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

Ashkan Golmohammadi
Yasuj University of Medical Sciences

Mahboobe Hosseinkia
Yasuj University of Medical Sciences

Mohammad Kazem Sadeghi
Yasuj University of Medical Sciences

Dariush Golampur
Yasuj University of Medical Sciences

Zahra Hosseinzadeh
Yasuj University of Medical Sciences

SeyedBahman Panahande
panahande.b@gmail.com
Yasuj University of Medical Sciences  https://orcid.org/0000-0002-7008-2449

Research Article

Keywords: nightshade, rheumatoid arthritis, randomized control trial (RCT), DAS-28, VAS, AIMS-2, WHOQOL-BREF

Posted Date: August 3rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3027968/v1

License: ©️ This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License

Version of Record: A version of this preprint was published at Trials on August 10th, 2024. See the published version at https://doi.org/10.1186/s13063-024-08372-7.
Abstract

Background and objectives

Rheumatoid arthritis (RA) is a chronic, auto-immune disease (AD) that is associated with progressive disability, systemic inflammation, early death, cartilage destruction, and other systemic complications (1, 2). RA is characterized by synovial inflammation, the production of auto-antibodies including rheumatoid factor (RF), and bone deformities (1). This disease is also associated with cardiovascular, pulmonary, psychological, skin, and skeletal disorders (2). The prevalence of RA varies globally, ranging from 0.4–1.3% with two to three times more prevalence in women (3). RA is also more prevalent in older populations and industrialized countries (3, 4).

RA symptoms significantly vary between early-stage and untreated later stages (3). The early stage is known for generalized disease symptoms such as tender and morning stiffness of joints, fatigue, and a flu-like feeling. The early stage of the disease is also accompanied by increased levels of C-reactive protein (CRP) and an erythrocyte sedimentation rate (ESR) (3, 5). Untreated later stages of RA are characterized by serious systemic manifestations such as lymphomas, atherosclerosis, hematologic abnormalities (such as anemia, leukopenia, thrombocytosis, or neutropenia), pleural effusions, and interstitial lung disease (3). A set of genetic and environmental factors such as smoking, obesity, diet, hormonal, immunological, infectious factors, type of delivery, and birth weight play a role in the occurrence and progression of RA (6, 7).

Early diagnosis and intervention are essential for the prevention of serious damage to these patients (7). The main goals of treatment for RA are to reduce joint pain and inflammation (7). The Treatment is usually carried out using pharmacological therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anti-rheumatic drugs (7). NSAIDs, which are used as the main treatment of RA, reduce prostaglandin synthesis by suppressing the cyclooxygenase enzymes 1 and 2 (COX-1 and COX-2) therefore reducing the inflammation (8). No matter how useful the effects of these drugs are, their side effects such as gastrointestinal toxicity (nausea in 20–70% of RA patients) still bother some RA patients (8). Many RA patients seek additional treatments with fewer side effects (5). In recent years, an increasing number of studies have suggested that diet may have an important role in modifying RA symptoms (9). Nutritional factors can be both a protective factor and a risk factor for the onset of the disease (5, 10, 11). This could be possibly related to epigenetic mechanisms, changing the metabolic profile, increasing the levels of antioxidants, and changing the intestinal microbiome (5, 10, 11). Several nutrients are proven to have positive effects on RA patients such as omega-3 polyunsaturated fatty acids, oleic acid, flavanoids, vitamin D, and vitamin C (1, 9–11). Some other nutrients might harm RA patients, such as red meat and high sodium and protein intake (11). Many RA patients acknowledge that consuming dairy products and foods such as tomatoes and eggplants adversely affect their symptoms (12).

Nightshades (Solanaceae family) are a group of plants including tomatoes, potatoes, eggplant, and some types of peppers (13–15). These plants contain toxic glycoalkaloids including Solanine, tomatine, chaconine, and solasonine, which are used by the plants to protect themselves against insects, animals, and bacteria (16). Small amounts of alpha-solanine can lead to symptoms such as confusion, nausea, abdominal pain, vomiting, and diarrhea, and excessive amounts can lead to seizures, coma, and even death (16). Solanine increases intestinal permeability and causes damage to bones and joints by increasing calcium loss from bones, so it has a destructive effect on the pathogenesis of arthritis (5, 15, 17). More than 10% of arthritis patients may have allergic reactions to the solanine family and a study suggests that the elimination of plants containing solanine from OA patient's diets for a period of 4–6 weeks could be useful (18).

Methods

A single-blinded controlled trial will be conducted to evaluate the effect of a NED on 36 participants for 8 weeks (2 months). The patients will be equally divided in two intervention and placebo groups. Both groups will receive general anti-inflammatory dietary recommendations and the intervention group will be undergone a NED during the study. Clinical symptoms will be determined using questionnaires. Moreover, blood samples will be collected from participants to measure desired indicators.

Discussion

To the best of our knowledge, this study will be the first RCT investigating the effect of NED on inflammatory and rheumatologic markers of rheumatoid arthritis patients. The possible results of this study could be useful for nutritionists and physicians in managing RA patients.

Trial registration

Iranian Registry of Clinical Trials (irct.ir) IRCT20230220057465N1. Registered on 8 April 2023.
Considering the lack of data about the nightshades effect on RA and increasing prevalence of rheumatology diseases and the heavy economic burden caused by current treatments, as well as the desire of patients to have alternatives or a supplementary treatment (19), this study aims to assess the impact of a NED on inflammatory and rheumatologic markers of rheumatoid arthritis patients.

**Objectives**

The primary objective of this study is to determine the possible effects of the nightshade elimination diet on clinical symptoms, inflammatory and rheumatological markers in rheumatoid arthritis patients.

Secondary outcomes are to determine the possible effects of the nightshade elimination diet on anthropometric variables, and the quality of life of these patients.

**Material and Methods**

**Design**

This study has a randomized single-blinded controlled trial design and will be carried out to evaluate the effect of NED on RA patients. Due to the nature of this study, there is no possibility of blinding the researchers, so this study will be done in a single-blinded manner to blind the patients from their treatment allocation until the end of the study. All patients who volunteered to participate in the study will be explained the purpose and procedure of the study and will be asked to sign a written informed consent form approved by the Ethics committee. All the information about the patients included in the questionnaires will remain confidential. This method has used the SPIRIT reporting guidelines (20). We also made some modifications to the baseline method of our research including changing sample size from 38 to 40 and removing the prohibition of nutritional supplements for participants.

**Participants**

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

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).
3. Not having a diet during the study and before sampling
4. Not having any other chronic diseases: allergies, CVD, asthma, cancer, depression, Alzheimer’s
5. Not taking psychoactive drugs
6. Not having any other rheumatoid diseases than RA.

The exclusion criteria are:

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 during the study.

**Sampling and randomization**

The sample size was calculated based on the mean difference formula and according to ESR changes from baseline to the end of treatment in a study conducted by Sadeghi et al. 2022 (21). Considering 25% dropout, the sample size was determined to be 40 patients (20 patients in each group). Participants will be then assigned to the groups using block random sampling by computer-generated random numbers based on sex and body mass index (BMI).

\[
\begin{align*}
\text{var} \frac{n}{Z_{1-\beta}} &= \left( \frac{\text{var} Z_1 - \text{var} Z_2 + \text{var} Z_{1-\beta}}{\text{var} \mu_1 - \text{var} \mu_2} \right)^{2} \times \left( \text{var} \delta_1^{2} + \text{var} \delta_2^{2} \right) \times 16 \\text{var} \delta_1 \\text{var} \delta_2 \\
Z_{1-\beta} &= 1.96 \\
Z_{1-\beta} &= 1.282 \\
\mu_1 &= 24.66 \quad \mu_2 = 9.23 \\
\delta_1 &= 16.4 \quad \delta_2 = 10.3
\end{align*}
\]

**Intervention**

The present study includes two groups. The intervention group will be put on the nightshade elimination diet for 8 weeks (2 months) (figure.1). Both groups will receive general dietary recommendations regarding their illness and the intervention group will be asked to avoid consuming any nightshade vegetables, including tomatoes, eggplants, potatoes, bell and chili peppers. Anyone who is willing to quit the trial, will be asked to give a blood sample for later analysis.
At the end of the study, analysis of food intake data will be done after converting raw and cooked ingredients to grams or milliliters through NUTRITIONIST IV nutritional software and then entering the information into SPSS version 26 software.

**Outcomes**

**Primary outcome**

Clinical symptoms will be determined by a rheumatologist using the number of tender and swollen joints, the visual pain intensity scale (VAS: visual analog scale), The AIMS-2 (Arthritis Impact Measurement Scale-2) questionnaire, and disease activity score (DAS-28) which all will be obtained from all participants at the beginning and end of the study.

Fasting Blood samples (10cc) will be taken from each participant in a sitting position at baseline and at the end of treatment. Hs-CRP and IL-1 variables will be measured by the ELISA method, and ESR will also be assessed by the Westergren-Katz method. CBC of the patients will be measured using a TB counter device.

**Secondary outcomes**

General information will be assessed using questionnaires containing demographic (name, age, gender) socioeconomic (marital status, level of education, occupation) and anthropometric (weight, height, and BMI), lifestyle/behavior (smoking), medical records (history of various diseases, weight loss surgeries, diets for lose weight or gain weight) and drugs (use of any type of chemical or herbal medicine). Weight will be measured using a Seka scale with minimal clothing while standing, with an error of 0.5 kg, and height will be measured using a Seka caliper while standing completely looking forward with an error of 0.1 cm. Finally, the body mass index will be obtained by calculating the ratio of weight to the square of the height. All data will be used to obtain our secondary objectives.

Quality of life will be assessed using the short form of WHOQOL (WHO Quality of Life) questionnaires which will be obtained from all participants at the beginning and end of the study.

**Dietary assessment**

Dietary assessment will be done using a three-day food questionnaire which will be filled out at the end of the study. Also, at the beginning of the study, patients will be given a notebook to record any type of food that causes them pain and swelling.

**Data management**

All the information about the patients included in the questionnaires and the results of blood tests will remain confidential. If requested, participants can access their individual results at the completion of the study period, by making a direct request.

**Statistical Methods**

The data will be analyzed by SPSS software version 26. After examining the normal distribution of variables using the Shapiro-wilk test, quantitative normal variables will be reported as mean ± standard deviation, quantitative non-normal variables will be reported as median IQR, and qualitative variables as number (percentage). The independent T-Test and Mann-Whitney test will be used to compare the mean of variables between the two groups for normal and unnormal distributions respectively. The paired T-test or Wilcoxon test will be used to analyze within groups means. missing data will be handled using the imputation method. P-Value < 0.05 will be considered statistically significant. If necessary, ANCOVA analysis will be implemented.

**Discussion**

As far as our knowledge goes, this study will be the first randomized controlled trial to investigate the effect of a nightshade elimination diet on inflammatory and rheumatologic markers of rheumatoid arthritis patients. Making a protocol publicly available helps us document our work and also helps other investigators to lay the foundation of their studies based on our protocol (22). Publishing study protocols will also inform the scientific community of the studies that are being conducted, which helps avoid duplication (22). After conducting this RCT, the effect of nightshades on RA patients will be clearer than before and the result may be useful for nutritionists and physicians to advise patients about dietary guidelines.

This study also has some limitations. The first one is the single-blinded design because there is no way to blind researchers to their treatments, which could have resulted in bias when completing the outcome (23). Secondly, this study used a food questionnaire, which relies on participants’ memory and can result in under or over-reporting intake of food groups (24).

**Trial status**

This is a paper protocol. The recruitment will start at 23 of July, 2023 and approximately will take 4 months to be completed.

**Declarations**

**Ethics approval and trial registration**

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. IRCT2023022005746SN1) before data collection and intervention administration.
Confidentiality of patient records

The names and personal information of study participants will remain confidential. All study records will only identify the patient by an assigned study identification number. We will maintain a confidential patient identification list (Master list) during the course of the study. Access to confidential information and the Master list is only permitted for direct patient management and for those involved in monitoring the conduct of the study. The patient’s name will not be used in any public report of the study.

Consent for publication

Not applicable

Availability of data and materials:

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.

Competing interests

All authors declared that they have no competing interests.

Funding

This study is funded by grants from the Yasuj University of Medical Sciences (ID:4010133).

Email: research@yums.ac.ir, Web page address: https://research.yums.ac.ir

Author’s contributions

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 data collection.

Acknowledgments

We will be grateful to all participants for their contribution to this research. This study is supported by grants from the Yasuj University of Medical Sciences, Yasuj, Iran.

References


10. Don't neglect nutrition in rheumatoid arthritis! | RMD Open [Internet]. [cited 2023 Mar 23]. Available from: https://rmdopen.bmj.com/content/4/1/e000591.abstract
Figures
<table>
<thead>
<tr>
<th>TIMEPOINT**</th>
<th>STUDY PERIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrolment</td>
</tr>
<tr>
<td>t&lt;sub&gt;-&lt;/sub&gt;</td>
<td>0</td>
</tr>
</tbody>
</table>

**ENROLMENT:**
- Eligibility screen: X
- Informed consent: X
- [List other procedures]: X
- Allocation: X

**INTERVENTIONS:**
- [Intervention group]: X X
- [Control group]: X X

**ASSESSMENTS:**
- [List baseline variables]: X X
- [List outcome variables]: X X
- [List other data variables]: X X

Figure 1

schedule of enrolment, interventions, and assessments

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- completedSPIRITchecklist.docx