

## ROMATOİD ARTRİTİN KLİNİK TEDAVİSİNDE KULLANILAN DİYET YAKLAŞIMLARININ DEĞERLENDİRİLMESİ

### AN EVALUATION OF DIETARY APPROACHES USED IN THE CLINICAL MANAGEMENT OF RHEUMATOID ARTHRITIS

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#### ÖZET

Romatoid Artrit (RA), populasyonun %0.5-1.0'ini etkileyen sistemik inflamasyon, kalıcı sinovit ve diğer komorbiditelerle karakterize bir kronik, otoimmün bozukluktur. Uzun süreli aktif RA şiddetli eklem hasarı, ağrının engellenememesi, yaşam kalitesinde düşüğe neden olmaktadır. RA'nın etiolojisi tam olarak anlaşılamamıştır ancak doğuştan gelen ve edinilmiş bağışıklık sistemlerinin tepkileri arasındaki etkileşimden kaynaklandığı düşünülmektedir. RA, kan dolaşımında Romatoid Faktör ve anti-sitüline peptid antikotlarının varlığı ile karakterize edilmektedir. Ayrıca Romatoid artrit ile ilişkili immünitelerde bağırsak mikrobiyomunun önemi olduğu vurgulanmaktadır. Mikrobiyotadaki değişikliklerin, hastalığın riski ve şiddeti ile ilgili olduğu düşünülmektedir. Başta akciğerler, ağız mukozası ve gastrointestinal sistem olmak üzere üç bölge, mikrobiyotada görülen değişiklikler ile ilişkilendirilmiştir. RA'nın farmasötik tedavisi genellikle; ağrıyı ve inflamasyonu yönetmek için kullanılan steroidal olmayan anti-inflamatuar ilaçları (NSAID's) ve hastalığı yavaşlatarak ağrıyı azaltan anti-romatizmal ilaçları içerir. Ne yazık ki birçok hastada remisyon olasılığı düşük olmakla birlikte, ilaçlarla ilgili yaygın yan etkiler rapor edilmektedir. Hastalarda bazı çevresel ve yaşamsal değişikliklerin semptomları şiddetlendirdiği ve dolayısıyla RA'nın şiddetini etkilediği düşünülmektedir. Örneğin RA hastaları, kırmızı et, alkollü ve alkolsüz içecek tüketiminin semptomlarını kötüleştirdiğini; balık ve yaban mersini gibi besinlerin ise semptomlarını hafifletmeye yardımcı olduğunu ifade etmektedir. RA'nın semptomlarını yönetmek amacıyla; inflamasyonu azaltmada, antioksidan seviyelerini artırmada ve lipid profillerini iyileştirmede potansiyel diyet değişiklikleri önerilmektedir. Romatoid Artrit'in hem başlangıcında hem de hastalığın şiddetinde, diyetle ilgili meydana gelen antijenik yük ve gıda sensitivitesinin rol oynadığı düşünülmektedir. Bunun yanında RA hastalarında kullanılan NSAID ilaçlar ile hastaların bağırsak mukozasının alerjenlere karşı daha geçirgen olduğu gösterilmektedir. Bu anlamda Eliminasyon diyeti, Akdeniz Diyeti, Vegan/vejetaryen Diyet yaklaşımı; Omega-3 yağ asidi, D vitamin ve probiyotik takviyesinin hastalık aktivitesini azalttığı düşünülmektedir. Bu derlemenin amacı, RA ile ilişkili semptomları azaltmak için kullanılan belirli diyet yaklaşımlarının ve besin takviyelerinin etkinliğini, literatürde bilimsel kanıtlara dayanarak değerlendirmektir.

**ANAHTAR KELİMELER:** Artrit Romatoid, Diyet yönetimi, Diyet, Akdeniz, Vejetaryen

#### ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by systemic inflammation, persistent synovitis, and other comorbidities, that affects 0.5-1.0% of the overall population. Long-term active RA causes severe joint damage, disabling pain and diminished life quality. The etiology of RA is not accurately understood, but it is thought to be due to an interaction between the responses of the innate and acquired immune systems. RA is characterized by the presence of Rheumatoid Factor (RF) and anti citrullinated peptide antibodies in the blood circulation. Also the composition of intestinal the gut microbiome is claimed to be critical in immune responses associated with RA. Changes in the microbiota are thought to be related to the risk and severity of the disease. Three regions; primarily the lungs, oral mucosa and gastrointestinal tract have been associated with changes in the microbiota. Commonly, the pharmaceutical treatment of RA includes non-steroidal anti-inflammatory drugs (NSAIDs) that are used to manage the pain and inflammation associated with RA and disease-modifying anti-rheumatic drugs that reduces pain by slowing down the disease. Unfortunately, remission is not likely in many patients. Moreover, side effects related to drugs are commonly reported. Some alterations in the patients' life and environment are thought to aggravate symptoms, thus influencing severity of RA. For example RA patients, the participants asserted that consumption of red meat, alcoholic and non-alcoholic beverages worsen their symptoms, while nutrients such as fish and blueberries help alleviate the symptoms. To manage the adverse effects of RA, particular dietary alterations are suggested to be effective in reducing inflammation, increasing antioxidant levels, and improving lipid profiles. Antigenic load and food intolerance are thought to play a role in both the onset of Rheumatoid Arthritis. Besides, it has been shown that the intestinal mucosa of the patients would have become more permeable to allergens due to long term NSAIDs use. In this sense, Elimination Diet, Mediterranean Diet, Vegan/Vegetarian Diet approach, Omega-3 Fatty acids, Vitamin D and probiotic supplementation is thought to reduce disease activity. The purpose of this review is to evaluate the efficiency of certain dietary approaches and supplements used for lessening the RA related symptoms, based on the scientific evidence found in the literature.

**KEYWORDS:** Arthritis Rheumatoid, Dietary management, Diet, Mediterranean, Vegetarian

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by systemic inflammation, persistent synovitis, structural bone damage and other comorbidities, that affects 0.5-1.0% of the overall population. Both genetic and environmental factors are believed to be play a role in the pathogenesis of RA (1). Fatigue, severe pain, loss in certain bodily functions due disabling effects in the bone structure are commonly reported symptoms. Besides, when it is the "end stage", in which inflammation ceases but the damage persists, surgical intervention may be necessary to alleviate joint pain (2).

The underlying pathogenic mechanism of RA is highly complex, involving an unhealthy interaction between innate and acquired immune responses. Immunological markers such as Rheumatoid Factor (RF) and anticitrullinated peptide antibodies are generally found in the patients' blood, even before any signs or symptoms of joint inflammation appear. Thus, it is thought that the activation of autoimmune responses may occur in regions, such as the gastrointestinal system, other than the usual location of inflammation, namely joints (3, 4). The first step in the treatment of RA is disease-modifying antirheumatic drugs (DMARDs) which suppress disease activity and reduce joint damage. With the development of more effective therapeutic agents such as tumor necrosis factor (TNF) alpha inhibitors or the combination of DMARDs with other drugs, some remission can be achieved in most patients. However, there are many patients whose disease symptoms persist despite the pharmacotherapy (5). Yet some alterations in personal life and environment are believed to alleviate the disease's severity. For instance, some "dietary approaches" are used to manage or lessen the symptoms of RA by reducing inflammation, increasing antioxidant levels, and improving lipid profiles (6, 7). Additionally, according to some recent study, there is strong evidence suggesting an association of the gastrointestinal microbiome with the immune system, pointing the significant role that intestinal microbiota may play in the pathogenesis of systemic inflammatory diseases such as RA (8).

## Relationship between RA and Intestinal Microbiota

The gastrointestinal tract (GIT) is the major entry route for various environmental agents such as food and microorganisms that in turn may affect metabolic homeostasis and microbiota within the GIT (9). Although, some microbiota located in host may have a beneficial effect on the host's health, certain host-microbiota interactions may result in adverse effects on the host's wellbeing. For instance, particular resident bacterial species may cause inflammatory diseases by activating the immune system unnecessarily (10). Thus, the composition of intestinal microbiome is claimed to be critical in immune responses associated with RA. It has been reported that changes in the microbiota found in lungs, oral mucosa, and GIT are associated with the predisposition to and severity of the disease (11).

In a series of studies evaluating the impact of intestinal flora on the etiopathogenesis of RA; it was found that the *faecal* culture of RA patients had a significantly higher rate of *Clostridium perfringens* in comparison to the control group. Besides, it was determined that patients in early stages of RA had a higher rate of *Lactobacillus spp.* in their *faecal* microbiota compared to that of healthy controls (12).

Recent *in vitro* and *in vivo* studies have suggested that some probiotic strains may have anti-inflammatory properties. Scientists then began to investigate whether some probiotics could ease RA-related symptoms. In two randomized double-blind clinical trials on female patients, who were diagnosed with RA more than one year ago (at time of the study), *Lactobacillus casei* supplementation caused a significant decrease C-reactive protein levels in patients' serum. Additionally, in comparison to the placebo group, in the group provided probiotic supplement, RA scores are demonstrated significant difference in terms immunological parameters such as interleukin (IL) 10, IL-12 and TNF-alpha, in favor of the group using probiotics (13, 14).

Mohammed et al. (15) reports that, different species of probiotics especially *Lactobacillus* including the strains supplementation in RA

reduces proinflammatory cytokines such as IL-6, but there is no proved statistically significant difference between effects of probiotics and placebo substances on disease activity score. In a similar line, it is stated that the clinical effect of probiotic supplementation is not definite begging for additional high-quality randomized controlled studies to confirm the alleged impact of probiotics. A meta-analysis which investigated the impact of probiotic supplementation on RA demonstrated that probiotic use did not alter inflammatory parameters such as TNF-alpha, IL-6, IL-10, and IL-12, or oxidative stress level parameters such as total antioxidant capacity and malondialdehyde. Nonetheless, this meta-analysis pointed a partial effect on reducing the disease activity scores and C-reactive protein levels, concluding that probiotic supplementation may have only a "low impact" on the course of RA (16).

Studies suggest that RA-related pathophysiological mechanisms associated with intestinal microbiota might be multifactorial. Activation of Antigen-Presenting Cells (APCs) through Toll-like receptors (TLRs) or NOD-like receptors (NLRs), control of the host immune system, initiation of T cell differentiation and alterations in the permeability of the intestinal mucosa are some of the suggested factors (17). In addition, it is stated that microbial imbalance in/on the body (i.e., dysbiosis) can provoke proinflammatory cells that trigger intestinal permeability which in turn result in the development of autoimmune response. Within this context, it is highly plausible to proclaim that the diet is one of the major elements of both the intestinal microbiota and the immune system (18).

#### **Dietary approaches in RA**

Both patients and researchers have wondered about the impact of the diet on RA-related symptoms for a long time. Recently, the effect of non-pharmacological interventions on the disease symptoms were widely studied. In a single-center survey study conducted with 217 RA patients, the participants asserted that consumption of red meat, alcohol and non-alcoholic beverages worsen their symptoms, while nutrients such as fish and blueberries help alleviate the symptoms (19). As an outcome of these

studies, it has been noticed that dietary means suggested to manage or minimize RA-related symptoms usually through various mechanisms such as reducing inflammation, increasing antioxidant levels, regulating lipid profiles to have an anti-inflammatory effect, and potentially regulating the intestinal flora (20).

Antigenic load and food intolerance are thought to play a role in both the onset of Rheumatoid Arthritis and the course of the disease for two main reasons. First one is the high number of mast cells activated in response to foreign antigens (mostly in an immunoglobulin E-mediated process) are present in the tissues of RA patients. Secondly, there are higher levels of cross-reactive antibodies displayed against various nutrients in the small intestine of patients with RA, in comparison to healthy individuals (21). Besides, it has been shown that the intestinal mucosa of the patients would have become more permeable to allergens due to long term non-steroidal anti-inflammatory drug (NSAIDs) use (22).

The elimination diet is a diet that purposefully avoids particular nutrients found to be associated with certain symptoms in a disease. It is generally based on the idea that removing a food from the diet should result in some improvement if it ever plays a role in the pathogenesis of the disease (8, 23). After a few weeks of deprivation, restricted nutrients are reintroduced to the patients gradually to determine if any of them has an aggravating effect on the RA. A study included 347 RA patients (27% of whom had food intolerance), reported that 9% of patients reacted against cow's milk protein while 4% reacted against wheat. Subsequently, when the "rectal protein food challenge" approach applied in the study, it is reported that mucosal reactivity shown against cow's milk and gluten was observed in only a small portion of RA patients (24).

It has been suggested that a low-fat vegetarian or vegan diet after a fasting period may be beneficial for RA patients. A systematic review on four controlled studies that had lasted at least three months, reports that such diets may have statistically significant clinical effects (25). Even though exact mechanisms (such as decrease

in the inflammatory cytokine release, reduced formation of leukotrienes, changes in intestinal permeability and consequently the penetration of immunostimulants from the intestines) of these diets are not fully understood, fasting is thought to suppress inflammation (26). It has been reported that with limited vitamin, mineral and carbohydrate supplementation, 7-day fasting results in (i) reduction of CD4+ lymphocyte count, (ii) decrease of CD4+ lymphocyte function, (iii) declined levels of specific inflammatory markers such as IL-6, CRP, and (iv) rise in the erythrocyte sedimentation rate (ESR). However, following reintroducing restricted nutrients, inflammation returns, and symptoms worsen. Hence, the therapeutic value of fasting is claimed to be limited unless accompanied with a vegetarian/vegan diet (27). In addition, it has been reported that substantial changes occurred in the intestinal flora of initially omnivorous RA patients only within one year after beginning a vegan diet. Therefore, it has been suggested that there is a noticeable correlation between vegan diet, faecal microbial flora, and disease activity in RA patients (28). Further controlled clinical studies are required to assess the safety and precise influences of fasting coupled with vegan/vegetarian diet on RA patients.

The Mediterranean diet includes three main groups. First group includes abundant vegetable-based foods such as unrefined grains, fruits, leguminous plants, and olive oil. Second group consists of poultry products, dairy products, and eggs. Third group involves sugar-based nutrients and red meat. Olive oil is main sources of fat, there is 1-2 times of month consumption of red meat, moderate intake of poultry. Also according to this dietary approach moderate amounts of wine are often recommended with meals. It is thought that Mediterranean diet, potentially, may alter inflammatory pathways in RA, as it contains nutrients with high amounts of antioxidants that may have anti-inflammatory effect (7, 29). In a three-months-long randomized study included 51 RA patients, a decrease in disease activity and improvement in physical function were observed following the introduction of Mediterranean diet. These results are proclaimed to be partially associated with deliberate choice of antioxidant-rich diet on the

course of Mediterranean diet in the study (8). A second research, aimed to assess the impact of adherence to the Mediterranean diet on RA patients on disease activity and the relationship between comorbidities, asserts that the Mediterranean diet score was found to be negatively correlated with the total score of "RA Impact of disease" (RAID). Additionally, results of the latter study suggested noticeable association between the Mediterranean diet and general health score, although the relationship between high Mediterranean diet score and low disease activity was statistically insignificant (30). A third study revealed that Mediterranean diet may cause only slight reduction in pain or disease activity. Consequently, taking the limited evidence into account, this final study stated that it is not possible to determine the impact of Mediterranean diet on the quality of life among RA patients (31).

Some researchers state that because some non-enzymatic antioxidants such as vitamins A, C, and E may be helpful in managing RA-related symptoms, an antioxidant-rich diet can reduce free radical damage in the joints resulting in decreased inflammation, swelling and pain (32). In a study involved RA patient women who were daily introduced with certain vitamin and minerals (namely, 50 µg selenium, 400 µg vitamin A, 8 mg zinc, 40 mg Vitamin E, and 125 mg Vitamin C) for three months, a significant betterment in disease activity was reported. However, the study suggested that the impact of these antioxidant substances was statistically insignificant on specific disease parameters such as joint swelling and pain (33).

The influence of omega-3 fatty acids on the clinical management of RA patients has also been documented. When the amount of omega-3 fatty acid in diet is increased, the amount of arachidonic acid binding to the cell membrane decreases. Such a decrease, in turn, have affect molecular inflammatory responses such as TNF-alpha positively (34). Park et al. (35) performed a double-blind placebo-controlled study on 109 RA patients. The results suggested that 2.1 gr EPA + 1.2 gr DHA supplementation for a four-months period reduced the need for NSAIDs. Furthermore, Proudman et al. (36) demon-



trated that when supplemented with 5.5 grams of fish oil supplementation for 12 months, the rate of therapeutic inefficacy decreased in 140 recently diagnosed RA patients. In a similar line, another study demonstrated that using omega-3 capsules daily that contain 1.8 EPA and 2.1 DHA led to a substantial improvement in disease activity as well as a significant decrease in the need for analgesic drugs, in comparison to the placebo group (37). Moreover, when omega-3 fatty acids along with low doses of vitamin E is given as supplementation, construction of inflammatory blood markers was decreased. This in turn led to an overall decline in lipid peroxidation of RA patients, as well as the therapeutic dose they need for symptom alleviation (38).

Recent studies suggested that vitamin D plays an immunomodulatory role within the immune system as blood vitamin D levels are shown to correlate with the immune activity. When researchers examined whether vitamin D plays such a role in the RA pathogenesis, serum 25-OH vitamin D levels were found to be inversely associated with the disease activity (39, 40). Additionally, a negative relationship between serum vitamin D and RA disease activity was reported as blood vitamin D levels of RA patients were found to be lower than the healthy controls (41). Another study was performed to evaluate the association of Vitamin D levels with RA disease activity in 15 different countries. The results were suggesting a statistically significant correlation between low levels of vitamin D and RA disease activity differing both in countries and at latitudes (42). In a recent double-blind placebo-controlled study conducted by Buondonno et al. (43), it was demonstrated that when 30000 IU combined cholecalciferol was given to patients for 12 weeks period, a considerable improvement was noticed in the disease activity and severity as well as a significant reduction in the level of RA associated immunological markers. Moreover, others demonstrated that when RA patients on the DMARDs therapy are given vitamin D supplementation for three months, disease activity score and CRP blood levels become significantly better (44). However, there are also contradicting results from another study investigating the efficacy of oral vitamin D supplementation in active RA patients who are on methotrexate therapy. According to this

study, there was no significant efficacy-related difference between the vitamin D supplemented patient group and the placebo group in terms of disease activity score at the end of the study period (45).

## CONCLUSION

As demonstrated in this review paper, studies examining the possible effects of various dietary approaches on the course of RA are conducted on small study populations. Besides, they have considerably poor design. Although both non-enzymatic antioxidants and high-antioxidant diets, such as the above-mentioned Mediterranean diet, have been illustrated to be beneficial by lessening the inflammation, no specific dietary guidelines for RA were prepared or introduced due to inadequate scientific evidence. In several countries, such as Sweden, RA patients are encouraged to follow healthy and balanced diet guidelines (46, 47).

There are several limitations of diet modification approach on RA related symptoms. For instance, fasting approaches are reported to provide significant yet short-term and highly subjective advantages. Moreover, vegetarian/vegan and elimination diets are claimed to be complicated and subjective as well. It is also stated that the efficacy of different diet plans, such as Mediterranean Diet, vegetarian/vegan diet and elimination diet, are asserted to be unsatisfactory because of the fact that they involve small-scale or singlet studies that are prone to medium-to-high bias levels (48). It is also noted that dietary manipulation studies failed to provide any long-term feedback on whether participants continued to follow experimental diet after dietary interventions. In addition, some dietary manipulations were also claimed to be responsible for the aggravation of present nutritional risks associated with weight loss and RA-specific therapies (49).

Finally, positive outcomes on the RA disease activity were obtained through the administration of high doses of Omega-3 polyunsaturated fatty acids (PUFAs). It is reported that the daily recommended safe intake dose of omega3 is 3g below. PUFAs administration was also associated with decreased failure rates of pharmacotherapy on the course of RA. Moreover, vitamin

D supplements are mostly proven to yield beneficial outcomes on the RA disease activity. Although former studies demonstrated positive impact of nutrients on clinical outcomes of RA, studies evaluating the combined effects of different ingredients within a particular nutrient are lacking, as food ingredients usually interact with each other. All in all, this review, based on the detailed review of literature, concludes that there is not sufficient data and evidence to adopt specific dietary advice on the course of RA.

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