

# Can dietary intervention be an auxiliary therapy for Rheumatoid Arthritis?

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Review

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**ABSTRACT**

Diet is an important environmental factor in the process of rheumatoid arthritis (RA) development. In the clinic, patients with RA often inquire about dietary advice. Dietary intervention has become an attractive alternative option for rheumatism because of dissatisfaction with pharmacological treatments and the increasing demands for therapeutic efficacy. Different nutrients in the diet and different dietary patterns affect RA in various ways. Some nutritional ingredients and dietary choices such as omega-3 polyunsaturated fatty acid, cheese lactobacillus, Mediterranean diet and vegetarian diet are beneficial for the control and mitigation of RA. Inappropriate iron supplement, high sugar and high fat diet have adverse effect on RA in patients. Though several recommendations on dietary intervention could be given based on existing research, more accurate and definitive studies are still needed to explore the auxiliary therapeutic effect of dietary intervention on RA.

**Keywords:** Rheumatoid arthritis; Dietary intervention/pattern; Nutritional supplements

**INTRODUCTION**

Rheumatoid arthritis (RA) is one of the most common rheumatic diseases, affecting about 0.5-1% of the global population[1]. It is a chronic autoimmune disease characterized by systemic inflammation and ensuing joint damage, which requires persistent drug intervention. How RA is initiated is still unclear, but initiation is widely considered to be the consequence of a combination of genetic and environmental events. Diet is an important environmental factor that received more close attention before the shift toward anti-rheumatic drugs development. A large number of earlier studies reported on the effects of dietary intervention on the initiation and progression of RA, although the efficacy of dietary change was relatively

weak[2]. With development and application of anti-rheumatic drugs, survival and prognosis of RA patients have been greatly improved, whereas some patients still achieve poor clinical remission. Nearly 30-40% of RA patients experienced a decline in working ability in 5 years after diagnosis, and one-third of RA patients terminated their occupation in advance[3]. With the increasing demands on the efficacy of RA treatment, dietary intervention has reemerged as a viable alternative for clinical research on RA therapy. Diet may affect RA processes by interfering with inflammatory activities, adjusting lipid metabolism, increasing antioxidant levels and changing intestinal flora[4]. In this review, we will summarize the latest studies on nutritional composition and dietary patterns, and explore the auxiliary therapeutic effect of dietary intervention on RA.

## 1. Nutritional Supplements

### 1.1 Fatty Acids

Fatty acids (FAs) are one of the important nutrients in the body. They are divided into short chain FA, medium chain FA and long chain FA according to respective carbon chain length. In addition, FA can also be categorized by respective degree of unsaturation: saturated fatty acid (SFA), monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA).

MUFA are the fatty acids containing single double bonds in the carbon chain, and include oleic acid abundant in olive oil. Intake of MUFA in RA patients was significantly lower than that in the healthy individuals, while RA patients with high MUFA intake tended to have lower disease activity[5]. MUFA may play an inhibitory role in disease activity of RA[5].

PUFA have more than one double bond in the carbon chain and can be divided into two series, omega-3 and omega-6, based on different positions of the first double bond. The omega-6 PUFA mainly includes arachidonic acid, linoleic acid and  $\gamma$ -linolenic acid. The omega-3 PUFA, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are important fatty acids unable to be synthesized in human but rich in deep-sea fishes. Omega-3 PUFA is able to reduce the production of pro-inflammatory cytokines, while omega-6 PUFA stimulates release

these cytokines[6]. Arachidonic acid, mainly derived from animal fat, is a semi-essential fatty acid in humans and can be metabolized into prostaglandins, leukotrienes, thromboxane and other eicosanoids, which promote the inflammation progression. However, EPA, DHA and other omega-3 PUFA can suppress inflammation by inhibiting the transformation of arachidonic acid into eicosanoid[6], synthesizing anti-inflammatory agents such as lysin and protectin, and down-regulating the expression of pro-inflammatory genes through G protein-coupled receptor 120 (GPR120)[7].

A large Swedish prospective study using food frequency questionnaires showed that long-term consumption of the long chain omega-3 PUFA reduced the risk of developing RA in middle-aged and older women[8]. With a daily intake of more than 0.21g of long-chain omega-3 PUFA, risk of RA decreased by 35% while the long-term continuous intake higher than 0.21g/day could lower the risk by 52%. This study also indicated that individuals who consumed one fish per week had 29% lower risk of developing RA than those who did not consume fish or ate less than one per week[8]. In addition, a nested, case-control study of disease-free first-degree relatives of RA patients and HLA-DR4 allele carriers showed that the intake of omega-3 fatty acids and its level on red blood cell membranes were inversely correlated with serum anti-cyclic citrullinated peptide type 2 (Anti-CCP2) antibody[9]. For RA patients, omega-3 PUFA supplements can alleviate pain, decrease the number of tender joints, improve morning stiffness and reduce the dosage of non-steroidal anti-inflammatory drugs (NSAIDs)[10]. A recent retrospective analysis also found that omega-3 PUFA reduced serum levels of leukotriene B4 and triglyceride in RA patients[11]. In summary, omega-3 PUFA has a protective effect on the general and RA-prone population.

### 1.2 Vitamins

Researchers have noticed the correlation between vitamin D deficiency and RA prevalence, especially as a consequence of solar exposure. This relationship was confirmed after taking into account abundant

sunshine and relatively low prevalence of RA in low latitudes[12, 13]. It has become clear that the role of vitamin D in the body exceeds the modulation of calcium absorption and bone metabolism. Vitamin D also has anti-inflammatory and immunoregulation function[14]. Vitamin D can block the differentiation of monocytes into dendritic cells, reduce antigen presentation by macrophages and induce the activation of regulatory T (Treg) cells. Moreover, it inhibits the function of T helper (Th)-1 cells, intervenes in the synthesis of interleukin (IL)-12, IL-1, IL-6 and tumor necrosis factor (TNF)- $\alpha$  and suppresses the proliferation of B cells, plasma cell differentiation and antibody production[14].

In collagen-induced arthritis(CIA) mice, vitamin D receptor agonist can not only prevent the occurrence of diseases, but also relieve symptoms of established arthritis[15]. In RA patients, the efficacy of vitamin D intervention is controversial. Indeed, a large number of studies have confirmed that vitamin D deficiency exists in RA patients in different countries and low levels of vitamin D are associated with increased disease activity, glucocorticoid dosage and RA complications[16]. Another study documented an inverse correlation between the severity of depression and anxiety in RA patients and the level of serum vitamin D3[17]. However, a randomized, double-blind, placebo-controlled trial indicated that vitamin D supplementation did not improve disease activity in RA patients[18]. Meanwhile, a prospective cohort study revealed that adolescent vitamin D intake does not reduce the incidence of adult-onset RA[19]. Although, vitamin D is currently mainly used to prevent and treat osteoporosis in RA patients, it may still be an alternative option for clinicians to supplement certain amounts of vitamin D for RA patients with vitamin D deficiency[16].

Previous studies have shown that high consumption of red meat is a risk factor for inflammatory polyarthritis (including RA), while the consumption of fruits and vegetables can reduce the risk[20, 21]. Research has suggested that antioxidant ingredients in plants such as vitamin A, C and E may play a protective role in RA[20, 22]. A prospective cohort study of 29,368 women reported that vitamin C and E supplement reduced the risk of RA developing[22]. Howev-

er, the effectiveness of supplemental antioxidants on disease activity of RA remains controversial. Jalili M et al. indicated that vitamin A, C and E supplement reduced the oxidative stress level and significantly improved the disease activity of RA, but had no effect on reducing the numbers of painful and swollen joints [23]. Some studies found that there was no significant change in RA activity after vitamin A and C supplement[24], and the clinical effect of vitamin E is very weak or unavailable[25].

### 1.3 Phytochemicals

Phytochemicals are bioactive chemical compounds existing in fruit, vegetables, grains, and other plant food. Over 5000 phytochemicals have been identified, but the effects of most of them on human remain unclear[26]. Other chemicals, such as phenolic acids, flavonoids, diarylheptanoids and stilbenes are well studied and were reported to have anti-inflammatory [27], anti-tumor[28] and immunomodulatory functions[29]. Considerable researches also reported the immunoregulatory effects on T and B cell immune response and inhibitory role in signal pathways such as NF- $\kappa$ B, MAPKs, and Jak-Stat in RA[30-32]. These suppressive effects of chemicals consequently reduce the production of cytokines, chemokines and inflammatory extracellular matrix enzymes[33]. In addition, phytochemicals may play a protective role in the occurrence and development of RA[25]. Unfortunately, current researches have only been conducted in animal experiments and cell experiments *in vitro*, the effectiveness of these substances in RA patients still needs further clinical trials.

### 1.4 Alcohol

It is interesting that moderate alcohol consumption in the general population can reduce the level of inflammatory cytokines[34]. However, the effect of alcohol on RA patients depends on several factors including alcohol quantity, the frequency and drugs taken concomitantly. Conventional disease-modifying antirheumatic drugs (DMARDs), glucocorticoid and NSAIDs are often used in the treatment of RA, however they have gastrointestinal side effects and liver toxicity. Alcohol intake can increase the chance of the

emergence and severity of these adverse effects[2]. Therefore, total abstinence from alcohol is recommended by clinical doctors during the application of these drugs. However, in the case of rebalancing potential confounding factors including drug use, a large study of the UK reported that alcohol intake could reduce the risk of RA. Meanwhile, the disease severity parameters of RA patients including C reactive protein (CRP), disease activity score of 28 joints (DAS28), visual analogue scale (VAS) score, Improved Health Assessment Questionnaire (MHAQ) and Larsen score were negatively related to alcohol intake frequency[35]. Another study drew a similar conclusion that moderate drinking (5.1-10.0g/day) can significantly reduce patients' MHAQ scores[36]. A multi-center study on early RA patients in Sweden also showed that alcohol consumption in female patients was associated with lower disease activity and higher quality of life. Interestingly, no correlation was observed in male patients[37]. Although the above studies show that alcohol consumption may have particular benefits for RA patients, the mechanism of alcohol influencing the pathological process of RA needs further detailed studies. Up to date, the rational advice seems to abstain from alcohol during drug therapy. Limit alcohol consumption to 5.1-10.0g/day is recommended during remission to maximize the benefits of alcohol[36].

### 1.5 Probiotics

Many studies have reported the changes in the intestinal flora of RA patients[38], indicating probiotics might be a wise intervention method to correct the imbalance of the patients' bacterial flora[39]. *Bifidobacteria* and *lactobacillus* are the most commonly used probiotics. Arthritis symptoms of CIA mice were significantly improved after feeding *lactobacillus casei*. The levels of pro-inflammatory cytokines IL-1 $\beta$ , IL-2, IL-6, IL-12, IL-17, interferon (IFN)- $\gamma$  and TNF- $\alpha$  were significantly decreased, while the expression of cytokines IL-10 and TGF- $\beta$  were significantly increased[40-42]. Similarly, the administration of *rhamnose GG lactobacillus (LGG)*, *bulgarian lactobacillus* and yogurt significantly reduced the joint score in rat tropomyosin arthritis

model[43]. *Escherichia coli O83* treatment was able to increase the anti-inflammatory effect of methotrexate in RA treatment[44].

In RA patients, a randomized double-blind study showed that *lactobacillus casei 01* can help alleviate symptoms in RA patients and reduce the expression of inflammatory cytokines compared with placebo [45]. The level of highly sensitive C reactive protein (hs-CRP), number of tenderness joints and swollen joints, overall health score and DAS28 score were significantly reduced after 8 weeks of treatment with *Lactobacillus*. IL-12 and TNF- $\alpha$  levels in serum were decreased, while IL-10 levels were increased[45]. Compared with placebo, taking *LGG* capsules twice a day could remarkably reduce the number of tenderness and swollen joints in RA patients, but there was no significant difference in the levels of serum IL-6, TNF, IL-10 and IL-12 between the two groups[46]. A recent meta-analysis showed that probiotics supplementation reduced the expression of IL-6 in RA patients versus the placebo group, but there was no significant difference in disease activity between the two groups[47].

These studies suggest that probiotics to the different extent affect the improvement of RA. Detailed studies are still needed on the development of specific probiotics targeting to remedy microbiota disturbance in RA.

### 1.6 Micronutrients

The content of micronutrients in the body is extremely low, but they play an important role in the physiological condition of the body. Some studies have showed that serum levels of zinc and selenium in RA patients were significantly decreased and negatively correlated with disease activity[48, 49]. On the other hand, serum copper in sera of RA patients was higher than that in healthy people, and positively correlated with disease activity[49]. A study showed that antioxidants including zinc, selenium, vitamins A, C and E could improve the oxidative stress of RA and reduce disease activity in patients[23]. In addition, the content of free iron, lactoferrin and other iron-binding proteins in joint synovial fluid of RA patients was higher than that of healthy people. Iron supple-

ment may have adverse effects on RA patients without deficiency[50].

## 2. Dietary Pattern

Dietary patterns vary in region, population and country. Different dietary pattern has the representative combination of elements which may affect RA development differently.

### 2.1 High sugar and high fat Diet

High sugar and fat are important features of the western diet model, which usually has adverse effects on RA patients. A large prospective study of American nurses found that sugary sodas could increase the risk of RA with serum rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPAs) positive. The risk of serum positive RA increased by 63% after drinking 1 bottle of carbonated beverage per day compared with no or less than 1 bottle per day[51]. At the same time, Jhun JY et al. found that a high fat diet did not affect arthritis occurrence in CIA mice, but continuous feeding mice with high fat diet would lead to more serious joint inflammation after successful modeling[52]. However, Kim SJ et al. found that the high fat diet did not affect the severity of joint inflammation in the CIA model but did lead to an earlier onset of arthritis[53]. Although the results of the two studies are not consistent, it is generally recognized that obesity caused by high sugar and high fat diet is a risk factor for RA[54]. Further studies revealed a gender bias for the impact of obesity on RA. Overweight and obese women have a higher risk of developing RA than women who are not over weight and among female RA patients diagnosed before 55 years of age, RA is correlated with obesity[55]. Obese men, on the other hand, have a reduced risk of RA[56]. Compared with non-obese patients, obese RA patients generally have worse disease activity (DAS28), inflammatory index, number of joint tenderness, overall pain score and physical function score[57]. Although obesity does not increase the mortality rate of RA patients, it is still believed that prevention and reversal of obesity can improve the prognosis and quality of life for RA patients[57].

### 2.2 Mediterranean Diet

Mediterranean diet is primarily a plant-based diet that includes plenty of fruit, vegetables, whole grains, fish, olive and canola oils, along with some red wine and low amounts of red meat, sugar and saturated fat. Its beneficial effects may come from a variety of sources, including unsaturated fatty acids in fish and olive oil, phytochemicals, moderate amounts of alcohol and probiotics in cheese and yoghurt.

It was reported that compared with conventional western diets, Mediterranean diet can reduce inflammatory activity in RA patients, improve their physical function and increase their vitality[58]. A British study showed that the VAS and HAQ scores of RA patients decreased significantly after 3 months of initiating a Mediterranean diet. After 6 months on the Mediterranean diet, the overall evaluation of disease activity, VAS score and morning stiffness were significantly improved[59]. However, an American study of nurses' health found no correlation between Mediterranean diet and the risk of RA[60]. Does Mediterranean diet have an effect on population with RA, but do not protect people where the disease has not yet appeared? More researches are required to answer this question[61].

### 2.3 Vegetarian Diet

Vegetarianism is a dietary mode that does not include animal products such as meat, birds, seafood, with or without consuming eggs, milk and honey. Some studies have confirmed the benefits of the vegetarian diet for RA[39]. Early in 2000, a study had found that the benefits of vegetarianism might come from antioxidants, dietary fiber and lactobacillus, which would change the gut microbiota and play a salutary role in the course of RA[62]. Results from a single-blinded diet intervention experiment showed that RA patients with moderate to severe disease activity had a significant loss of weight after four weeks of low fat (less than 10%) vegetarian diets, and all measures of clinical symptoms improved significantly except for the duration of morning stiffness. Erythrocyte sedimentation rate (ESR) was not changed, and the serum CRP and RF decreased although there was no statistical difference[63]. Further study revealed that RA im-

provement from non-dairy vegetarianism, strict vegetarianism and Mediterranean diet was independent of weight loss[64].

**Table 1:** The effects of diets on rheumatoid arthritis and relevant suggestions

	Impact on Mor-	Impact on Disease Activity	Advice
<b>Nutritional Supplements</b>			
MUFA		Good for remission[5]	Moderate supplementation
Omega-3 PUFA	Reduce the risk of the disease[8]	Improve pain, number of tenderness joints and morning stiffness, and reduce the dosage of	Long-term supplementation is recommended, and preferably greater than 0.21g/ day[8]
Vitamin D	Controversial[16-19]	Controversial[16-19]	Recommend long-term regular supplementation to prevent and treat osteoporosis, Recommend moderate supplementation to improve Vitamin D deficiency in RA patients
Vitamin A,C,E	Reduce the risk of the disease[21,	No significant improvement[23, 24]	Only need to satisfy self nutrition demand
Phenols, Flavonoids, Diarylheptanes and		Improve the disease in animal experiments[30-33]	More researches are needed
Alcohol	Reduce the risk of the disease[35]	Moderate doses can improve disease activity and quality of life[35, 36]	Alcohol is still not recommended during drug therapy given its hepatotoxicity and gastrointestinal side effects. Moderate drinking during remission
Probiotics		Debated, <i>lactobacillus casei 01</i> can relieve RA symptoms[45]	Moderate supplementation
Zn/Se		Serum levels are negatively correlated with disease activity[48,	Only need to satisfy self nutrition demand
Cu		Serum levels are positively correlated with disease activity[49]	Only need to satisfy self nutrition demand
Fe		Levels increase in synovial fluid during disease activity[50]	No recommendation without iron deficiency[50]
<b>Dietary Pattern</b>			
High sugar diet	Increase the risk of serum positive RA[51]		Obesity is a risk factor for women with RA[55], and obesity reduces the odds of disease remission[57]. Therefore, body weight control and less high sugar and high fat diet intake are necessary for RA patients.
High fat diet	Controversial[52,	Controversial[52, 53]	
Mediterranean Diet	Do not reduce the risk of disease [60]	Reduce inflammatory activity, improve VAS score and morning stiffness[58, 59]	Recommend
Vegetarian diet		Improve RA symptoms expect for morning stiffness[63]	Recommend only when meeting nutritional requirements
Fasting		Improve RA symptoms temporarily[65]	Do not recommend, because there are no special benefits
Gluten-free Diet		Uncertain[68]	If not combined with celiac disease and gluten allergy, do not recommend
Dairy-free Diet		Temporarily alleviate disease conditions[71, 72]	If not dairy products intolerance, do not recommend

## 2.4 Fasting

Although a balanced diet is nutritionally important, short-term fasting can be beneficial. Fasting is thought to reduce the pain and inflammation of RA patients[65], but the effect is temporary, and may disappear after resuming regular diets. It was reported that fasting followed by a vegetarian diet may have a longer-term therapeutic effect on the RA, but similar studies have been rare and more evidence is needed[66]. Additional research suggested that the mitigation of inflammation may be due to the increased mobilization of fat after fasting and the large amount of anti-oxidative ketone bodies had been by metabolism of fatty acids in the liver[67].

## 2.5 Gluten-free Diet

A gluten-free diet is a diet that excludes the protein gluten. It is essential for people with gluten-related medical conditions like celiac disease. Many people with celiac disease may suffer from joint pain, meanwhile RA patients may have gastrointestinal manifestations. Although the specific antibodies of the two diseases and the HLA susceptibilities are different, the two diseases share multiple non-HLA genetic loci as recently reviewed[68]. There may be correlations between two diseases[68]. After initiating a gluten-free diet, joint symptoms of celiac patients were significantly improved, however, a role for gluten in RA has not been determined[68]. Although there were studies showing that antibodies against  $\beta$  lactoglobulin and gliadin in the serum notably declined[69], and serum levels of low density lipoprotein and oxidized low density lipoprotein significantly decreased[70], the effectiveness of this diet needs to be further confirmed.

## 2.6 Dairy-free Diet

Dairy products are rich in nutrients such as proteins and calcium. According to research by Panush RS, symptoms of RA patients could be temporarily eased after a fully removal of dairy products from the diet, while joint swelling and stiffness returned when dairy products were re-introduced[71, 72]. It is still not recommended to use a completely dairy-free diet to

control RA[73].

## CONCLUSION

As an important environmental factor, the impact of the diet on RA is bidirectional. Some nutritional ingredients and dietary patterns such as omega-3 PUFA, cheese lactobacillus, Mediterranean diet, vegetarian diet are beneficial for the control and mitigation of RA, while high sugar and high fat diet, inappropriate iron supplements have adverse effects on RA patients (Table 1). Due to the insufficiency of research methods, low compliance of experimental subjects, less attention paid by researchers, the impact of many nutrients on RA are still controversial. Dietary recommendations exclusively belonging to RA patients are still difficult to make. But clinicians can give RA patients some dietary guidelines based on existing researches (Table 1). More accurate and detailed studies are worth expecting to develop more effective nutritional additives, or to exploit recipes and dietary patterns that are more reasonable and beneficial to RA therapy.

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