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Efficacy of therapeutic fasting and plant-based diet in patients with rheumatoid arthritis (NutriFast): study protocol for a randomised controlled clinical trial

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ABSTRACT

Background Previous studies have shown beneficial effects of therapeutic fasting and plant-based dietary interventions on disease activity in patients with rheumatoid arthritis (RA) for a duration of up to 1 year. To date, the effects of such interventions on the gut microbiome and on modern diagnostic markers in patients with RA have not been studied. This trial aims to investigate the clinical effects of therapeutic fasting and a plant-based diet in patients with RA, additionally considering current immunological diagnostic tools and microbiome analyses.

Methods/design This trial is an open-label, single-centre, randomised, controlled, parallel-group clinical trial. We will randomly assign 84 patients with RA under a stable standard therapy to either (1) therapeutic fasting followed by a plant-based dietary intervention or (2) to a conventional nutritional counselling focusing on an anti-inflammatory dietary pattern according to the recommendations of the Deutsche Gesellschaft für Ernährung (German society for nutrition). Primary outcome parameter is the group difference from baseline to 12 weeks on the Health Assessment Questionnaire (HAQ). Other secondary outcomes include established clinical criteria for disease activity and treatment response in RA (Disease Activity Score 28, Simple Disease Activity Index, ACR-Response Criteria), changes in self-reported health and physical functional ability, mood, stress, quality of life, dietary behaviour via 3-day food records and a modified Food Frequency Questionnaire, body composition, changes in the gut microbiome, metabolomics and cytometric parameters. Outcomes will be assessed at baseline and day 7, after 6 weeks, 12 weeks and after 6 months.

Ethics and dissemination Ethical approval to process and analyse data, and to publish the results was obtained through the institutional review board of Charité-Universitätsmedizin Berlin. Results of this trial will be disseminated through peer-reviewed publications and scientific presentations.

Trial registration number NCT03856190.

Strengths and limitations of this study

- This is the first approach to generate a dietary therapeutic concept for patients with rheumatoid arthritis (RA) involving therapeutic fasting.
- Fasting has emerged as an effective, economic and safe therapeutic intervention for patients with rheumatoid arthritis.
- This study design can contribute to the understanding of pathomechanisms in RA, especially in the context of diet and the microbiome, through an extensive biorepository of blood and stool samples and large amounts of data to be collected.
- A limitation is the open-label dietary intervention, which may not exclude bias like non-specific treatment effects, confirmation and observer bias.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterised by a destructive inflammation of the joints. With a prevalence of approximately 1% in Europe and the US RA is the most common rheumatic disorder, affecting several million people worldwide.[1] Patients with RA experience painful, swollen joints which can severely impair physical function and quality of life; untreated it may lead to irreversible articular deformation and stiffness as well as to increased cardiovascular risk and mortality.[2]

So far, disease progression can only be stopped by permanent suppression of the inflammatory response.[3] In recent years, therapeutic concepts with non-steroidal anti-inflammatory drugs and conventional disease modifying antirheumatic drugs (DMARDs) have been extended by targeted antibody therapies that can specifically block various inflammatory pathways (biological DMARDs).[4–6] Although being more efficient

in comparison to conventional DMARDs, individual treatment responses can differ widely; as a result, the optimal drug needs to be identified for each patient individually and has to be monitored for habituation and side effects.[6] Nutritional medicine (NM) as well as Complementary and Integrative Medicine (CIM) alongside conventional drug therapy might be a supportive and possibly cost-effective way to relieve RA symptoms, limit adverse effects of conventional drug therapies or even influence the course of the disease.[7] Patients increasingly demand CIM and NM approaches; surveys indicate that up to two-thirds of patients with rheumatological conditions already use CIM, mainly for pain control.[8 9]

A complex interplay of genetic predispositions, lifestyle-related factors and environmental aspects is thought to account for the not yet fully understood pathogenesis of RA.[10] Moreover, interactions with the intestinal microbiota have increasingly been discussed over the last three decades.[11–15] A gut microbial imbalance (dysbiosis), characterised by the loss of metabolically and immunologically beneficial bacteria and a concomitant increase in potentially pathogenic microbes (pathobionts), is associated with several chronic inflammatory syndromes.[16–22] In the case of RA, a predominance of *Prevotella* species in the intestinal microbiota has been associated with early-stage patients with RA in previous studies.[23–25] Recent translational publications suggest that such an altered microbiota might be associated with the formation of RA-specific autoantibodies, that is, anticitrullinated protein antibodies (ACPAs), possibly triggering autoinflammatory disease in predisposed individuals.[26–29]

Nutrition is a pivotal variable in shaping the gut microbiota composition and function. It influences the complex host-microbiota cross-talk and hence affects host metabolism and the immune system in a multifaceted fashion; thus, changes in dietary regimens may have either beneficial or detrimental consequences for the gut microbiota and thus for overall health.[11 30] This also applies to caloric restriction or fasting, an element which can be implemented in different types of diets.[31 32]

In the past few decades, mounting experimental and translational evidence regarding the biological fundamentals of caloric restriction and different fasting regimes, such as periodic and intermittent fasting, has evolved. It encompasses a broad spectrum of cellular and molecular mechanisms affecting health and disease processes; fasting not only involves ketogenesis to fuel cellular energy production but also elicits a coordinated adaptive stress response: signalling pathways are activated, which bolster mitochondrial health, DNA repair and autophagy. Fasting also seems to enhance immune functions by downregulating proinflammatory cytokine expression.[33–36] These well-orchestrated processes may hold promising therapeutic options for a variety of fields in medicine, including autoimmune diseases such as RA.[35 37–40]

By contrast, robust clinical evidence on the therapeutic effects of dietary and fasting interventions in patients wih RA has been sparse; in 2009 a Cochrane review concluded 'uncertain effects' of specific dietary regimens on RA due to a lack of sufficient data.[41] Currently, a growing body of literature reports on clinical improvement through plant-based nutrition and fasting in inflammatory arthritis.[42–45]

In early clinical trials, modified fasting (up to 500 kcal energy intake per day) for 7–10 days followed by plant-based diet showed positive effects such as decreased morning stiffness, reduced pain and increased function in RA patients for up to 1 year.[22 46] For this reason, it is already in regular use by a number of clinical departments in Europe for the integrative treatment of RA.[47] Kjeldsen-Kragh *et al*[22] and Sköldstam *et al*[48 49] were able to demonstrate the effectiveness of such an approach in clinical studies, of which occurred two in a randomised setting.[46]

Data from several clinical trials have already suggested that therapeutic fasting produces anti-inflammatory effects.[21 22 47 50] However, in the period following fasting interventions, inflammation and symptoms frequently reoccur. Previous studies have demonstrated that this process can be delayed by the implementation of specific diets or food items.[46 51 52] However, until now no standardised recommendations for long-term stabilisation of the positive fasting effects have been developed.

In what follows, we present the protocol of a randomised, controlled clinical trial comparing an experimental anti-rheumatic fasting and nutrition protocol to a conventional guideline-based anti-inflammatory diet.

We hypothesise that the experimental protocol will improve RA symptoms in the mid-term and long term. In an additional experimental context, we will investigate changes (1) in metabolism and (2) in the microbiome. We further hypothesise that the anti-inflammatory effects of fasting and plant-based diets are related to changes in the composition of the individual gut microbiota.

Thereby, this trial aims to contribute to an improved understanding of underlying pathophysiological processes and to extend non-pharmacological therapeutic options for patients with RA.

METHODS AND ANALYSIS

Study design

In this prospective, open-label, clinical, randomised, controlled trial, we intend to recruit and randomise 84 participants between 18 and 70 years of age, diagnosed with RA, into two groups (figure 1). This protocol meets the standard recommendations and guidelines for randomised clinical trials.[53]

Patient and public involvement

Patients are not involved in the design, or conduct, or reporting, or dissemination plans of our research, but they are a key element in the choice of our outcome measures. Both the primary and several secondary endpoints consist of patient-reported outcomes (PROs). Furthermore, we provide basic educational material to promote long-term

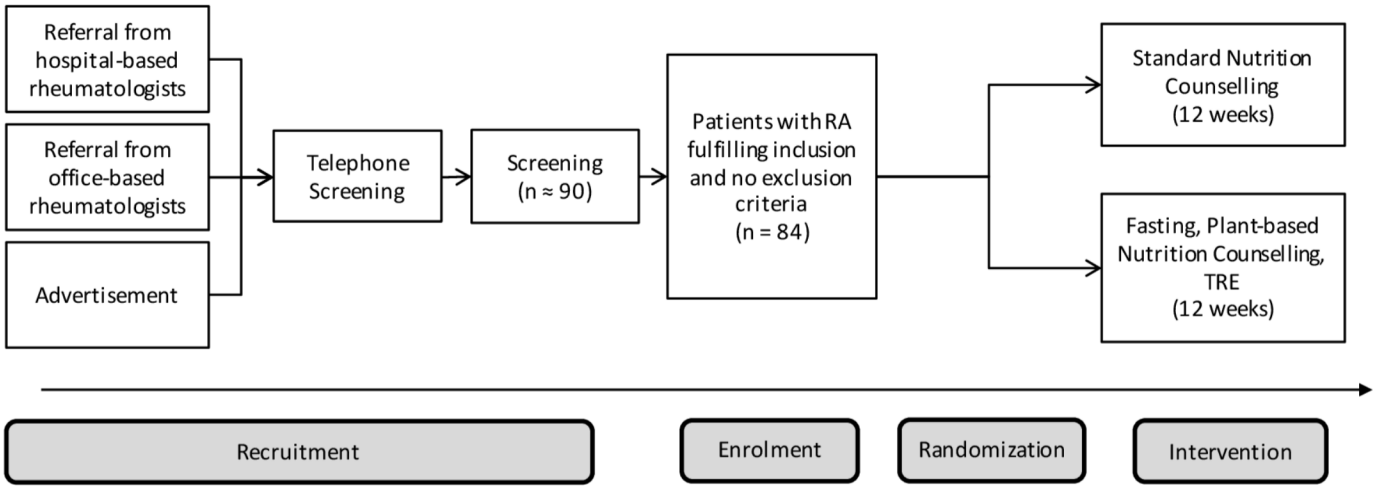

Figure 1 Study design. RA, rheumatoid arthritis; TRE, time restricted eating.

health literacy (online supplemental file 1) and assess regularly the burden of the trial interventions on participants. Once the trial has been published, we intend to inform participants of the results through a newsletter suitable for a non-specialist audience.

Recruitment and randomisation

Participants are recruited using three sources (figure 2): (1) by direct referral from either physicians at the Immanuel Hospital Berlin and the Charité-Universitätsmedizin Berlin, Department of Rheumatology and Clinical Immunology Berlin or (2) by direct referral from office-based rheumatologists and (3) by non-personal advertising strategies (eg, flyers, social media).

Eligibility criteria are designed to target patients with RA who are sufficiently healthy to participate safely in the interventional fasting trial-arm (table 1). Participants meeting all inclusion and no exclusion criteria are randomly assigned to one of the two treatment arms, using a 1:1 ratio. An independent research team member, outside of the project, has generated the randomisation list using blockrand library (V.1.4) with a randomised variable block approach within the statistical computing language R (V.3.5). The computer-generated randomisation allocation sequence has been consecutively numbered, sealed in opaque envelopes and concealed from the study personnel responsible for conducting the studies. Participants are allocated after written informed consent (online supplemental file 1 and successful screening by the responsible study physician.

Discontinuation and adherence criteria are displayed in table 2. Missed consultation appointments can either be made up in the following groups or the omitted topic must be worked on at home. Food records measure adherence to the prescribed intervention (see outcome parameters).

Study settings

This is a single-centre trial: screening visits, blood collection and dietary counselling are conducted at the Charité-Universitätsmedizin Berlin, Department of Internal and Complementary Medicine in Berlin, Germany, located at the Department of Internal and Integrative Medicine, Immanuel Hospital Berlin, Germany.

Interventions

Dietary counselling for both trial arms is carried out in small groups of up to 10 persons within 3 individual and 9 group sessions over 3 months (figure 2). The entire intervention takes place in an outpatient setting.

Both groups begin with a 7-day intensive course (corresponds to a fasting week in the intervention group) with daily group coaching sessions of 2 hours each and one individual coaching of 60 min per participant. Afterwards, participants receive one group coaching of 1.5 hours and 30 min of individual phone coaching in the second

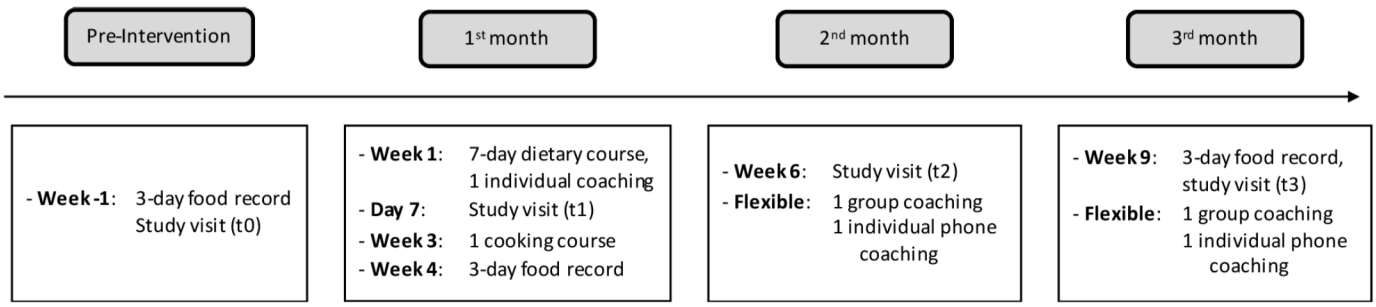

Figure 2 Schedule for both interventions.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
► Prediagnosed RA* ► Age 18–70 years ► Ability to fully understand the trial concept and written informed consent to participate ► Willingness to accept randomisation, to undergo testing and intervention procedures, and to deliver stool, blood and urine samples for testing	► Diagnosed gout or septic arthritis ► Known psychiatric disorders limiting an understanding of the protocol (unable to give consent) ► Pregnancy or breast feeding ► BMI <18.5 kg/m^2 ► Eating disorder (bulimia, anorexia nervosa) within the past 5 years ► Severe internal diseases (eg, renal insufficiency with creatinine >2 mg/dL) ► Participation in another study ► Currently practising or having practised plant-based diet or fasting within the previous 6 months to enrolment ► Implementation of a rheumatological therapy with biologicals or biosimilars within the last 8 weeks prior to enrolment ► Absence of email address and internet access

*Prediagnosed by a medical specialist.
BMI, body mass index; RA, rheumatoid arthritis.

month and third month of the study. Additionally, a cooking lesson of 3 hours is hosted in the second month. Due to the spread of COVID-19, the study protocol is being changed to maintain social distancing measures. Face-to-face consultations are carried out online using secured web-based video conferences. The cooking course is replaced by a tasting with max. 5 participants respecting hygiene measures (preparation by a single person wearing gloves, listing of the participants, distance rule, mouth covering in between tasting).

No changes to existing drug therapies are made in the course of the trial, unless undertaken by the treating rheumatologist.

Fasting and plant-based dietary counselling

The experimental intervention group undergoes a 7-day therapeutic fasting regime (2 days of light plant-based diet, 7 days of fasting, 3 days of light plant-based diet), and a following period of 11 weeks with a specific plant-based normocaloric nutrition.

During the first 2 days of light plant-based before fasting, the subjects are given a low-calorie (approx. 1200 kcal) diet with reduced intake of salt, fat and protein (online supplemental file 2). During the following fasting period, participants can consume unlimited amounts of water or herbal tea (no black or green tea, no caffeine, no alcohol), 2×150 mL of vegetable juice low in sugar and 250 mL of light vegetable broth with a maximum total daily energy intake of 1.255 kJ (300 kcal). Participants are encouraged to drink at least 2.5 litres of fluid daily (online supplemental file 2).

In the event that a participant regularly takes medication for other diseases, his/her medication may have to be adjusted during the fasting days. Fasting is known to lower blood pressure, affect electrolyte balance and blood sugar levels. It may also prolong bleeding time and trigger migraine attacks.[54–56] For this reason, diuretic, antihypertensive and antidiabetic drugs as well as coumarins are adapted by the responsible study physician (online supplemental file 3).

Fasting is followed by 3 days of light plant-based diet with successive reintroduction of plant-based solid food. Afterwards, a specific plant-based normocaloric diet is to be resumed. The latter is enriched with kitchen herbs and kitchen spices known for their anti-inflammatory potential. The recommended diet is also high in prebiotics and integrates the concept of time restricted eating (TRE), with 16 hours of fasting overnight for at least 6 days per week.

Standard dietary counselling

The control group receives a wholefood diet considered to be fundamentally health-promoting according to the current recommendations of the Deutsche Gesellschaft für Ernährung (DGE, German society for nutrition; online supplemental file 4).[57]

The omega-6-fatty acid arachidonic acid (AA), which is particularly found in animal derived protein, has been

Table 2 Discontinuation and adherence criteria

Discontinuation criteria	Adherence criteria
► Withdrawal of consent ► Medical reasons for terminating the intervention	► ≥ 2 of 3 individual consultations ► ≥ 9 of 11 group consultations ► 1 cooking course

suggested to play a role in RA as it leads to the formation of inflammation-promoting messenger substances. Therefore, a reduction of the former is thought to have an anti-inflammatory effect.[58 59] Thus the focus of the control intervention is a lower intake of this substance, meaning a maximum of 2 portions per week of foods such pork lard, liver, and egg yolk. If consumption of dairy products cannot be avoided, low-fat dairy products should be preferred. High amounts of salt, sugar and alcohol should be avoided (online supplemental file 4).

The three main omega-3 fatty acids alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been described to have anti-inflammatory effects.[60 61]

An enzymatic desaturation step of variable efficiency (1%–5%), is required to convert dietary ALA to EPA and DHA.[62] Acting as competitive inhibitors for AA, the intake of these long-chain omega-3 fatty acids in therapeutic doses of 3 g/day inhibits the production of proinflammatory eicosanoids.

ALA is mainly found in oilseeds such as canola, flaxseed, soybean, chia as well as walnut. DHA and EPA are found in fish like mackerel, salmon and herring. In accordance with the current recommendation of the DGE, an optimal ratio of 1:5 omega-3 to omega-6 FA is considered. The recommended daily dose of 250 mg EPA and DHA can be met with two servings per week of the above fish species; that of ALA using 20 g of walnuts, 10 g of linseed or 15 mL of either rapeseed or linseed oil per day.

An adequate supply of antioxidants, vitamins, minerals and secondary plant compounds can be achieved with five portions of fruit and vegetables daily.

Adverse events

There are no major risks expected for participants in this trial. Fasting without underlying conditions is considered safe and there are no reports of major risks whatsoever.[63] Minor adverse effects of fasting therapy are described as initial headaches (coffee withdrawal, etc), mild circulatory reactions, feelings of hunger and increased sensitivity to cold. These side effects are known, occur mostly during the first 3 days of fasting and are self-limiting.[63 64]

Occurring adverse events are recorded at each clinical visit using open questions. Adverse events are also documented at any time between visits whenever a participant communicates such an event to study personnel. Serious adverse events are announced to the study coordinator and the principal investigator within 24 hours of their report.

Outcome parameters

The primary endpoint is the group difference of the Health Assessment Questionnaire (HAQ) after 12 weeks compared with baseline. Target parameters are surveyed at baseline, on day 7, after 6 and 12 weeks and on follow-up after 6 months (table 3).

Additional secondary outcomes are standard RA assessment tools (Disease Activity Score 28, DAS28; ACR-Response-Criteria; Simple Disease Activity Index) and questionnaires for functional ability (Funktionsfragebogen Hannover), mood (Profile of Mood States), stress (Cohen's Perceived Stress Scale-10), quality of life (WHO-5) and subjective strength of the main complaint on the Visual Analogue Scale. Both groups keep a pain diary also recording pain medication intake. Occupational stress, domestic stress, interpersonal conflicts, digestion, menstruation, adherence on diet and extraordinary events are documented by means of a diary containing verbal numerical rating scale scores.

For safety monitoring, body weight and composition, food intake and vital signs are surveyed at regular intervals as well as urinalysis and a clinical standard laboratory, including blood count, liver and kidney values, vitamin B_{12}, erythrocyte sedimentation rate and CrP (Biospecimen and data collection). ACPA and rheumatoid factor (IgM) are collected at baseline to complete the rheumatological assessment.

Cytometric parameters indicating changes in cell activation are determined to analyse the immunological effects of the intervention: detailed changes in subpopulations of immunological importance for inflammation (eg, monocytes) are quantified by transcriptome analysis of immune cells (microarray /RNAseq). A preliminary study by the same research group identified inflammatory profiles of individual foods as well as molecular markers of disease activity in RA, whose diagnostic value has been tested and interpreted under the influence of fasting.[65] In this trial, these markers are being clinically evaluated.

Moreover, polar metabolic plasma metabolites are of interest and are analysed using a GC/MS metabolomics platform. Stool samples are collected in a subgroup of participants for 16s-18s rRNA sequencing.

Individual dietary habits are surveyed in week −1, 4 and 9. Each measurement consists of a weighed 3-day food record (two weekdays and one weekend day) where all consumed food and drinks are recorded by the participants themselves. Exact time, mood and location during food intake are also to be recorded.

All surveys and endpoints shall be collected and assessed by trained and experienced staff. Participants are informed about any abnormal findings and referred to their general practitioner for further treatment as soon as such findings may occur.

Biospecimen and data collection

Clinical data

Clinical visits are carried out by study personnel at the Institute of Social Medicine, Epidemiology and Health Economics, Charité-Universitätsmedizin Berlin, Germany. Study participants are called in with an empty stomach between 8:00 am and 2:00 pm.

Diet and lifestyle assessment

Standardised electronic questionnaires (LimeSurvey V.3) are used to assess baseline data and deviations over the

Table 3 SPIRIT flow diagram of the NutriFast trial

	Study period					
Visit	t_{-1}	t_0	t_1	t_2	t_3	t_4
Assessment	Screening	Baseline	7 days	6 weeks	12 weeks	Follow-up
Study week	-2	0	1	6±1	12±1	26
Eligibility screen	x					
Informed consent	x					
Enrolment and allocation	x					
Interventions						
Fasting and plant-based diet, TRE		←	—	—	→	
Standard dietary counselling		←	- - -	- - -	→	
Assessments						
Sociodemographics		x				
Case history		x		x	x	
Concomitant medication	x	x		x	x	
Vital signs	x	x	x	x	x	
Physical examination	x	x	x	x	x	
Disease Activity Score 28		x	x	x	x	
Simple Disease Activity Index		x	x	x	x	
AE/SAE query			x	x	x	
Bioelectrical impedance analysis		x		x	x	
Anthropometric data		x		x	x	
Laboratory parameters		x	x	x	x	
Cytometry		x	x	x	x	
Metabolic plasma metabolites		x	x	x	x	
Urine sample		x	x	x	x	
Stool sample		x	x	x	x	
Questionnaires						
Health Assessment Questionnaire		x	x	x	x	x
The Hannover Functional Ability Questionnaire		x	x	x	x	x
Profile of Mood States		x		x	x	x
Cohen Perceived Stress Scale		x		x	x	x
WHO-Five Well-Being Index		x		x	x	x
Subjective strength of the main complaint (Visual Analogue Scale)		x		x	x	x
Food Frequency Questionnaire		x		x	x	x
Final questionnaire						x
Behavioural factors and drug intake						
Tobacco habits		x		x	x	x
Alcohol habits		x		x	x	x
Physical activity		x		x	x	x
Coffee		x		x	x	x
Analgetics via diary		←	—	—	→	
Stress, menstruation, adherence and extraordinary events via diary		←	—	—	→	
3-day food record				Week –1, 4, 9		

AE, adverse event; SAE, serious adverse event; TRE, time restricted eating.

study period. Questionnaires are sent out online via email and completed on the day of the respective visit (table 3).

Adherence

Daily group consultations with a nutritionist support adherence to the initial fasting week. The study team examines 3-day food records in week −1, 4 and 9 as well as disseminates electronic questionnaires at the time of study visits to assess applicability (table 2). Food records are analysed for nutrient content using NutriGuide software. This software's database is based on the German Federal Food Code (BLS) of the German Federal Institute for the Protection of Consumer Health and Veterinary Medicine (BGVV) and provides comprehensive information about the composition/ingredients of more than 15 000 foods. Participants are further asked to provide information on their lifestyle factors (including physical activity, nicotine, alcohol and illicit drug consumption) and complete a modified Food Frequency Questionnaire (FFQ) which queries the consumption frequency of certain spices and herbs at all three food recording points. The FFQ has been generated for the purpose of this trial on the basis of the clinically used FFQ of our department for integrative medicine. Its focus lies on nutrition, fasting and chronobiology.

Anthropometric measurements and body composition

Weight and height are determined at baseline, 6 weeks and 12 weeks with regularly calibrated personal scales (seca, model 920). Body composition is assessed using a bioelectrical impedance analyser (Data Input, Nutriguard M/S, model BIA-2000S) and the corresponding software by the same supplier (Data Input, NutriPlus 6.0) at each clinical evaluation.

Blood samples

Blood samples are taken at each clinical visit (baseline, 7 days, 6 weeks, 12 weeks). These are either transported directly to the study laboratory or centrifuged and frozen. Serum and EDTA samples are centrifuged at 2800 rpm for 10 min to obtain serum and plasma, aliquoted (minimum 200 µL per aliquot) and then stored at −80°C for subsequent analysis. Samples from this study are only used for the ongoing process. Should further research with biological samples obtained be planned in the future, renewed informed consent will be sought.

Metabolomics

Blood samples are collected as dried blood spots and metabolites will be extracted using an established protocol[66] before assessment via GC/MS. The raw GC/MS data will be analysed using the MetaboliteDetector software (http://metabolitedetector.tu-bs.de) to extract pure mass spectra and semi-quantitative values for all detected compounds in a non-targeted approach.[67] If possible, the software will perform an identification of compounds present in a reference library. Finally, statistical analyses of the results will yield metabolites significantly affected by our treatments.

Urine and stool samples

Midstream urine samples are collected at each clinical visit (baseline, 7 days, 6 weeks, 12 weeks) and analysed immediately using semiquantitative urine dipsticks. Stool samples are collected in a subgroup of participants (n=20) to the indicated timepoints (table 3). Longitudinal changes in the composition of the intestinal microbiome will be assessed using 16S rDNA gene-based next-generation sequencing on the Illumina MiSeq platform. The V4 region of 16S rDNA will be amplified by PCR, normalised, pooled and sequenced with the Illumina MiSeq 2×250 bp paired end as described.[68 69] Analysis of the 16S sequencing results will be performed as described.[70]

Statistical analysis

Sample size and power calculation

Based on the estimated yearly turnover of the associated hospitals and clinics in Berlin, 84 patients were enclosed in this pilot study. Under the standard assumptions of a significance level of alpha=0.05, a beta=0.20 (corresponding to a power of 80 %) and a repeated analysis of variance design with a hypothesis only for the interaction term, a nonsphericity correction of epsilon=1, an assumed correlation among repeated measures of 0.5, and a drop-out rate of 10%, the number is sufficient to discover all effects with effect sizes of f=0.20 (d=0.40) or higher, and thus all medium and large effects. The number is thus apt to decide whether the effect is larger or smaller than the critical effect size of d=0.5, indicating whether the treatment effect is to be termed clinically important.

Blinding

This is an open-label randomised controlled trial. Complete blinding of both the participants and the nutritionist to the treatments in this study is not possible due to obvious differences between the intervention arms.

Data management

Each participant receives his/her individual study ID (pseudonym) when enrolling in the study. In order to guarantee the confidentiality of participant's personal data this pseudonym is used for all data documentation. Initially, data are collected in source documents and transferred to analogue case report forms. Data sheets relating the participant's study ID to the person's contact details are stored in a locked cabinet in a locked office to which only members of the research team have access. Later, data are digitised and stored in a central database at Charité-Universitätsmedizin Berlin, Germany. Accuracy of the data entry is to be improved by double-checking the entries for expected scope and correct format. Participant files and other source data (including copies of protocols, questionnaires, original reports of test results, informed consent records and other documents concerning the conduct of the study) will be kept for at least 10 years after completion of the study. Any modifications to the

current study protocol will be communicated to the institutional review board, all study participants and the study investigator.

Data monitoring

Given the minimal risks of the dietary interventions, this trial is monitored on a regular basis by the protocol team, without the use of a formal data monitoring committee.

The principal investigator, in close cooperation with the study coordinator and protocol team, may take the decision to discontinue the study. Such decision may be based either on adverse or serious adverse events attributed to the study intervention or for the reasons mentioned in the section 'Exclusion criteria' or because not enough participants could be recruited. Further details about its operating procedures can be obtained by contacting the corresponding author via email. The protocol team and the principal investigators meet every 3–6 months to monitor, review and discuss the study progress and trial related issues.

There is no endpoint assessment committee and no study steering committee. There are no stakeholder and public involvement groups involved.

Data analysis

The primary endpoint is the group difference in the HAQ after 12 weeks. Baseline variables with prognostic and demographic relevance, as well as the totality of the target criteria, are described accordingly and compared by Student's t-test. Statistical variables included are, in addition to absolute and relative frequency, the number of valid values, the formation of the SD, minimum, maximum, median and mean value (depending on the numerical scale used). For the protocol calculation of a primary endpoint, a repeated variance analysis is performed.

Based on prior publications, no detrimental effects of the study intervention are expected that would result in a premature termination of the study.[63 64] Hence, we do not plan an interim analysis. For an intention to treat analysis, we intend to replace missing values by multiple imputation using the amelia II package.[71]

Due to the consultation methods initiated to meet the restrictions associated with COVID-19, we introduced the additional covariate of 'rate of visits/consultations done only virtually' (ie, online video conferences or telephone calls). These additional tests will be done as a sensitivity analysis, and are therefore separate from the analysis of the primary outcome.

Follow-up and evaluation of data

In order to investigate the feasibility and the long-term effects of a dietary change after the study, we conduct a follow-up of all participants who have completed the study after 6 months. Electronic questionnaires are used to collect follow-up outcomes including HAQ, health questionnaires and questionnaires on function and diet/lifestyle (table 3).

Ethics and dissemination

The trial, including participant information and informed consent, has been approved by the institutional review board of Charité-Universitätsmedizin Berlin and is conducted in accordance with the Declaration of Helsinki in its currently valid version, the guidelines of the International Conference on Harmonisation of Good Clinical Practice and the applicable German laws. An amendment for adaptations to our trial due to the COVID-19 pandemic was approved by the same ethics committee. Written informed consent is obtained from all participants preceding study entry by the responsible study physician (online supplemental file 1). We only ask for consent to use data and samples for the research subject described in this protocol, and do not intend to use participant data or biological samples in further future studies.

Results will be presented at national and international conferences, published in peer-reviewed journals and disseminated to rheumatologists and medical laymen. We will follow the official eligibility guidelines for authorship in all publications and do not intend to use professional writers.

DISCUSSION

To the authors' knowledge, this is the first approach to generate a dietary therapeutic concept for patients with RA involving therapeutic fasting. The study aims to provide additional evidence on promising existing laboratory research and clinical data on this dietary approach in patients with RA.

Previous nutritional recommendations, such as a gluten-free or Mediterranean diet, have remained rather experimental therapeutic approaches due to insufficient data regarding their mechanisms and clinical effectiveness.[72–74] Likewise, a recently published Swedish trial of an anti-inflammatory, primarily pesco-vegetarian, diet in rheumatoid arthritis has shown potential efficacy but lacked significant clinical relevance regarding the chosen endpoint (DAS28-ESR).[75] In this study, we aim to fill the the knowledge and quality gap on both preclinical and clinical sides of fasting and a plant-based diet in RA.

A meta-analysis by Genel *et al*[76] suggests health benefits of a low-inflammatory diet for adults with arthritis (calorie-reduced regimens or fasting excluded). However, the quality of existing clinical trials is questionable—what is missing are professionally led nutritional interventions and a combined evaluation of laboratory and PROs. This structural aspect is reflected in the selection of certified nutritionists in this study design, together with the wide-ranging chosen endpoints. In addition, recent epidemiological studies on risk for RA under Mediterranean diet appear controversial and call for a specification into seropositive and seronegative RA,[77 78] which will be implemented in the statistical analysis of the results of this study.

As far as mechanisms of action are concerned, caloric restrictions harbour potential immunological consequences for patients with RA. As Häupl *et al*[65] have recently

suggested, there is an enhanced turnover of monocytes with accelerated monocytopoiesis to be seen in RA; the prematurely released monocytes from the bone marrow migrate into, then inflamed, joints.[79] Fasting in turn reduces the number and activity of circulating inflammatory monocytes in healthy humans and mice, without compromising the acute inflammatory response to infectious agents.[80] The influence of fasting on the specific activity of monocytes in humans with RA shall now be the subject of this study.

Moreover, the study group of Jordan *et al*[80] revealed that metabolic activity and gene expression patterns predicting improvement of chronic inflammatory and autoimmune disorders, such as RA and multiple sclerosis, are modifiable by fasting in mice. Using GC/MS metabolomics, this study shall point out the metabolic consequences of fasting in human subjects with RA as an example of chronic inflammatory conditions.

Growing evidence endorses the influence of diet on the imbalanced immune system in RA, which is also characterised by an increased number of proinflammatory T-helper cells 17 (Th17) and hence by a decreased Th1/Th17 ratio compared with healthy subjects.[81] Protective regulatory T-cells (Treg) on the other hand tend to malfunction.[81] A recent study showed that 28-day high-fibre supplementation induces an uplift in circulating Treg, favourable Th1/Th17 ratios and improvement in symptoms in RA patients.[82] Interestingly, a ketogenic diet induces similar effects: not only does it result in alteration of the human and murine gut microbiota, but also reduces the levels of intestinal Th17 cells after human microbiome transplantations into germ-free mice.[83] This translational study suggests that Th17 cell-promoting bifidobacteria may be suppressed not only by a ketogenic diet, but also fasting. *Prevotella copri*, implicated in the pathogenesis of RA, was also shown to induce Th17 cells in an arthritis model and might therefore be suppressed during fasting and ketosis.[23] As ketone bodies directly inhibit bacterial growth,[83] other taxa may be affected as well. According to Ang *et al*, these should include *Lactobacillus* species that were sensitive not only to a ketogenic diet, but also to ketone ester supplementation in mice. Some *Lactobacillus* species have been linked to translocation to internal organs in lupus-prone models; a mechanism which may be also involved in the pathogenesis of RA that is characterised by a dysfunctional gut barrier.[84 85] *Lactobacillus* also grows out in collagen-induced arthritis that is alleviated by another dietary intervention with resistant starch.[86] One can thus speculate that these potentially disease-promoting taxa may be repressed in their niche within the gastrointestinal tract by the fasting protocol applied to patients with RA in this study. Similarly, the gut barrier dysfunction may improve by this intervention, being comparable to a high-fibre diet that was shown to ameliorate this aspect by increasing the mucus layer in the gastrointestinal tract and preventing from gut commensals to translocate to secondary lymphoid organs.[84 87]

Aside from fasting, a plant-based diet also seems to result in a significant shift in the microbiota in some studies.[88 89] However, a recent review of Trefflich *et al*[90] could not identify a consistent association between a vegan or vegetarian diet and a specific microbiota composition compared with omnivores. Eventually, the interplay of diet, microbiota and host physiology may be unique and person-specific, eliciting individual responses to dietary inputs.[91] Therefore, future microbiome study designs should consider individual microbiome stability and evaluate such data rather on the basis of longitudinal intraindividual basis than on interindividual comparison.[92] We will adopt this approach in the evaluation and interpretation of gut microbiota composition over the individual course of the study intervention.

Given the epidemiological and preclinical data on the one hand and the lack of consistent clinical data on the other, this trial has the potential to generate substantial data on the mechansims as well as on the efficacy of fasting and diet. It aims to target key issues on nutrition and microbiota research and its translation into clinical RA contexts.

A major strength of the study design is the comprehensive amount of data to be collected as well as a sizeable biorepository of blood and stool samples to be generated. Laboratory tests on inflammation and metabolic processes may contribute to further illuminate the mechanism of fasting in RA. Blood-based biomarkers will enable us to identify subgroups of RA patients that benefit to varying extents from our dietary intervention. The longitudinal collection of samples for microbiome analysis will provide further valuable information on the relationship between the microbiota and inflammatory activity in RA patients. Linkage to extensive clinical, dietary and lifestyle data will us provide further information to perform secondary epidemiological analyses to generate new hypotheses for testing in future studies.

Another strength is the avoidance of performance bias. We designed the trial in such a way that both intervention arms receive the same amount of coaching and medical visits, so that no systematic distortion of the study results should occur from this.

In addition, the experimental intervention presented, with the support of nutritional experts, is realistically feasible. The short coaching intervals in the first week of intervention as well as the outpatient study design is more likely to be accepted and put into practice by patients than regular dietary consultations that have to be planned in the long term. It is cost-effective and— in view of the recent research on the positive effects of plant-based foods[42 93 94] or the adverse effects of animal products[95]—has an overall health benefit most likely without serious side effects, if communicated by a professional nutritionist.

However, there are some limitations to our study design. First, the intervention of a plant-based diet

itself includes a reduced intake in AA as the recommendations of the control interventions do. The latter, similar to other studied dietary forms, has indicated trends toward clinical improvement of RA in other clinical trials, although without reaching statistical significance.[52 75] A plant-based diet though represents not only a reduced, but almost negligible consumption of AA. Nevertheless, this aspect might influence our resulting outcomes. Second, our dietary intervention is not blinded. The study, therefore, may be prone to bias like non-specific treatment effects, confirmation and observer bias. This is a general problem among studies aiming to investigate comprehensive dietary interventions and must be taken into account when interpreting results. From past studies in our facility, it is known that many patients apply for studies with a clear preference for one specific intervention. This expectation alone can lead to a change in behaviour and can bias the outcome. Currently, we expect people to favour the fasting-intervention. Patients who are assigned to the control group may not want to participate all together, thus distorting the drop-out rate.[96] On the other hand, rater and subject-expectation bias can increase placebo response and affect study outcome.[97] We try to evaluate the degree of this effect by assessing both the rater's and the participant's expectation for both intervention arms before randomisation.

In summary, fasting and a subsequent specific diet may have the potential to provide a safe and cost-effective complementary treatment option for RA. A better understanding of the underlying mechanisms could also be applicable to other rheumatic diseases. We hope this study will help bridge the gap between promising preclinical data and the lack of clinical data.

Trial status

The NutriFast trial is active with patient recruitment. Recruitment started May 2019 and will be approximately finished in the first quarter of 2021.

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Declaration of consent

for participation in the scientific study on

'Randomized, controlled clinical trial on the efficacy of therapeutic fasting and specific diet in patients with rheumatoid arthritis'

Patient: _____
(surname, firstname)

Date of birth (DD/MM/YY): __ __ . __ __ . __ __ Pat.-No._____

Address: _____

Email: _____

Phone number:_____

The information about the clinical study was given to the patient by:

_____
(Name of the doctor providing information in block capitals)

and covered the following points:

- Type and objective of the clinical trial.
- Type and implementation of treatment related to the study, medical evaluations, including questionnaires, enrolment and final assessments
- Right to withdraw from the clinical trial.
- Data protection: Documentation, transfer and publication of patient data takes place in pseudonymized form, right to deletion of personal data and responsible authorities for right of appeal.
- A copy of the written patient information and the signed consent form was given to me.

With his/her signature the patient declares:

I wish to participate in nutritional therapy with random allocation to the intervention group of therapeutic fasting and specific diet or to the control group with nutritional training on the recommendations of the DGE.

I agree to participate in this study and certify that the consent procedure covered the above points. I was informed verbally and in writing about the nature, significance, scope and risks of the scientific investigation in the context of the aforementioned study and had sufficient opportunity to clarify my questions in an interview with the study physician. In particular, I have understood the patient information presented to me and have received a copy of it and this declaration of consent.

Furthermore, in order to enable the regular surveys in the context of the questionnaire dispatch and follow-up, I agree that my contact data such as name, telephone number, email address and home address may be passed on to the responsible colleagues at the study center (see below). These colleagues may then contact me either by phone, SMS or email if appointments or reminders regarding the questionnaires become necessary.

I understand that I may revoke my consent to participate in this clinical trial at any time without giving reasons and that this will not adversely affect my further treatment. All my questions about the trial have been answered.

Privacy policy

The processing of your personal data takes place on the basis of the basic data protection regulation of the EU and the Berlin Data Protection Act.

The study physician is the data processor within the meaning of the EU Data Protection Regulation. By signing the declaration of consent, you agree that the study physician and his or her colleagues may collect and use your personal data for the purpose of the above-mentioned study for the conduct of the study and for research purposes in the field of integrative oncology. Personal data is, for example, your name, date of birth, your address and data on your health or illness or other personal data that was collected during your participation in the study or in one of the follow-up examinations for a specific purpose.

The study physician gives personal and medical data, which have been generated in relation to the study, as well as the data of your treatment, to the study supervisor Prof. Dr. Andreas Michalsen (see address below) and his working group for the central administration of the data, for cases of adverse events, for data monitoring, for contacting for the necessary purposes of the study and for statistical analysis.

Your personal and health-related data will be stored exclusively on the in-house servers of your treatment centre or servers of the Charité or Immanuel Diakonie. Health-related data is stored and processed exclusively under a pseudonym that replaces your name.

The blood and/or tissue samples taken from you within the scope of the above-mentioned study are also examined pseudonymized in the laboratory of PD Dr. Thomas Häupl. In addition, they will be sent in this form to the laboratory in Berlin for examination there for the purpose of the above-mentioned study. The samples are stored in the laboratory for a period of 5 days and then destroyed. Furthermore, the samples will be sent to Prof. Dr. K. Hiller, Prof. Paul Wilmes and Prof. Dr. med. (all addresses see below).

The study supervisor provides pseudonymized study-related data collected during the study for statistical evaluation to:

Prof. Dr. Manfred Wischnewsky
Department of Mathematics and Computer Science
University of Bremen
Universitätsallee 10-12
28359 Bremen

Tel.:+4942121861400
wischnewsky@escience.uni-bremen.de

The data available at the aforementioned locations will be stored for a period of 10 years and then destroyed.

You have the right to access (including a free copy) all personal data about you that is held by the study physician or the study sponsor. You also have the right to have incorrect personal data corrected. Furthermore, you have the right to revoke your consent to data processing at any time; in the event of such a withdrawal, you can demand the deletion of your personal data. The health and study related data would also in this case be used anonymously (no longer related to your person) for statistical evaluation. To exercise these rights, please contact your study physician. You will find the address and telephone number at the end of this form.

Please note that the results of the study may be published in medical literature, but every effort will be made to maintain your anonymity.

You may at any time object to the further processing of your data collected within the scope of the above-mentioned study and/or further examination of the samples taken from you and demand their deletion or destruction.

You also have the right to appeal to the supervisory authority responsible for data protection.

If you have any questions regarding data processing and compliance with data protection requirements, please contact the Charité Data Protection Office:
Stabsstelle Datenschutz
Charitéplatz 1
10117 Berlin
Tel. +4930450580016
E-Mail: datenschutz@charite.de

You have the right to file a complaint with the regulatory authority if you believe that your study data is being used in violation of applicable data protection laws.

For Berlin, this is the following regulatory authority:
Berliner Beauftragte für Datenschutz und Informationsfreiheit
Friedrichstraße 219
Tel.: +493013889-0
Fax: +49302155050
E-Mail: mailbox@datenschutz-berlin.de

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Prof Dr. K. Hiller
Technische Universität Braunschweig
Braunschweig Integrated Centre of Systems Biology (BRICS)
Institut für Biochemie, Biotechnologie und Bioinformatik
Abteilung Bioinformatik und Biochemie
Rebenring 56
38106 Braunschweig

Herr Prof Paul Wilmes, Prof. Dr. med. J. Schneider Luxembourg Centre for Systems Biomedicine (LCSB),
6 Ave. Du Swing,
L-4367 Esch/Alzette,
Luxembourg

Patient's consent to study participation and data processing:

_____
Place, Date

_____
Patient's signature

Declaration of the study physician:

Hereby I declare that on _____

I have informed the above-mentioned participant orally and in writing about the nature, significance, scope and risks of the above-mentioned study and that I have provided her with a copy of the information and this declaration of consent.

_____
Place, Date

_____
Signature of physician obtaining consent

Zentrum für Naturheilkunde im Immanuel Krankenhaus Berlin
CHARITÉ

Stiftungsprofessur für Klinische Naturheilkunde
Charité – Universitätsmedizin Berlin
Klinik für Innere Medizin, Abt. für Naturheilkunde
Chefarzt Prof. Dr. med. A. Michalsen

Handout

Fasting and

Plant-based Nutrition

Content

Hartmann AM, *et al. BMJ Open* 2021; 11:e047758. doi: 10.1136/bmjopen-2020-047758

Dear participant,

Nutrition is on everyone's lips! Many studies of the last years deal with the influence of nutrition on various medical conditions. Meanwhile there is scientific consensus that an unfavourable diet - low in fibre, rich in refined sugar, an excess of animal fats and calories - plays a major role in the fact that the number of widespread diseases such as diabetes and cardiovascular diseases has risen so sharply. Whereas in the past, nutrition was often neglected in the treatment of diseases, it is now becoming increasingly apparent that a healthy, wholesome plant-based diet not only helps to alleviate symptoms, but also has a significant impact on the prevention of many diseases.

Research shows that symptoms of rheumatoid arthritis (RA) can be significantly relieved by a consistent change in diet. Fasting followed by healthy diet, rich in plant-based foods, can lead to an improvement of the clinical picture in many patients with RA. In our study we would like to accompany you in taking a critical look at your own diet and help you redesign and maintain it according to the rules of a healthy lifestyle.

Making changes to old, entrenched habits can sometimes be quite tedious. Please try to implement the recommendations on these pages without putting yourself under pressure.

Our main concern is to work with you to develop a plan that will lead to a **long-term and lasting improvement** in your health. Therefore, it is better to proceed slowly and step-by-step, but with a lot of joy and lasting effect. If you have any questions, please feel free to contact us at any time and let us know where you have problems with the implementation or where you are unsure - we will support you and find solutions together.

In the following pages you will find explanations of the form of nutrition and suggestions regarding creating a healthy eating and living routine. This information should serve you as a supplement to your nutritional coaching.

We wish you much success and pleasure in implementing them!

Preparing for Fasting

Dear participant,

in a few days your study group will start. You were randomly assigned to the fasting group. Before the fasting week starts, we ask you to follow a light plant-based diet.

While preparing for fasting it is recommended that you consume easily digestible food rich in fibre, which positively affects stool consistency for cleansing of the bowels on the first fasting day. In addition, in these days quantities of food are reduced, in order to prepare you and your digestive tract carefully for the subsequent period of food deprivation. Food and luxury food such as coffee, black tea, nicotine, sweets and alcohol should already be off the menu in these days. Reduce coffee by one cup a day to maximum one cup a day before the fasting starts. The start of the fasting week will be easier for you and unpleasant side effects such as headaches, nausea and circulation problems may be prevented.

In general: **Drink plenty of fluids**! You should drink about 2-3 litres of water (e.g. with herbs, ginger or cucumber slices) or herbal teas per day. Lemonades or alcohol should not be consumed.

Our first coaching takes place on the day before fasting starts. Here you will receive all the information about bowel cleansing and the fasting week. **It is advisable that you obtain the recommended items on the following shopping list in advance**. Your fasting week begins with a weekend; during the first days of fasting, it is also a good idea to avoid stressful activities such as shopping. Below you will find examples of recipes that are suitable for a light plant-based diet.

We wish you a successful start to the fasting week; if you have any questions, please contact the study team at any time!

Daily Schedules

1. Day of light plant-based diet

Breakfast: 1 cup of herbal tea (or special fasting tea), 1 small bowl of porridge (prepared with water or oat milk) with 1 grated apple

Lunch: 1 small portion of natural rice pan with steamed vegetables (e.g. carrot, zucchini, tomato, pumpkin, parsnip...) and herbs

Dinner: 1 slice of wholemeal bread with tomato spread, 1 small bowl of carrot salad (steam carrots slightly before serving, with roasted sunflower seeds and sesame seeds)

2. Day of light plant-based diet

Breakfast: 1 cup of herbal tea (or special fasting tea), 1 small bowl of porridge (prepared with water or oat milk) with berries

Lunch: 1 medium-sized potato with steamed vegetables (e.g. carrot, zucchini, tomato, pumpkin, parsnip...)

Dinner: 200g steamed cauliflower and 100g steamed broccoli with herbs or 1 plate of vegetable soup

3. Day of light plant-based diet

Breakfast: 1 cup of herbal tea (or special fasting tea), 1 small bowl of porridge (prepared with water or oat milk) with berries or apple

Lunch: 1 small portion of natural rice pan with steamed vegetables or 50g lettuce (e.g. chicory, iceberg lettuce, lamb's lettuce), 1 medium-sized tomato, 6 radishes, ¼ green cucumber with lemon juice, fresh herbs, white pepper, some sea salt, if necessary seasoning with 1 teaspoon olive or linseed oil

Dinner: 1 bowl of vegetable soup, pureed into cream soup

√	**Shopping List I**
Foods – organic products recommended	
☐	Food for light plant-based diet (e.g. rice, oatmeal, vegetables) (see recipes for quantities)
☐	Fresh vegetables as desired (for homemade vegetable broth) (see recipes for quantities)
☐	Fresh herbs as desired (for homemade vegetable broth) (see recipes for quantities)
☐	Freshly squeezed vegetable juices without added sugar, preferably self-pressed or organic direct juice (e.g. tomato juice, carrot juice, mixed vegetable juices) ca. 2,1 litres for 7 fasting days
☐	Herbal teas as desired: – Teas to relax (e.g. lemon balm, lavender, lime blossom, hops, St. John's wort) – Teas for circulatory problems (e.g. rosemary, ginseng, lemongrass) – Teas for digestive complaints (e.g. chamomile, sage, fennel, cinnamon, liquorice, oats) – fresh ginger or turmeric – Liquorice tea can be helpful in case of craving for sweets ca. 2,0 litres water/herbal tea per day
☐	Non-carbonated mineral water (low sodium) or tap water
☐	Sauerkraut juice - optional
☐	Oatmeal or flaxseed (for digestive complaints or increased sensation of cold) - optional
☐	Lemons, unwaxed - optional
☐	Fresh ginger - optional

√	**Shopping List II**
Fasting Aids	
☐	Disposable enema (minimum 500ml, 3-4 pieces) or enema aids for intestinal cleansing (Irrigator OROS for multiple use) in the pharmacy
☐	Massage glove/brush (for dry massage)
☐	Warm blanket and warm socks
☐	2 hot water bottles (for liver compress)
☐	Tongue Scratcher
☐	Organic olive or sesame oil for oil extraction

Fasting meals

Breakfast: 150 ml vegetable juice (e.g. carrot juice, beet)
Lunch: 150 ml vegetable juice (e.g. tomato juice)
Dinner: ca. 250 ml homemade vegetable broth

The juice and broth can also be swapped in time.

Throughout the day, drink 2-3 litres of water and herbal tea, feel free to squeeze a lemon and drink or bite on lemon slices.

Some tips:

- The vegetable broth can also be replaced with tomato juice diluted with hot water.
- Spoon your juice mindfully as you would eat a meal.
- Bring variety to your meals by using different types of vegetables
- If you want a little more flavour to your water, you can add cucumber slices, lemon slices or mint leaves ("infused water")
- If your stomach is sensitive or you are prone to feeling cold, warm oatmeal or flaxseed mucilage can also be taken instead of juice. To do this, add 1-2 tablespoons of fine oatmeal or preferably light-coloured, ground flaxseed to 250 ml of water. Boil this for 5 min or let it stand longer in the hot boiled water and stir. Before drinking, sieve off the solid components!

Some suggestions for fresh, home-squeezed juices:

- Carrot - Lemon – Ginger
- Cucumber - Celery – Mint
- Beetroot - fennel

Broth recipes

Recipes for 4 servings each

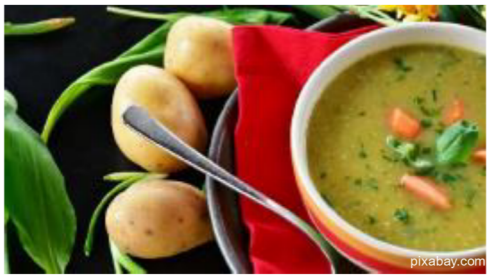
Basic vegetable broth recipe

1 Litre	water
1 kg	vegetables (e.g. carrots, tomatoes, pumpkin, broccoli, zucchini)
1	clove
3-4	bay leaves
4-5	juniper berries
1 – 2 tblsp	fresh herbs (e.g. parsley, oregano, marjoram, basil, dill, lovage)
Optional:	sea salt

Wash the vegetables well, chop them and bring to a boil with the water. Cook the broth on the lowest heat for 60-90 minutes. After 15 minutes of cooking, add bay leaf, clove and juniper berry and let steep. Strain, season with fresh herbs and a pinch of sea salt optionally.

TIP: Add fresh tomatoes to the vegetables, season with 1 - 2 tsp tomato paste and fresh basil to create a tomato broth.

Potato broth



1 Litre	water
250 g	potatoes
250 g	carrots
1 stick	leek
1	large parsley root
½ tsp	caraway
3-4	bay leaves
4-5	juniper berries
Optional:	parsley, sea salt (ca. 1 tsp)

Wash the vegetables well, chop them and bring to a boil with the water. Cook on the lowest heat for 60-90 minutes. After 15 minutes of cooking, add the caraway seeds and let the soup simmer. Strain and season with finely chopped parsley and a pinch of sea salt optionally.

Other seasoning options are dill, basil, lovage, nutmeg, marjoram or oregano.

Bowel Cleansing with Sodium Sulfate

(only on the 1st day of fasting)

Fasting is initiated with bowel emptying on the first day of fasting, so that the body can switch more quickly and better from food intake to elimination. It reduces the feeling of hunger and supports the regeneration of the digestive system.

Bowel cleansing is initiated by taking sodium sulfate. The dosage and intake will be discussed in the first session of the dietary coaching.

How does it work?

Sodium sulfate is an osmotically acting laxative. This means that large amounts of water diffuse through the intestinal walls while it is being transported in the gut. The intestines additionally react with increased activity. The desired result is thorough emptying of the small and large intestines. To make up for the increased, diarrheal fluid loss from the body, please drink plenty of fluids after taking the salt.

Preparation

- Stir sodium sulfate into ½ litre of well-warmed water until dissolved. At best, drink in the morning within approx. 20 minutes - determine the right amount together with the study staff.
- In addition, drink about 1 litre of peppermint tea; a good balance for fluid loss and preventive against stomach cramps.
- If necessary, squeeze an untreated organic lemon and either mix it with the sodium sulfate drink or drink it straight in between sips - this binds the strong taste.
- Light physical activity or exercises support bowel cleansing.
- **The time it takes for the bowel cleansing to start varies individually, but it usually occurs after 1-3 hours depending on the physical constitution.**
- Take time and rest.

If bowel cleansing has not set on by the evening, help with an enema.

Bowel Cleansing with Enema

An enema is recommended every two days. It can also be used as an alternative to laxative salts such as sodium sulfate in certain cases.

The intestine reduces its activity during fasting. To eliminate residual stool, dead intestinal cells and bacteria, the enema is highly recommended.

The enema can reduce feelings of hunger, discomfort or headaches and can be used regularly if needed.

What do you need?

- 1 irrigator with long flexible intestinal tube
- Vaseline or body oil
- 1 large towel

Preparation

- Place the towel on your bathroom floor.
- Familiarize yourself with how the irrigator works.
- Fill lukewarm water (about 750 ml) into the irrigator, then drain a little water to remove air bubbles.
- Grease the end piece of the flexible bowel tube.
- Hang the irrigator on a hook or on the bathroom door (the higher it hangs, the faster the water will flow in).
- Find your optimal position to insert the intestinal tube (about 15-20 cm, do not force if there is resistance, possibly pull back a little, turn and try again). It is recommended to lie on your left side, or on your back and place your feet on the edge of the bathtub or against the wall or stay in the all-fours position. It is important that you can open and close the irrigator tap in your position.
- Open the irrigator tap and let the water run in (you may be able to push the intestinal tube in a little further as the water runs in).
- **Breathe calmly.**
- When the water has run in, close the tap and remove the intestinal tube.
- If you are lying on your left side, turn on your back and then to your right side.
- If the pressure is not yet too great, stand up and move your upper body to the right and left. At any time, give in to the emptying pressure on the toilet if it is no longer possible.

Exercise and Relax

During your fasting week, both sufficient exercise in fresh air and rest periods are important to support the optimal fasting process.

Exercise promotes fat burning, good circulatory function and respiratory activity. You prevent muscle loss by doing gymnastic exercises and walking, cycling or swimming. If you are used to other sports, you can do them carefully even during fasting. If possible, move at least one hour every day.

Along going, relaxing is just as important. In addition to resting during the liver compress, other relaxation exercises such as autogenic training, light yoga, QiGong exercises or meditation are ideal. If possible, make sure you breathe deeply.

Liver Compress

The liver compress is a well-known household remedy that is used in fasting as a liver-supporting measure. The humid-hot compress promotes the blood circulation of the liver and thus leads to a faster elimination of metabolic decomposition products.

The liver wrap can be done with hot water or with brewed yarrow tea. The essential oils in yarrow have an antispasmodic and mild blood circulation stimulating effect and thus support the function of the liver wrap. And, as with every compress, it provides a good opportunity to get some rest.

What do you need?

- Inner cloth (e.g. washcloth, kitchen towel or gauze diaper)
- Intermediate cloth (kitchen towel)
- Outer cloth (e.g. wool scarf, bath towel)
- Wringing cloth (another kitchen towel)
- Yarrow tea or hot tap water
- Bowl
- 2 hot water bottles filled with hot tap water
- Blanket
- Household gloves

Instructions

- Fill the hot water bottles with hot (not boiling!) tap water.
- Check if they are properly closed.
- Roll the inner cloth from both sides inwards and place it inside the wringing cloth.
- Then roll the wringing cloth and grab it by both sides to create the shape of a candy. The ears of the wringing cloth will stay dry.
- Place both cloths in a bowl leaving the ears outside the bowl.
- Pour yarrow tea or hot (not boiling!) water over it.
- Put the household gloves on and wring it out to create a hot, dry cloth. Hot water may burn the skin where applied and lets the compress cool faster.
- Remove the wringing cloth.
- Place the inner cloth (test temperature compatibility on the skin) on the right upper abdomen and cover with the intermediate cloth.
- For a longer lasting warmth place the hot water bottle on the intermediate cloth and wrap everything tightly around the body with the outer cloth.
- Fix the hot water bottle with the towel or a tight t-shirt.
- The second hot water bottle can be used to warm the feet.
- Cover up with the blanket so that you feel comfortably warm.
- Stay in this position for 30 minutes and enjoy the rest.

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Reintroduction of Solid Foods

Important, but also more difficult than fasting is the introduction of solid foods in form of a light plant-based diet. Therefore, special attention should be paid to these days. The transition should be slow, gentle, and gradual. The digestive tract must first gradually get used to eating again.

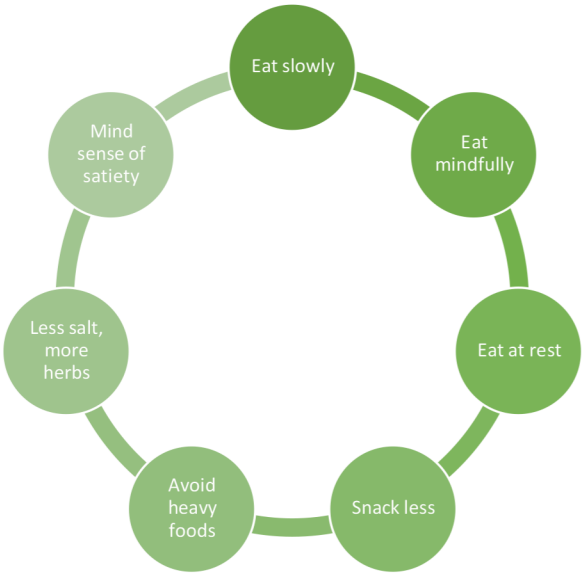
Please eat small portions, chew the food thoroughly and enjoy it consciously. Use as many herbs as possible and very little salt during the rebuilding days.

To stimulate the intestines again, eat lots of fibre. A cup of flaxseed mucilage, preferably light-coloured, is also recommended in the morning. Soak 1 tablespoon of flaxseed in 250 ml overnight or boil 1 tablespoon in 250ml of water briefly and let it swell well.

Continue to ensure adequate drinking, light exercise and relaxation.

1. Day after Fasting	2. Day after Fasting	3. Day after Fasting
High carbohydrate foods	High carbohydrate foods, little protein	High carbohydrate foods, little protein, little fat
Example: **Breakfast:** Apple, flaxseed mucilage optionally **Lunch:** Vegetable soup **Dinner:** stewed carrot with herbs, a crispbread optionally	Example: **Breakfast:** Porridge with fruit **Lunch:** Potatoes or millet with vegetables **Dinner:** Potato and vegetable soup with pumpkin seeds or crispbread with plant-based toppings and vegetables	Example: **Breakfast:** Porridge with fruit **Lunch:** Raw vegetable salad or brown rice and vegetables pan, 1 tbsp. oil **Dinner:** Crispbread/whole flour bread with natural tofu or plant-based cream cheese or other toppings plus vegetables; alternatively: potato soup

Simple rules for reintroducing foods (and afterwards):



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Schedule for the Fasting Week

	Light plant-based diet	**1st day of fasting**	**2nd – 6th day of fasting**	**Last day of fasting**	**Reintroducing solid foods – 1st day of light plant-based diet**	**Reintroducing solid foods – 2nd and 3rd day of light plant-based diet**
Intake	Drink plenty: at least 2.5 litres e.g. tap water, non-carbonated mineral water, unsweetened herbal teas or ginger water*. Meals see script	Drink plenty: at least 2.5 litres e.g. tap water, non-carbonated mineral water, unsweetened herbal teas or ginger water*. **Breakfast:** Bowel cleansing & peppermint tea **Lunch:** 250 ml vegetable juice **Dinner:** 250 ml vegetable broth**	Drink plenty: at least 2.5 litres e.g. tap water, non-carbonated mineral water, unsweetened herbal teas or ginger water*. **Breakfast:** 150ml vegetable juice **Lunch:** 150ml vegetable juice **Dinner:** 250 ml vegetable broth**	Drink plenty: at least 2.5 litres e.g. tap water, non-carbonated mineral water, unsweetened herbal teas or ginger water*. **Breakfast:** 150ml vegetable juice **Lunch:** 150ml vegetable juice **Dinner:** 250 ml vegetable broth**	Continue drinking plenty **Breaking the fast** Meals see script, e.g.: **Breakfast:** tea, apple **Lunch:** vegetable soup **Dinner:** stewed carrot*	Continue drinking plenty Meals see script, e.g.: **Breakfast:** porridge with fruit **Lunch: p**otatoes with vegetables **Dinner:** crispbread with plant-based toppings
Output	Good intestinal filling due to a high-fibre diet	**Morning:** Start fasting with bowel cleansing **Midday:** Promote elimination of metabolic decomposition products with liver compress + **Evening:** Enema if bowel cleansing has not begun	**Midday:** Liver compress + **Every 2nd day:** Enema	Liver compress +	Liver compress +	Liver compress +
Exercise and Relax	Exercise outside, come to rest, relax from everyday life	**Morning:** exercise outside **After enema:** supportive gymnastics at home, mindful rest periods	Exercise outside, mindful rest periods	Exercise outside, mindful rest periods	Moderate exercise, mindful rest periods, avoid physical effort	Keep exercise implemented in everyday life
Other	**Prepare:** - Fasting food and drinks - Fasting aids (warm blanket and hot water bottles)	Mindful start of fasting	Increased body care and fasting supporting measures (e.g. tongue cleansing, body oil, water applications).	Farewell to fasting, experiencing change	Paying attention to body signals, eating consciously, paying attention to satiety	Slowly increase the amount of cereals and, if necessary, add some protein (e.g. plant-based yoghurt) and some fat (e.g. virgin oil) on the 3rd day, eat low-salt food.

* Pour 2-3 slices of fresh peeled ginger with 1 litre of boiling water and let it infuse

** See recipes

\+ See supplemental instructions

Nutritional Concept for Rheumatoid Arthritis

The aim of the study is to change your diet to a plant-based diet that is individually adapted by traditional medical knowledge. In what follows, we offer an explanation of the basics.

What is a plant-based diet?

A plant-based nutrition excludes the consumption of animal products and is therefore enriched with vegetable food, which is rich in vitamins and minerals. Studies in recent years indicate that excessive consumption of animal proteins is associated with an increased risk of type 2 diabetes and cardiovascular disease. In addition, there is evidence from research that diseases such as rheumatism or type 2 diabetes can be positively influenced by a plant-based diet.

A well-planned whole plant diet ensures the supply of all essential nutrients and also provides nutrients that are beneficial to physical health, which are often neglected in a mixed diet with animal products, as they are found in these foods on average in little or no quantity. These include:

- Vitamins, especially provitamin A (ß-carotene), vitamin C, vitamin E, folate, pantothenic acid, biotin
- dietary fibres
- secondary plant compounds

With a balanced plant-based diet, high levels of vitamins, fibre and secondary plant substances are consumed and can thus prevent the development of various diseases or alleviate their course.

A plant-based wholefood diet has a positive influence on the course of:	A plant-based wholefood diet reduces the disease risk for:
• **Obesity** • **Hypertension** • **Lipometabolic disorders** • **Insulin resistance** • **Chronic inflammation (e.g. arthrosis)** • **Metabolic syndrome** • **Cardiovascular diseases (e.g. chronic heart failure, atherosclerosis, coronary heart disease)**	• Type 2 diabetes • Colorectal cancer • Gastric cancer • Prostate cancer • Breast cancer • Alzheimer's disease • Chronic inflammation

The specially developed food pyramid for a plant-based diet can be used to support the daily food planning.

Group 1a: Bread, cereals, potatoes

Cereals and potatoes are important sources of protein in the plant-based diet. They should therefore be consumed in 2-3 portions daily. Whole grains are very important - they contain dietary fibres, complex carbohydrates, important B vitamins as well as minerals such as iron, zinc and magnesium. Potatoes also are an excellent supply of vitamin C, potassium and magnesium.

Group 1b: Legumes, protein products

In a plant-based diet, legumes (1-2 meals) and soy products (such as tofu, seitan, tempeh: 50-150g) should have a special place in your daily diet. They provide high-quality vegetable protein as well as dietary fibres, vitamins, minerals and secondary plant substances.

Group 2: Vegetables and Group 3: Fruit

A plant-based diet is based on plant-based nutrition, so at least 3 portions of vegetables per day should be consumed. Fruit and vegetables provide plenty of fibre, minerals and vitamins. It is recommended that you eat as colourfully as possible: the colours of fruits are often caused by secondary plant compounds, which are beneficial to health in many ways. Dark green vegetables are also of great value, as they are rich in calcium. Fruit contains many essential vitamins and minerals and should therefore be eaten in 2 portions daily. Fruit smoothies also count as a fruit portion, but usually exceed the recommended serving quantities. It is therefore recommended to choose dark green vegetables as the base of the smoothies and mix them with a portion of fruit. More portions of fruit are not recommended in the long run due to high sugar content.

Group 4: Dairy alternatives

Dairy products, especially cheese, are very good sources of protein and calcium. If these are not available in the chosen diet, they must be replaced by alternative foods. In addition to calcium and protein-rich vegetables, seeds or legumes, a wide range of vegetable drinks, yoghurts or fresh creams on a vegetable basis are available. Particularly soy products, such as soy drinks and soy yoghurt, provide high-quality vegetable protein. Enriched vegetable drinks help cover your calcium need and supply you with important vitamins, whose supply is more difficult with a purely plant-based nutrition (above all Vitamin B12, Vitamin B2, Vitamin D and Vitamin E). Vegetable cheese alternatives can make the changeover easier for you and make your diet more

varied, but they usually do not have much nutritional value (exceptions here are products enriched with vitamins or minerals). To ensure a sufficient supply, you should take 1-3 servings (200-300g) of the milk alternatives daily and make sure to choose a wide selection of calcium-rich plant-based foods.

Group 6: Fats and oils

If the consumption of fat-rich sea fish is left out, it is important to ensure the supply of polyunsaturated fatty acids through the sufficient supply of plant-derived fats. For this you should have a daily intake of 30-60g nuts (especially walnuts) and additionally 3-5 tablespoons of high-quality plant oil. Particularly recommendable here are flax, hemp and rape seed oil due to their very good omega-3-fatty acid content. Omega-3-fatty acids enriched vegetable oils represent a reasonable supplement. It is recommended to avoid the use of omega-6-rich oils such as sunflower, thistle or maize germ oil as far as possible in a purely plant-based food form because of the unfavourable fatty acid ratio. A spoonful of ground flax seeds in muesli not only has an excellent fat composition, but also ensures healthy intestinal function thanks to its high fibre content.

Group 7: Beverages

The plant-based diet, like any dietary form, is based on an adequate intake of fluids. Again, water and tea as well as highly diluted fruit juices (one part juice - three parts water) are recommended. Due to the critical supply of calcium-rich food, it is advisable to choose a calcium-rich mineral or medicinal water (>150mg/L). Coffee and black tea can be used as a supplement to cover the liquid requirements. However, undiluted fruit juices, lemonades and wellness drinks are among the extras due to their high sugar content.

„Extras“:

A purely plant-based diet can offer an advantage regarding the daily caloric intake. Nevertheless, you should not replenish saved calories with sweets, snacks or sugar-rich drinks. If you are not able to cover your daily requirements and weight loss is not desired, try integrating more energy-rich foods such as avocado, nuts and high-quality vegetable fats into your daily plan. Alcohol is tolerated in moderate amounts.

„Supplements“:

With a purely plant-based diet it is extremely difficult to ensure a sufficient supply of vitamin B12 with food alone. Supplementation and the consumption of enriched products are therefore strongly recommended. In addition, care must be taken to ensure an adequate supply of iodine. Ideally, you should take 1 teaspoon of Nori algae daily. If this is out of the question, use alternatively max. 3g iodized table salt daily. The additional intake of vitamin D (preferably in combination with vitamin K) is also highly recommended in Germany due to the low number of hours of sunshine. During

summer time, it is also advisable to stay outside for 10-15 minutes a day in light clothing and without the use of sunscreen.

Basically, you should discuss the intake of dietary supplements with your family doctor (or in our case also with your study physician) and adjust them to your needs and any underlying diseases. The intake of isolated secondary plant substances such as ß-carotene is not recommended. When taking such complementary products, an opposite effect to the one observed in food has often been observed, since the positive effect of secondary plant substances depends strongly on the other nutrients present.

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Critical nutrients - a selection of favourable food products

Some essential nutrients count in the plant-based diet as so-called "critical nutrients" (protein, zinc, calcium, vitamin B2, vitamin B12, omega-3 fatty acids). These are nutrients, which occur in vegetable food on the average in smaller quantity than in certain animal products, for example iron and protein from animal muscle meat or calcium from cow's milk. Nevertheless, it is possible to ensure a sufficient supply of these nutrients through the right choice of food and the planned combination of food components. We include Vitamin D and iodine likewise among the critical nutrients. This applies however not only to a plant-based diet, but also to the healthy mixed diet recommended by the Deutsche Gesellschaft für Ernährung (DGE, German society for nutrition). The same recommendations apply here (see above "Supplements"). Vitamin B12 takes on a special role, as it is not or not sufficiently contained in plant-based foods under current hygiene and processing methods and must be supplied via food supplements (see above "Supplements").

Below you will find a selection of foods that should make it easier for you to choose alternatives to animal products.

These products are now available in almost every supermarket or organic food store.

	Protein in g/100g,[1,4]	**Usual average portion size**	**Protein in g/portion**
Pumpkin seed	35	15g (1 tbsp)	5,25
Wheat germs	28	10g (1 tbsp)	2,8
Peanut	25	50g	12,5
Lenses, dry	24	60g	14,4
Flax seeds	24	15g (1 tbsp)	3,6
Peas, green	6	200g	12
Poppy seed	20	15	3
Almond, sweet	19	15g (10 almonds)	2,85
Sesame seeds	18	15g (1 tbsp)	2,7
Tofu, roasted	16	100g	16
Amaranth	15	20g	3
Quinoa	15	20g	3
Nettle	8	50g	4
Dandelion	3	50g	1,5

For comparison: the average daily protein requirement of an average heavy adult aged 25 to under 51 years is 57g/day for men and 48g/day for women (0.8g/kg body weight/day).

	Omega-3 fatty acids in g/100g[2,4]	**Usual average portion size**	**Omega-3 fatty acids in g/portion**
Linseed oil	54	10g (1 tbsp)	5,4
Hemp oil	18	10g (1 tbsp)	1,8

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Chia seeds	19[3]	15g (1 tbsp)	2,85
Flax seeds	13[4]	15g (1 tbsp)	2
Walnut oil	13	10g (1 tbsp)	1,3
Canola oil	9	10g (1 tbsp)	0,9
Walnuts	8	20g (5 pieces)	1,6
Soya Oil	8	10g (1 tbsp)	0,8

	Iron in mg/100g[1]	**Usual average portion size**	**Iron in mg/portion**
Wheat bran	16,6	6g (1 tbsp)	1,0
Sesame seeds	10,0	15g (1 tbsp)	1,5
Poppy seed	9,5	15g (1 tbsp)	1,4
Amaranth	9	20g	1,8
Flax seeds	8,2	15g (1 tbsp)	1,2
Pistachios	7,3	40g	2,9
Savory	6,2	2g (1 tsp)	0,12
Oat flakes, hulled	5,8	60g	3,5
Basil	5,5	2g	0,11
Pumpkin seeds	4,9	15g	0,74
Apricot, dried	4,4	10g (1 piece)	0,44
Rye meal	3,7	10g (1 tbsp)	0,37
Spinach, raw	3,4	200g	6,8

For comparison: the average daily iron requirement of an average adult aged 25 to under 51 years is 10mg/day for men and 15mg/day for women.

	Zinc in mg/100g[1]	**Usual average portion size**	**Zinc in mg/portion**
Wheat bran	9,0	6g (1 tbsp)	0,54
Poppy seed	8,0	15g (1 tbsp)	1,2
Sesame seeds	7,7	15g (1 tbsp)	1,2
Wild rice	6,0	30g	1,8
Flax seeds	5,5	15g (1 tbsp)	0,8
pecan nut	5,3	40g	2,1
Lentils, dry	3,4	60g	2,0
Muesli with nuts	3,4	90g	3,1
Buckwheat, hulled	2,7	15g	0,4
Rye crispbread	2,3	10	0,23

For comparison: the average daily zinc requirement of an average adult aged 25 to under 51 years is 10mg/day for men and 7mg/day for women.

	Calcium in mg/100g[1]	**Usual average portion size**	**Calcium in mg/portion**
Poppy seed	1460	15g (1 tbsp)	219
Sesame seeds	780	15g (1 tbsp)	117
Nettle	710	50g	355
Savory	350	2g (1 tsp)	7
Flax seeds	250	15g (1 tbsp)	37,5
Hazelnut	225	40g	90
Kale	210	200g	420

Tofu, roasted	195	100g	195
Fig, dried	190	20g	38
Arugula	160	50g	80

For comparison: the average daily calcium requirement of an average adult aged 25 to under 51 years is 1000mg/day.

	Vitamin B2 in mg/100g[1]	**Usual average portion size**	**Vitamin B2 in mg/portion**
Wheat germs	0,72	10g (1 tbsp)	0,072
Almond, sweet	0,62	15g (10 pieces)	0,093
Wheat bran	0,51	6g (1 tbsp)	0,031
Dill	0,43	2g (1 tsp)	0,009
Mushroom	0,42	150g	0,63
Rosemary	0,40	2g (1 tsp)	0,008
Cashew nuts	0,26	40g	0,104
Kale	0,25	200g	0,5
Spinach, raw	0,20	200g	0,4
Dandelion	0,17	50g	0,085

For comparison: The average daily vitamin B2 requirement of an average adult aged 25 to under 51 years is 1.4mg/day for men and 1.1mg/day for women.

Note: Flours from the above-mentioned nuts, legumes, grains, and seeds usually have even higher concentrated nutrient contents. Dried products also have a higher nutrient density (e.g. dried fruit).

For our health it is not only important **what** we eat, but also **how** we eat. Furthermore, the following elements contribute to your well-being when practiced regularly:

1. **Enjoy food variety:**
   Try to eat in a varied and diverse way.
2. **Vegetables and fruit – "take 5 a day"**
   Have at least 3 servings of vegetables and 2 servings of fruit a day.
3. **Choose whole grain:**
   Choose the whole grain option of bread, noodles, rice, and flour.
4. **Use healthy fats:**
   Preferably use high-quality vegetable oils and spreadable fats made from them. Watch out for hidden fats in baked goods, sweets, and other convenience products.
5. **Save salt and sugar:**
   Avoid foods and drinks with added sugar and be sparing in your use of sugar. Try to limit the use of salt and salty products and season with herbs and spices instead.

6. **Drink water:**
   Drink about 1.5 litres of water and other calorie-free beverages like tea a day.
7. **Prepare gently:**
   Cook with little water and little fat and only as long as necessary. Burning food (roasting, grilling and other forms of preparation at very high temperatures) produces substances that are harmful to health.
8. **Mindful eating:**
   Take time for your meal and refrain from doing other activities simultaneously. Do not eat while walking or in a hurry.
9. **Watch your weight and keep moving:**
   Integrate regular sport into an active everyday life with cycling or walking.
10. Try to get used to a maximum of **three meals**. Pay attention to eating little early in the morning, the main meal at noon, and lightly in the evening and not after 7 pm. Try to **avoid snacks** and only eat again when the previous meal has been digested (after about 4-5 hours).
11. **Pure, ripe, and fresh:** Food from organic farming methods and fresh home-prepared meals are ideal for you. If possible, avoid convenience foods, canned foods, foods containing colorants and preservatives, frozen foods, foods containing industrial sugar and foods that have been reheated several times.
12. **Enjoy your food**!

External applications for Rheumatoid Arthritis

In rheumatoid arthritis, not only does nutrition play an important role in its development, but other reinforcing factors are also involved.

In order to treat your symptoms as holistically as possible, you should integrate the following things, which can have a positive effect on the course of the disease, into your daily routine as often as possible:

- Keep the affected joint **warm** by exposing it to dry heat, at least as long as it seems comfortable to you and there is no worsening due to the heat. This can be done, for example, with spelt cushions or sandbags by "dabbing" the joint.
- Silk glove massage: This massage is performed with a silk glove and should be done daily if possible. Circular movements are performed around the joints, along the legs and arms in long stroking movements. The heart and the chest are left out.
- Integrate **gentle movements** / **sports** into your everyday life. Yoga exercises are especially suitable for this. Swimming and cycling are also suitable, although you should focus less on strength and more on endurance.
- Avoid **extreme positions** of legs and feet. Try to cross your legs less.
- Reduce periods of one-sided, longer standing and sitting.

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Spices

Spices should play a special role in the diet, because they not only improve the taste, but also promote good digestion, reduce flatulence and have various other healing effects. For many of the spices an anti-inflammatory effect has been proven by studies. It is recommended to have a small selection of spices on the kitchen shelf. The most important spices that you should include in your diet especially often are listed here below in order:

Curcuma	blood cleansing, good for the liver and anti-inflammatory
Fenugreek	warming, weight-reducing, lowers blood sugar and cholesterol, especially good for rheumatoid arthritis
Ginger	warming, helps against flatulence and nausea
Kalonji (black cumin)	blood cleansing, good for rheumatoid arthritis
Cumin	helps against flatulence, digestive
Coriander	cooling, pain-relieving, calming. Coriander is available fresh or dried. Dried it loses its intense flavour and is well suited for cooking.
Cardamom	soothing, heating, binds acidity, good for refining desserts
Cinnamon	warming, sweetishly hot, stimulates the circulation
Nutmeg	Strengthens the nervous system, good for sleep disorders (do not use more than a trace), binds the stool
Ajwan (wild celery seeds)	effective in the treatment of flatulence, intestinal cleansing (not with heat in the joints!)
Pippali (long pepper)	heating, stimulates digestion, supports the body in the elimination of metabolic toxins
Carnations	analgesic, blood cleansing
Fennel	cooling, sweet, helps with stomach and intestinal colic
Asafoetida (Hing)	effective in the treatment of flatulence, good for loss of appetite (do not use in hot joints!)
Saffron	cooling, cleansing, good for the immune system

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Spice blends

Curry Pulver

Ingredients
2 tablespoons cumin seed
1 tablespoon fennel seeds
1 tablespoon black mustard seeds
1 tablespoon turmeric powder
1 teaspoon black peppercorns
1 teaspoon fenugreek seed
6-8 cloves

Preparation
Heat a heavy pan and add all the spices except turmeric. Stir until the spices start to smell and brown slightly (approx. 2-3 min). Leave to cool and grind as fine as possible in a mortar or coffee grinder. Mix with turmeric. Stored airtight in a glass jar, the spice mixture lasts up to 3 months. This spice mixture is ready and should not be roasted again, but added to the dishes at the end.

8 Winds Powder

This spice blend supports the digestion of the meal and prevents gas formation. Please do not use this mixture with hot and reddened joints.

Ingredients (fine powders):
Hing/Asafötida (from the Ayurveda store)
Cumin
Caraway seeds
Pepper
Ginger
Pippali (long pepper: Piper longum; from the Ayurveda store)
Ajwain (Trachyspermum ammi; from the Ayurveda or Asia store)
Himalayan salt (pink rock salt)

Preparation:
Mix fine powder in equal parts. Before the meal, warm a level teaspoon of the mixture in coconut oil and take with the meal.

Warming spice powder

Ingredients
8 cardamom capsules
4 cinnamon sticks (each 6cm long and in small pieces)
4 tablespoons coriander seeds
2 tablespoons cumin

1 ½ tablespoons black peppercorns
1 teaspoon cloves

Preparation
Roast cardamom capsules, cinnamon sticks, coriander seeds, cumin, black peppercorns and cloves together in a pan or wok until they smell nice. Then put aside to cool.
Peel the cardamom seeds from the capsules and throw the capsules away. Grind all the spices in a mixer or with a mortar to a fine powder and then mix in ½ teaspoon grated nutmeg. Stored airtight in a glass jar, the spice mixture lasts up to 3 months. This spice mixture is ready and should not be roasted again, but added to the dishes at the end.

Garam Masala

Another spice blend that you can buy ready to use or make yourself is Garam Masala. It consists typically of cardamom, pepper, cinnamon, cumin, nutmeg and cloves.

Example for the use of spices

Turmeric Tea

Turmeric is anti-inflammatory. We recommend you prepare and drink this tea twice a day.

Ingredients	*Preparation*
- 250 ml water - 1 teaspoon curcuma powder - 1 pinch of black pepper	Bring water to the boil, add turmeric and pepper, cool to drinking temperature and drink.

Ginger Water

Ginger water stimulates the digestion. However, it should not be drunk when there is a sensation of heat or hot joints.

Ingredients	*Preparation*
- 1 l water - 1 slice of fresh ginger	Boil water with peeled ginger with open lid until the liquid has reduced by about half. Remove ginger, let it cool down to drinking temperature and drink 1 cup. People with heat symptoms should not drink too much of the water, because otherwise - especially in summer - too much heat can build up in the body.

Chai Tea

In the afternoon, a tea made of stimulating spices called chai is recommended. It can be drunk instead of coffee and refined with a milk alternative (e.g. rice milk or soy milk). Chai tea blends are also available in stores as an alternative to the recipe below. Mixtures in organic quality and without black tea are preferable. The spices are also beneficial for the digestive system.

Ingredients	*Preparation*
- 1 litre water - 2 cinnamon sticks - 5 cardamom capsules - 4 cloves - 1 teaspoon freshly grated ginger - (1 teaspoon of rooibus tea) - 200 ml milk alternative - 1 teaspoon raw cane sugar	Simmer all ingredients except the milk alternative, rooibos tea and raw cane sugar for about 10-20 minutes until the liquid has reduced by about half. Add the remaining ingredients, bring to the boil again and then strain.

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Spice Milk

A spice milk is particularly suitable in the evening, as it promotes sleep. Saffron strengthens our immune system, the other spices ensure good digestion.

Ingredients	*Preparation*
- 200 ml almond milk - 1 pinch of nutmeg - ¼ teaspoon cinnamon - ¼ teaspoon cardamom - 4 saffron threads	Soak the saffron threads in 1 teaspoon of milk. Bring the remaining milk and the other spices to the boil briefly. Remove from heat and add the saffron threads.

Notes

SOP
Fasting and Medication

In case a participant takes medication and is randomized to the fasting group, the following should be noted:

1. Antihypertensives

- ACE inhibitors, angiotensin receptor and calcium channel blockers: ½ dose during fasting days. If reducing is not possible due to low dose, pause this medication during fasting days. If blood pressure lowers to less than 120/80 mmHg, pause as well.
- Diuretics: Due to shifts in fluid and electrolyte balance when fasting, diuretics should be paused completely during fasting.
- Combination preparations (with diuretic): Since diuretics must be paused, please give the participant the additional single substances in half dosage for the fasting days.
- **Do not pause beta blockers!**

If participants have their own blood pressure monitor, encourage them to self-monitor their blood pressure at home.

2. Oral antidiabetics

Stop from the 1st day of fasting until the end of the fast (applies to biguanide/metformin, sulfonylureas, glinides, glitazones, α glucosidase inhibitors, DPP-4 inhibitors, SGLT-2 inhibitors). Starting with the first fasting day, participants should measure their blood glucose daily for three days and seek medical advice if their blood glucose exceeds 12 mmol/l (216 mg/dl). Please clearly inform the participant that temporarily high blood glucose levels of up to 12 mmol/l are harmless. **Hypoglycemia, which can occur if a participant takes his medication while fasting, can be life-threatening!**

3. Anticoagulants

- Phenprocoumon: ½ dose from the 1st day of fasting, INR controlled dose adjustment every 1-2 days, then return to normal dosage.
- Direct oral anticoagulants: No changes in medication necessary during fasting.

4. Gout treatment and prophylaxis

Participants with a prior history of gout should ideally start on allopurinol 300 mg/day 3 weeks before fasting. Continue existing medication. Colchicine may lead to more side effects during fasting due to its narrow therapeutic range and may be paused in this case.

5. Procedure for participants known to suffer from migraines

Inform the participant of the increased likelihood of migraine attacks during fasting. The participant should therefore take his/her usual prophylaxis (e.g. triptans) as **early** as possible at the onset of symptoms.

SOP Fasting and Medication
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Handout

Heathy Mixed Diet and

Dietary Routine

Content

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Dear participant,

Nutrition is on everyone's lips! Many studies of the last years deal with the influence of nutrition on various medical conditions. Meanwhile there is scientific consensus that an unfavourable diet - low in fiber, rich in refined sugar, an excess of animal fats and calories - plays a major role in the fact that the number of widespread diseases such as diabetes and cardiovascular diseases has risen so sharply. Whereas in the past, nutrition was often neglected in the treatment of diseases, it is now becoming increasingly apparent that a healthy, wholesome mixed diet not only helps to alleviate symptoms, but also has a significant impact on the prevention of many diseases.

Research shows that symptoms of rheumatoid arthritis (RA) can be significantly relieved by a consistent change in diet. A healthy, rich mixed diet according to the rules of the Deutsche Gesellschaft für Ernährung (DGE, German society for nutrition) and the reduction of arachidonic acid-containing foods can lead to an improvement of the clinical picture in many patients with RA. In our study we would like to accompany you in taking a critical look at your own diet and help you to redesign and maintain it according to the rules of a healthy lifestyle.

Making changes to old, entrenched habits can sometimes be quite tedious. Please try to implement the recommendations on these pages without putting yourself under pressure.

Our main concern is to work with you to develop a plan that will lead to a **long-term and lasting improvement** in your health. Therefore, it is better to proceed slowly and step-by-step, but with a lot of joy and lasting effect. If you have any questions, please feel free to contact us at any time and let us know where you have problems with the implementation or where you are unsure - we will support you and find solutions together.

In the following pages you will find explanations of the form of nutrition and suggestions for creating a healthy eating and living routine. This information should serve you as a supplement to your nutritional coaching.

We wish you much success and pleasure in implementing them!

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Nutritional Concept for Rheumatoid Arthritis

The aim of the study is to change your diet to a healthy mixed diet according to the rules of the Deutsche Gesellschaft für Ernährung (DGE, German society for nutrition), which is reduced in arachidonic acid in the sense of an anti-inflammatory diet. For this purpose, we will explain the basics in the following.

What is a healthy mixed diet?

A healthy mixed diet consists of a rich mixture of vegetable foods such as cereal products, fruits, vegetables and legumes, and animal products such as meat, fish, dairy and milk products and vegetable or animal fats.

The specially developed food pyramid or the nutrition circle of the DGE can be used to support the daily food planning.

Group 1: Bread, cereals, potatoes

Cereals, pseudo-cereals (such as amaranth or quinoa) and potatoes are important energy suppliers due to the carbohydrates they contain and also provide us with high-quality plant-derived protein. They should therefore be consumed daily in 4 portions. Whole grains are very important - they contain dietary fibre, complex carbohydrates, important B vitamins as well as minerals such as iron, zinc and magnesium. Potatoes also are an excellent supply of vitamin C, potassium and magnesium.

Group 2: Vegetables and Group 3: Fruit

The healthy mixed diet according to the DGE is based on a rich selection of vegetable foods: At least 3 portions of vegetables (including herbs, edible mushrooms and legumes) should be eaten per day. Fruits and vegetables provide plenty of fibre, minerals and vitamins. It is recommended to eat as colourful as possible: the colours of fruits are often caused by secondary plant substances, which are beneficial to health in many ways. Dark green vegetables are also very important, as they are rich in calcium. Legumes are rich in fibre and plant-based protein, and complement the proteins of cereals and meat very well. Fruit contains many essential vitamins, secondary plant substances and minerals and should therefore be eaten in 2 portions daily. Group 3 also includes dried fruits and nuts, which are rich in unsaturated fatty acids and protein. Smoothies made from fruit also count as fruit portions, but usually exceed the recommended portions in terms of quantity. It is therefore recommended to choose dark green vegetables as the basis of smoothies and mix them with a portion

of fruit. More portions of fruit are not recommended in the long run due to the high sugar content.

Group 4: Milk and dairy products

Dairy products, especially cheese, are very good sources of protein and calcium. Calcium from animal products in can be ideally utilized by the human body and is therefore the most important source of this mineral. This is why 3 portions of milk or dairy products should be consumed daily. Here you can choose from the wide range of milk drinks, yoghurts, cheese, quarks etc. (e.g. 250g milk, 250g yoghurt or quark, 30g). Since butter is almost exclusively fat, it does not belong to group 4, but is assigned to edible fats. Also make sure that milk is not a drink, but a food that is dense in energy and nutrients.

Group 5: Meat, sausages, fish and eggs

Animal products such as meat, sausage, fish and eggs can be a useful addition to a healthy, mixed diet if they are consumed in small quantities. Meat and sausage provide not only high-quality protein but also B vitamins, iron and zinc. Eggs provide large quantities of high-quality protein, vitamins and minerals. However, these products should be consumed in moderation, as they also contain substances that are harmful to health, such as saturated fatty acids, cholesterol and purines, which are triggers for many of the diseases of modern society. For this reason, these foods should not be on the menu daily and even in small quantities; an average weekly value of 300g (i.e. a total of 3 portions of sausage or meat of 100g each) is sufficient. Eggs are also rich in fat and cholesterol and contain substances whose negative health effects are being discussed. For this reason, they should only be served occasionally.
Sea fish contains proteins, iodine and long-chain omega-3 fatty acids. Recommended here are mackerel, salmon and tuna, which are high-fat sea fish. Moderate consumption of 1 to 2 portions per week is also recommended when eating fish. Fish from sustainable fishing or sustainable aquaculture is of particular value..

Group 6: Fats and oils

Animal fats also contain large quantities of saturated fatty acids, which affect the blood fats unfavourably and are the calorie-richest nutrient. By contrast, plant-based fats and oils have quite wrongly acquired a bad reputation when consumed reasonably and in moderation. They provide important vitamins and essential (poly)unsaturated fatty acids. Rape, walnut, hemp and linseed oil are suitable for daily use due to their fatty acid composition (3-5 tablespoons). Other high-quality oils such as olive oil or pumpkin seed oil should also be consumed regularly.

Group 7: Beverages

The healthy mixed diet is based, like any dietary form, on a sufficient fluid intake of approx. 1.5 litres. Water and tea as well as highly diluted fruit juices (one part juice -

three parts water) are recommended. Depending on the source, water can contribute to a good supply of minerals. Coffee and black tea can be used as a supplement to cover the need for fluids but are considered to be stimulants because of their effect on the body. However, undiluted fruit juices, lemonades and wellness drinks belong to the extras due to their high sugar content.

„Extras“:

Extras include all highly processed and sugar-rich foods such as sweets, cake, jam, chips, lemonade, etc. These generally have no positive nutritional value and have few health benefits. In addition, they provide large amounts of calories and contain substances that have a negative impact on health, such as saturated fatty acids, highly processed industrial sugars, colorants, additives or flavours. They should therefore only make up one portion per day. Alcohol is also a luxury food without any additional health benefits and should therefore only be consumed in moderate amounts and not on a daily basis.

„Supplements“:

With a well-balanced mixed diet, the intake of nutrients through supplements is usually not necessary. Only the additional supply of vitamin D (preferably in combination with vitamin K) is highly recommended due to the shortage of sunshine hours in Germany. During summer time it is also advisable to stay outside for 10-15 minutes in light clothing and without the use of sunscreen.
Since iodine is a nutrient that is found in our domestic food in rather small quantities (exception: fish, seafood and algae), you should ensure a sufficient supply of iodine, for example, by eating a maximum of 3g of iodized table salt daily.

Basically, you should discuss the intake of dietary supplements with your family doctor (or in our case also with your study doctor) and adjust them to your needs and any underlying diseases. It is not recommended to take isolated secondary plant substances such as ß-carotene. When taking such complementary products, an opposite effect to the one observed in food has often been documented, since the positive effect of secondary plant substances in particular depends strongly on other nutrients present.

Recommendations for a healthy eating routine

For our health it is not only important **what** we eat, but also **how** we eat. The DGE recommends 10 Golden Rules:

1. **Enjoy food variety:**
   Try to eat in a diverse way and choose predominantly plant-based foods.
2. **Vegetables and fruit – "take 5 a day"**
   Have at least 3 servings of vegetables (this also includes legumes) and 2 servings of fruit a day (this also includes nuts).
3. **Choose whole grain:**
   Choose the whole grain option of bread, noodles, rice, and flour.
4. **Enrich with animal-based foods**
   Consume milk and dairy products daily, fish once or twice a week and meat only 300-600g maximum per week.
5. **Use healthy fats:**
   Preferably use high-quality vegetable oils and spreadable fats made from them. Watch out for hidden fats in baked goods, sweets and other convenience products.
6. **Save salt and sugar:**
   Avoid foods and drinks with added sugar and be sparing in your use of sugar. Try to limit the use of salt and salty products and season with herbs and spices instead.
7. **Drink water:**
   Drink about 1.5 litres of water and other calorie-free beverages like tea a day.
8. **Prepare gently:**
   Cook with little water and little fat and only as long as necessary. Burning food (roasting, grilling and other forms of preparation at very high temperatures) produces substances that are harmful to health.
9. **Mindful eating:**
   Take time for your meal and refrain from doing other activities simultaneously. Do not eat while walking or in a hurry.
10. **Watch your weight and keep moving:**
    Integrate regular sport into an active everyday life with cycling or walking.

Critical nutrients – a selection of (un)favourable food products

In rheumatoid arthritis, an arachidonic acid-reduced diet is recommended.

Arachidonic acid

Arachidonic acid is a fatty acid in food, which is broken down in the human body into inflammatory eicosanoids (thromboxane A2; prostaglandin E2; leukotriene B4). Arachidonic acid is exclusively contained in animal food groups. The following is an overview of the contents in selected foods (after Adam, 1994):

	Arachidonic acid in mg/100g
Lard	1700
Egg Yolk	300
Tuna	280
Pork	120
Beef	70
Chicken	42
Cow's milk (1,5%)	2
Plant-based food	0

The DGE does not recommend a purely plant-based diet but emphasizes the health benefits of animal foods consumed in small quantities. With rheumatoid arthritis is imperative to avoid strongly arachidonic acid-containing food. This leads to an average daily intake of 200-400mg/day, which is an effective compromise compared to the health benefits of milk, dairy products and meat.

Fatty acids

The omega-3 fatty acid eicosapentaenoic acid has a chemical structure very similar to that of arachidonic acid. For this reason, it can greatly reduce the conversion of arachidonic acid to eicosanoids by attaching itself to the enzyme responsible for the conversion.

For this reason, the consumption of 2 portions of fish per week is very beneficial for patients with rheumatoid arthritis. Fatty sea fish contain large amounts of omega-3 fatty acids:

	Eicosapentaenoic acid in g/kg
Herring	20,7
Salmon	6,2
Baltic Sea Herring	3,1
Trout	2,4
Turbot	2,8
Cod	0,8

Alternatively, 30mg fish oil fatty acids/kg body weight/day in capsule form can be used.

Alpha-linolenic acids

Alpha-linolenic acid can be converted to eicosapentaen in the human body. This in turn leads to the positive influence that can also be achieved with omega 3 fatty acids. The effect can be strengthened by consuming foods rich in alpha-linolenic acid such as linseed oil, canola oil, wheat germ oil, Soya oil or walnut oil.

Dihomo-gamma-linolenic acids

Dihomo-gamma-linolenic acid is a precursor of arachidonic acid, which, in contrast to arachidonic acid, has an anti-inflammatory effect and additionally reduces the formation of the substances leading to inflammation. A daily intake of 2-3g via for example evening primrose oil, currant oil or borage oil is recommended.

Vitamins

Vitamin E is a substance that can reduce the formation of substances that promote inflammation. An increased supply is recommended for patients with rheumatoid arthritis.

Vitamin C in connection with selenium can still strengthen the effect of Vitamin E, since they can reactivate inactive Vitamin E. A supply of 200mg/day is recommended for patients with rheumatoid arthritis.

Selenium

Selenium acts in antioxidative systems and thus has a positive influence on inflammatory processes. It should be taken in the form of fish, nuts or supplements.

External applications for Rheumatoid Arthritis

In rheumatoid arthritis, not only does nutrition play an important role in its development, but other reinforcing factors are also involved.

You can try the following recommendations to relieve your symptoms:

- Keep the affected joint **warm** by exposing it to dry heat, at least as long as it seems comfortable to you and there is no worsening due to the heat. This can be done, for example, with spelt cushions or sandbags by "dabbing" the joint.
- Silk glove massage: This massage is performed with a silk glove and should be done daily if possible. Circular movements are performed around the joints, along the legs and arms in long stroking movements. The heart and the chest are left out.
- Integrate **gentle movements** / **sports** into your everyday life. Yoga exercises are especially suitable for this. Swimming and cycling are also suitable, although you should focus less on strength and more on endurance.
- Avoid **extreme positions** of legs and feet. Try to cross your legs less.
- Reduce your exposure to cold and wind in all situations.

Notes