Nutritional Factors for Etiology and Course of RA

Subjects: Rheumatology

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A possible association of lifestyle factors with rheumatoid arthritis (RA) has attracted increasing public interest. Nutritional habits determine the composition of our microbiome, which is increasingly recognized as a major player in the etiology of inflammatory rheumatic diseases (IRDs). In a non-RA cohort, a diet with high fiber content resulted in a reduced level of inflammatory cytokines. In addition, polyunsaturated fatty acids may exert anti-inflammatory and immunomodulatory effects, as illustrated by the inverse correlation between n-3-fatty acids and autoantibodies in individuals at high risk for RA.

rheumatoid arthritis lifestyle diet Mediterranean diet smoking

1. Fish and Polyunsaturated Fatty Acids (PUFA)

Polyunsaturated oils such as fish oil and various plant oils exert anti-inflammatory and antiarteriosclerotic effects. Several studies have reported a trend towards a protective role of fish, especially oily fish species, although the observed effects did not achieve statistical significance [1][2][3]. The analysis of more than half a million subjects registered in the British Biobank demonstrated that the consumption of oily fish, breakfast cereals and a moderate alcohol intake was negatively associated with the risk of RA [4]. In addition, a dose-dependent effect of the intake of polyunsaturated fatty acids (PUFA) was observed among 32,232 elderly women, showing that a long-term intake of more than 0.21 g/d was associated with a risk reduction for RA of 52% [5]. In a cohort of pre-RA patients, the erythrocyte levels of n-6-PUFA were inversely correlated with the risk of RA, with an odds ratio (OR) for definite RA of 0.29 for patients with the highest tertile of PUFA compared with the lowest [6]. The content of n-3-PUFA in erythrocytes is also inversely correlated with the prevalence of rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibodies in sera of patients genetically at risk for RA [7].

2. Adiposity and the Risk for RA

By correlating the intake of 39 predefined food items with the levels of inflammatory markers measured in the Nurses Health Study (NHS), the Empirical Dietary Inflammatory Index (EDII) was developed in a non-RA cohort to identify a dietary pattern most predictive of increased values of interleukin 6, C-reactive protein (CRP) and tumor necrosis factor alpha receptor 2 [11].The effect of a high EDII on RA risk mentioned above was attenuated after adjusting for body mass index (BMI) [8]. In addition, a recent analysis of the NHS cohort revealed that obesity had the most marked effect on RA risk [9]. A high score in the Alternative Healthy Eating Index (AHEI 2010) indicates a

diet that is rich in fruits, vegetables, nuts, highly unsaturated fatty acids and whole-grain products. After adjustment for the BMI, the AHEI 2010 did not contribute independently to the hazard ratio for RA [9]. By analyzing the data of 108,000 women who were followed-up prospectively between 1989 and 2017, the NHS demonstrated that weight gain from baseline was quantitatively associated with the risk for seropositive and seronegative RA. Women gaining more than 20 kg had a relative risk (RR) of 3.8 for seropositive RA compared with women who maintained a stable weight [10]. Therefore, this study elegantly confirms previous data that suggested a connection between the BMI and the risk of RA, albeit with considerable heterogeneity [11]. Significantly, the combination of adiposity and smoking was disproportionally associated with the development of definite RA in a preselected cohort of persons without arthritis but positive for RA-associated autoantibodies compared with each component alone [12].

It was hypothesized that central adiposity may be of prominent importance for an elevated RA risk. A British cohort analysis revealed that central adiposity, assessed by waist circumference, was associated with an elevated odds ratio for the prevalence of RA and psoriatic arthritis. This association was stable, even after adjustment for confounders and BMI [13]. However, these data were collected in a sample with established RA. A prospective study of the NHS cohort did not reveal an independent contribution of abdominal adiposity in comparison to general adiposity [14].

3. Alcohol

It is now well accepted that low-to-moderate alcohol consumption is a protective factor with respect to RA (review in [15]). According to data from 30,447 participants of the Malmö Diet and Cancer Study, persons with moderate baseline alcohol consumption (3.5–15.2 g/day vs. <3.5 g/day) tended to have a reduced risk of RA (OR 0.48) compared to participants who drank less than 3.5 g alcohol per day. The study was adjusted for smoking and the level of education [16]. A meta-analysis of eight prospective studies involving more than 195,000 participants concluded that low-to-moderate alcohol consumption lowered the risk for RA to a RR of 0.86 compared with the risk of abstinent persons. The same analysis described a non-linear relationship between alcohol consumption and RA- risk. The protective effect was largest with an average daily consumption of 9 g alcohol per day, compared with 3 g or 12 g per day. The effect waned and even trended towards a negative influence with doses reaching 30 g alcohol per day [17]. The type of the preferred alcoholic beverage was of no significance [17].

4. Nutritional Intervention for the Treatment of RA

Nutritional studies to investigate the impact of food on the activity of IRD are difficult to perform. A blinding of treatment arms is not possible, and the risk of selection bias is high. In 2009, a Cochrane analysis of 14 clinical trials including 837 patients concluded, “The effects of dietary manipulation… on rheumatoid arthritis are still uncertain due to the included studies being small, single trials with moderate to high risk of bias” ([18], page 2). Recent systematic reviews of the literature came to the same conclusion, i.e., the role and the efficacy of dietary interventions are not clearly defined, and heterogeneity and bias remain significant problems [19]. The evidence for any dietary intervention in RA has to be graded as low or very low, primarily owing to the limited number of studies

with small sample sizes [20]. The main impact of dietary interventions on RA, if any, is pain reduction rather than objective measures of disease activity [21].

In general, dietary interventions are not suitable to replace effective disease-modifying antirheumatic drugs (DMARDs). In addition, no data demonstrate the ability of diet to either prevent structural damage or to be effective against highly active disease. Significantly, a far-reaching interference into accustomed dietary habits may be difficult to tolerate for patients and may lead to early discontinuation of clinical studies [22]. Therefore, the recently published recommendations of the European League Against Rheumatism (EULAR) regarding lifestyle behaviors for IRD patients are very cautious in recommending any specific diet besides a “healthy balanced diet” and a “healthy weight” [23]. Nevertheless, some studies make the cautious conclusion that Mediterranean and anti-inflammatory diets may be recommended for patients with IRD. A Mediterranean diet (MD) leads to reduced levels of inflammatory cytokines in RA patients compared with controls [24]. In addition, there is now evidence that diets rich in anti-inflammatory components such as olive oil, nuts or fatty fish reduce cardiovascular risk [25][26][27]. Although these data were generated in non-RA samples, the researchers assume that this finding is of major importance for patients with inflammatory arthritis, given that these patients have significantly elevated risk for major cardiovascular events [28].

One of the earliest studies that investigated the role of nutrition in RA was a randomized controlled trial that combined a fasting period of approximately one week with three to five months of a vegan diet, followed by lactovegetarian nutrition. The study demonstrated small but significant improvements in swollen joint count and patient global assessment, which were mainly achieved during the fasting and maintained thereafter. However, 40 of 53 participants in the study did not receive DMARD treatment. Therefore, the disease activity of the sample was probably very low [29].

In 2003, a randomized controlled trial investigated the impact of an MD on RA disease activity over 12 weeks. The intervention resulted in a small albeit significant improvement in the Disease Activity Score (DAS28) [30]. The effect correlated with the extent of the uptake of n-3-PUFA [31] and was not dependent on the weight reduction that occurred during this and other dietary interventions [32]. More recently, in a randomized cross-over study, the anti-inflammatory diet in RA (ADIRA) trial, the participating RA patients consumed a diet designed to exert anti-inflammatory effects. The diet was rich in legumes, fruits and fish and was supplemented with probiotics [33]. The primary endpoint was not met, probably because the study was underpowered. However, the DAS28 improved in an unadjusted analysis.

Taking these studies together, it can only be speculated whether the association of inflammatory markers with nutrition observed healthy subjects [34][35] translates into reduced disease activity in RA patients. Although [30][33] both point in this direction, definitive evidence supporting this hypothesis is still pending.

5. Fasting and the Activity of RA

Besides the study mentioned above that included a fasting period [29], a meta-analysis of this and three other clinical trials argued for pain reduction after controlled fasting not exceeding 12 weeks [36]. However, there is neither evidence for long-term effects, especially with respect to structural damage, nor for a benefit of repeated fasting.

6. Exclusion Studies in RA

In recent decades, the possibility of food allergens contributing to the pathogenesis of RA was discussed intensely. However, a study eliminating milk allergens and azo dyes in a double-blinded fashion did not convincingly demonstrate a clinical effect in RA [37], although these phenomena could be relevant for subgroups of patients. In a 2001 randomized study, RA patients were put on a vegan, gluten free diet. The intervention resulted in an improvement in the American College of Rheumatology response criteria (ACR20) and a decrease in CRP levels. However, more than 40% of the study population terminated the trial ahead of schedule, indicating the low tolerability of this rather radical dietary regimen [22]. A small study on obese RA patients with stable disease revealed that weight reduction resulted in additional benefit if the balanced diet was deprived of meat, gluten, lactose and all dairy products, compared with a balanced diet alone. Patients consuming the privative diet achieved reduced blood pressure, as well as improvements in physical and mental health, compared with the control group [38]. However, potential drawbacks of these exclusion diets, namely a lack of dietary fiber, calcium or essential amino acids, outweigh the potential advantages. Therefore, the exclusion of gluten (for non-celiac patients) and dairy products is explicitly not recommended for patients with IRD [39].

7. Interventions Aiming at Weight Reduction in RA

A retrospective analysis of RA patients who underwent bariatric surgery demonstrated a marked reduction in inflammatory markers, as well as reduced RA disease activity after the surgical intervention [40]. In a randomized study, RA patients were put on a hypocaloric diet of 1000–1500 kcal/day for 12 weeks. Besides a weight loss of 9.5 kg, these patients experienced significant improvements in disease activity (DAS28) and the health assessment questionnaire (HAQ) disability index [41].

8. Nutritional Supplements

Reports arguing for beneficial effects of nutritional supplements for IRD have been published in large numbers. In a broader sense, some components of daily food may be considered a supplement, namely spices such as curcumin, cinnamon, garlic and saffron. These food ingredients possess multiple anti-inflammatory and antioxidative features in vitro and in experimental models [42][43]. However, interventional studies applying these compounds in RA are of poor quality and have a high risk of bias [42].

Probiotics contain living microorganisms such as lactobacilli or yeast. Several smaller studies have claimed a symptom-modifying effect of probiotics in IRD [44]. However, in general, these studies are highly heterogeneous

and include small patient groups with low disease activity [45][46][47]. Therefore, the application of probiotics is not recommended for the adjuvant treatment of RA [48].

Of all nutritional supplements, omega-3 PUFAs have been studied most extensively in RA patients [49]. In a Cochrane meta-analysis, omega-3-PUFAs were found to significantly reduce patient-reported joint pain intensity, morning stiffness and non-steroidal anti-inflammatory drug (NSAID) consumption [49].

Experimental studies argue for a pathogenetic role of trace elements such as zinc and cadmium in RA [50], and deficiencies of zinc, copper, magnesium and selenium have been described in the sera or in the diet of RA patients [50][51][52][53]. However, there is no convincing evidence that the supplementation of either trace elements alone or a mixture of micronutrients is of any benefit with respect to disease activity in RA [54][55][56].

Vitamin E was formerly regarded as an antioxidant with anti-inflammatory potential. However, vitamin E supplementation was not associated with a reduced risk of RA development in the Women's Health Study [57], and an excessive consumption was even linked to an increase in all-cause mortality [58]. Although a recent meta-analysis argued for the beneficial effect vitamin E in RA [59], the dietary recommendations of the French Society for Rheumatology explicitly advise against the supplementation of vitamins, including vitamin E or trace elements [39].

It is common sense that a relevant deficiency of vitamin D and iron has to be treated in RA patients. Beyond that, however, an over-supplementation is of no use and should be avoided [39].

9. Nutrition and Rheumatoid Arthritis: Current Recommendations

With respect to the literature presented, it would be beyond the scope of the article to derive firm recommendations for patients with established RA or for persons at risk of developing this disease. However, recent efforts have been made to develop nutritional recommendations for RA patients on the basis of the current scientific evidence. The European League Against Rheumatism (EULAR) recommends a healthy balanced diet and a healthy weight for patients with rheumatic and musculoskeletal disease [23]. Recently, the French Society for Rheumatology formulated nutritional recommendations for RA patients in more detail [39], including eight general principles and nine recommendations. The general principles stress the importance of a healthy diet as one component of the overall care. The importance of nutrition with respect to cardiovascular risk is addressed, as well as the consideration of the cultural and socioeconomic background of the patient. Recommendations include a reduction in overweight, a Mediterranean diet and supplementation with polyunsaturated fatty acids. Explicitly, the recommendations do not include supplementation with vitamins, trace elements or probiotics, nor the application of a vegan or gluten-free diet. Furthermore, the elimination of dairy products is not advised [39].

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