a) Definition of the keywords (RA, foods, inflammation, oxidative stress, nutrients, malnutrition), allowing the definition of the interest field of the documents to be searched, grouped in inverted commas (“…”) and used separately or in combination; b) use of: the Boolean (a data type with only two possible values: true or false) AND operator, that allows the establishments of logical relations among concepts; c) Research modalities: advanced search; d) Limits: time limits: papers published in the last 20 years; humans; languages: English; e) Manual search performed by senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on management of inflammation and oxidative stress by dietary approach in RA published in journals qualified in the Index Medicus. 4. The analysis was carried out in the form of a narrative review of the reports. We evaluated, as suitable for the narrative review, the studies of any design, which considered the relevance of diet, foods, or nutrients for RA management.

The strength of evidence of the single study, of each food and supplementation [23,24] has been reported in Table 1.

The keywords considered and the kinds of studies chosen for specific foods are as below.

3. Results

3.1. Energy intake, body mass index (BMI), body composition, physical activity and rheumatoid arthritis

This research was conducted based on the keywords: “Rheumatoid Arthritis” AND “Energy intake” AND “Body Mass Index” AND “Body composition” AND “Physical Activity”; 28 articles were sourced: 6 case–control studies, 4 observational study, 2 cohort studies, 1 position paper, 4 narrative reviews, 2 meta-analysis, 1 systematic review, 2 systematic reviews & meta-analysis, 2 guidelines, 1 1ongitudinal study, 1 cross-sectional study, 1 in vitro study and 1 comment on an article.

3.2. Fruits and vegetables

This research was conducted based on the keywords: “Rheumatoid Arthritis” AND “Fruits” AND “Vegetables”. 16 articles were sourced: 3 case–control studies, 3 cohort studies, 3 observational studies, 2 cross-sectional studies, 1 narrative review, 1 book chapter, 1 randomized controlled trial, 1 clinical trial and 1 animal study.

3.3. Carbohydrates

This research was conducted based on the keywords: “Rheumatoid Arthritis” AND “Carbohydrates”. 12 articles were sourced: 3 cohort studies, 2 cross-sectional studies, 2 narrative review, 1 systematic review, 1 meta-analysis, 2 case-reports and 1 case-control-study.

Table 1
Strenght of evidence.

Author, year	Type of study	Strenght of evidence	Conclusions
Energy intake, BMI, body composition, physical activity			
Strenght of evidence: MODERATE			
Versini et al., 2014 [25]	Narrative review	Low	Obesity appears to be a major environmental factor contributing to the onset and progression of autoimmune diseases
Fantuzzi et al., 2005 [26]	Narrative review	Low	A cross-talk between lymphocytes and adipocytes can lead to immune regulation
Qin et al., 2015 [27]	Systematic review & meta-analysis	High	An increase in body mass index can contribute to a higher risk for rheumatoid arthritis development
Feng et al., 2016 [28]	Meta-analysis	High	There is evidence that obesity is a risk factor for developing of RA. Furthermore, the positive association between BMI and RA risk may be stronger among women than men
Feng et al., 2019 [29]	Meta-analysis	High	An increased BMI is associated with an increased risk for rheumatoid arthritis
Bae et al., 2019 [30]	Observational study	Moderate	BMI may be causally associated with an increased risk of RA
Dar et al., 2018 [31]	Case-control study	Moderate	Obesity is significantly associated with RA
Naranjo et al., 2008 [32]	Cohort study	Moderate	Prolonged use of treatments such as methotrexate for RA appears to be associated with a reduced risk of CV disease
Armstrong et al., 2006 [33]	Comment on an article	Low	RA ought to be treated as an additional risk factor when calculating 10-yr risk of a CHD-related event
Nikiphorou et al., 2017 [10]	Cohort study	Moderate	Obesity has increased at RA presentation over 25 years
Henchoz et al., 2012 [34]	Case-control study	Moderate	Daily energy expenditure is significantly lower in RA patients compared with matched controls
Bustos Rivera-Bahena et al., 2016 [35]	Observational study	Moderate	Circulating Leptin, Resistin, IL-6 and IL-17 levels positively correlate with RA clinical activity in a manner independent of the subject's BMI
Xibillé-Friedmann et al., 2010 [36]	Observational study	Moderate	Leptin levels change in direct relation to disease progression and in close relation to changes in Interleukin-17
Olama et al., 2012 [37]	Case-control study	Moderate	In RA, there is a significant increase in circulating leptin levels and synovial/serum leptin ratio compared to non-RA controls
Ngeuleu et al., 2017 [38]	Observational study	Moderate	RA patients with sarcopenia had an increased cardiometabolic risk which is added to high cardiovascular risk already associated with the disease. 39,8% of subjects with RA suffers with sarcopenia
Ceyhan Doğan et al., 2015 [40]	Case-control study	Moderate	SMI is decreased and sarcopenia risk was elevated in patients with RA
Giles et al., 2008 [41]	Case-control study	Moderate	Abnormal body composition phenotypes are overrepresented in patients with RA, particularly in those in the normal weight BMI range
Reina et al., 2019 [43]	Case-control study	Moderate	In RA patients, regarding SMI, BMI showed a high specificity to detect sarcopenia (94% of the patients with low BMI had sarcopenia) but low sensitivity (47% of the patients with normal BMI or overweight had sarcopenia)
Sanada et al., 2010 [44]	Cross-sectional study	Moderate	There is a relationship between sarcopenia and high cardiovascular risk in the general population; RA increases the risk of cardiovascular mortality
Gallagher et al., 2000 [45]	Longitudinal study	Moderate	RA increases the risk of cardiovascular (CV) mortality up to 50% compared to the general population
Meune et al., 2009 [46]	Systematic review & meta-analysis	High	RA is associated with a 60% increase in risk of CV death compared with general population
Gabriel, 2008 [47]	Narrative review	Moderate	An increased inflammation associated with RA appears to contribute substantially to the increased CV mortality
Deutz et al., 2014 [48]	Guidelines	High	It is estimated that the percentage of sarcopenic RA patients ranges from 25 to 43%: for the prevention of sarcopenia, a protein quota of 1–1.2 g/kg/body weight is recommended
Bauer et al., 2013 [49]	Position paper	High	It is estimated that the percentage of sarcopenic RA patients ranges from 25 to 43%: for the prevention of sarcopenia, a protein quota of 1–1.2 g/kg/body weight is recommended
Varma et al., 2007 [50]	In vitro study	Low	Overweight and obesity are associated with a worsening of the symptomatology due to the inflammation, especially in RA patients
Russell et al., 1999 [51]	Guidelines	High	For the patient with RA, therefore, a personalized diet with an adequate amount of protein and controlled in energy (25–30 kcal per kg of body weight at most) is essential, like elderly patients
Cramp et al., 2013 [52]	Systematic review	High	The physical activity and psychosocial interventions provide benefit in relation to self-reported fatigue in adults with RA
Dreher et al., 2019 [53]	Narrative review	Low	The increase of physical activity, regular physical training and the adaptation of diet should be a basic additive component of the treatment of inflammatory rheumatic diseases
Fruits and vegetables			
Strenght of evidence: MODERATE			
Linos et al., 1999 [54]	Case-control study	Moderate	Consumption of both cooked vegetables and olive oil is inversely and independently associated with risk of RA
Hu et al., 2017 [55]	Cohort study	Moderate	A healthier diet is associated with a reduced risk of RA occurring at 55 years of age or younger, particularly seropositive RA
Veronese et al., 2016 [56]	Observational study	Moderate	An higher adherence to the Mediterranean diet is associated with better Quality Of Life and decreased pain, disability, and depressive symptoms
Oliviero et al., 2015 [57]	Narrative review	Low	Arthritis patients may potentially benefit from adherence to the Mediterranean diet in view of their increased cardiovascular risk
Han et al., 2017 [58]	Cross-sectional study	Moderate	Intake of whole fruits and vegetables may help improve pain, especially knee pain, in older adults
Hagfors et al., 2003 [59]	Randomized controlled study	High	The plasma levels of vitamin C, retinol and uric acid are inversely correlated to variables related to RA disease activity
Tedeschi et al., 2017 [21]	Cohort study	Moderate	Nearly one-quarter of RA subjects with longstanding disease has reported that ah healthy diet had an effect on their RA symptoms
Basu et al., 2018 [60]	Book chapter	Low	Blueberries, raspberries and strawberries, as well as pomegranates are among the commonly available fruits that may offer some protection against arthritis
Zhong et al., 2015 [61]	Clinical trial	High	A combination therapy of blueberry and etanercept can reduce the severity of Juvenile idiopathic arthritis (JIA) and should be developed as a new method for JIA therapy

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Table 1 (*continued*)

Author, year	Type of study	Strenght of evidence	Conclusions
He et al., 2016 [62]	Cross sectional study	Moderate	Several dietary items may have protective effects on RA development, such a citrus fruits
Kawaguchi et al., 2011 [63]	Animal study	Low	Oal administration of naringin (Citrus flavanone) might be effective for treating human patients with RA
Oben et al., 2009 [64]	Case-control study	Moderate	NP 06-1 (a combination of two botanical extracts: *Phellodendron amurense* bark and *Citrus sinensis* pee) has beneficial effects on symptoms of osteoarthritis
Gough et al., 1964 [65]	Cohort study	Moderate	There is a significant increase in the incidence of anaemia and of biochemical evidence of folic-acid deficiency in the patients with RA
Stone et al., 1997 [66]	Observational study	Moderate	Patients with RA should receive dietary education or supplementation to bring their intake of calcium, folic acid, vitamin E, zinc, and selenium up to the recommended dietary intake (RDI). Patients on methotrexate had a significantly reduced intake of folic acid as a percentage of RDI compared with those on other therapies
Cehran et al., 2003 [67]	Cohort study	Moderate	Intake of certain antioxidant micronutrients, particularly beta-cryptoxanthin and supplemental zinc, and possibly diets high in fruits and cruciferous vegetables, may be protective against the development of RA
Tanner et al., 1990 [68]	Observational study	Moderate	A subset of RA patients might have food sensitivity as a component of clinical activity
Carbohydrates			
Strenght of evidence: MODERATE			
Zhernakova et al., 2011 [69]	Meta-analysis	High	Some gene loci established in either celiac disease (CD) or RA are associated with the other autoimmune disease
Voight et al., 2012 [70]	Narrative review	Low	Autoimmune and inflammatory diseases share an underlying genetic basis in common
Lerner et al., 2015 [71]	Narrative review	Low	The intestinal mucosa have all the necessary tools to produce neo-epitopes, breaking tolerance to self-antigens, by citrullination (PAD) and crosslinking (tTg, neo-epitope tTg, mTg) initiating autoimmunogenic dysregulation and autoantibody generation in RA
Collin et al., 1994 [72]	Case-control study	Moderate	RA can present with several other concomitant disorders such as CD
Lodhi et al., 2018 [73]	Case report	Low	RA can present with several other concomitant disorders such as CD
Warjri et al., 2015 [74]	Case report	Low	Gut-derived antigens of CD may have a role in the pathogenesis of other autoimmune disorders including RA
He et al., 2016 [62]	Cross sectional study	Moderate	High intakes of carbohydrates (e.g., potatoes) might be associated with increased RA risks
Hu et al., 2017 [55]	Cohort study	Moderate	A healthier diet, with fruits and whole grains, is associated with a reduced risk of RA occurring at 55 years of age or younger, particularly seropositive RA
Hu et al., 2014 [75]	Cohort study	Moderate	Regular consumption of sugar-sweetened soda, but not diet soda, is associated with increased risk of seropositive RA in women
De Christopher et al., 2016 [76]	Cross sectional study	Moderate	Beverages with excess free fructose intake are significantly associated with arthritis in US adults aged 20–30 years
Barber et al., 2015 [77]	Systematic Review	High	Regular screening for CV disease risk factors is an important part of care in patients with RA
Lindhardsen et al., 2011 [78]	Cohort study	Moderate	RA is associated with the same risk of myocardial infarction as diabetes mellitus
Extra-virgin olive oil			
Strenght of evidence: MODERATE			
Linos et al., 1999 [54]	Case-control study	Moderate	Consumption of both cooked vegetables and olive oil is inversely and independently associated with risk of RA
Hu et al., 2017 [55]	Cohort study	Moderate	A healthier diet, with extra virgin olive oil, is associated with a reduced risk of RA occurring at 55 years of age or younger, particularly seropositive RA
Rosell et al., 2009 [79]	Case-control study	Moderate	An high intake of olive oil, together with alcohol, fish and cooked vegetables confer a protective effect against the development of RA
Santangelo et al., 2017 [80]	Narrative review	Low	EVOO and its polyphenols can improve diseases symptoms
Casas et al., 2018 [81]	Narrative review	Low	Olive polyphenols are potential candidates to combat chronic inflammatory states
Grimstvedt et al., 2010 [19]	Case-control study	Moderate	Living with RA is associated with significantly lower dietary quality
Sköldstam et al., 2003 [82]	Case-control study	Moderate	Patients with RA, by adjusting to a Mediterranean diet, obtain a reduction in inflammatory activity, an increase in physical function, and improved vitality
McKellar et al., 2007 [83]	Case-control study	Moderate	A Mediterranean-type diet rich in fish, fruit and vegetables shows a significant benefit in patients with RA for patient global assessment at 6 months, pain score at 3 and 6 months, early morning stiffness at 6 months and Health Assessment Questionnaire score at 3 months
Nocella et al., 2017 [85]	Narrative review	Low	EVOO as anti-inflammatory, antioxidant and vasodilatory nutrient that may contribute to lower the atherosclerotic burden
McEntegart et al., 2001 [86]	Case-control study	Moderate	RA patients have a significantly higher prevalence of angina pectoris and diastolic pressure
Forsyth et al., 2018 [84]	Systematic review	High	There are beneficial effects of the Mediterranean diet in reducing pain and increasing physical function in people living with RA
Seeds			
Strenght of evidence: LOW			
Ivanov et al., 2011 [87]	Poster presentation	Low	Flaxseeds have nutritional characteristics and are rich source of ω-3 fatty acid: α-linolenic acid (ALA), PUFA, soluble and insoluble fibers, phytoestrogenic lignans, proteins and an array of antioxidants
Singh et al., 2011 [88]	Narrative review	Low	Flaxseeds have nutritional characteristics and are rich source of ω-3 fatty acid: α-linolenic acid (ALA), PUFA, soluble and insoluble fibers, phytoestrogenic lignans, proteins and an array of antioxidants
Oomah et al., 2001 [89]	Narrative review	Low	Flaxseed oil inhibits interleukin and TNF-α production, even in supplementation of ALA for 3 months in patients with RA has shown no beneficial effects
Touré et al., 2010 [90]	Narrative review	Low	Flaxseeds have nutritional characteristics and are rich source of ω-3 fatty acid: α-linolenic acid (ALA), PUFA, soluble and insoluble fibers, phytoestrogenic lignans, proteins and an array of antioxidants
Bhatty, 1995 [91]	Narrative review	Low	Flaxseed is a multicomponent system with bio-active plant substances
Heimbach, 2009 [92]	Report	Low	Flaxseed is a multicomponent system with bio-active plant substances

Table 1 (*continued*)

Author, year	Type of study	Strenght of evidence	Conclusions
Oomah et al., 1993 [93]	Narrative review	Low	Whole flaxseed, flaxseed meals and isolated proteins are rich sources of glutamic acid/ glutamine, arginine, branched-chain amino acids (valine and leucine) and aromatic amino acid (tyrosine and phenylalanine)
Morris et al., 2003 [94]	Narrative review	Low	The proportion of soluble to insoluble fiber in flaxseeds varies between 20:80 and 40:60
Mazza et al., 1995 [95]	Book chapter	Low	The proportion of soluble to insoluble fiber in flaxseeds varies between 20:80 and 40:60
Vaisey-Genser et al., 2003 [96]	Book chapter	Low	The major insoluble fiber fraction in flaxseeds consists of cellulose and lignin, and the soluble fiber fractions are the mucilage gums
Mazza et al., 1989 [97]	Narrative review	Low	The major insoluble fiber fraction in flaxseeds consists of cellulose and lignin, and the soluble fiber fractions are the mucilage gums
Mazur et al., 1996 [98]	In vitro study	Low	Flaxseeds contain up to 800 times more lignans than other plant foods
Westcott et al., 1998 [99]	Narrative review	Low	Flaxseeds contain up to 800 times more lignans than other plant foods
Adlercreutz, 2007 [100]	Narrative review	Low	Lignan –and flaxseed- rich diets may be beneficial, particularly if consumed for life
Bozan et al., 2008 [101]	In vitro study	Low	Seeds provide an healthy oil profile
U.S. Department of Agriculture, 2010 [102]	Guidelines	High	Flaxseed contains approximately 23 g ALA per 100 g and thus, the recommended dietary amounts can be obtained by consuming about 9 g of flaxseed per day
Pellizzon et al., 2007 [103]	Animal study	Low	Flaxseed reduces plasma and hepatic cholesterol in human apolipoprotein B-100 transgenic mice
Cloughley et al., 1997 [104]	In vitro study	Low	The organoleptic quality of ω-3 enriched eggs was acceptable without off-flavors when hens were fed 5% (or less) flaxseed oil in diet
Parker et al., 2018 [105]	Narrative review	Low	Chia seeds have some beneficial effects on healthy outcomes, but they are too limited or preliminary to make any substantive conclusions
Mohamed et al., 2020 [106]	Animal study	Low	Chia seeds oil and mucilage, more promisingly the oil, attenuate TNF-α and the swelling of the paw, improve lipid profile, and decrease the oxidative stress both in obese and non-obese arthritic rats
Jin et al., 2012 [107]	Observational study	Moderate	The ingestion of 25 g/day milled chia seeds for 7 weeks by postmenopausal women results in significant increases in plasma ALA and EPA but not DPA and DHA
Nuts			
Strenght of evidence: MODERATE			
Perna et al., 2016 [108]	Systematic review & meta-analysis	High	Hazelnut-enriched diet is associated with a decrease of LDL and total cholesterol, while HDL cholesterol, triglycerides and BMI remain substantially unchanged
Wu et al., 2012 [109]	Narrative review	Low	Certain dietary components, including polyphenols and other types of compounds, found in various dietary factors including nuts, can play an important role in attenuating and mitigating chronic pro-inflammatory processes associated with chronic disease
Chehade et al., 2019 [110]	Narrative review	Low	Lifestyle modification programme should be considered as the basis of any treatment, (i.e., pharmacological treatment), in patients with RA
U.S. Department of Health and Human Services, 2015 [111]	Guidelines	High	Nuts must be eaten daily, in the portion equal to 30 g
Spices			
Strenght of evidence: LOW			
Islam et al., 2016 [112]	Narrative review	Low	Some of phytochemicals compounds have shown good promise for development into novel agents for treating RA, diabetes mellitus, and CVD by targeting oxidative stress and inflammation
Ramadan et al., 2013 [113]	Animal study	Low	Ginger-turmeric rhizomes mixture may be effective against RA severity and complications as shown in adjuvant-induced arthritis rats
Ramadan et al., 2011 [114]	Animal study	Low	Turmeric has the anti-inflammatory/anti-oxidant activity, and may has beneficial effects against RA onset/progression as shown in adjuvant-induced arthritis rats
Rathi et al., 2013 [115]	Animal study	Low	Cinnamon bark has demonstrated prominent action in animal models of inflammation and arthritis and therefore can be considered as a potential anti-rheumatic agent
Deng et al., 2016 [116]	Narrative review	Low	The specific block of capsaicin pathway has been proved to have potential beneficial effects on various of autoimmune conditions like RA
Frias et al., 2016 [117]	Narrative review	Low	An injectable highly purified form of capsaicin is currently under investigation for treatment of neurogenic pain
Lee et al., 2013 [118]	Narrative review	Low	The therapeutic benefits of curcumin for neurodegenerative diseases appear multifactorial via regulation of transcription factors, cytokines and enzymes associated with (Nuclear factor kappa beta) NFKB activity
Kocaadam et al., 2017 [119]	Narrative review	Low	Curcumin has antioxidant and anti-inflammatory effects on many outcomes, like autoimmune diseases
Oliviero et al., 2018 [120]	Narrative review	Low	Polyphenolic compounds are able to inhibit the expression and the release of a number of pro-inflammatory mediators and proteolytic enzymes, the activity of different transcriptional factors and the production of reactive oxygen species (in vitro studies)
Park et al., 2007 [121]	In vitro study	Low	Curcumin might help identify a new therapeutic pathway against hyperplasia of the synovial fibroblasts in RA
Kloesh et al., 2013 [122]	In vitro study	Low	Curcumin represents strong anti-inflammatory properties and induces apoptosis in fibroblast-like synoviocytes
Funk et al., 2006 [123]	Narrative review	Low	3 major curcuminoids are responsible for antiarthritic effects
Zheng et al., 2015 [124]	Animal study	Low	Curcumin is an effective antiarthritic agent
Di Silvestro et al., 2012 [125]	Case-control study	Moderate	A low dose of a curcumin-lipid preparation can produce a variety of potentially health promoting effects in healthy middle aged people
Yang et al., 2019 [126]	Narrative review	Low	Curcumin supplementation emerges as an effective therapeutic agent with minimal-to-no side effects, which can be added in conjunction to current standard of care
Amalraj et al., 2017 [127]	Randomized Case-control study	High	A novel curcumin in a turmeric matrix acts as an analgesic and anti-inflammatory agent for the management of RA at a dose as low as 250 mg twice daily
Rahman et al., 2008 [128]	Book Chapter	Low	Curcumin allows the negative regulation of proinflammatory interleukins

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Table 1 (*continued*)

Author, year	Type of study	Strenght of evidence	Conclusions
Jurenka, 2009 [129]	Narrative review	Low	Curcumin may have potential as a therapeutic agent in diseases such as arthritis
Bisht et al., 2010 [130]	Narrative review	Low	Curcumin allows the negative regulation of proinflammatory interleukins
Moon et al., 2010 [131]	Animal study	Low	Curcumin can effectively suppress inflammatory response by inhibiting pro-inflammatory mediators and regulating humoral and cellular immune responses
Huang et al., 2013 [132]	Animal study	Low	Suppression of B cell-activating factor belonging to the TNF family production may be a novel mechanism by which curcumin improves RA
Chandran et al., 2012 [133]	Randomized controlled trial	High	Curcumin assumption (500 mg/die) shows the highest percentage of improvement in Disease Activity Score and American College of Rheumatology criteria
Daily et al., 2016 [134]	Systematic review & meta-analysis	High	Turmeric extract (about 1000 mg/day of curcumin) in the treatment of arthritis is effective
Joint FAO/WHO Committee on Food Additives [135]	Report	Low	An adequate daily intake value of curcumin is 0.3 mg per kg of body weight
European Food Safety Authority, 2014 [136]	Report	Low	An adequate daily intake value of curcumin is 0.3 mg per kg of body weight
Lao et al., 2006 [137]	Clinical trial	High	The tolerance of curcumin in high single oral doses appears to be excellent
Fan et al., 2013 [138]	Narrative review	Low	Adjuvant drug delivery system and structural modification have been demonstrated to have a potential effect to improve the bioavailability of curcumin
Aggarwal et al., 2009 [139]	Narrative review	Low	Curcumin has a potential role in the prevention and treatment of various proinflammatory chronic diseases
Mirzaei et al., 2017 [140]	Narrative review	Low	The efficacy and safety of curcumin phytosomes have been shown against several human diseases, osteoarthritis and inflammatory diseases
Bresciani et al., 2020 [141]	In vitro study	Low	Curcumin-based botanical extracts (demethoxycurcumin and bis-demethoxycurcumin) can be considered important sources of curcuminoids
Shen et al., 2012 [142]	Narrative review	Low	Dietary polyphenols benefit the management of inflammatory arthritis
Alcohol			
Strenght of evidence: MODERATE			
Källberg et al., 2009 [143]	Case-control study	Moderate	Alcohol may protect against RA
Di Giuseppe et al., 2012 [144]	Cohort study	Moderate	Moderate consumption of alcohol is associated with reduced risk of RA
Maxwell et al., 2010 [145]	Case-control study	Moderate	Alcohol consumption has an inverse and dose-related association with both risk and severity of RA
Lu et al., 2014 [146]	Prospective study	Moderate	There is a modest association between long-term moderate alcohol drinking and reduced risk of RA
Nissen et al., 2010 [147]	Cohort study	Moderate	There is a trend toward reduced radiographic progression of joint damage by RA in alcohol drinkers compared with nondrinkers, specifically in occasional and daily alcohol consumers
Bergman et al., 2013 [148]	Cohort study	Moderate	There is an association between alcohol consumption and both lower self-reported disease activity and higher health related quality of life in female, but not in male, RA patients
NHS_Choices, 2018 [149]	Report	Low	There is no risk of increasing transaminases if alcohol consumption equals 14 units of alcohol per week
Perrino et al., 2008 [150]	Randomized controlled trial	High	Intravenous ethanol administration has a concentration effect on pain tolerance but not on pain threshold
Szabo et al., 1996 [151]	In vitro study	Low	Intake of low to moderate amounts of alcohol over a long period of time (years) has been shown to decrease TNF-α, IL-1 and CRP levels
Dairy foods			
Strenght of evidence: MODERATE			
Dean et al., 2012 [152]	Narrative review	Low	Consumption of dairy foods has pro-inflammatory effects
Nestel et al., 2012 [153]	Randomized controlled trial	High	Single high-fat meals containing sequentially four different full-fat dairy foods did not increase eight circulating biomarkers related to inflammation or atherogenesis
Labonté et al., 2014 [154]	Randomized crossover study	High	A short-term consumption of a combination of low- and high-fat dairy products as part of a healthy diet has no adverse effects on inflammation
Lawrence, 2013 [155]	Narrative review	Low	Proteins, fats and calcium in milk are beneficial in inflammation
Li et al., 2016 [156]	Animal study	Low	The pathogenesis of RA correlates closely to increased egg- or milk-specific antibodies
Merlino et al., 2004 [157]	Cohort study	Moderate	Greater intake of vitamin D may be associated with a lower risk of RA in older women
Benito-Garcia et al., 2007 [158]	Cohort study	Moderate	There is a trend towards an inverse association between the consumption of dairy products and risk for RA
Sundström et al., 2019 [159]	Cohort study	Moderate	No associations are observed between dietary intake of meat and dairy products and the risk of RA development
Lu et al., 2014 [160]	Observational study	Moderate	A frequent milk consumption may be associated with reduced arthritis progression in women
He et al., 2016 [62]	Cross sectional study	Moderate	Several dietary items may have protective effects on RA development, such a dairy products
Gossec et al., 2006 [161]	Guidelines	High	Elimination diets, particularly those with low intakes of dairy products, should be discouraged in patients with early RA
Rozenberg et al., 2016 [162]	Narrative review	Low	The intake of up to 3 servings of dairy products per day appears to be safe and may confer a favourable benefit with regard to bone health
Fish			
Strenght of evidence: MODERATE			
Rosell et al., 2009 [79]	Case-control study	Moderate	An high intake of olive oil, together with alcohol, fish and cooked vegetables confer a protective effect against the development of RA
Tedeschi et al., 2018 [163]	Cross-sectional study	Moderate	An higher intake of fish may be associated with lower disease activity in RA patients
Pedersen et al., 2005 [164]	Cohort study	Moderate	An increase in intake of 30 g fat fish (>or = 8 g fat/100 g fish) per day is associated with 49% reduction in the risk of RA, whereas medium fat fish (3–7 g fat/100 g fish) is associated with significantly increased risk of RA
Venter et al., 2020 [165]	Narrative review	Low	The preventive role of fish regarding RA is due to omega 3, which is an immune-modulating dietary component
Sparks et al., 2019 [166]	Cohort study	Moderate	Fish intake attenuated the strong association of smoking for RA diagnosed $\leq$55 years of age
di Giuseppe et al., 2014 [167]	Meta-analysis	High	There is a non-statistically significant inverse association between fish consumption and RA

Table 1 (*continued*)

Author, year	Type of study	Strenght of evidence	Conclusions
Manor et al., 2018 [168]	Cohort study	Moderate	In fish there is a high content of molecule trimethylamine-N-oxide (TMAO), that promotes RA
Chan et al., 2019 [169]	Narrative review	Low	Consumption of about two servings of marine fish can raise the urinary excreted TMAO to millimolar levels. Microbial Dysbiosis and TMAO promote RA
Brusca et al., 2014 [170]	Narrative review	Low	Mucosal sites exposed to a high load of bacterial antigens–such as the periodontium, lung, and gut–may represent the initial site of autoimmune generation
Chung et al., 2005 [171]	Case-control study	Moderate	TMAO may alter the metabolism of the microbiota to reduce the effectiveness of the common DMARD methotrexate
Hagfors et al., 2005 [172]	Randomized controlled trial		A lower ratio of ω-6 to ω −3 fatty acids is observed in RA patients with a Mediterranean diet
Meat			
Strenght of evidence: MODERATE			
Benito-Garcia et al., 2007 [158]	Cohort study	Moderate	Red meat, poultry, and fish arent't associated with RA risk
Sundström et al., 2019 [159]	Cohort study	Moderate	No associations are observed between dietary intake of meat and dairy products and the risk of RA development.
He et al., 2016 [62]	Cross sectional study	Moderate	There are no significant differences in red meat intakes between RA patients and healthy controls
Pedersen et al., 2005 [164]	Cohort study	Moderate	No associations are found between risk of RA and intake of meat
Lahiri et al., 2014 [173]	Cohort study	Moderate	There is an association between meat consumption and risk of developing RA, but that it is the high consumption of meat that increases the risk
Philippou et al., 2018 [174]	Narrative review	Low	It's the Western-type diet, rich in energy intake, total and saturated fat, an unbalanced ratio of n-3 to n-6 fatty acids, high in refined carbohydrates and sugar and low in fiber and antioxidants, that might increase the risk of RA
D'Amelio et al., 2018 [175]	Narrative review	Low	Indole derivatives from meat act on intestinal mucous membranes, increase the development and maintenance of the mucous membranes but also of the immune cells residing in them
Frericks et al., 2007 [176]	In vitro study	Low	Indole derivatives are aryl hydrocarbon receptor (AhR) ligands, and activation of AhR in innate lymphoid cells subsequently promotes the production of Interleukin-22
Zelante et al., 2013 [177]	In vitro study	Low	Activation of AhR in innate lymphoid cells subsequently promotes the production of Interleukin-22
Postler et al., 2017 [178]	Narrative review	Low	The cells of the immune system depend critically on a diverse array of microbial metabolites for normal development and behavior
Legumes			
Strenght of evidence: MODERATE			
Sköldstam et al., 2003 [82]	Case-control study	Moderate	The patients with RA, by adjusting to a Mediterranean diet, obtain a reduction in inflammatory activity, an increase in physical function, and improved vitality
Philippou et al., 2018 [174]	Narrative review	Low	The Mediterranean diet (MD), rich in plant-based foods such as wholegrains, legumes, fruit, vegetables, extra-virgin olive oil and low in red meat consumption, might have the potential to reduce the risk of RA
He et al., 2016 [62]	Cross sectional study	Moderate	Several dietary items may have protective effects on RA development
U.S. Department of Health and Human Services, 2015 [111]	Guidelines	High	3 servings per week are the recommended amount
Eggs			
Strenght of evidence: MODERATE			
Andersen, 2015 [179]	Narrative review	Low	Bioactive egg components possess a variety of pro- and/or anti-inflammatory properties
U.S. Department of Health and Human Services, 2015 [111]	Guidelines	High	2 eggs/week, preferably soft boiled or boiled or omelet baked (never fried) are recommended
Coffee and tea			
Strenght of evidence: MODERATE			
Heliovaara et al., 2000 [180]	Cross sectional study	Moderate	Coffee consumption may be a risk factor for RA, possibly through mechanisms contributing to the production of rheumatoid factor
Mikuls et al., 2002 [181]	Cohort study	Moderate	Decaffeinated coffee intake is independently and positively associated with RA onset, while tea consumption shows an inverse association with disease onset
Karslon et al., 2003 [182]	Cohort study	Moderate	There is a little evidence of an association between coffee, decaffeinated coffee, or tea consumption and the risk of RA among women
Lee et al., 2014 [183]	Meta-analysis	High	There is a significant association between coffee consumption and seropositive RA risk but not seronegative RA risk
Cutolo et al., 2001 [184]	Narrative review	Low	The caffeine leads to a reduced efficacy of MTX through inhibitory effects on extracellular adenosine.
Tedeschi et al., 2017 [21]	Cohort study	Moderate	Nearly one-quarter of RA subjects with longstanding disease has reported that ah healthy diet had an effect on their RA symptoms
Nesher et al., 2003 [185]	Observational study	Moderate	In subjects use MTX, nobody reported that coffee or tea containing caffeine worsened RA
Benito-Garcia et al., 2006 [186]	Cohort study	Moderate	Caffeine intake among patients taking high doses of MTX for RA did not affect MTX efficacy and RA disease activity over time
ω-3 supplementation			
Strenght of evidence: HIGH			
Kremer et al., 1985 [187]	Case-control study	Moderate	Patients with RA with an experimental diet high in polyunsaturated fat and low in saturated fat, with a daily supplement (1.8 g) of EPA improve morning stiffness and number of tender joints
Kremer et al., 1987 [188]	Crossover study	Moderate	Fish-oil ingestion results in subjective alleviation of active RA and reduction in neutrophil leukotriene B4 production
Kremer, 2000 [189]	Narrative review	Low	It is recommended that patients consume dietary supplements containing 3−6 g ω-3 fatty acids daily for ≥ 12 wk
Van Der Tempel et al., 1990 [190]	Randomized crossover trial	High	The mean neutrophil leucotriene B4 production showed a reduction after 12 weeks of fish oil supplementation

(*continued on next page*)

Table 1 (*continued*)

Author, year	Type of study	Strenght of evidence	Conclusions
Nielsen et al., 1992 [191]	Randomized controlled trial	High	Dietary supplementation with ω −3 PUFA in patients with rheumatoid arthritis improved two out of six patient reported disease parameters (morning stiffness and joint tenderness)
Geusens et al., 1994 [192]	Randomized controlled trial	High	Daily supplementation with 2.6 gm of ω −3 results in significant clinical benefit and may reduce the need for concomitant antirheumatic medication
Remans et al., 2004 [193]	Randomized controlled trial	High	There is not superior clinical benefit of daily nutrient supplementation with EPA, GLA and micronutrients at the doses tested (1.4 g EPA - 0.211 g DHA - 0.5 g GLA)
Gioxari et al., 2018 [194]	Systematic review & meta-analysis	High	There are beneficial properties of ω-3 PUFA on RA disease activity
Lee et al., 2012 [195]	Meta-analysis	High	The use of ω-3 PUFAs at dosages >2.7 g/day for >3 months reduces DMARD consumption by RA patients
Vitamin D supplementation			
Strenght of evidence: MODERATE			
Adami et al., 2019 [196]	Narrative review	Low	Bone tissue is commonly involved in many rheumatic diseases, and osteoporosis represents the most frequent bone disease in rheumatic conditions
Islander et al., 2011 [197]	Narrative review	Low	An hormone replacement therapy (HRT) decreases disease activity, improves bone mineral density, and in addition, has an indication of a joint protective effect in postmenopausal women with RA. Also, the bone and cartilage turnover is reduced by HRT
Spector et al., 1993 [198]	Case-control study	Moderate	The rate of vertebral fracture in the women with RA is over twice that in the healthy subjects. There is also an increased risk of osteoporotic fractures at the spine and hip
Gough et al., 1994 [199]	Case-control study	Moderate	In patients with RA significant amounts of generalised skeletal bone are lost early in the disease and the loss is associated with disease activity
Baskan et al., 2007 [200]	Case-control study	Moderate	RA is a risk factor on its own for the development of osteoporosis and vertebral deformity and this risk increases by age, excess number of deformed joints and severe course of disease
Cooper et al., 1995 [201]	Case-control study	Moderate	Hip fracture risk is approximately doubled amongst patients with RA and among those taking steroids
Rossini et al., 2015 Clin Exp Rheumatol [202]	Case-control study	Moderate	In patients with RA, serum levels of Dickkopf-1 are significantly increased, correlate with PTH and are associated with increased risk of bone erosions and osteoporosis
Hippisley-Cox et al., 2009 [203]	Cohort study	Moderate	RA is an independent risk factor in fracture risk assessment
Rossini et al., 2015 Endocrine [204]	Narrative review	Low	The use of Bisphosphonates is recommended at the earliest by all major scientific societies in postmenopausal women and men ≥50 years at high risk of fracture receiving glucocorticoid therapy, as in RA
Rizzoli et al., 2013 [205]	Guidelines	High	Serum levels of 25-hydroxyvitamin D (25 (OH) D) < 50 nmol/L are associated with increased bone turnover, bone loss and mineralization defects resulting in increased fragility and fractures
Holickm 2007	Narrative review	Low	Vitamin D deficiency is implicated in the pathogenesis of several autoimmune conditions
Neve et al., 2014 [207]	In vitro study	Low	IL-1 α, IL-1β and IL-6 levels were reduced by 1,25$(OH)^2$D3 at higher concentrations in all cell populations
De Santis et al., 2015 [208]	Narrative review	Low	Vitamin D shows protective effects on intestinal permeability
Guerreiro et al., 2018 [209]	Narrative review	Low	High levels of *Prevotella copri* and similar species are present in microbiota of patients with RA. Vitamin D helps with protective effects on intestinal permeability
Merlino et al., 2004 [157]	Cohort study	Moderate	Greater intake of vitamin D may be associated with a lower risk of RA in older women
Kostoglou-Athanassiou et al., 2012 [210]	Cohort study	Moderate	Vitamin D deficiency is highly prevalent in patients with RA, and vitamin D deficiency may be linked to disease severity in RA
Costenbader et al., 2008 [211]	Cohort study	Moderate	Vitamin D intake is not associated with risk of systemic lupus erythematosus or RA in these large prospective cohorts of women.
Lee et al., 2016 [212]	Meta-analysis	High	Serum vitamin D level is significantly low in patients with RA, vitamin D deficiency is prevalent in RA patients compared to controls, and the vitamin D level correlates inversely with RA activity
Lin et al., 2016 [213]	Systematic review & meta-analysis	High	RA patients have lower vitamin D values than healthy controls. There is a negative association between serum vitamin D and RA disease activity
Franco et al., 2017 [214]	Systematic review & meta-analysis	High	Vitamin D supplementation reduces anti-dsDNA positivity on systemic lupus erythematosus and could possibly reduce RA recurrence
Wu et al., 2018 [215]	Systematic review & meta-analysis	High	A significantly lower 25(OH)D concentration is observed in patients with RA
Antioxidants supplementation			
Strenght of evidence: MODERATE			
Cehran et al., 2003 [67]	Cohort study	Moderate	Intake of certain antioxidant micronutrients, particularly beta-cryptoxanthin and supplemental Zn, and possibly diets high in fruits and cruciferous vegetables, may be protective against the development of RA
Costenbader et al., 2010 [216]	Cohort study	Moderate	Antioxidant intake is not associated with the risk of developing either RA or systemic lupus erythematosus
Comstock et al., 1997 [217]	Case-control study	Moderate	A low antioxidant status is a risk factor for RA
Heliövaara et al., 1994 [218]	Case-control study	Moderate	A low antioxidant level is a risk factor for RA
Pattison et al., 2004 [219]	Case-control study	Moderate	Patients which consume less fruit and vitamin C have an increased risk of developing inflammatory diseases
Jalili et al., 2014 [220]	Pre-post clinical trial	Moderate	Antioxidants may improve disease activity significantly, but it don't affect the number of painful and swollen joints and increased erythrocyte antioxidant levels
Yu et al., 2016 [221]	Meta-analysis	High	There is a significant association between low serum Se concentration with RA
Sahebari et al., 2016 [222]	Case-control study	Moderate	Low serum concentrations of Zn and Se, and high serum Cu concentrations may be associated with the presence of RA or be a consequence of this condition. Of the trace elements investigated, only serum Cu is positively correlated with disease activity
Baker et al., 2009 [223]	Narrative review	Low	An altered Fe homoeostasis may represent a purposeful response to inflammation
Fraenkel, 2017 [224]	Narrative review	Low	The proinflammatory cytokine, interleukin-6, the Fe regulatory hormone, hepcidin, and the Fe exporter, ferroportin, interact to cause Fe sequestration in the setting of inflammation
Weiss et al., 2013 [225]	Narrative review	Low	Anaemia in systemic rheumatic diseases is often multifactorial and a careful diagnostic work-up is mandatory

Table 1 (*continued*)

Author, year	Type of study	Strenght of evidence	Conclusions
Alam et al., 2014 [226]	Animal study	Low	Quercetin ameliorates oxidative stress
McAnulty et al., 2013 [227]	Randomized crossover trial	High	A resveratrol and quercetin combination significantly reduces exercise-induced lipid peroxidation without associated changes in inflammation or plasma antioxidant status
Choi et al., 2009 [228]	Animal study	Low	A dietary deficiency of vitamin E increases inflammatory responses and antioxidants successfully suppress the inflammatory responses
Ji et al., 2013 [229]	Narrative review	Low	Quercitin may be an adjuvant natural drug for treatment of RA
Javadi et al., 2017 [230]	Randomized controlled trial	High	500 mg per day of quercetin supplementation for 8 weeks result in significant improvements in clinical symptoms, disease activity, hs-TNFα, and health assessment questionnaire in women with RA
Jackson et al., 2006 [231]	In vitro study	Low	Curcumin and to a lesser extent quercetin may offer therapeutic potential for the treatment of crystal-induced arthritis or RA
Elliott et al., 2008 [232]	Narrative review	Low	Enhanced sirtuins status has a protective effect against diabetes mellitus
Yoo et al., 2016 [233]	In vitro study	Low	Hypoxic and inflammatory condition in synovium perpetuates Reactive oxygen species generation, and oxidative stress reshapes the immune system into the development of pre-clinical RA
Khojah et al., 2018 [234]	Randomized controlled trial	High	Clinical markers (i.e., the 28-joint count for swelling and tenderness) and the disease activity score assessment for 28 joints are significantly lowered in patients with RA treated with resveratrol (1 g)
Di Giuseppe et al., 2012 [144]	Cohort study	Moderate	Moderate consumption of alcohol is associated with reduced risk of RA
Salt/sodium			
Strenght of evidence: LOW			
Kleinewietfeld et al., 2013 [235]	In vitro study	Low	An increased dietary salt intake might represent an environmental risk factor for the development of autoimmune diseases through the induction of pathogenic interleukin (IL)-17-producing CD4 (+) helper T (TH17) cells
van der Meer et al., 2013 [236]	In vitro study	Low	Salt enhances the inflammatory responses of Th17 cells
Marouen et al., 2017 [237]	Case-control study	Moderate	Patients with early RA show increased sodium excretion which may have contributed to autoimmunity
Jung et al., 2019 [238]	In vitro study	Low	Salt can aggravate arthritis by affecting Th17 differentiation. Limiting salt intake may be helpful for treating inflammatory arthritis, such as RA
Sundström et al., 2015 [239]	Case-control study	Moderate	High Na consumption among smokers is associated with the risk of RA may provide new insights into the impact of smoking in RA development
Hernandez et al., 2015 [240]	In vitro study	Low	There is a putative role for NaCl that promotes autoimmunity by inducing proinflammatory responses
Kleinewietfeld et al., 2013 [241]	Narrative review	Low	The plasticity of human Treg and Th17 cells may play a role in autoimmune diseases
Luo et al., 2016 [242]	In vitro study	Low	A short-term increase in dietary salt intake could induce reciprocal switches in Th17/Treg ratio and related cytokines
Fasting			
Strenght of evidence: MODERATE			
Philippou et al., 2020 [243]	Systematic review	High	Some dietary approaches may improve RA symptoms, in particular fasting results in significant but transient subjective improvements
Venetsanopoulou et al., 2020 [244]	Narrative review	Low	Fasting mimicking diets have beneficial effects on symptoms and disease progression in RA patients
Müller et al., 2001 [245]	Systematic review	High	Fasting diets might be useful in the treatment of RA
Smedslund et al., 2010 [246]	Systematic review	High	Fasting followed by a vegetarian eating plan and a Cretan Mediterranean-style eating plan may improve pain
Badsha et al., 2018 [247]	Narrative review	Low	The benefits with fasting in RA, if any, are transient and may not have long-term implications in disease activity

3.4. Extra virgin olive oil

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Extra Virgin Olive Oil"; 11 articles were sourced: 6 case–control studies, 3 narrative reviews, 1 systematic review and 1 cohort study.

3.5. Seeds

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Flaxseeds" AND "Chia seeds"; 21 articles were sourced: 10 narrative review, 3 in vitro studies, 2 book chapters, 1 report, 1 poster presentation, 1 observational study, 2 animal studies and 1 guidelines.

3.6. Nuts

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Nuts"; 4 articles were sourced: 2 narrative reviews, 1 systematic review and meta-analysis and 1 guidelines.

3.7. Spices

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Spices" AND "Ginger" AND "Cinnamon" AND "Capsaicin" AND "Curcumin"; 31 articles were sourced: 14 narrative reviews, 6 animal studies, 2 report, 3 in vitro study, 1 case control study, 1 randomized case control study, 1 clinical trial, 1 randomized controlled trial, 1 systematic review and meta-analysis and 1 book chapter.

3.8. Alcohol

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Alcohol"; 9 articles were sourced: 3 cohort studies, 2 case–control studies, 1 randomized controlled trial, 1 prospective study, 1 report and 1 in vitro study.

3.9. Dairy foods

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Dairy". 12 articles were sourced: 3 narrative

reviews, 3 cohort studies, 1 randomized crossover study, 1 randomized controlled trial, 1 observational study, 1 cross-sectional study, 1 guidelines and animal study.

3.10. Fish

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Fish". 11 articles were sourced: 3 cohort studies, 3 narrative reviews, 2 case–control studies, 1 cross-sectional study, 1 randomized controlled trial and 1 meta-analysis.

3.11. Meat

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Meat". 10 articles were sourced: 4 cohort studies, 2 in vitro study, 1 cross-sectional study and 3 narrative reviews.

3.12. Legumes

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Legumes"; 4 articles were sourced: 1 narrative review, 1 cross sectional study, 1 case–control study and 1 guidelines.

3.13. Eggs

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Eggs"; 2 articles were sourced: 1 narrative review and 1 guidelines.

3.14. Coffee and tea

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Coffee" AND "Tea"; 8 articles were sourced: 4 cohort studies, 1 cross-sectional study, 1 observational study, 1 meta-analysis and 1 narrative review.

3.15. Omega (ω) 3 supplementation

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Polyunsaturated fatty acids" AND"Omega 3" AND "supplementation"; 9 articles were sourced: 4 randomized controlled trials, 1 crossover study, 1 narrative review, 1 systematic review & meta-analysis, 1 meta-analysis and 1 randomized crossover trial.

3.16. Vitamin D supplementation and osteoporosis

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Vitamin D" AND "Osteoporosis"; 21 articles were sourced: 5 case–control studies, 4 cohort studies, 6 narrative reviews, 3 systematic reviews and meta-analysis, 1 meta-analysis, 1 guidelines and 1 in vitro study.

3.17. Antioxidants supplementation

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Antioxidants" AND "Supplementation"; 21 articles were sourced: 5 case–control studies, 5 narrative reviews, 2 randomized controlled trial, 2 animal studies, 2 in vitro studies, 2 cohort studies, 1 meta-analysis, 1 pre-post clinical trial, 1 randomized crossover study.

3.18. Salt/sodium

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Sodium" AND "Salt"; 8 articles were sourced: 5 in vitro studies, 2 case–control studies, and 1 narrative review.

3.19. Fasting

This research was conducted based on the keywords: "Rheumatoid Arthritis" AND "Fasting" AND "Diet"; 5 articles were sourced: 3 systematic reviews and 2 narrative reviews.

This review included 227 eligible studies and the dedicated flowchart is shown in Fig. 1, which represents graphically, in a simple and intuitive way, proper nutrition for rheumatoid arthritis, specifying the quality and amount of food, in order to reduce oxidative stress, counteract inflammation and alteration in immune system.

As shown in Fig. 2, the pyramid shows that carbohydrates should be consumed every day (3 portions of whole grains, preferably gluten free), together with fruits and vegetables (5 portions; among the fruit, berries and citrus fruit are to be preferred, and among the vegetables, green leafy ones.), light yogurt (125 ml), low-fat milk (200 ml), 1 glass (125 ml) of wine and extra virgin olive oil; weekly, fish (3 portions), white meat (3 portions), legumes (2 portions) eggs (2 portions), fresh cheeses (2 portions), and red or processed meats (once a week). At the top of the pyramid, there are two pennants: one green means that subjects with RA need some personalized supplementation (vitamin D and omega 3) and one red means that there are some foods that are banned (salt and sugar).

4. Discussion

4.1. Energy intake, body mass index (BMI), body composition, physical activity and rheumatoid arthritis

Overweight/obesity is associated with a high incidence of chronic autoimmune and inflammatory pathologies, such as RA [25].

Adipose tissue now is considered as an active participant contributing to physiological and pathological processes associated with inflammation and immunity [26].

Given this background, numerous studies have assessed both the correlation between obesity and risk of developing rheumatoid arthritis, and the proportion of obese subjects among RA patients, by comparing this proportion with respect to healthy subjects of the same age and gender. Considering the association between Body Mass Index (BMI) and the risk of RA, three meta-analyses, that of Qin in 2015 (which included 11 studies) [27], that of Feng in 2016 [28] and finally dose–response meta-analysis of Feng in 2019 (which broadened Quin's and 2016 Feng's meta-analysis, by including 16 papers, 406,584 participants) [29], have assessed this topic.

The most recent dose–response meta-analysis demonstrated a 12% increase in RA risk in overweight participants and a 23% increase in obese participants compared to normal weight participants; by stratifying the results according to gender, it was found that the risk of RA for obese participants compared to normal weight was higher in women than the risk for both sexes combined [29]. Moreover, the dose response meta-analysis revealed that each 5 kg/m2 increase in BMI resulted in an 8% increase in the risk of RA. In addition, a significant nonlinear relationship between BMI and RA was found in the overall studies, as well as in case–control studies and cohort studies. Also, a very recently Mendelian

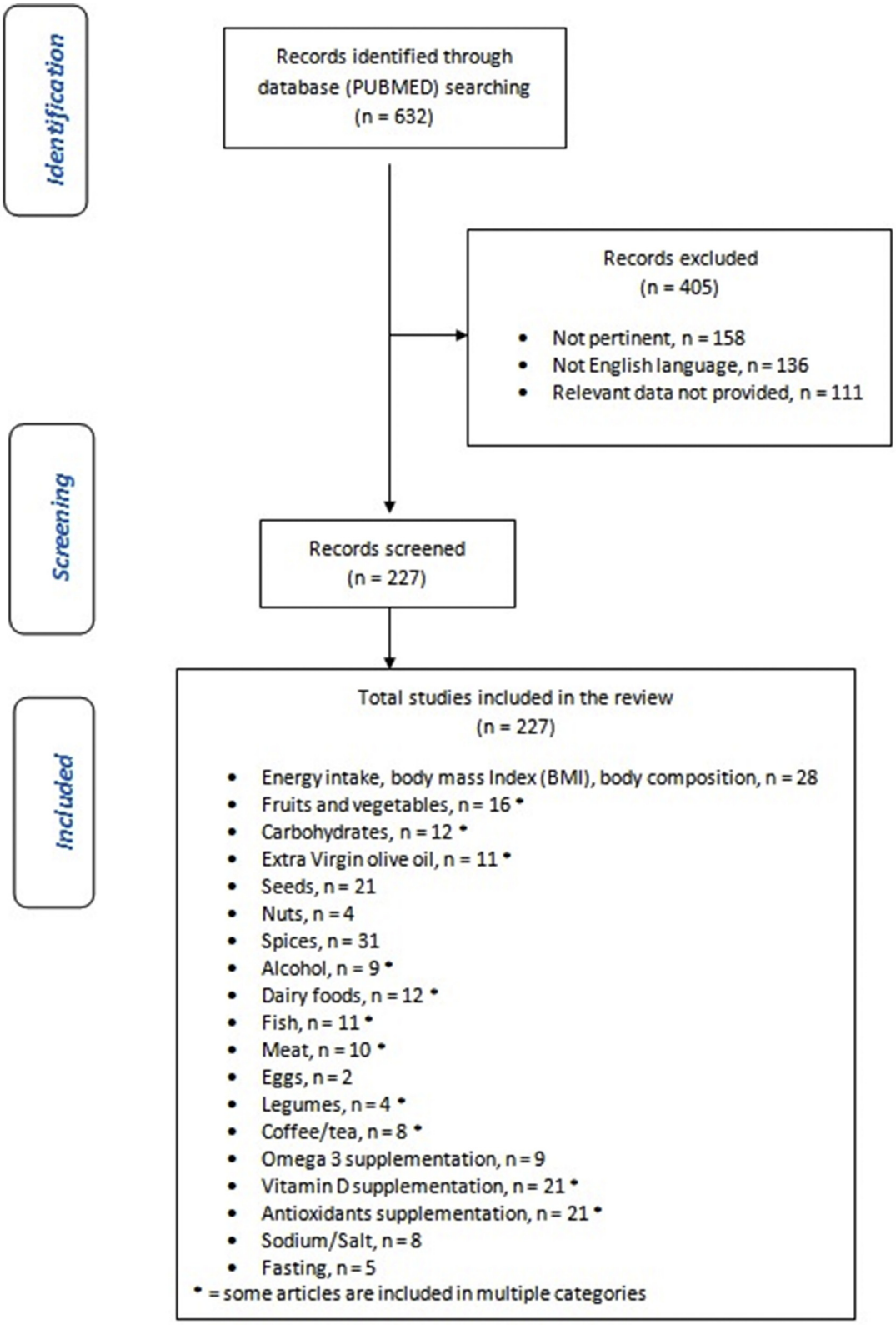

Fig. 1. Flow diagram of the literature search and filtering results for a narrative review of the effectiveness of diet on Rheumatoid Arthritis.

Randomization Study demonstrated that BMI may be causally associated with an increased risk of RA [30].

Considering patients who were diagnosed with RA, if they were compared with population-based controls, matched for age and sex, a cross-sectional analysis, performed in 11,406 patients with RA and 54,701 controls, demonstrated that the proportion of obese subjects among RA patients was higher in comparison with controls, (33.4% vs 31.6%, respectively) [31].

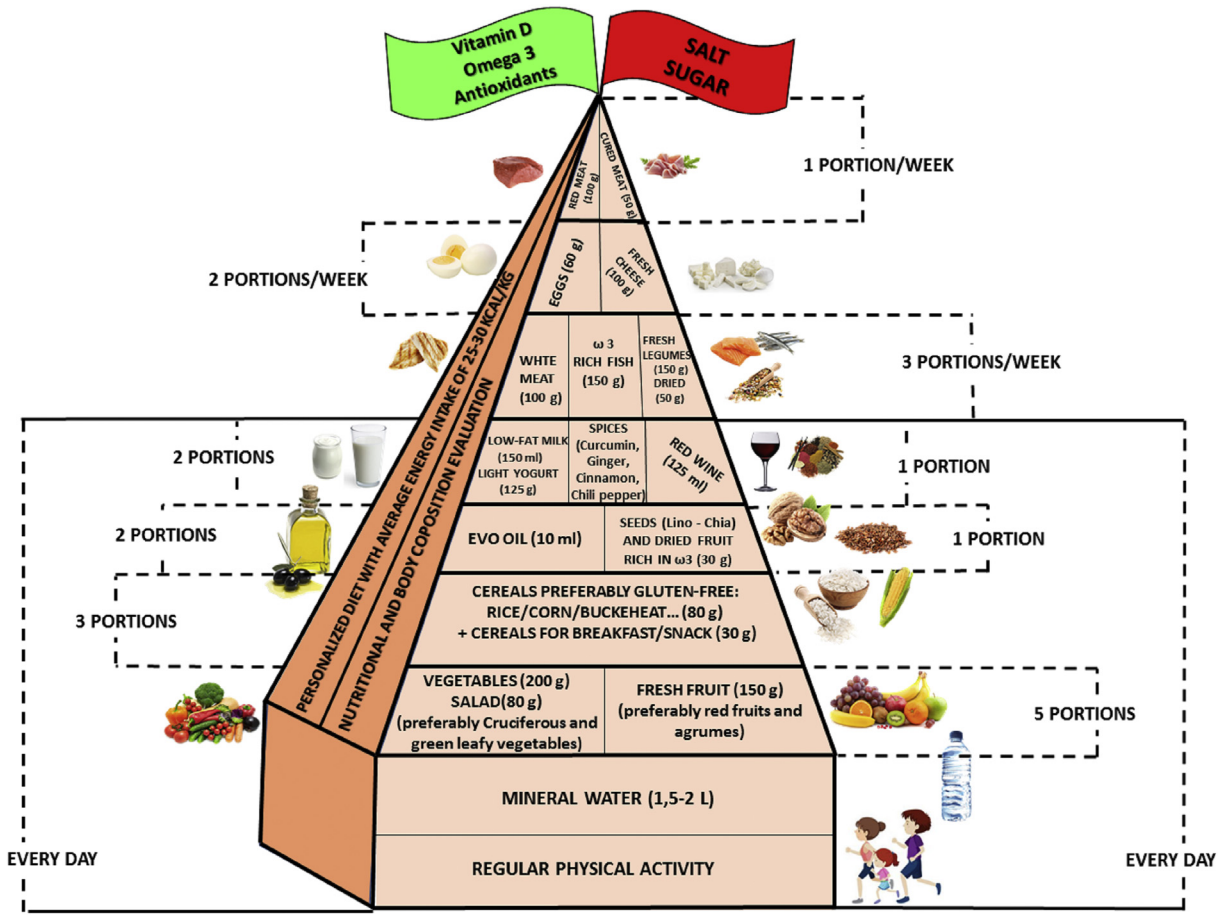

Fig. 2. Ideal food pyramid for patients with Rheumatoid Arthritis.

The study by Dar et al. confirmed what has been shown in 2 previous studies: the study by Naranjo and the study by Armstrong reported that more than 60% of patients with RA are classified as overweight or obese by body mass index (BMI≥25 kg/m2) [32,33].

In addition, obesity represents an important and increasingly prevalent comorbidity even at the first presentation of RA [10].

The cause of the higher incidence of obesity in subjects with RA could also depend on a reduction in daily energy expenditure. In the study of Henchoz et al., 110 patients with RA (with the same disabling condition) and 440 age- and sex-matched were compared: subjects with RA recorded a lower daily energy expenditure of about 100 kcal. This share of daily energy expenditure reduction over time may be sufficient to cause the gradual weight gain observed in most people with RA [34]. This study also indicated that physical activity is lower in RA patients.

In recent years there has been a lot of interest in studying the relationship between adipose tissue, adipocytokines, inflammation and disease activity in RA, and the results are very amazing, although not always in agreement.

The most recent study on this topic demonstrated that circulating Leptin, Resistin, IL-6 and IL-17 levels positively correlated with the clinical activity of RA patients in a BMI-independent way and, while Resistin showed a limited correlation with other inflammatory cytokines, Leptin showed a positive association with IL-1β [35].

These results are in agreement with previous longitudinal study by Xibille-Friedmann, and with a study by Olama [36,37].

Due to the many inflammatory and metabolic pathways involved, these complex relationships warrant further study, also because the studies conducted to date have several limitations, including a small sample size, the heterogeneity of disease-modifying anti-rheumatic drug (DMARD) treatment and the limitations in treatment.

The non-linear trend of the correlation between BMI and risk of developing RA demonstrated in the dose response meta-analysis by Feng [29] can be explained by the fact that BMI does not reflect body composition, not distinguishing between lean and fat mass quantities. In a study by Ngeuleu [38] 123 subjects with RA were evaluated, for whom body composition was analyzed with the use of the dual X-ray densitometer (DXA) (gold standard for the evaluation body composition); of these 39.8% (49 subjects) were sarcopenic according to the Baumgartner equation [39] according to which a subject is sarcopenic if the relative skeletal muscle mass index (RSMI) is < 5.5 kg/m2 for women and <7.26 kg/m2 for men). Other previous studies have investigated the prevalence of sarcopenia in RA patients, with percentages of 43.3% [40] and 25.9% respectively [41]. In the latter two papers, however, sarcopenia was defined using the criteria proposed by Janssen et al. [42], as the relative skeletal muscle index ≤5.75 kg/m2 for women and ≤8.50 kg/m2 for men.

Another study by Reina, demonstrated that RA patients fulfilled criteria of sarcopenia in 44% of cases versus 19% of controls (100 subjects); moreover, this study demonstrated that RA disability is inversely correlated to lean mass and directly to fat trunk; also, that RA time of evolution correlates inversely with lean mass in limbs and SMI: more long and aggressive disease provokes a loss of muscle mass [43].

According to the study by Sanada et al. [44] there is a relationship between sarcopenia and high cardiovascular risk in the

general population; it is also already known that RA increases the risk of cardiovascular (CV) mortality up to 50% compared to the general population [45,46] and CV disease (CVD) is the main cause of death in RA patients [45–47]. This means that the increased cardiovascular risk already associated with the pathology is added to the cardiovascular risk given by the condition of sarcopenia [38].

In conclusion, the evaluation of body composition by DXA is an essential point of the patient's assessment with RA in order to prevent the onset of loss of lean mass.

Considering that it is estimated that the percentage of sarcopenic RA patients ranges from 25 to 43%, for the prevention of sarcopenia, a protein quota of 1–1.2 g/kg/body weight is recommended, while in the patient with overt sarcopenia the protein intake should be 1.5 g/kg of body weight, as reported in the guidelines of the European artificial nutrition society [48] and in the position paper of the PROT-AGE study group [49].

It is equally important to avoid weight gain, reminding the patient that he must remain in the normal weight range, as overweight and obesity are associated with a worsening of the symptomatology due to the inflammation that is present in the obese patient [50].

For the patient with RA, therefore, a personalized diet with an adequate amount of protein and controlled in energy (25–30 kcal per kg of body weight at most) is essential, which must be built after evaluating the patient's basal metabolism by indirect calorimetry, since it has been shown that the patient with RA can have a slowed basal metabolic rate of about 100 kcal/day [34]. Considering then the energy intake, the base of the food pyramid is narrower, precisely to emphasize how the energy intake should be controlled in patients with RA, as it is for food pyramid specific for the elderly patient [51].

Finally, at the base of the pyramid the importance of physical activity was reported because, together with diet, it represents an important part of the lifestyle, as also reported in the pyramid of Mediterranean diet.

A Cochrane demonstrate that physical activity (n = 6 studies; 388 participants), was statistically significantly more effective than the control at the end of the intervention period [52].

A recent review reported that physical activity and training show positive effects on the disease itself and also on its comorbidities with existing certainty. In addition, the exercise and training recommendations of the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) provide recommendations, which were adapted by the European League Against Rheumatism (EULAR) to control intensity, duration and training extent [53].

4.2. Fruits and vegetables

Consumption of fruits and vegetables has several health benefits, which may be largely related to their antioxidant properties. Linos et al. have reported that high intake of cooked vegetables confer a protective effect against the development of RA [54].

Moreover, Hu et al., thought the Alternative Healthy Eating Index (AHEI-2010), a dietary quality score based on the recent Dietary Guidelines for Americans, demonstrated that fruits and vegetables, that were considered as healthy items, reduce the risk of developing RA in women [55].

Epidemiological data is further substantiating the protective associations of a dietary pattern, such as the Mediterranean diet rich in a combination of dietary polyphenols derived from fruits, vegetables, olives and red wine in osteoarthritis (OA) [56,57].

A recently reported cross-sectional study from Korean National Health and Nutrition Examination Survey revealed higher intake of fruits and vegetables to be significantly associated with lower prevalence of keen pain in older adults with knee OA [58].

Hagfors et al. demonstrated, in a study in which RA patients randomized to either a Mediterranean type diet, with significantly higher intake frequencies of antioxidant-rich foods, (n = 26 significantly higher intake frequencies of antioxidant-rich foods) or a control diet (n = 25) were compared during a three months dietary intervention study, demonstrated that the plasma levels of vitamin C, retinol and uric acid were inversely correlated to variables related to RA disease activity [59].

In another cross-sectional report among patients with RA, 20 commonly-consumed foods were associated with varying levels of pain and RA symptoms. Interestingly, among these foods identified by the participants to be associated with improving RA symptoms, blueberries and strawberries were ranked high on the list of 'anti-inflammatory foods' based on Disease activity scores [21]. These emerging observational data support the role of dietary berries in alleviating arthritis symptom; berries are a rich source of several phytochemicals and nutrients, which may explain much of their physiological effects as antioxidants and anti-inflammatory agents, as reported in a recent interesting review by Basu et al. [60].

Finally, regarding blueberries, an interesting randomized clinical study on juvenile idiopathic arthritis (AIG) has been published that has tested the efficacy and safety of a combined therapy of blueberry juice and etanercept for AIG. 201 patients with AIG, randomly and uniformly assigned to three groups, were enrolled in the study: ETA (50 mg of etanercept twice a week), ETABJ (50 mg of etanercept and 50 ml of blueberry juice per day), and ETAPJ (50 mg of etanercept and placebo juice). After a 6-month follow-up, clinically-significant improvement in symptoms was demonstrated only in the ETABJ group. At the same time, the symptoms and side effects were significantly reduced or absent in the ETABJ group and there was evidence of a decrease in the levels of IL1 alpha and beta and an increase in the level of Interleukin 1 Receptor Antagonist (IL1RA) [61].

Citrus fruits also have a protective role in the pathogenesis of RA, as demonstrated by He et al. [62]. Citrus fruits are rich in hesperidin. Kawaguchi reported that the consumption of citrus flavanone and naringin suppressed inflammatory responses in collagen-induced arthritis in mice, possibly by decreasing tumor necrosis factor-α (TNF-α) levels [63]. In an 8-week, placebo-controlled, randomized, double-blind clinical trial, Oben et al. reported that citrus extracts improved knee joint pain and flexibility and reduced C-reactive protein (CRP) levels [21,64].

Considering vegetables, the aforementioned study by Tedeschi et al. reported that the intake of spinach, therefore green leafy vegetables, was related to a reduction in symptoms [21]. The intake of green leafy vegetables is also recommended because they are rich in folic acid and low serum folic acid levels have been observed in RA patients [65,66].

Finally, green leafy vegetables, in particular cruciferous vegetables, are rich in cryptoxanthin and cryptoxanthin, supplemental zinc, and possibly diets high in fruits and cruciferous vegetables, may be protective against the development of RA [67].

Among the vegetables that could worsen symptoms are tomatoes, as two studies agree that RA patients report a worsening of symptoms after intake of tomatoes. Patients are therefore advised to assess whether tomato intake worsens symptoms [21,68].

In conclusion, it is favorably useful to modify the lifestyle by adding large quantities of fruit and vegetables (5 portions per day: 3 of fruit and 2 of vegetables, 1 raw and cooked). Among the fruit, berries and citrus fruit are to be preferred, and among the vegetables, green leafy ones. Patients are advised to assess whether tomato intake worsens symptoms.

4.3. Carbohydrates

Many of the susceptibility genetic loci for coeliac disease (CD) are shared with those for RA suggesting shared immunological and autoimmune mechanisms [69,70].

In 2015, Lerner and Matthias determined that there was a significant amount of symptomatic and physiology overlap between CD and RA. Starting at the fundamental level, both CD and RA are autoimmune disorders that stereotypically affect certain aspects of the human body more so than other areas; RA affects the joints and CD affects the small intestine. At the genetic level, RA and CD have different predispositions, RA is related to human leukocyte antigen HLA DRB1 haplotypes and CD is related to HLA DQ2 and DQ8 haplotypes [71].

RA can also present with several other concomitant disorders (at the time of diagnosis or during the course of celiac disease) such as celiac disease, type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, thyroid disorders, nutritional deficiencies, and gram-negative sepsis [72,73].

The systemic immune response in celiac disease may be directed toward sites other than the gut. Gut-derived antigens are the key initiators and drivers of dysimmunity in RA. These shared immunological mechanisms explain the concomitant occurrence of celiac disease and RA [74].

The results a study by He et al. revealed that high intakes of carbohydrates (e.g., potatoes) might be associated with increased RA risks. High carbohydrate and lower fiber intakes lead to excess energy intake [62].

Most recently, Hu et al. thought the Alternative Healthy Eating Index (AHEI-2010), a dietary quality score based on the recent Dietary Guidelines for Americans, demonstrated that fruits, vegetables, whole grains, nuts, long-chain (n-3) fat (% of total energy), polyunsaturated fat (% of total energy) and moderate alcohol consumption were considered as healthy items [55].

Regarding simple carbohydrates, intake of sugar sweetened soda is associated with an increased risk of developing RA [75].

Indeed, De Christopher discussed the role of ingested fructose leading to the formation of advanced glycation end products that travel beyond the intestinal boundaries to other tissues and may play a role in the etiology of auto-immune arthritis [76].

Finally, patients with RA face an approximate 50% increased risk of myocardial infarction and stroke compared to the general population, and their risk of CVD is comparable to that of patients with diabetes [77]. Consequently, life expectancy among patients with RA is reduced by 5–10 years, compared to non-diseased individuals [78].

In conclusion, considering this evidence, and given the specific nutritional indications for cardiovascular prevention as regards the indication for carbohydrates, the intake of 3 portions a day of whole grains, preferably gluten-free, is recommended. The intake of sugar and sweeteners must be excluded from the diet.

4.4. Extra virgin olive oil

Linos et al. have reported that high intake of olive oil confers a protective effect against the development of RA [54].

Most recent, Hu et al. thought the AHEI-2010, demonstrated that fruits, vegetables, whole grains, nuts, long-chain (n-3) fat (% of total energy), polyunsaturated fat (% of total energy) and moderate alcohol consumption were considered as healthy items [55].

Rossel et al. have also reported that high intake of olive oil, together with alcohol, fish and cooked vegetables confer a protective effect against the development of RA [79].

The beneficial effects of extra-virgin olive oil (EVOO) on RA have been linked to its fatty acid composition, which is very rich in monounsaturated fatty acids (MUFA), and has moderate saturated (SFA) and polyunsaturated fatty acids (PUFA), and to its high content in polyphenols and in vitamin E. All these nutrients have anti-inflammatory activity and have Protective Effects on Immune-mediated Inflammatory Response [80,81].

Moreover, all the studies that evaluated the effectiveness in terms of improving symptomatology, as well as the quality of life and inflammatory parameters, in patients who followed a Mediterranean diet, of which EVOO is a cornerstone, agree in showing that this type of diet is effective [19,82,83]. A recent review confirmed that the Mediterranean Diet may provide benefit for patients with RA in conjunction with medical treatment, even if there is insufficient evidence to support the use of the MD for the prevention of RA [84].

Finally, the cardio-protective properties of EVOO were well demonstrated [85], and this is an additional beneficial effect useful for RA patients who have an increased cardiovascular risk compared to the healthy population [86].

In conclusion, the intake of EVOO is the preferable choice as a condiment, preferably raw, in the dose of 2–3 servings per day.

4.5. Seeds

4.5.1. Flaxseeds

Flaxseeds (both brown and yellow varieties) have nutritional characteristics and are rich source of ω-3 fatty acid: α-linolenic acid (ALA), PUFA, soluble and insoluble fibers, phytoestrogenic lignans (secoisolariciresinol diglucoside-SDG), proteins and an array of antioxidants [87–90]. Various edible forms of flax are available in the food market—whole flaxseeds, milled flax, roasted flax and flax oil. According to its physico-chemical composition, flaxseed is a multi-component system with bio-active plant substances, such as oil, protein, dietary fiber, soluble polysaccharides, lignans, phenolic compounds, vitamins (A, C, F and E) and minerals (Phosporus - P, Magnesium - Mg, Potassium - K, Sodium - Na, Iron - Fe, Copper - Cu, Manganese - Mn and Zinc - Zn) [91,92]. Although flaxseed oil, unlike fish oil, does not contain Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), and it is gaining popularity due to its high ALA content. Whole flaxseed, flaxseed meals and isolated proteins are rich sources of glutamic acid/glutamine, arginine, branched-chain amino acids (valine and leucine) and aromatic amino acid (tyrosine and phenylalanine) [93]. Flax fibers include both soluble and insoluble dietary fibers. The proportion of soluble to insoluble fiber varies between 20:80 and 40:60 [94,95]. The major insoluble fiber fraction consists of cellulose and lignin, and the soluble fiber fractions are the mucilage gums [96,97]. Only 10 g of flaxseed in the daily diet increases the daily fiber intake by 1 g of soluble fiber and by 3 g of insoluble fiber. Flax contains up to 800 times more lignans than other plant foods [98,99]. Lignans act as both antioxidants and phytoestrogens [100]. In relation to composition of minerals, the contents of calcium, magnesium and phosphorus are highlighted being that a 30 g portion of the seed constitutes 7%–30% of the recommended dietary allowances (RDAs) for these minerals [101]. Flaxseed contains approximately 23 g ALA per 100 g [102] and thus, the recommended dietary amounts can be obtained by consuming about 9 g of flaxseed per day. Flaxseed provides an excellent omega 6 (ω-6): omega 3 (ω-3) fatty acid ratio of approximately 0.3:1 [103]. ω-3 enriched eggs from laying hens fed a special flax diet are gaining in popularity amongst consumers on the North American continent and abroad. The organoleptic quality of ω-3 enriched eggs was acceptable without off-flavors when hens were fed 5% (or less) flaxseed oil in diet [104].

4.5.2. Chia seeds

Chia seed is a natural source of antioxidants and is rich in ALA. Because the body cannot synthesize ALA, chia has a newfound and

instrumental role in diet [105]. The oil and mucilage of chia seed, more promisingly the oil, attenuated TNF-α and the swelling of the paw, improved lipid profile, and diminished the oxidative stress both in obese and non-obese rats; so, exhibited anti-inflammatory effects against adjuvant-induced arthritis in obese and non-obese rats [106]. Ingestion of 25 g/day milled chia seeds for seven weeks by postmenopausal women resulted in significant increases in plasma ALA and EPA but not DPA and DHA [107].

In conclusion, the intake of 10 g/day of flax or chia seeds can be a useful support for taking adequate quantities of PUFAs.

4.6. Nuts

Nuts are rich in MUFAs (in particular hazelnuts), antioxidant and mitigating chronic pro-inflammatory processes bioactive substances, like EVOO [108,109].

Nuts are a cornerstone of the Mediterranean diet and all literature agrees that a low-fat low-sodium Mediterranean diet rich in fruits, vegetables, whole grains and nuts reduces the risk of developing RA and better controls the symptoms [110].

In conclusion, nuts must be eaten daily, in the portion equal to 30 g [111].

4.7. Spices

Spices are rich in important phytochemicals that can attenuate oxidative stress and inflammation and relieve RA. Studies on animal models of RA, OA and gout show interesting results in terms of reduced tissue damage, restored cartilage homeostasis, and decreased levels of uric acid, respectively [112].

4.7.1. Ginger

An in-vivo study revealed the beneficial effects of using a mixture of blended ginger, which is rich in pungent phenolic compounds (e.g., shogaols and gingerols), and turmeric, which is rich in phenolic curcuminoids (including curcumin, bisdemethoxycurcumin, and demethoxycurcumin), against extra-articular complications of RA including hematological, metabolic, and cardiovascular complications in adjuvant-induced arthritic rats (male Wistar albino) [113]. Earlier, the same group of researchers confirmed that both ginger and turmeric could independently and significantly protect against RA in adjuvant-induced arthritic male Wistar albino rats [114].

4.7.2. Cinnamon

Cinnamon bark (*Cinnamomum zeylanicum*), one of the most common spices used in Indian, Bangladeshi, Burmese, and Sri Lankan dishes, can confer some protective effects against RA. Rathi et al. observed a significantly-higher level of anti-inflammatory activities (inhibition of cytokines: IL-2, IL-4, and IFN-γ and reduction of TNF-α concentration) upon the treatment of RA animal models (male Wistar rat and Swiss albino mice) with the polyphenolic fractions of cinnamon bark [115].

4.7.3. Capsaicin

Red hot chili peppers (capsaicin) have been suggested to play anti-inflammatory roles by increasing anti-inflammatory macrophages (M2), modulating the neuroimmune response and decreasing neurogenic pain, even if the studies are only on topical effect [116,117].

4.7.4. Curcumin

4.7.4.1. Turmeric intake in the prevention of RA. The most important bioactive chemical constituents of turmeric are curcuminoids, including curcumin, demethoxycurcumin and bisdemethoxycurcumin, which are extracted from the rhizome of the herb *Curcuma longa* which belongs to the Zingiberaceae family [118]. The best known, curcumin, is a hydrophobic polyphenol which, thanks to its antioxidant and anti-inflammatory properties, seems to be effective in the prevention of various pathologies, including autoimmune and inflammatory ones, going to interact with numerous molecular targets [119].

Curcumin, in particular, has shown an interesting preventive effect, proving effective in the prevention of RA [120]. In vitro, curcumin showed antiproliferative and anti-inflammatory action in fibroblast-like synoviocytes in rheumatoid arthritis (RA-FLS) inducing apoptosis and causing inhibition of COX-2 pathways leading to the production of prostaglandin E2 (PGE2) [121]. Furthermore, the exposure of RA-FLS to curcumin led to the decrease of cytokines and growth factors, such as Interleukin-6 (IL-6) and the growth factor of the vascular endothelium and the deactivation of the nuclear factor kB (NF-kB) [122]. The influence of curcumin on specific signal transduction pathways is therefore an interesting point, because the activation of these pathways can alter the threshold for immune activation in rheumatoid arthritis [120]. In animal model studies, curcumin has been shown to increase anti-inflammatory cytokines, reduce pro-inflammatory cytokines and activate the antioxidant defense system [114,123,124].

A human study also investigated the beneficial effects of taking a low dose of supplement of lipidet curcumin (equivalent to 80 mg/day of curcumin) for four weeks in a population of healthy adults. This supplementation has resulted in numerous positive effects for health promotion. In particular, curcumin increased the body's antioxidant capacity, assessed through the activity of certain enzymes in the plasma (increase in catalase activity) and in saliva (increase in the salivary ability of “radical scavenging”) [125].

4.7.4.2. Taking turmeric in the patient with full-blown RA. The consumption of curcumin represents a valid strategy in the reduction of the typical symptoms of inflammatory diseases, such as RA. The mechanism of action of curcumin is similar to that of nonsteroidal anti-inflammatory drugs, commonly used in the treatment of OA [126].

Since the long-term use of drugs available for the treatment of RA seems to have different side effects, natural phytonutrients could represent a valid, safe and effective alternative for the treatment of RA; in particular, curcuminoids have been used for centuries by Ayurvedic medicine for the improvement of inflammatory conditions [127]. Curcuminoids exert a pleiotropic action, interacting with numerous molecular targets involved in inflammation. In particular, curcumin allows the negative regulation of proinflammatory interleukins (IL-1β, IL1, IL-2, -IL-6, IL-8, IL-12), and of cytokines, including TNF-α; in addition, it regulates the inflammatory response down-regulating enzymes such as iNOS, cyclooxygenase-2 (COX-2), lipoxygenase and xanthine oxidase, thus suppressing the activation of the NF-kB [128–130]. Studies in cell culture and animal model have shown that curcumin is a potential effective agent in RA [131,132]. A murine model study has shown interesting efficacy of curcumin, similar to the well-known drug methotrexate (MTX), in the reduction of TNF-α and IL-1β values in blood and synovial fluid both by intravenous and oral administration [124].

With regard to human studies, RA patients treated with 500 mg of curcumin per day for 8 weeks showed a greater reduction in clinical symptoms than subjects treated with diclofenac sodium (50 mg). In particular, the test scores for knee pain and swelling were reduced, according to the criteria of the American College of Rheumatology (ACR) and the Disease Activity Score (DAS). CRP, as a

marker of inflammation, also decreased, while there were no significant improvements in erythrocyte sedimentation rate (ESR) or in other blood parameters [133]. In the Amalraj et al. study, patients with active rheumatoid arthritis who had received a curcumin-based product, both low-dose (250 g) and high (500 mg), twice daily for 3 months, showed a significant relief of clinical symptoms. This improvement emerged from the results of the ACR, DAS tests and the visual analogue pain scale (VAS). In addition, significant improvements in CRP, ESR and rheumatic factors were recorded for blood chemists [127].

The beneficial effect of turmeric has been confirmed by a systematic review and meta-analysis [134]. This study shows that the oral intake of turmeric extract (about 1000 mg per day of curcumin) reduces the typical symptoms of arthritis, assessed through the WOMAC index (Western Ontario and McMaster Universities Osteoarthritis) and VAS of pain, as a pain reliever. Specifically, the meta-analysis of four studies showed a reduction in WOMAC (−15.36; $P = 0.009$) in subjects treated with turmeric extract and curcumin. In addition, the analysis of five studies on the pain showed no difference in patients treated with turmeric and curcumin extract and pain relieving drugs [134]. However, it is difficult to translate the results obtained into a definitive recommendation, given the low number of studies considered and the small sample size. Rather, the authors recommend taking it in combination with conventional therapy [134].

According to the Joint FAO/WHO Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA), an adequate daily intake value of curcumin is 0.3 mg per kg of body weight [135,136]. No toxicological effects have been reported in the long-term use of curcumin and up to 12 g per day the intake was safe [137]. Side effects have been reported only with the consumption of high doses of curcumin (8–12 g) and concern mild nausea and diarrhea [138].

However, it should be underlined that curcumin has a very low bioavailability in the body and in order to optimize its absorption, a lot of affords have been spent for new formulations. Examples are the association of curcumin with pepper as adjuvant [139], or the applications of proprietary technologies, including phytosomes, liposomes, and micelles [140,141]. In conclusion, there is evidence from clinical studies, together with the results of in-vitro experiments, that demonstrate the effectiveness of dietary supplementation with curcumin in RA. However, it remains to be determined what the optimal dose may be consumed and the type of formulations [142]. Despite the multiple protective effects of the polyphenols contained in spices, there are no specific dietary recommendations for patients affected by rheumatic diseases. However, given the numerous studies in vitro and on the animal model, it is advisable for RA patients to daily consume spices such as ginger, cinnamon, and turmeric.

4.8. Alcohol

Regarding studies conducted to evaluate the correlation between alcohol intake and risk of developing RA, a Swedish study by Kallberg et al., of 2009 describes how alcohol consumption 2.9 drinks/week can lead to a reduced risk of RA; two independent RA case control studies were compared, the Swedish EIRA (1204 cases and 871 controls) and the Danish CACORA- (444 cases and 533 controls) to estimate the probability ratios (OR) of developing RA for different amounts of alcohol consumed [143].

In particular, among alcohol users, those who had a consumption of 4.1–9 drinks/week had the risk of RA reduced by 40–50% compared to those with a lower consumption. In addition, for the RA patient subgroup that was seropositive for anti-citrullinated peptide antibodies, alcohol consumption was observed to reduce the risk more in smokers carrying HLA-DRB1 alleles. The authors of the present study conclude that there is an observed reverse association between alcohol intake and the risk of RA, and the demonstration of a preventive effect of alcohol in experimental arthritis indicates that alcohol can protect against RA. This highlights the potential role of lifestyle in determining the risk of developing RA, and the advice not to necessarily refrain from alcohol to reduce the risk.

Also in the study of Di Giuseppe et al. the authors showed a statistically-significant 37% reduction in RA risk among women who drank> 4 glasses of alcohol (1 glass = 15 g ethanol) per week compared to women who drank <1 glass per week or had never drunk alcohol ($P = 0.04$). Drinking all types of alcohol (beer, wine and spirits) was associated, not inversely significantly, with the risk of RA. Long-term alcohol consumption analysis showed that women who reported drinking more than 3 glasses of alcohol per week had a 52% reduced risk of RA compared to those who had never drunk. Therefore, the authors concluded that moderate alcohol consumption is associated with reduced risk of developing RA [144]. Maxwell's study also showed that alcohol intake can protect against RA development [145].

Finally, Lu et al. have reported that high intake of alcohol, fish, olive oil and cooked vegetables confer a protective effect against the development of RA [146].

As for the studies that considered alcohol intake in RA patients, the Nissen study showed that alcohol intake is associated with lower radiographic progression. The study included 2908 RA patients with an average of 4 sequential radiographs and 3.9 years of follow-up. A trend toward reduced radiographic progression existed in drinkers versus non-drinkers, with an average erosive progression rate of 0.99% at 1 year. Alcohol consumption showed a J-shaped dose–response effect, with a more favorable evolution in occasional consumers ($P = 0.01$) and daily consumers ($P = 0.001$) compared to non-drinkers, while heavy drinkers have shown worse radiographic evolution [147].

Bergman's study also demonstrated a positive correlation between moderate alcohol consumption and disease activity and quality of life in RA patients, albeit only in women. Alcohol intake was assessed in 1238 patients: 11% were non-drinkers, 67% had non-hazardous consumption and 21% were classified as dangerous drinkers. Women who drank alcohol reported lower disease activity and better Health-Related Quality of Life (HRQL), but there was no association between alcohol consumption and disease activity in men. For current smokers, alcohol use was associated only with fewer swollen joints reported by patients. The result was not influenced by the type of alcohol consumed [148].

Even for patients taking MTX, who may be at risk of increasing transaminases due to the hepatotoxic effect of the drug, there is no risk of increasing transaminases if alcohol consumption equals 14 units of alcohol per week (1 alcohol unit is 10 mL or 8 g according to NHS_Choices) [149].

There is a theoretical background for the association of alcohol consumption and reduction of inflammation in RA. Intake of low to moderate amounts of alcohol over a long period of time (years) has been shown to decrease TNF-α, IL-1 and CRP levels [150,151].

In conclusion, the intake of moderate quantities of alcohol (on average 14 units of alcohol per week, 1 unit of alcohol is equal to 10 mL or 8 g as is found on average in 125 ml of red wine at 11° or 330 ml of beer) is useful in preventing the risk of developing RA and

in controlling symptoms, and therefore the quality of life in patients with RA.

4.9. Dairy foods

Although dairy foods have in the past been considered pro-inflammatory [152], studies of dairy consumption demonstrate that dairy products have either a neutral or inverse effect on levels of circulating inflammatory biomarkers [153,154]. Dairy products contain a high content of saturated fatty acids, but also many of the shorter chain fatty acids found in milk fat have beneficial health effects, with important immune response functions. There is also evidence that the proteins, fats and calcium in milk are beneficial in inflammation [155]. However, for the high content of saturated fatty acids, milk and dairy products have been suggested as risk factors for OA, as reported in a rat model of inflammatory arthritis [156], but, prospective studies in humans have not been able to verify this; instead, a trend towards an inverse association between the consumption of dairy products and risk for RA has been described in some prospective cohort studies [157–159].

Regarding dairy products in the diet of patients with RA, a single observational study suggested a reduction in OA progression associated with frequent milk consumption among women [160]. Moreover, a cross section multicenter study demonstrated that dairy products, such as milk and yogurt, had protective roles against RA [62]. So total elimination of dairy from diet is not recommended for control of symptoms in RA [161].

In conclusion, intake of up to three servings of dairy products per day appears to be safe and may confer a favourable benefit with regard to patients with OA and, consequently. also RA [162].

4.10. Fish

Multiple studies have reported decreased risk of incident RA associated with greater fish consumption, although categorizations of fish intake varied [79].

A cross-sectional analysis by Tedeschi on fish consumption in a cohort of RA patients demonstrated that DAS28-CRP was significantly lower among subjects consuming fish $\geq$2 times per week compared with those eating fish <1/month after adjusting for confounders. One additional serving of fish/week was associated with significantly lower DAS28-CRP [163].

In multivariate models studied by Pedersen et al., each increase in intake of 30 g fat fish (>or = 8 g fat/100 g fish) per day was associated with 49% reduction in the risk of RA, whereas medium fat fish (3–7 g fat/100 g fish) was associated with significantly increased risk of RA [164]. The preventive role of fish regarding RA is due to omega 3, which is an immune-modulating dietary component [165].

However, Sparks found no clear protective effect of fish intake on RA risk [166], confirming the results of a previous meta-analysis that showed a non-statistically significant inverse association between fish consumption and RA [167].

There may be different reasons for these conflicting results. Among these, one could be the fact that in fish there is a high content of molecule trimethylamine-N-oxide (TMAO) [168].

TMAO, together with microbial dysbiosis, promote RA [169].

TMAO is recognized as a risk factor for CVD and could be a diagnostic marker because of the strong association between the two. TMAO interferes with cholesterol metabolism and induces inflammation. Atherosclerosis and chronic inflammation underlie many autoimmune diseases [170].

RA patients harbor the TMAO-producing anaerobic, Gram-negative Bacteroidetes, *Prevotella copri*.

Furthermore, it may alter the metabolism of the microbiota to reduce the effectiveness of the common DMARD MTX [171].

Considering the effect of dietary intake omega 3 on symptoms in patients with RA, a study by Hagfors demonstrated that patients with AR that have a higher reported intake of n-3 fatty acids and a lower ratio of n-6 to n-3 fatty acids showed a moderate or better clinical improvement during the study [172].

In conclusion, three portions a week of fish, preferably fatty, is the right amount of fish to eat for prevention of RA and for improving clinical symptoms in RA patients.

4.11. Meat

The association between meat consumption and the risk for RA has been evaluated in numerous prospective cohort studies. The Nurse's Health Study [158], and the Danish Diet, Cancer, and Health cohort [164] demonstrated that there is no association between meat consumption and the risk for RA. Moreover, other studies confirm this result: a recent study, conducted on a large prospective population cohort, the Swedish Mammography Cohort, confirm that no associations were observed between dietary intake of meat and the risk of RA development [159]. a cross section multicenter study by He et al. demonstrated that there were no significant differences in red meat intakes between RA patients and healthy controls [62].

Some studies do not agree, and have shown an association between meat consumption and risk of developing RA, but these studies specify that it is the high consumption of meat that increases the risk [173].

But more than anything, it is the Western-type diet, rich in energy intake, total and saturated fat, an unbalanced ratio of n-3 to n-6 fatty acids, high in refined carbohydrates and sugar and low in fiber and antioxidants, that might increase the risk of RA, both directly through increasing inflammation and indirectly through increasing insulin resistance and obesity [174].

It is important to underline that meat contains numerous nutrients useful for counterbalancing immune alterations, such as such as tryptophan and arginine. In fact, indole derivatives and polyamines are produced by the microbiota through transformations starting from tryptophan and arginine, and these two molecules are beneficial for the immune system. Indole derivatives act on intestinal mucous membranes, promoting their integrity by stimulating the production of mucins, antimicrobial peptides and intestinal calyx cells, while polyamines (such as putrescine, spermidine and spermine) increase the development and maintenance of the mucous membranes but also of the immune cells residing in them [175].

Indole derivatives, in particular, are formed, by the microbiota, within the tryptophan metabolism cycle. Some of these derivatives are aryl hydrocarbon receptor (AhR) ligands, transcription factors widely expressed throughout the body including immune and bone marrow cells [176]. The activation of AhR in innate lymphoid cells subsequently promotes the production of Interleukin-22 (IL-22), a cytokine that improves epithelial integrity and resistance to infection [177].

Like Tryptophan, Arginine, from which polyamines derive, also thanks to the microbiota, has a central role as modulator of the immunometabolism of macrophages and T cells [178].

In conclusion, we recommend consuming 4 portions of meat per week, including 3 portions of white meat and 1 portion of red meat. Especially for red meat, lean cuts must be chosen, in order to reduce the intake of saturated fat.

4.12. Legumes

Common legumes are rich in dietary fiber, starch, protein and phenolic compounds with demonstrated antioxidant and anti-inflammatory potential.

A 2-year study on the effects of the Mediterranean diet on RA patients revealed that consumption of cereals, vegetables, legumes, fruits, and olive oil decreased the risk of new onset of inflammatory polyarthritis [82].

A recent review confirms that all literature agrees that the Mediterranean diet, rich in plant-based foods such as wholegrains, legumes, fruit, vegetables, and EVOO, might have the potential to reduce the risk of RA [174].

Unfortunately, compared to healthy individuals, RA patients had decreased consumption of beans [62].

In conclusion, legume intake should be encouraged in RA patients; 3 servings per week are the recommended amount, as per guidelines [111].

In order to improve tolerability, legumes can be consumed dehulled or in smoothies.

4.13. Eggs

To date, surprisingly, no studies have investigated the relationship between egg intake and risk of developing RA. There are also no studies that have considered whether the intake of eggs has a negative or positive effect on the symptoms.

Eggs are actually recognized as a functional food and contain a variety of bioactive compounds that can influence pro- and anti-inflammatory pathways (e.g., egg phospholipids, cholesterol, the carotenoids lutein and zeaxanthin, and bioactive proteins) [179].

For these reasons, 2 eggs/week, preferably soft boiled or boiled or omelet baked (never fried) are recommended, as per guidelines [111].

4.14. Coffee and tea

Heliövaara et al. recently reported an association between coffee consumption, rheumatoid factor (RF) status and subsequent onset of RA. In a cross-sectional survey of subjects without arthritis, the number of cups of coffee consumed daily was directly proportional to the prevalence of positivity. In the same study, subjects who consumed more than 4 cups/day of coffee were more than twice as likely to develop seropositive RA during follow-up than those who drank less than that amount. Although the specific type of coffee (caffeinated versus decaffeinated) was not specified in this provocative study, this was the first investigation to suggest an association between coffee consumption and RA. In this prospective cohort study of older women, the consumption of decaffeinated coffee was independently and positively associated with an increased risk for RA development, while tea intake was inversely associated with the onset of the disease. The extent of the association between the intake of decaffeinated coffee and RA, as well as between the consumption of tea and RA, was even more pronounced in the development of HIV-positive disease [180]. Their results do not support an association between caffeinated coffee or caffeine intake and RA development [181].

In a study of the following year, a significant association was not found between the consumption of decaffeinated coffee of4 or more cups/day (compared to the consumption of non-decaffeinated coffee) and the subsequent risk of incident RA, in both multivariate models adequate (relative risk [RR] 1.1, 95% confidence interval [CI 95%] 0.5–2.2) or a multivariate model using only basic ratios of decaffeinated coffee consumption (RR 1.0, IC 95% 0.6–1.7). Similarly, there was no relationship between the cumulative consumption of caffeinated coffee and the risk of RA (RR 1.1, 95% CI 0.8–1.6 for>/= 4 cups a day compared to none) or between tea consumption and RA risk (RR 1.1, 95% CI 0.7–1.8 for> 3 cups/day against none). Total caffeine and caffeine consumption was also not associated with RA risk [182].

A meta-analysis of cohort studies revealed a trend of association between total coffee intake and the incidence of RA (RR of the highest group compared to the lowest group = 1.309, 95% confidence interval [CI] = 0.967–1.771, p = 0.085). The meta-analysis of the case–control studies showed a significant association between total coffee intake and the incidence of RA (RR = 1.201, 95% CI = 1.058–1.361, p = 0.005). There were differences in the target groups (all coffee categories) between the case–control meta-analysis which showed a significant association and the cohort studies where the meta-analysis results were not significant. Furthermore, the highest category of coffee intake varied between the Heliovaara et al. cohort study from Finland, where the highest category included drinking up to 13 cups a day, compared to US studies in which it was very unusual to consume more than 4 cups of coffee a day [180]. The combination of data from the cohort and case–control studies showed a significant association between total coffee intake and the incidence of RA (RR = 1.217, 95% CI = 1.083–1.368, p = 0.001). The meta-analysis stratified by seropositivity indicated a significant association between coffee consumption and seropositive risk of RA (RR = 1.309, CI 95% = 1.142–1.499, p = 1.1 × 10-5), but not risk of seronegative RA (RR = 1.097, 95% CI = 0.886–1.357, p = 0.396). There was no significant association between the consumption of decaffeinated coffee and the incidence of RA (RR = 1.709, 95% CI 0.786–3.715), or between the consumption of coffee with caffeine and the incidence of RA (RR = 1.055, 95% CI 0.782–1.421) [183].

The literature is conflicting that caffeine leads to a reduced efficacy of MTX through inhibitory effects on extracellular adenosine. Adenosine modulates cellular functions by interacting with specific receptors on the cell membrane, with consequent anti-inflammatory effects [184].

In the study of Tedeschi et al. among 54.8% of the subjects who used MTX, nobody reported that coffee or tea containing caffeine worsened RA. In the era of powerful DMARD therapy, it is interesting to note that a similar percentage of subjects with RA report that diet has an impact on their RA, compared to the results of 25 years ago when Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and hydroxychloroquine were among the pillars of therapy [21].

Since caffeine consumption is very common, the authors evaluated in one study whether caffeine intake affected the efficacy of MTX in patients with RA. In particular, RA patients underwent MTX treatment, 7.5 mg/week, without folic acid supplementation. Each patient had received a stable dosage of NSAID for at least 1 month. Five parameters of disease activity (tender joint count, swollen joint count, joint pain assessment, duration of morning stiffness, and ESR) were assessed prior to initiation of MXT therapy, and at monthly intervals. When reporting a dietary diary, the amount of caffeine consumed by each patient was calculated, and they were then divided into three groups (A, B, C) according to the amount of daily caffeine intake. The authors highlighted that the patients in group C (high caffeine intake) had a significantly lower improvement in morning stiffness and joint pain compared to patients in group A (low caffeine consumption). The difference between group C and the other 2 groups did not reach a meaning The authors suggest that caffeine, in particular an amount of 180 mg/day, interferes with the efficacy of MTX in RA patients, compared to patients consuming 120 mg/day, although other studies are needed to further evaluate the possible interaction of adenosine receptor antagonists with MTX in RA patients [185].

Another study by Garcia B et al. investigated whether RA patients and those taking MTX with higher dietary caffeine consumption had a worse clinical response to MTX than those with lower intake [186]. RA patients were enrolled in a prospective cohort study and were on MTX therapy. They have been divided

equally into low, moderate and high caffeine users. The clinical response to MTX was defined by DAS-28, multidimensional health assessment questionnaire score (MDHAQ), and duration of morning stiffness. The authors found that 264 RA patients taking MTX had an average caffeine consumption of 211.7 mg and an average MTX dose of 16.0 mg/week. The low caffeine group included 87 patients, the moderate caffeine group 86 and high 91. There was no statistical difference in MTX efficacy between the groups, measured by the DAS-28 score, the MDHAQ score and the duration of stiffness in the morning at the start of the study. The moderate and high caffeine group had DAS-28 scores and higher swollen joint counts, but the differences were not significant. The authors conclude that caffeine intake among patients taking high doses of MTX for RA did not affect MTX efficacy and disease activity over time [186].

In conclusion, the intake of coffee, even decaffeinated, and it does not correlate with the risk of RA, nor with the symptoms if the patient is suffering from RA. Even in RA patients taking MTX, considering that caffeine can act through inhibitory effects on extracellular adenosine, a correlation with symptoms has not been demonstrated. RA patients can therefore freely take coffee in adequate quantities, for a healthy adult, a maximum of 4–5 cups a day.

4.15. ω 3 supplementation

PUFAs play an important role in the structural and metabolic function of cell membranes; competitively inhibit the formation of prostanoids (PGE2) and leukotrienes (LTB4), eicosanoids derived from arachidonic acid (AA) with powerful proinflammatory effects. The beneficial effects of dietary supplementation with ω-3 fatty acids in patients with RA were initially demonstrated in the late 1980s by Kremer et al. [187,188] on short-term clinical studies; when integrated, these fatty acids which contain EPA and DHA, compete AA for incorporation into cell membranes, with consequent reduction in synthesis specific leukotrienes and prostaglandins with proinflammatory activity [189].

In the 90s the studies continued and in the van der Tempel et al. study. (1990) the clinical and biochemical effects of dietary supplementation with fractionated fatty acids of fish oil on patients with RA are described, and it is shown that the administration of ω-3 fatty acids is effective in suppressing the clinical symptoms of RA. The randomized, double-blind, placebo-controlled study included 16 patients (9 females, 7 males, average age 53 years, average disease duration 12 years); 15 of them received nonsteroidal anti-inflammatory drugs; 11 patients also received disease-modifying drugs (gold, antimalarial drugs and D penicillamine), while none of the patients received steroids or cytostatic drugs. The duration of the study was 12 weeks.

Patients were randomly assigned to receive 12 capsules of fractionated fish oil or fractionated coconut oil, flavored with fish as placebo, each day. The fish oil capsules contained a majority of 20: 5, ω-3 (31 mol/100 mol fatty acids (% mol)) and 22: 6, ω-3 (22% mol), resulting in a daily supply of 2, 04 g 20: 5, ω-3 and 1.32 g 22: 6, ω-3, while the coconut oil capsules mainly contained C8: 0 (63 mol %) and C10: 0 (36 mol%). After a 12-week period, without fatty acid supplementation, to confirm the stability of the pathology, after week 13, the integration with fish oil or placebo began. Patients had to continue their regular drug treatment program, dietary fat intake was constant throughout the study, and patients were observed by the rheumatologist, biometrist and dietician every two weeks. For the clinical evaluation, the following were monitored: duration of morning stiffness (in minutes), joint pain, joint swelling and pain index assessed with a visual analogical scale and grip force, measured with a pressure gauge (kPa), while laboratory evaluations included a complete blood cell count, ESR and plasma concentrations of CRP, fibrinogen, amyloid serum A and rheumatoid factor IgM. From a clinical point of view, after the 12 weeks of treatment with fish oil, a decrease in the joint swelling index was observed ($p = 0.01$), the morning stiffness had decreased by an average of 35 min ($p < 005$) and the pain index showed a tendency to improve without achieving statistical significance, while strength and pain were not altered. Regarding laboratory evaluations, the authors observed after treatment differences between leukotrienes B4 of neutrophils with significantly-decreased values of neutrophils and increased significant production of leukotrienes B5 from amounts not detectable at an average production of 13 ng/10 ^ 7 ($p < 0.01$). In conclusion, this study shows that the administration of ω-3 fatty acids at indicated doses is effective in suppressing the clinical symptoms of RA [190].

Similarly, Nielsen et al. in a randomized, double-blind, placebo-controlled study for 12 weeks on 57 patients with active RA, (29 treated with ω-3 PUFA and 28 in the control group) determined the effects of a dietary supplementation with ω-3 [191]. In the treatment group, patients took 6 capsules that contained a daily amount of 2 g of EPA, 20: 5 ω-3 and 1.2 g of DHA 22: 6 ω-3. In addition, each patient enrolled continued drug therapy with NSAIDs, corticosteroids and DMARD. Clinical assessments were made that included grip strength, joint swelling, joint weakness, morning stiffness, overall pain, and biochemical assessments such as total blood cell count, ESR, PCR, and leukocyte fatty acid composition. In addition, the serum values of type I and III procollagen peptides (PICP and PIIINP) were measured at baseline and at the end of the study. Regarding clinical evaluations, the authors observed that in the ω-3 PUFA group there was a significant reduction in morning stiffness from 120 to 75 min ($p = 0.0007$); in addition, there was a significant improvement in the pain score ($p = 0.002$). Biochemical analyses demonstrated a significant decrease in CRP ($p = 0.04$) in the treated group compared to placebo, but not in ESR, while serum PICP levels in the treated group and PIIINP in both groups remained unchanged, indicating that collagen metabolism was not essentially affected. The study showed that supplementation with ω-3 PUFA at concentrations of 2 g of EPA and 1.2 g of DHA significantly improves patient well-being, without clinically significant effects on the biochemical parameters traditionally used for the activity of the disease, therefore it can be used in RA patients treated with traditional drugs [191].

In the study of Geusens et al., the long-term effects of ω-3 fatty acid supplementation were studied in patients with active rheumatoid arthritis [192]. 90 patients were enrolled for a 12-month period in a randomized double-blind study; patients were randomly assigned to 1 of the following 3 daily regimens: 6 capsules containing 1 g of olive oil each (placebo), 3 capsules containing 1 g of fish oil (I. 3 g of ω-3) each, plus 3 placebo capsules or 6 capsules containing 1 g of fish oil each (2.6 g of ω-3). The fish oil capsules that contained 1 g of oil consisted primarily of EPA (28%) and DHA (6%). The evaluation criteria were ranked in order of importance at the start of the study. The characteristics that were evaluated at baseline and after 3,6,9, and 12 months were: overall evaluation of the disease activity by the doctor (scale 0–4, 0 = without symptoms and 4 = very serious), evaluation overall by the patient of the disease activity (0–10) VAS, (0 = without symptoms and 10 = very severe), pain assessment by the doctor and the patient (0–4 scale, 0 = none pain and 4 = very severe), duration of morning stiffness (in minutes), grip strength (in mm Hg; average of 3 measurements), Ritchie joint index for pain (number of painful joints and number of joint swellings and concomitant medications (NSAID and/or DMARD). Laboratory assessments included ESR and RF. Furthermore, radiological evaluations were performed for the proximal and distal interphalangeal joints, and for the metacarpophalangeal and wrist joints of both

hands. The authors observed a significant improvement from baseline in the overall patient assessment only in the group taking 2.6 g/day of ω-3 ($P < 0.05$ according to Friedman's test) and for the duration of the study, these changes were significantly different from those noted in the placebo group ($P < 0.01$, Mann–Whitney Test). At 12 months, this parameter was significantly improved in the group taking 2.6 g/day compared to those taking 1.3 g/day ($P < 0.05$). The pain score, assessed by the doctor, was constantly improved from baseline in all 3 intervention groups, but the changes were significant only in the group taking 2.6 g/day of ω-3 ($P < 0.05$, according to Friedman's test). The patient-assessed pain score improved on all visits in both ω-3 dosage groups, but these changes from baseline were not significant and were not statistically different from those in the placebo group. In each treatment group, significant reductions were observed for the Ritchie joint pain index and the number of painful joints ($P < 0.01$, from Friedman's test). No significant differences were found between the treatment groups. Friedman's test indicated a significant worsening of the grip strength in the placebo group ($P < 0.01$) and a significant improvement in the treatment group with 2.6 g/day of omega-3 ($P < 0.05$). A significant increase in RF titre was observed in the 1.3 g/day group treated with ω-3 ($P < 0.05$, according to Friedman's test) while this was not observed in the 2.6 g group/day of ω-3. Regarding pain assessment and overall assessment, patients treated with 2.6 g/day, but not those treated with 1.3 g/day, reported an overall improvement and a reduction in their estimated pain score by the doctor, compared with the placebo group. This was consistent with the observed proportions of patients whose NSAID and/or DMARD dosages could be reduced, particularly in the 2.6 g/day ω-3 group, 47% of patients were able to reduce these drugs, compared 15% of the placebo group ($P < 0.05$); in the ω-3 group 1.3 g/day, 29% of patients could reduce these drugs. The results of this double-blind study, on the effect of integrating fish oil in patients with active RA, confirms the positive results obtained in previous short-term studies [187,188]. The most interesting result was the overall improvement reported by patients treated with 2.6 g/day of ω-3. This improvement was significantly different from the change observed in the group of patients taking placebo and tended to increase with increasing treatment period. The proportions of patients in whom improvement was observed were significantly higher in the 2.6 g/day ω-3 group than in the placebo group, and a significant reduction in the need for NSAIDs and/or DMARDs was also observed. In conclusion, the observations of this long-term study in patients with active RA treated with NSAIDs and/or DMARDs indicate that dietary supplementation with ω-3 fatty acids (2.6 g/day) can have significant beneficial clinical effects and may reduce the need for NSAIDs or DMARDs [192].

The study by Remans et al. highlights how ω-3 supplementation can have beneficial effects based on the daily dose taken, in patients with RA [193]; this is a double-blind, placebo-controlled parallel group study on the effects of a nutritional supplement, in the form of a drink, (200 ml) containing, among other ingredients, ω-3 fatty acids (1.4 g EPA and 0.211 g DHA), gamma-linolenic acid of ω-6 fatty acids (0.5 g GLA) and micronutrients (vitamins C and E), the duration of the study was 4 months. A total of 66 patients were enrolled (33 treated and 33 placebo); patients were instructed to continue their eating habits and clinical parameters were assessed at baseline and after 2 and 4 months by the same observer. The primary end point was the change in the 2- and 4-month joint weakness count. Other clinical variables considered were swollen joint counts, visual analog scales for pain and disease activity, grip strength, and morning stiffness. Biochemical parameters included plasma concentrations of PUFA and vitamins C and E. A total of 11 patients (17%) dropped out of the study during the treatment period, 5% for gastrointestinal intolerance and 12% for lack of efficacy; a total of 55 patients completed the 4 months of treatment: 29 received the placebo and 26 the supplement. No significant changes were observed in the clinical parameters considered between the two patient groups. Disease activity measured with DAS-28 worsened in both groups after 4 months, but this only gained statistical significance in the control group, not in the experimental group or between the groups. No difference in NSAID intake was observed, while a statistically-significant increase in body weight was observed in the 2-month treated group, but the changes in weight and BMI were not significant between the groups. All patients receiving nutrient supplementation had a significant increase in ω-3 PUFA (EPA, docosapentaenoic acid − DPA and DHA) compared to baseline and compared to changes in the placebo group. The mean concentration of ω-6 PUFA (GLA, DGLA dihomogammalinolenic acid) did not change in both groups. Plasma concentrations of AA were significantly decreased in patients taking the nutritional supplement, but not in the placebo group. EPA concentrations were inversely correlated with AA ($r -0.66$, $P = 0.001$) and positively with DPA and DHA (r 0.83 for both, $P < 0.0001$), while DPA concentrations with DHA and GLA with DGLA they were significantly correlated (r 0.75, $P < 0.0001$, r 0.59, $P = 0.003$, respectively). Significant increases were observed in serum concentrations of vitamin E ($p = 0.015$) EPA, DHA and DPA concomitantly with a decrease in AA ($p = 0.01$) in the intervention group, also differences intergroup for PUFA and vitamin E were significantly different ($p = 0.01$ and 0.03 respectively). This double-blind, placebo-controlled study of RA patients did not show a clinical benefit, higher than the nutrients taken daily, of the integration with EPA, GLA and micronutrients at the doses tested compared to placebo but nevertheless provides information regarding omega-3 fatty acid doses, below which no anti-inflammatory effects are observed in RA [193].

In conclusion, as the meta-analyses on the subject also show, it was found that consumption of ω-3 fatty acids significantly improves the markers related to the activity of the disease and, as regards inflammation, reduces leukotriene B4 [194].

Regarding the dosage to be taken, Lee's meta-analysis suggests that the use of ω-3 PUFA at dosages> 2.7 g/day for> 3 months reduces the consumption of NSAIDs by patients with RA; this meta-analysis evaluated 10 RCTs that considered 183 patients with RA and 187 placebo [195].

4.16. Vitamin D supplementation and osteoporosis

Bone tissue is commonly involved in RA, and osteoporosis represents the most frequent bone disease in rheumatic conditions [196]. The peak incidence of RA in women coincides with the perimenopausal period, suggesting a relationship between estrogen deficiency and development of RA [197].

Osteoporosis is a well-known extra-articular complication in RA [198,199], and an increased risk of fractures has been clearly documented in RA patients [200].

Treatment with chronic glucocorticoids (GC), together with the functional impairment associated with RA, appear to be the most relevant determinants [201], although the disease itself may also play an important role [202].

RA was considered as an independent risk factor in fracture risk assessment [203] and postmenopausal women, in whom estrogen deficiency may amplify the negative effect of RA and corticosteroid therapy on skeletal health, is representative of a high-risk population. Therefore, major scientific societies recommend specific treatment in postmenopausal women receiving glucocorticoid therapy, particularly when they have RA [204].

Vitamin D is known to play a role in calcium homeostasis and skeletal mineralization through endocrine effects on the bones,

intestines, parathyroid glands and kidneys. Vitamin D insufficiency has direct effects on bone health, through the liberalization of calcium homeostasis and an increase in serum parathyroid hormone, which negatively affects bone remodeling with increased bone resorption. In older or postmenopausal women this can exacerbate osteoporosis. Serum levels of 25-hydroxyvitamin D (25 (OH) D) < 50 nmol/L are associated with increased bone turnover, bone loss and mineralization defects resulting in increased fragility, fractures and all cause mortality [205].

There is growing evidence that vitamin D regulates many other cellular functions: Vitamin D deficiency is implicated in the pathogenesis of several autoimmune conditions. Its role as an immunoregulatory hormone is also documented [206,207].

Moreover, vitamin D shows protective effects on intestinal permeability [208] that is crucial in RA modulation [209].

Considering vitamin D dietary intake, some dietary intake-based prospective studies have failed to show any association between vitamin D and RA, except for the Iowa WHS [157,206,210].

Greater intake of vitamin D may be associated with lower risk of RA in older women, although this finding is hypothesis generating [211].

However, dietary intake is not the sole determinant of vitamin D status, because it may also be affected by latitude and sunlight exposure. If instead we consider vitamin D levels in RA and its correlation with disease activity, all meta-analyses on this topic agree in showing that serum vitamin D level is significantly low in patients with RA, vitamin D deficiency is prevalent in RA patients compared to controls, and the vitamin D level correlates inversely with RA activity [212,213].

Concerning clinical benefits of vitamin D supplementation on rheumatic diseases, a meta-analysis demonstrated a trend of reduction in rheumatic disease activity using vitamin D supplementation in RA, with a possible reduction in its recurrence [214].

In conclusion, low 25(OH)D concentrations may be associated with pain conditions and that there is a higher prevalence of osteoporosis in RA patients. The evaluation of vitamin D in the blood is mandatory in patients with RA, and supplementation must be carried out considering the blood values for the dosage [215].

4.17. Antioxidants supplementation

Free oxygen radicals (e.g. superoxide and hydrogen peroxide) as well as proinflammatory cytokines (e.g. TNF-α) are mediators of tissue damage in RA patients and have been identified in the synovial fluid of these patients. Free radicals (ROS) are generated by activated macrophages, monocytes and granulocytes and by the anoxic reperfusion reactions that can occur with the movement of the affected joints. Antioxidant micronutrients play an important role in protecting tissues from damage caused by reactive oxygen species, as they suppress the expression of cytokines and collagenase induced by TNF- α and therefore represent an additional protection mechanism for development or the progression of the RA [67,216].

4.17.1. Supplementation in RA prevention

Regarding antioxidant supplementation in preventing RA development, there are studies such as that of Cehran et al. [67] where the relationship between vitamin C and E, carotenoids and antioxidant micronutrients with the incidence of RA in elderly women is assessed, and it is shown how the intake of some antioxidant micronutrients, in particular β-cryptoxanthin and Zn, if associated with a diet rich in fruits and vegetables of the cruciferous family, can be protective against the development of RA. The prospective cohort study was conducted on 29,368 women between the ages of 55 and 69 at baseline in 1986 and follow-up surveys were subsequently performed between 1987 and 1997; the diet was assessed using a semi-quantitative questionnaire on the frequency of the foods, specifying the size of the portion or the unit for each food. Furthermore, it was asked if supplements containing vitamin C, vitamin E, selenium (Se) or Zn were used, and the dosage used on a daily basis. During 1997, 152 cases of RA were identified and the average age of onset of symptoms was 68 years with an average time of onset of symptoms from the basic survey of 1986 of 5.9 years. The study showed weak inverse associations, statistically insignificant, between the intake of total vitamin C, (food and supplement), vitamin E (supplement) and carotenoids (supplement) and risk of RA, while there was no association for the vitamin E or the carotenoids obtained from food. There was no association between α-carotene, β-carotene, lycopene or lutein/zeaxanthin with risk of RA, while on the contrary, a statistically significant inverse association was observed between beta-cryptoxanthin and risk of RA ($p = 0.005$). Compared to women who consumed quantities <40 μg/day, women who consumed quantities> 86.9 μg/day beta-cryptoxanthin were at lower risk of developing RA. Foods that contain higher amounts of beta-cryptoxanthin are 1) Red hot pepper (cayenne) 6252 μg; 2) Paprika 6186 μg; 3) Winter squash 3471 μg; 4) Khaki 1447 μg; 5) Hot pepper 1103 μg; 6) Papaya 589 μg; 7) Red peppers 490 μg; 8) Mandarin 407 μg; 9) Tangerine juice 214 μg; 10) Orange juice 169 μg.

Subsequently, the authors evaluated the role of antioxidant trace elements with the risk of RA, in particular Zn, Cu, Mn and Se were considered. They observed a statistically significant association ($p = 0.03$) between the use of zinc supplements (a dose> 15 mg/day is significantly associated with the lowest risk of RA, this reverse association was not observed considering the Zn was coming from the diet. Cu and Mn showed similar patterns, i.e. there was little association between the dietary intake of these trace elements and the risk of developing RA, while the use of Cu, Mn and Se in the form of supplements was inversely associated with the risk of RA; Cu (RR = 0.54, 95% CI: 0.28, 1.03), at an amount >1.70 mg/day, Mn an amount >3.17 mg/day (RR = 0.50, 95% CI: 0.23, 1.07), Se (RR = 0.63, 95% CI: 0.32, 1.23) (Normal supplement values: Se usually contains 100 or 200 μg/dose; Cu 0.9 mg, which corresponds to 100% of the daily value; Mn 10 mg).

Dietary intake of fruit and vegetables and the risk of developing RA was also considered, and the authors observed an inverse association, statistically significant ($p = 0.03$) with a greater consumption of fruit with quantities >83 portions per month (therefore >3 servings per day of fruit) and in particular with the consumption of oranges, the source of beta-cryptoxanthin, although for oranges, the inverse association with the risk of RA was not statistically significant. As for the consumption of vegetables, only those belonging to the cruciferous family, and in particular broccoli, has shown an inverse association with the risk of developing RA, about 35% lower, even after adjustment for other factors of risk (age, total energy intake, history of smoking, menopausal age, use of hormone replacement therapy, consumption of coffee and tea). In conclusion, the observations of this prospective cohort study have shown that the intake of certain antioxidant micronutrients, in particular beta-cryptoxanthin at a dose >86.9 μg/day, Zn supplementation, at a dose >15 mg/day, a consumption of fruit >83 servings per month and broccoli >3 servings per month or cruciferous vegetables in general >11 servings per month, can protect against the development of RA [67]. Regarding the role of vitamins C and E, the study reveals a weak protective role in the etiology of rheumatoid arthritis in accordance with other studies [217,218]. Conversely, another study found no correlation between risk and intake of antioxidants; the study by Costenbader KH et al. [216] highlights that the intake of antioxidants was not associated with the risk of developing rheumatoid arthritis or

systemic lupus erythematosus. The authors identified and confirmed cases of RA and systemic lupus erythematosus among 184,643 US women followed in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts in the 1980–2004 period; the final group included 90,721 women followed from 1980 to 2004 in the NHS and 93,922 women followed from 1991 to 2003 in NHSII. Participants in both cohorts filled out these semi-quantitative food frequency questionnaire where they reported the intake of vitamins A, C, E, alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein and zeaxanthin both from food and from supplements. The total intake of antioxidants was evaluated by calculating the "FRAP (" ferric plasma reduction capacity ") score, a method for quantifying the total antioxidant effect of a food based on the direct evaluation of the reduction of ferric iron (Fe 3 +) in ferrous iron (Fe 2+) in the presence of antioxidants. The associations between the intake of each nutrient and the risk of RA or LES was examined in proportional Cox risk models adjusted for age and multivariable of the risks. The cohort results were grouped meta-analytically using random effect models, and 787 cases of rheumatoid arthritis and 192 cases of systemic lupus erythematosus for which dietary information was available were identified. In these cohorts of women, the antioxidant intake was not associated with the risk of developing rheumatoid arthritis or systemic lupus erythematosus. In relation to other risk factors or like smoking or alcohol intake, there have been no associations between average cumulative intake of vitamins A, C or E, both from foods and supplements, in a combined or separate way [216]. In conclusion, these results do not exclude the possibility that deficiencies of one or more of these antioxidants may contribute to the pathogenesis of these autoimmune diseases, but many factors other than dietary intake, such as genetic differences in absorption or homeostatic mechanisms and environmental exposures, may influence interperson variations in plasma antioxidant levels and oxidative stress. Therefore, oxidative stress may be involved in the pathogenesis of one or both of these diseases, but this prospective longitudinal cohort study does not support the hypothesis that regular intake of a range of antioxidants in food or in the form of supplements is related to the future risk of RA or SLE development in women.

As a demonstration that antioxidant deficiencies can still contribute to the pathogenesis of inflammatory diseases such as inflammatory polyarthritis, the study by Pattison DJ et al. [219] highlights how higher consumption of fruits and vegetables, foods rich in antioxidants, can be associated with a lower risk of developing inflammatory polyarthritis (PI). This is a prospective case–control study made possible by the random investigation of the same population of two independent studies (Norfolk European Prospective Investigation of Cancer (EPIC-Norfolk) and Norfolk Arthritis Register (NOAR). The study recruited participants, men and women aged 45 to 74, between 1993 and 1997, who provided data such as age, weight, BMI height and a general lifestyle questionnaire. The dietary intake of all participants was evaluated at baseline, using a 7-day dietary diary, to get an indication of the diet, before the onset of symptoms in new PI cases. The diets of the cases were compared to the diets of a target group who had not developed inflammatory polyarthritis. Participants were asked to estimate the amount of food and drink consumed, including through photographs of the portions of various foods that illustrated whether they were small, medium or large portions. The intake of food and nutrients was expressed as the median and interquartile interval (IQR) and the Wilcoxon Sign Evaluation Test was used to compare the medians between the two groups, keeping the sets matched, while the chi square test was used to compare the proportion of cases and controls that were smokers and obese (BMI> 30). Cases reported a lower, but not statistically significant, level of average daily fruit and vegetable consumption compared to controls: cases: (g/day) 187.4 (110.0–312.5); controls: (g/day) 228.7 (162.5–326.2) and, studying the tertiles of individual fruit and vegetable intake and as a fruit + vegetable association in relation to the risk of IP, it was seen that the intake of smaller doses of fruit alone <78 g/day were associated with an increased risk of IP 1.8 (0.9–3.6) OR 95% CI p = 0.3 compared to taking higher doses> 176 g/day (1.0 OR 95% C). A significant difference in dietary intake of vitamin C was observed between cases and controls, but not for other antioxidants. In addition, 21% of cases and 7% of controls had a daily dietary intake of vitamin C below the UK RNI reference value of 40 mg/day. For those with vitamin C intake below 40 mg/day, the risk of developing PI was almost four times greater than those with intake greater than 40 mg/day (3.9 (1.5–9.7) OR 95% CI.

Low intake of vitamin E and beta-carotene were weakly associated with an increased risk of PI: Vitamin E < 5.3 (mg/day) 1.3 (0.6–3.2) OR 95% CI p = 0.5; beta-carotene <1305 (micrograms/day) 1.3 (0.6–2.7) p = 0.6. In conclusion, this study shows that the consumption of fruit and vegetables and, in particular, the dietary intake of vitamin C, can play an important role in the development of PI; people who consumed less than 56 mg of vitamin C per day (while higher than the UK reference RNI of 40 mg/day) had a 3 times higher risk of PI risk compared to those who consumed more. These observations could have implications in the primary prevention of inflammatory pathologies [219].

In conclusion, although the literature is not completely concordant, supplementation with antioxidants (selenium: 100 or 200 μg/dose; copper 0.9 mg; manganese 10 mg; > 86.9 μg/day beta-cryptoxanthin; zinc: > 15 mg/day; vitamin C: >40 mg/day) can be a useful strategy to prevent the development of RA.

4.17.2. Supplementation with antioxidants in the symptoms of RA

4.17.2.1. Vitamins and minerals. In a study in 40 women with RA, daily supplementation with 50 μg Se, 8 mg Zn, 400 μg vitamin A, 125 mg vitamin C, and 40 mg vitamin E improved clinical outcomes and alleviated oxidative stress in RA. In this study, there was a significant improvement in disease activity but not in the number of painful and swollen joints. The antioxidant levels in erythrocytes were increased [220].

There is a significant association of low serum selenium levels and RA. Serum copper levels are reported to be positively correlated with disease activity in RA. There is a significant association of low serum selenium levels and RA [221].

Low serum concentrations of albumin, Zn, and Se were independently related to disease activity index in an evaluation of trace elements in 110 patients with RA [222].

Fe also has an important role in maintaining normal immune function. Deficiency of Fe and anaemia may hamper the immunological balance in RA [223].

Complex interactions of the pro-inflammatory cytokine, IL-6, the iron regulatory hormone, hepcidin, and the iron exporter, ferroportin, underlie the impaired iron homeostasis in anaemia associated with inflammation [224]. Correction of anaemia can help improve the physical activity and quality of life in patients with rheumatic diseases [225].

4.17.2.2. Dietary antioxidant botanical supplement: quercetin and resveratrol. There are studies that have shown that quercetin has strong antioxidant and anti-inflammatory effects, including the inhibition of immune cells such as macrophages and the secretion of inflammatory cytokines such as interferon-gamma (IFNg), TNF-α and IL-2 [226,227]. In some studies, quercetin has been shown to reduce RA in animal models and reduced sensitivity to pain [228,229]. In the study of Javadi J et al. [230] the authors studied the effect of quercetin supplementation on inflammation, disease

severity, and clinical symptoms in women with RA, and showed that 500 mg/day supplementation of quercetin for 8 weeks demonstrated significant results, with improvements in clinical symptoms, disease activity, inflammation factor-TNF-α, and the well-being of those women. This was a randomized, double-blind, placebo-controlled clinical trial in which 50 women with RA were assigned to a group treated with 500 mg/day of quercetin (25) or placebo (25) for 8 weeks; average age 48 years. Plasma levels of TNF-α with high sensitivity, ESR, and clinical symptoms including morning stiffness (EMS), morning pain, post-activity pain and joint swelling were measured. Disease activity and functional disability were assessed with the score DAS-28, the overall assessment was assessed by a doctor, and a health assessment questionnaire was made at the start and end of the study. There was no significant difference in baseline characteristics such as BMI, age, disease duration, physical activity and medications between 2 two groups and there was no significant difference in macro and micronutrient intake between the 2 groups. After intervention a significant difference in hs- TNF-α levels was observed between the 2 groups and in the quercetin group compared to the start of the study, and it was also observed a significant reduction of morning stiffness in the intervention group compared to placebo and compared to baseline. Quercetin supplementation reduced the DAS-28 and Health Assessment Questionnaire (HAQ) score in the treated group and the differences were significant compared to the placebo group. The results of this study showed that quercetin supplementation at a dose of 500 mg per day as an adjunctive treatment had beneficial effects on pain, stiffness, disease activity, hs-TNF-α and well-being in women with RA [230].

In conclusion, as demonstrated by other studies on the subject, quercetin supplementation had positive effects on synovial cells, controlling and reducing the clinical symptoms and severity of arthritis [231].

Resveratrol (RSV), a naturally occurring polyphenol, also has powerful antioxidant, anti-inflammatory and anti-cancer effects. Studies have shown that it exerts a variety of beneficial actions such as prolonged lifespan in animal models and a protective effect against diabetes mellitus has been found [232,233].

In the study of Hani M. Khojah et al. [234] a randomized controlled clinical trial, the aim of the authors was to shed light on the therapeutic benefits of RSV in the treatment of RA in patients with different stages of disease activity. In particular, 100 RA patients (68 females, 32 males) were recruited, randomly enrolled and divided into two groups, each consisting of 50 patients: one group treated with RSV, who received one capsule of RSV per day of 1 g with the conventional treatment (DMARDs) for 3 months, and a control group that received only conventional treatment. Biochemical markers such as RF, matrix metalloproteinase-3 (MMP-3), osteocalcin under carboxylated (UCOC), IL-6, TNF-α, CRP and ESR and the clinical symptoms of RA (joint count for swelling and tenderness SJC-28 and TJC28) have been evaluated in both groups. Clinical and biochemical indices have changed dramatically, in favor of RSV treatment after the treatment period. Except positivity to the rheumatoid factor, which had decreased significantly in the group receiving RSV, CRP had decreased significantly and the other biochemical markers (e.g. ESR, ucOC, MMP-3, TNF-α, IL-6) were significantly decreased, in the group being treated. Similarly, the clinical markers (SJC-28 and TJC28) and DAS-28-ESR had significantly decreased in the RSV group. The highest and lowest DAS28-ESR score for the treated group was 4.89 and 1.74 respectively, while the highest and lowest values for the control group were 6.31 and 3.17, respectively. Therefore, in this study, the RSV group showed a significant drop in the main clinical and biochemical markers involved in the mechanism of disease activity.

In conclusion, the administration of oral resveratrol in the dose of 1 g per day in patients with RA improved management of the disease by reducing its activity and some of its clinical and biochemical markers [234]. The improvement in disease activity may be the result of changes in bone mineral metabolism and actions of cytokines involved in the etiopathogenesis of RA, supported by the antioxidant effect of RSV through the reduction of oxidative stress. Therefore, the suggested use could be 1 g of resveratrol as an adjuvant to conventional antirheumatic agents. The results may also confirm the beneficial effect of wine, which is rich in RSV, on the activity of RA disease as seen by Di Giuseppe D et al. [144].

In conclusion, the antioxidant supplements (literature recommends: 50 μg of Se, 8 mg of Zn, 400 μg of vitamin A, 125 mg of vitamin C and 40 mg of vitamin E per day) and dietary botanical supplement with quercetin (500 mg/day) and resveratrol (1 g/day) have a reasonable probability of ameliorating symptoms.

4.18. Salt/sodium

Studies in animal models and on human cells have shown the effect of sodium chloride (NaCl) on T_H17 cells in promoting inflammation, which may be the reason for its proposed association with RA [235].

Moreover, there is evidence that increased NaCl, activates proinflammatory macrophages (M1), Th17 cells and decrease T-regulator cells, all crucial players in RA pathogenesis [236]. In addition, sodium excretion was recently found to be higher in patients with early RA than in matched controls [237].

Finally, a recent study suggests that NaCl can aggravate arthritis by affecting Th17 differentiation, and so this study demonstrates a pro-arthritic effect of salt in an animal model [238].

In humans, a study links excessive salt consumption with a greater risk of developing rheumatoid arthritis [239].

The high consumption of salt also appears to be correlated with the inhibition of the secretion of Treg cells responsible for tolerance towards “self” antigens [240].

Excessive salt intake also seems to make Treg acquire the Th1, Th2 or Th17 phenotype [241]. This mechanism seems to be related to SGK1 kinase (serum/glucocorticoid regulated kinase 1), which plays a central role in many pro-inflammatory cascades and in many regulatory mechanisms [240].

It is also involved in the activation of the K, chlorine (Cl) and Na channels and in the response to cellular stress, and also in the induction of Th17 cells; the activation of SGK1 by high NaCl intake causes Treg cells to acquire the phenotype of Th1 type cells with an increased proliferation [242].

In conclusion, limiting salt intake may be helpful for treating RA.

4.19. The impact of fasting on RA

In recent years, numerous new therapeutic concepts for RA have been developed; between these, there is fasting mimicking diets. Two very recent reviews considered this topic and demonstrated that fasting resulted in significant, but transient subjective improvements [243,244] confirming the results reported in previous reviews [245–247].

5. Conclusions

Recent literature suggests that diet plays a pivotal role in therapy of RA, through management of inflammation, immunity and oxidative stress. Considering that a specific diet can be helpful support for patients suffering from RA, this narrative built a food

pyramid on this topic, as the food pyramid allows patients to easily understand what best to eat.

The proposed pyramid is very similar to that recommended for the general population [248], however, there are significant differences: 1. at the base there are the 5 portions of fruit and vegetables (specifying the most useful types of vegetables to eat) instead of the carbohydrates; 2. with regard to carbohydrates it is noted that glute-free carbohydrates are preferable for patients with RA; 3. the seeds have been introduced as daily consumption: 4. 2 flags have been added that underline that patients with RA must avoid the intake of salt and simple sugars and that it is useful to take a supplement of vitamin D, omega 3 and antioxidants.

The main limitation of this narrative review is that this nutritional pyramid is hypothetical, because clinical trials are few and consequently the levels of evidence are predominantly between moderate and low. In any way, we hope that it can serve the valuable purpose of helping researchers focus on the often-ignored possible connections between immunity, nutrition and RA, as already reported in the Cochrane of 2009 [249].

Further future investigation is needed; specifically, more randomized clinical trials should be conducted that directly study nutrition, symptoms, and/or progression of RA, in order to understand the specific mechanisms that interconnect the regulation of immunity, inflammation, oxidative stress and nutrition.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare non conflict of interests.

Acknowledgments

None.

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