Trials

STUDY PROTOCOL

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The evaluation of nightshade elimination diet (NED) on inflammatory and rheumatologic markers of rheumatoid arthritis patients: study protocol for a randomized controlled trial

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Abstract

Background Rheumatoid arthritis (RA) is a chronic disease with a global prevalence rate of 1%. Patients with RA often associate specific foods like tomatoes and eggplants with adverse symptoms. These plants contain solanine, which could potentially contribute to bone and joint damage. Despite patient reports, there is a lack of randomized controlled trials (RCTs) investigating the effects of nightshades on patients with RA. This study aims to assess the effect of nightshade elimination diet (NED) on inflammatory and rheumatologic marker levels in rheumatoid arthritis patients for the first time.

Methods A single-blinded controlled trial will be conducted to evaluate the effect of an NED on 40 participants over 8 weeks (2 months). Participants will be equally divided into intervention and placebo groups. Both groups will receive general anti-inflammatory dietary recommendations, with the intervention group undergoing an NED during the study. Clinical symptoms will be assessed using questionnaires, and blood samples will be collected to measure relevant indicators.

Discussion This RCT signifies a groundbreaking exploration into NED effects on RA markers, potentially initiating crucial discussions in the field. Its outcomes could serve as a cornerstone for larger and more robust trials, offering pivotal insights to nutritionists and physicians for the nuanced management of patients with RA.

Trial registration Iranian Registry of Clinical Trials IRCT20230220057465N1 (https://irct.behdasht.gov.ir/trial/68959). Registered on 8 April 2023.

Keywords Nightshade elimination diet, Rheumatoid arthritis, Randomized controlled trial (RCT), Study protocol

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Introduction

Background and rationale {6a}

Rheumatoid arthritis (RA) is an autoimmune disease that is linked to progressive disability, systemic inflammation, early mortality, cartilage destruction, and other systemic complications [1, 2]. Featuring synovial inflammation, autoantibody production (like rheumatoid factor (RF)), and bone deformities, RA also associates with cardiovascular, pulmonary, psychological, skin, and skeletal disorders [1, 2]. The global incidence of RA varies from 0.4 to 1.3%, exhibiting higher rates in women and older populations in industrialized nations [3, 4].

Symptoms in patients with RA considerably differ between early and untreated later stages [3]. Early stages showcase generalized symptoms: joint tenderness, morning stiffness, fatigue, and flu-like sensations, often alongside elevated C-reactive protein (CRP) and increased erythrocyte sedimentation rate (ESR) [3, 5]. Untreated later stages may bring severe systemic complications such as lymphoma, atherosclerosis, hematologic abnormalities, pleural effusions, and interstitial lung disease [3]. Understanding these variations, especially in relation to dietary interventions, holds critical importance, as emphasized in a recent review highlighting uncertainties regarding the effects of different diets on treating RA [6]. Multiple factors—genetic, environmental (like smoking, obesity, diet, hormonal influences), immunological factors, infections, type of delivery, and birth weight—contribute to both the occurrence and progression of RA [7, 8].

Early diagnosis and intervention are pivotal in preventing severe damage, with the primary treatment goal centered around reducing joint pain and inflammation [8]. Common pharmacological therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and antirheumatic drugs, despite NSAIDs, the primary treatment, carrying gastrointestinal side effects that prompt some patients to seek alternative, less side effect-prone treatments [5, 8, 9]. Recent evidence suggests a significant role for diet in modifying RA symptoms [10]. Nutritional factors act as either protective or risk factors for disease onset, potentially through epigenetic mechanisms, metabolic profile changes, increased antioxidant levels, and alterations in the intestinal microbiome [11–13]. Certain nutrients—like omega-3 polyunsaturated fatty acids, oleic acid, flavonoids, and vitamin C—have demonstrated positive effects on patients with RA [1, 10, 12, 13]. Individual interventions such as fasting followed by a vegetarian diet or a Cretan Mediterranean diet have shown substantial improvements in pain levels [6]. Conversely, intake of nutrients like red meat, high sodium, and high protein may detrimentally affect patients with RA [13]. Many patients with RA report adverse effects from consuming dairy products and nightshade plants like tomatoes and eggplants [14].

Nightshades—comprising tomatoes, potatoes, eggplants, and certain peppers [15, 16]—contain toxic glycoalkaloids, including solanine, tomatine, chaconine, and solasonine, used by plants as protection against insects, animals, and bacteria [17]. Even a small amount of alpha-solanine can cause symptoms such as confusion, nausea, abdominal pain, vomiting, and diarrhea; excessive amounts can lead to seizures, coma, and death [17]. Solanine escalates intestinal permeability and induces bone and joint damage by enhancing calcium loss from bones, thereby affecting arthritis pathogenesis [11, 16, 18]. Over 10% of arthritis patients may experience allergic reactions to the solanine family [19], with a study suggesting that eliminating solanine-containing plants from osteoarthritis (OA) patients' diets for 4–6 weeks could be beneficial [19]. Given the scarcity of data on nightshades' effects on RA, the escalating prevalence of rheumatological diseases, the substantial economic burden of current treatments, and patients' inclination toward alternative or supplementary treatments [20], this study aims to evaluate the impact of a nightshade elimination diet (NED) on inflammatory and rheumatologic markers in patients with rheumatoid arthritis.

Objectives {7}

The primary aim of this study is to investigate the potential impact of a nightshade elimination diet (NED) on the clinical symptoms, inflammatory responses, and rheumatological marker levels among individuals diagnosed with rheumatoid arthritis.

The secondary objectives encompass assessing the potential effects of the NED on anthropometric variables and evaluating its influence on the quality of life among the participants.

Trial design {8}

This study adopts a randomized, single-blinded controlled trial design to assess the impact of the nightshade elimination diet (NED) on individuals diagnosed with rheumatoid arthritis (RA). The trial adheres to a parallel-group format with an allocation ratio of 1:1. Given the exploratory nature of the investigation, the study framework is considered exploratory.

Achieving complete blinding of the researchers is not feasible due to the nature of the intervention. However, the trial will be conducted in a single-blinded manner to ensure that participants remain unaware of their treatment allocation. Prior to enrollment, all participants will sign a written informed consent form, approved by the ethics committee, to ensure their voluntary participation.

Stringent measures will be in place to uphold the confidentiality of the information gathered through questionnaires.

Some adjustments have been made to the baseline methodology, including increasing the sample size from 36 to 40 participants. Both intervention and placebo groups will now receive a placebo. Additionally, restrictions on the intake of nutritional supplements for participants have been lifted.

Methods: participants, interventions, and outcomes

Study setting {9}

The study will be conducted in a personal clinic under the authority of Yasuj University of Medical Sciences in Kohgiluyeh Va Boyerahmad province, in Yasuj city.

Eligibility criteria {10}

Participants who meet our inclusion criteria will be included in the study by availability sampling. The inclusion criteria are as follows:

1. ˃ 18 years of age
2. A definite diagnosis of the disease by a rheumatologist using the criteria of the American College of Rheumatology (ACR) [21]
3. Not having a specific diet (any prescribed diet plan provided by a dietitian or any diet that restricts certain types of food such as weight loss, fasting, ketogenic, vegetarian, and Mediterranean diet) during the study and before sampling
4. Not having any other chronic diseases: allergies, cardiovascular disease (CVD), asthma, cancer, depression, Alzheimer's
5. Not taking psychoactive drugs
6. Not having any other rheumatoid diseases than RA

The exclusion criteria are as follows:

1. Smoking
2. Changing therapeutic drugs
3. Contracting any other disease during the study
4. Not being committed to the study protocol
5. Occurrence of serious complications and adverse reactions during the study

Who will take informed consent? {26a}

Informed consent will be obtained by Dariush Golampur (DG) and Zahra Hosseinzadeh (ZH). All related documents can be requested and will be uploaded if possible.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

We will request consent for the review of participants' medical records and collection of fasting blood samples to assess high-sensitivity C-reactive protein (Hs-CRP) and interleukin-1 (IL-1) variables as well as for the administration of quality of life assessments, dietary assessments, and Disease Activity Score-28 (DAS-28) questionnaires.

Interventions

Explanation for the choice of comparators {6b}

The choice of the nightshade elimination diet as the intervention stems from its unprecedented evaluation in randomized controlled trials for rheumatoid arthritis (RA) patients. Ethical considerations and the need for effective blinding led to the selection of a standard anti-inflammatory diet for both groups, complemented by a placebo to enhance blinding. This decision ensures transparency in our study design and aligns with the ethical principles guiding clinical research.

Intervention description {11a}

The process begins with the rheumatologist assessing patients based on the entry criteria. Patients meeting these criteria undergo the DAS-28 questionnaire. Upon completion, eligible patients are introduced to the randomization manager, who allocates them to either the intervention or control group, each comprising 20 participants.

The randomization manager then introduces the patients to their respective group leaders. Each leader provides detailed explanations specific to their group, obtains consent, and assists in completing questionnaires. This approach ensures that participants are only aware of their assigned group.

In the intervention group, the leader explains the elimination of nightshades (tomatoes, potatoes, eggplants, bell peppers, chili peppers, paprika, tobacco) from the diet and the daily intake of a placebo tablet over the 8-week intervention period, in addition to general anti-inflammatory dietary recommendations. For the control group, the leader explains the requirement of taking a placebo tablet daily, in addition to adhering to general anti-inflammatory dietary recommendations.

Following the explanation, all participants complete the necessary questionnaires and receive a letter introducing them to a laboratory. At the laboratory, blood samples are collected, tests are conducted, and the results are reported back to the research team.

Throughout the 8-week intervention period, participants are continuously followed up by the team. Team managers conduct regular weekend check-ins with the entire team through meetings or calls to ensure that the

study is progressing smoothly and address any emerging issues or concerns.

Criteria for discontinuing or modifying allocated interventions {11b}

In this trial, allocated interventions might be altered or halted based on predetermined criteria established to manage different circumstances affecting participants in the trial. These criteria encompass various situations such as adverse reactions, participant requests, disease progression, and other clinical reasons.

Strategies to improve adherence to interventions {11c}

1. *Clear communication*: Participants will receive thorough and clear explanations of the intervention protocols from the designated group leaders during the initial explanation session.
2. *Written instructions*: Participants will be provided with written instructions summarizing the key aspects of their allocated interventions. These written instructions will serve as a reference for participants to follow the prescribed protocols at home.
3. *Regular follow-ups*: The group leaders will conduct regular follow-up sessions with participants to address any concerns, provide additional guidance, and reinforce adherence to the intervention protocols. This follow-ups will be done through phone calls and text.
4. *Adverse event monitoring*: Continuous monitoring of adverse events will be performed to identify and manage any issues that may impact participant adherence. This includes monitoring for potential side effects and promptly addressing participant queries or concerns.
5. *Feedback mechanism*: Participants will be encouraged to provide feedback on their experiences with the interventions, allowing for adjustments and improvements to enhance overall adherence.
6. *Laboratory tests*: The laboratory will play a crucial role in monitoring adherence, as participants will be required to present the introduction letter to the laboratory for blood sample collection. This serves as both a procedural check and a measure of participant engagement.

Relevant concomitant care permitted or prohibited during the trial {11d}

In the context of this trial, participants are encouraged to maintain their routine healthcare and concomitant care throughout the study period. Standard medical care, including routine medications, consultations, and necessary medical interventions for managing rheumatoid arthritis or any other pre-existing conditions, is permitted. However, participants are advised not to initiate any new or substantial changes to their healthcare regimen during the trial without consulting the research team.

Prohibited concomitant care includes initiation of new dietary supplements, significant changes to existing medications, or engagement in any other therapeutic interventions aimed at managing rheumatoid arthritis symptoms, unless explicitly recommended or approved by the treating physician or the research team.

The research team will maintain open communication with participants to monitor and address any changes in concomitant care, ensuring that these changes are documented and appropriately considered in the analysis of trial outcomes. Participants will be instructed to report any modifications or additions to their healthcare routine promptly to ensure accurate tracking and monitoring throughout the study.

Provisions for post-trial care {30}

While we do not anticipate harm from our intervention, in the event that participants experience any issues directly related to our study, we are committed to providing necessary care and support.

Outcomes {12}

Regarding the primary outcome, in this trial, clinical symptoms will be evaluated by a rheumatologist using various measures including the count of tender and swollen joints, the visual analog scale (VAS) [22], the Persian version of Arthritis Impact Measurement Scale 2-Short Form (AIMS2-SF) questionnaire [23], and the disease activity score (DAS-28) [24]. These assessments will occur at the start (baseline) and after 2 months.

Fasting blood samples of 10 cc will be collected from participants in a seated position both at baseline and at the end of the 2-month treatment. The levels of Hs-CRP and IL-1 will be measured through the enzyme-linked immunosorbent assay (ELISA) method, while ESR will be assessed via the Westergren-Katz method. Complete blood count (CBC) of the patients will be measured using a TB counter device.

Secondary outcomes will involve gathering general information through questionnaires covering demographics (name, age, gender), socioeconomic status (marital status, level of education, occupation), anthropometric measures (weight, height, BMI), lifestyle/behavior (smoking), medical history (various diseases, weight loss surgeries, diets for weight loss or gain), and drug use (chemical or herbal medicines). Weight will be measured using a Seka scale with minimal clothing, while

height will be measured using a Seka caliper with participants standing upright. Body mass index will be calculated from weight and height measurements. Dietary assessment will involve participants completing a 3-day food questionnaire at the end of the study. Additionally, participants will receive a notebook at the study's commencement to record any food types causing pain and swelling.

Participant timeline {13}

This intervention timeline is structured around a comprehensive baseline assessment conducted by rheumatologists and the determination of DAS-28 scores. Following randomization, group leaders provide tailored explanations and secure consent while maintaining participant blindness to group assignments.

Over the 2-month intervention period, the intervention group adheres to a nightshade-excluded diet and daily placebo intake, while the control group follows general anti-inflammatory dietary recommendations alongside the same placebo.

Post-intervention, participants complete questionnaires and receive an introduction letter for a laboratory visit where blood tests are conducted. After the 2-month period, another assessment is scheduled to evaluate the intervention's impact on relevant outcomes, ensuring a comprehensive evaluation of the study intervention.

For visual representation, a Standard Protocol Items for Clinical Trials (SPIRIT) diagram illustrating this timeline is included as Fig. 1.

Sample size {14}

The sample size calculation was based on the mean difference formula, considering ESR changes from baseline to the end of treatment, as observed in a study conducted by Sadeghi et al. in 2022 [25].

To ensure adequate power and account for potential dropouts, a 25% dropout rate was considered. This led to a determined sample size of 40 patients (20 in each group). The assignment of participants to groups will be carried out using block random sampling, employing computer-generated random numbers based on age (with the threshold of 50) and body mass index (with the threshold of 30). The choice of Sadeghi et al.'s study as a reference is grounded in

$$n = \frac{\left(\left(Z_{(1-(\alpha/2))} + Z_{(1-\beta)}\right)^2 \times \left({\delta_1}^2 + {\delta_2}^2\right)\right)}{\left((\mu_1 - \mu_2)^2\right)}$$

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT**	$-t_1$	0	t_1	*t2 (2 months)*	t_3
ENROLMENT:					
Eligibility screen	X				
Informed consent			X		
Allocation		X			
INTERVENTIONS:					
NED group				X	
Control group				X	
ASSESSMENTS:					
Age, Weight, Hight, BMI, Gender, Das-28	X				X
VAS, AIMS2-SF, ESR Hs-CRP, IL-1, CBC			X		X
socioeconomic status, lifestyle/behavior, medical history, drug use			X		X

Fig. 1 Schedule of enrolment, interventions, and assessments

$$Z_{1-\alpha 2} = 1.96$$

$$Z_{1-\beta} = 1.282$$

$$\mu_1 = 24.66\, \mu_2 = 9.23$$

$$\delta_1 = 16.4\, \delta_2 = 10.3$$

- n is sample size
- $Z\_(1—(\alpha/2))$: this term involves the standard normal distribution and is used in determining the critical value for a confidence interval. Here, α represents the significance level
- $Z\_(1—\beta)$: this term involves the standard normal distribution and is used in determining the critical value for a power analysis. β represents the probability of committing a type II error, which is failing to reject the null hypothesis when it is actually false

Recruitment {15}

We will employ various recruitment strategies to ensure we enroll a sufficient number of participants meeting our predetermined sample size. These strategies involve the following:

- Collaboration with rheumatologists: establishing partnerships with rheumatologists and healthcare providers in the local clinic to pinpoint eligible participants who meet our inclusion criteria
- Advertisement in the clinic: showcasing study details within the clinic premises to reach out to potential participants attending rheumatology appointments

Our emphasis on collaborating with rheumatologists and employing clinic-based advertisements aims to enhance participant recruitment, ensuring we meet our target sample size essential for the successful execution of the study.

Assignment of interventions: allocation

Sequence generation {16a}

The allocation sequence will be produced using computer-generated random numbers. To heighten the unpredictability of this sequence, we will separately record details outlining the planned restrictions (blocking). This record will be treated confidentially and inaccessible to individuals engaged in participant enrollment or intervention assignment.

Concealment mechanism {16b}

The allocation sequence will be executed through sequentially numbered, opaque, sealed envelopes. These envelopes will be prepared beforehand and opened solely at the moment of intervention assignment. This process guarantees that the sequence remains concealed until the interventions are allocated.

Implementation {16c}

The allocation sequence will be devised by MH, an individual not directly engaged in participant enrollment or intervention assignment, ensuring impartiality. The rheumatologist will oversee participant enrollment, while the assignment to interventions will be facilitated by the randomization manager (AG). AG will utilize sealed envelopes containing the allocation sequence to perform the assignments.

Assignment of interventions: blinding

Who will be blinded {17a}

The intervention's nature, involving dietary changes, presents inherent challenges for achieving double-blinding in this study. Unlike pharmaceutical trials using identical-looking placebos, dietary modifications are observable, making it hard to conceal from researchers whether they are leading the intervention or control group. Hence, we have chosen a single-blinded approach to ensure participants remain unaware of their treatment allocation throughout the study. To enhance the blinding process, we incorporated additional measures to increase similarity between groups. Despite our design being single-blind, we included a placebo to further mimic conditions. Additionally, both groups were assigned a basic anti-inflammatory diet. Furthermore, we ensured that participants from each group were handled separately to minimize any potential connections between them.

Procedure for unblinding if needed {17b}

In our study, unblinding will be reserved for specific situations where knowing the participant's treatment allocation becomes critical for their safety or well-being. The decision to unblind will rest with the principal investigator or another authorized member of the research team. The unblinding process involves accessing a secure document containing treatment allocations, stored separately from study records and accessible only to authorized personnel not directly involved in trial procedures. Participant identities and allocated interventions will be revealed solely when essential for their medical care.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Outcome assessment

The evaluation of clinical symptoms and primary and secondary outcomes will be conducted by a rheumatologist using standardized measures. These include assessing the number of tender and swollen joints, employing the visual pain intensity scale (VAS), utilizing The AIMS2-SF questionnaire, and calculating the disease activity score (DAS-28). Additionally, fasting blood samples will be collected at both the study's outset and the conclusion of the treatment period to measure relevant biomarkers.

Data quality processes

To ensure the quality of data, we have chosen experienced assessors, including the rheumatologist and laboratory personnel, who bring a wealth of expertise to the assessments.

Study instruments

The data collection instruments include validated questionnaires like The AIMS2-SF which gauge different aspects of health. Lab tests for Hs-CRP, IL-1, and ESR will follow established methods such as ELISA and the Westergren-Katz method. Weight measurements will be taken using a Seka scale with minimal clothing while standing, having an error margin of 0.5 kg, while height will be measured with a Seka caliper while standing and looking forward, with an error margin of 0.1 cm. The body mass index will then be calculated by dividing weight by the square of the height.

Plans to promote participant retention and complete follow-up {18b}

To maintain participant engagement and ensure consistent follow-up, we have established multiple strategies. Group leaders (ZH and DG) will conduct regular check-ins via phone calls and text messages, supplemented by weekend follow-ups from team managers BP and MH. Should a participant discontinue or deviate from the intervention, we will make efforts to gather pertinent outcome data and document reasons for discontinuation.

Moreover, participants will have their rheumatologist visits covered, removing any financial burden associated with these aspects. This support is intended to facilitate and encourage ongoing participation in the study.

Data management {19}

We are committed to rigorous data quality assurance. We will conduct double data entry and range checks to guarantee the accuracy and reliability of all entered information. Participant confidentiality remains a priority, and all personal details and names will be treated as strictly confidential. Additionally, participants can request access to their individual results upon completion of the study by making a direct inquiry.

Confidentiality {27}

Privacy and security are of paramount importance. We will collect names, contact information, and other necessary identifiers solely for research purposes. Personal data will only be shared with explicit consent from participants and managed with robust security measures. This includes encryption protocols for online sharing and secure, encrypted methods for offline sharing. The corresponding author will securely store physical records in a designated area and digital records in encrypted files or drives. After the trial concludes, access to personal data will be strictly restricted, maintaining ongoing privacy and security while adhering to participant consent.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Biological specimens, in the form of fasting blood samples (10 cc), will be collected from each participant at baseline and at the end of the treatment. These samples will undergo processing and evaluation for specific variables, including Hs-CRP and IL-1 measured by the ELISA method, and ESR assessed by the Westergren-Katz method. Additionally, CBC of the patients will be measured using a TB counter device. It is important to note that there are no intentions to retain or store these biological specimens for future use in ancillary studies. The primary focus of the current trial is on clinical assessments, and any collected samples will be appropriately disposed of after the necessary analyses are completed.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Data analysis will be conducted using the Statistical Package for the Social Sciences (SPSS) software version 26. The normality of variables will be assessed using the Shapiro–Wilk test, in conjunction with additional methods such as histograms, skewness measures, and tests for kurtosis for a more comprehensive evaluation. Quantitative normal variables will be presented as mean ± standard deviation, while quantitative non-normal variables will be reported as median IQR. Qualitative variables will be expressed as number (percentage). Group comparisons will be performed using the independent *T*-test

or Mann–Whitney test for normal and non-normal distributions, respectively. Within-group analyses will utilize the paired *T*-test or Wilcoxon test. Missing data will be imputed, with statistical significance set at $P<0.05$. ANCOVA analysis will be applied if deemed necessary.

Interim analyses {21b}

No interim analyses are planned for this trial. Stopping guidelines are not applicable, as the study involves a low-risk intervention. Decisions to terminate the trial will be made by the principal investigators based on overall trial progress and ethical considerations."

Methods for additional analyses (e.g., subgroup analyses) {20b}

Given the small sample size of our study, there may be insufficient statistical power for meaningful subgroup analyses. Any exploratory analyses conducted will be interpreted with caution, considering the limitations inherent in the study's sample size.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

For missing data, the imputation method will be used, ensuring a robust analysis.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

Due to confidentiality and privacy concerns, access to the full protocol, participant-level dataset, and statistical code will not be publicly granted. Any requests for access can be considered on an individual basis and will be subject to ethical and legal considerations. Please refer to the confidential section for further details.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

In our study, the coordinating center is led by the research team, with responsibilities including site setup, training, monitoring, data management, and overall operational support. The trial steering committee (TSC) comprises key investigators, a statistician, and consumer representatives. The chief principal investigator chairs the TSC, providing leadership, overseeing trial conduct, and ensuring integrity.

Composition of the data monitoring committee, its role and reporting structure {21a}

Given the low-risk nature of our intervention, a formal data monitoring committee was not deemed necessary. Internal monitoring by the research team, independent of investigators and sponsors, will ensure protocol adherence.

Adverse event reporting and harms {22}

In case of adverse reactions or unexpected challenges arising from the dietary changes prescribed in the intervention, the intervention may be modified or discontinued as necessary for the participant's well-being. Any adverse events that are both related and unexpected will be promptly reported to The Human Ethics Committee of Yasuj University of Medical Sciences. This reporting will be carried out in accordance with standard operating procedures to ensure comprehensive oversight and appropriate follow-up measures.

Frequency and plans for auditing trial conduct {23}

In consideration of the low-risk nature of this intervention, a data monitoring committee was not deemed necessary. The trial conduct will be monitored internally by the research team to ensure adherence to the protocol and ethical standards. The auditing process will be conducted by members of the research team and will remain independent from investigators and the sponsor. However, if circumstances warrant, the establishment of a data monitoring committee will be reevaluated to enhance oversight."

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Ensuring transparency and accountability, our study has a well-defined plan for communicating important protocol amendments to relevant parties. This includes notifying investigators, research ethics committees (REC), trial participants, trial registries (IRCT), the chosen journal (Trials), and regulatory authorities. The communication process will be systematic and timely, following established guidelines and ethical considerations. In the event of significant modifications, such as changes to eligibility criteria, outcomes, or analyses, all stakeholders will be promptly informed to maintain the integrity of the trial and uphold ethical standards. Communication channels will include official letters, email notifications, and updates on trial registries to ensure comprehensive awareness and understanding of any protocol amendments.

Dissemination plans {31a}

Trial results will be communicated via publication in scientific journals, through presentations at International Clinical Nutrition Congress. The target journals will be chosen to reach specific academic audiences interested in rheumatology, nutrition, and related fields.

Discussion

To our knowledge, this study represents the first exploration of the impact of NED on inflammatory and rheumatologic markers in patients with rheumatoid arthritis through a randomized controlled trial. The protocol publication serves as a resource for researchers, promoting transparency and preventing duplication [26]. While our study sheds light on the nightshade-RA relationship, limitations include a small sample size ($n=40$), a single-blinded design, and reliance on a food questionnaire [27]. Caution is advised in interpreting claims about widespread dietary recommendations, as larger studies are essential for validation [28, 29]. Moreover, regional specificity (limited to an area in Iran) pose challenges in generalizing results. Financial constraints prevented measurement of additional inflammation biomarkers. Future research should encompass diverse settings and demographics for broader applicability, contributing to a more nuanced understanding of NED in managing RA.

Trial status

This is Version 3.3 of this protocol (2024–05-29). The recruitment will commence on July 23, 2023.

Abbreviations

ACR	American College of Rheumatology
AIMS2-SF	Arthritis Impact Measurement Scale 2-Short Form
AG	Ashkan Golmohammadi
ANOVA	Analysis of variance
BMI	Body mass index
BP	Bahman Panahandeh
CBC	Complete blood count
CVD	Cardiovascular disease
DAS-28	Disease Activity Score-28
DG	Dariush Golampur
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
Hs-CRP	High-sensitivity C-reactive protein
IL-1	Interleukin-1
IRCT	Iranian Registry of Clinical Trials
MH	Mahak Hosseinikia
MKS	Mohammad Kazem Sadeghi
NED	Nightshade elimination diet
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SBP	Saeed Baghbanian Pulsani
SPSS	Statistical Package for the Social Sciences
SPIRIT	Standard Protocol Items for Clinical Trials
TSC	Trial steering committee
VAS	Visual analog scale
WHO	World Health Organization
ZH	Zahra Hosseinzadeh

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08372-7.

Supplementary Material 1

Acknowledgements

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Authors' contributions {31b}

AG wrote the draft, MH revised the manuscript, and SBP had full access to all of the data in the study and took responsibility for the integrity and accuracy of the data. All authors read and approved the final manuscript. MH and SBP are the study co-principal investigators who devised the study and will provide guidance and supervision during the data collection, processing, and analysis. MKS is the rheumatologist of the team which advices and assists us with diagnosis. DG and ZH will assist with the data collection. ZH and DG are group leaders for the intervention and control groups, respectively.

Funding{4}

This study is funded by grants from the Yasuj University of Medical Sciences (ID:4,010,133[Aikira1]) that played no role in the design of this study and will not be involved in its execution, analysis, interpretation of the data, or the decision to submit the results. The comprehensive details of our mutual responsibilities with the university are outlined in the contract file. [Aikira1]CE: Thousand comma separators added.
Email: research@yums.ac.ir, Web page address: https://research.yums.ac.ir.

Availability of data and materials {29}

The authors plan to publish the results of these studies at a later date after patient enrollment and follow-up is completed and the associated data is analyzed. Data will be available upon request from anyone. Access to personal data will be strictly restricted with ongoing adherence to participant consent.

Declarations

Ethics approval and consent to participate {24}

Ethics approval for the study protocol was confirmed by The Human Ethics Committee of Yasuj University of Medical Sciences (Ethics Number: IR.YUMS.REC.1401.172). This study was also registered on the Iranian Registry of Clinical Trials (IRCT No. IRCT20230220057465N1) before data collection and intervention administration.

Consent for publication {32}

Not applicable—no identifying images or personal/clinical participant details are included in this document, nor will they be featured in any trial result reports. Access to participant information materials and the informed consent form can be obtained from the corresponding author upon request.

Competing interests{28}

The authors declare no competing interests.

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References

1. Mazzucca CB, Scotti L, Cappellano G, Barone-Adesi F, Chiocchetti A. Nutrition and rheumatoid arthritis onset: a prospective analysis using the UK Biobank. Nutrients. 2022;14(8):1554. Available from: https://www.mdpi.com/2072-6643/14/8/1554. Cited 2023 Mar 23.
2. Jang S, Kwon EJ, Lee JJ. Rheumatoid arthritis: pathogenic roles of diverse immune cells. International Journal of Molecular Sciences. 2022;23(2):905.

Available from: https://www.mdpi.com/1422-0067/23/2/905. Cited 2023 May 7.
3. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020;9(4):880. Available from: https://www.mdpi.com/2073-4409/9/4/880. Cited 2023 Mar 26.
4. van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2018;32(2):174–87. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1521694218300688. Cited 2023 Mar 24
5. Bustamante MF, Agustín-Perez M, Cedola F, Coras R, Narasimhan R, Golshan S, et al. Design of an anti-inflammatory diet (ITIS diet) for patients with rheumatoid arthritis. Contemporary clinical trials communications. 2020;17:100524.
6. Hagen KB, Byfuglien MG, Falzon L, Olsen SU, Smedslund G. Dietary interventions for rheumatoid arthritis. Cochrane Database Syst Rev. 2009;(1). Available from: https://www.cochranelibrary.com/cdsr/doi/https://doi.org/10.1002/14651858.CD006400.pub2/abstract. Cited 2023 Dec 27.
7. Petrovská N, Prajzlerová K, Vencovský J, Šenolt L, Filková M. The preclinical phase of rheumatoid arthritis: from risk factors to prevention of arthritis. Autoimmunity Reviews. 2021;20(5):102797. Available from: https://www.sciencedirect.com/science/article/pii/S1568997221000616Cited 2023 Mar 23
8. Rheumatoid Arthritis: a brief overview of the treatment - Abstract - Medical Principles and Practice. 2018;27(6). Karger Publishers. Available from: https://www.karger.com/Article/Abstract/493390. Cited 2023 Mar 23
9. Bungau SG, Behl T, Singh A, Sehgal A, Singh S, Chigurupati S, et al. Targeting probiotics in rheumatoid arthritis. Nutrients. 2021;13(10). Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85115612599anddoi=10.3390%2fnu13103376andpartnerID=40andmd5=ec03ff170f4f613acffda031c12d0611.
10. Badsha H. Role of diet in influencing rheumatoid arthritis disease activity. Open Rheumatol J. 2018;12:19–28. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5827298/. Cited 2023 May 7.
11. Design of an anti-inflammatory diet (ITIS diet) for patients with rheumatoid arthritis - ScienceDirect. Available from: https://www.sciencedirect.com/science/article/pii/S2451865420300089. Cited 2023 May 7.
12. Don't neglect nutrition in rheumatoid arthritis! | RMD Open. Available from: https://rmdopen.bmj.com/content/4/1/e000591.abstract. Cited 2023 Mar 23.
13. Gioia C, Lucchino B, Tarsitano MG, Iannuccelli C, Di Franco M. Dietary habits and nutrition in rheumatoid arthritis: can diet influence disease development and clinical manifestations? Nutrients. 2020;12(5):1456. Available from: https://www.mdpi.com/2072-6643/12/5/1456. Cited 2023 Mar 23.
14. Masud Parvez GM, Akanda KM. Chapter 1 - foods and arthritis: an overview. In: Watson RR, Preedy VR, editors. Bioactive food as dietary interventions for arthritis and related inflammatory diseases (Second Edition). Academic Press; 2019. p. 3–22. Available from: https://www.sciencedirect.com/science/article/pii/B9780128138205000015. Cited 2023 Mar 23.
15. Salehi B, Sharifi-Rad R, Sharopov F, Namiesnik J, Roointan A, Kamle M, et al. Beneficial effects and potential risks of tomato consumption for human health: an overview. Nutrition. 2019;62:201–8. Available from: https://www.sciencedirect.com/science/article/pii/S0899900718312577. Cited 2023 Mar 23.
16. Krause's Food & The Nutrition Care Process - Journal of Nutrition Education and Behavior. Available from: https://www.jneb.org/article/S1499-4046(19)30909-1/fulltext. Cited 2023 Mar 28.
17. Chen Z, Li C, Yuan A, Gu T, Zhang F, Fan X, et al. α-Solanine causes cellular dysfunction of human trophoblast cells via apoptosis and autophagy. Toxins. 2021;13(1):67. Available from: https://www.mdpi.com/2072-6651/13/1/67. Cited 2023 Mar 23.
18. Paolino S, Pacini G, Patanè M, Alessandri E, Cattelan F, Goegan F, et al. Interactions between microbiota, diet/nutrients and immune/inflammatory response in rheumatic diseases: focus on rheumatoid arthritis. Reumatologia. 2019;57(3):151–7. Available from: https://reu.termedia.pl/Interactions-between-microbiota-diet-nutrients-and-immune-inflammatory-response-in,109692,0,2.html. Cited 2023 Mar 23.
19. Prousky JE. The use of Niacinamide and Solanaceae (Nightshade) Elimination in the Treatment of Osteoarthritis. J Orthomolecular Med. 2015;30(1). https://isom.ca/wp-content/uploads/The-Use-of-Niacinamide-and-Solanaceae-Nightshade-Elimination-in-the-Treatment-of-Osteoarthritis-30.1.pdf.
20. Rezaee M, Lotfi F, Gholami A, Azizpoor J, Aflaki E, Vazin A, et al. Economic burden of rheumatoid arthritis in Iran: a societal perspective economic burden of R.A. In Review; 2022 Jan. Available from: https://www.researchsquare.com/article/rs-1257689/v1/. Cited 2023 Mar 23
21. Fraenkel L, Bathon JM, England BR, StClair EW, Arayssi T, Carandang K, et al. American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care & Research. 2021;73(7):924–39. Available from: https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24596. Cited 2023 Dec 27.
22. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Academic Emergency Medicine. 2001;8(12):1153–7. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1553-2712.2001.tb01132.x. Cited 2023 Dec 27.
23. Askary-Ashtiani AR, Mousavi SJ, Parnianpour M, Montazeri A. Translation and validation of the Persian version of the Arthritis Impact Measurement Scales 2-Short Form (AIMS2-SF) in patients with rheumatoid arthritis. Clin Rheumatol. 2009;28(5):521–7.
24. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44–8.
25. Alireza Sadeghi, Mojtaba Tabatabaiee, Mir Ali Mousavi, Seyedeh Neda Mousavi, Somayae Abdollahi Sabet, Nooshin Jalili AS. Dietary pattern or weight loss: which one is more important to reduce disease activity score in patients with rheumatoid arthritis? A Randomized Feeding Trial. 2023. Available from: https://www.hindawi.com/journals/ijclp/2022/6004916/. Cited 2023 May 7
26. Classen S, Li Y, Giang W, Winter S, Wei J, Patel B, et al. RCT protocol for driving performance in people with Parkinson's using autonomous in-vehicle technologies. Contemp Clin Trials Commun. 2022;28:100954. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9256542/. Cited 2023 Apr 14
27. Golmohammadi A, Ebrahimi S, Shiraseb F, Asjodi F, Hosseini AM, Mirzaei K. The association between dietary polyphenols intake and sleep quality, and mental health in overweight and obese women. PharmaNutrition. 2023;24:100338.
28. Ioannidis JPA. Why most published research findings are false. PLoS Med. 2005;2(8):e124. Available from:https://dx.plos.org/10.1371/journal.pmed.0020124. Cited 2023 Dec 28]
29. Wachsmuth NB, Aberer F, Haupt S, Schierbauer JR, Zimmer RT, Eckstein ML, et al. The impact of a high-carbohydrate/low fat vs. low-carbohydrate diet on performance and body composition in physically active adults: a cross-over controlled trial. nutrients 2022 14(3):423. Available from: https://www.mdpi.com/2072-6643/14/3/423. Cited 2023 Dec 28

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