

## **Study Protocol**

### **Official**

### **Title:**

Evaluation of the Effect of the Mediterranean Diet on Disease Activity and Treatment Response in Patients With Axial Spondyloarthritis Receiving Biologic Therapy

**Protocol Number:** AS01

### **Sponsor/Institution:**

Erciyes University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology

### **Principal**

### **Investigator:**

Assoc. Prof. Gizem Cengiz

### **Date:**

24 January 2025

### **Aim**

This study aims to investigate the effects of the Mediterranean diet on disease activity, quality of life, inflammation levels, pain scores, and the frequency of biologic DMARD (bDMARD) use in patients with ankylosing spondylitis (AS) receiving biologic therapy.

### **Potential Risks**

There are no anticipated risks associated with this study.

### **Background**

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown etiology that typically begins with inflammation in the sacroiliac joints in the early stages and later affects the axial spine.<sup>1</sup> It can lead to significant reductions in quality of life due to inflammatory back pain, structural, and functional impairments. Genetic factors, gut microbiota, mechanical effects on the spine and peripheral joints, innate immunity, oxidative stress, lifestyle, and environmental factors are thought to play an important role in AS pathogenesis.<sup>2</sup> Accordingly, diet has increasingly been investigated as a potential factor influencing the pathogenesis and progression of AS.

Both pharmacological and non-pharmacological approaches should be used in AS management.<sup>3</sup> The main goals of treatment are to control symptoms and inflammation, prevent

structural damage progression, and maximize quality of life.<sup>4</sup> However, there is limited evidence supporting the impact of lifestyle modifications. Among environmental factors, diet stands out as a modifiable factor with potential to reduce inflammation.<sup>5</sup> Inflammation can alter metabolism, potentially modifying dietary habits and directly influencing disease activity.<sup>6</sup> While some foods may trigger inflammatory processes, nutrients such as antioxidants and omega-3 fatty acids demonstrate anti-inflammatory properties.

A study on axial spondyloarthritis (axSpA) patients suggested that diet could have beneficial effects; however, this study also included axSpA patients beyond AS.<sup>7</sup> Diets rich in fiber and antioxidants may provide protective effects in gastrointestinal and inflammatory processes.<sup>8</sup>

The Mediterranean diet (MD), with its anti-inflammatory and antioxidant potential, is thought to delay the onset and progression of chronic inflammation.<sup>9</sup> This diet has also been linked to the prevention and management of cardiovascular diseases.<sup>10</sup> The MD includes high intake of olive oil, unrefined carbohydrates, fresh and dried fruits, vegetables, and fish; low intake of dairy products and red meat; and moderate consumption of red wine. It is particularly rich in antioxidants and polyunsaturated fats.

In AS, these nutritional components may reduce inflammation, pain, and structural damage, and potentially lower disease prevalence.<sup>7</sup> However, to date, no study has compared the effects of the Mediterranean diet in AS patients receiving bDMARDs with a control group. Therefore, our study aims to evaluate the efficacy of the Mediterranean diet in this patient group, contributing to disease management and supporting a therapeutic approach that improves quality of life.

### **Hypothesis:**

The Mediterranean diet will reduce disease activity, improve quality of life, and decrease inflammation in AS patients.

## **Methods**

### **Study Design and Participants**

This is a prospective, single-blind, randomized controlled trial.

Sample size calculation determined that 51 participants per group were required. With an additional 10% dropout allowance, the total target enrollment is 55 participants per group (110 total). Eligible participants will be adults over 18 years old, diagnosed with AS according to ASAS criteria, and providing written informed consent.

**Inclusion Criteria:**

1. Diagnosis of AS according to ASAS criteria
2. Age  $\geq 18$  years
3. No recent dietary changes in the past 3 months
4. Stable treatment with NSAIDs or DMARDs in the past 4 months
5. Voluntary participation with signed informed consent

**Exclusion Criteria:**

1. Pregnancy or breastfeeding
2. Dietary restrictions preventing adherence to the Mediterranean diet (e.g., severe food allergies)
3. Participation in another diet or exercise-based intervention within the past 6 months
4. History of another rheumatologic or neurological disorder

**Randomization**

Participants will be randomized into intervention and control groups using stratified randomization by age, body mass index, and disease activity (ASDAS-CRP). Randomization will be conducted through <https://www.randomizer.org/> by an independent researcher not involved in the study.

Outcome assessors will be blinded to group allocation. The physiotherapist implementing the intervention will not be blinded, but will not participate in outcome assessments.

**Interventions**

- **Control Group (Standard Care):** Patients will continue their standard medical treatment and receive general healthy nutrition recommendations.
- **Mediterranean Diet Group:** Patients will follow a Mediterranean diet plan supervised by a dietitian. Compliance will be monitored via phone calls every 10 days.

Assessments will be performed at baseline and at 3 months.

## **Outcomes**

### **Primary Outcome Measure:**

- Change in Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) from baseline to 3 months.<sup>13</sup>

### **Secondary Outcome Measures:**

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)<sup>11 12</sup>
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Hospital Anxiety and Depression Scale (HADS)<sup>14 15</sup>
- Short Form-36 (SF-36)<sup>16</sup>
- International Physical Activity Questionnaire (IPAQ)<sup>17</sup>
- Pittsburgh Sleep Quality Index (PSQI)<sup>18</sup>
- FACIT-Fatigue Scale<sup>19</sup>
- Health Assessment Questionnaire (HAQ)<sup>20</sup>
- Morisky Medication Adherence Scale-8 (MMAS-8)<sup>21 22</sup>
- PREDIMED Mediterranean Diet Adherence Questionnaire<sup>23 24</sup>
- Handgrip strength (Jamar Hydraulic Hand Dynamometer)
- Body composition (InBody270 Analyzer)

## Statistical Analysis

Sample size was calculated using **G\*Power version 3.1.9.7** with 80% power and a 5% type I error, yielding 51 participants per group. With a 10% dropout rate, 55 participants per group will be recruited.

All analyses will be conducted using **SPSS version 22.0**. Normality will be tested with Shapiro-Wilk. Baseline group comparisons will be done using independent t-tests or Mann-Whitney U tests. Repeated measures will be analyzed with mixed-model ANOVA, with Bonferroni correction for multiple comparisons. Categorical variables will be analyzed using Chi-square or Fisher's exact tests. A p-value <0.05 will be considered statistically significant.

## References

1. van der Linden S, van der Heijde D. Ankylosing spondylitis: clinical features. *Rheumatic Disease Clinics of North America*. 1998;24(4):663-676.
2. Zhang L, Han R, Zhang X, Fang G, Chen J, Li J, Xu S, Qian L, Chen W, Pan F. Fecal microbiota in patients with ankylosing spondylitis: Correlation with dietary factors and disease activity. *Clinica Chimica Acta*. 2019;497:189-196.
3. Weisman M, RJ HD. Ankilozan Spondilit ve Spondiloartropatiler. *Ankara: Veri Medikal Yayıncılık*. 2008.
4. Lavie F, Pavy S, Dernis E, Goupille P, Cantagrel A, Tebib J, Claudepierre P, Flipo RM, Le Loët X, Maillefert J-F. Pharmacotherapy (excluding biotherapies) for ankylosing spondylitis: development of recommendations for clinical practice based on published evidence and expert opinion. *Joint Bone Spine*. 2007;74(4):346-352.
5. Macfarlane TV, Abbood HM, Pathan E, Gordon K, Hinz J, Macfarlane GJ. Relationship between diet and ankylosing spondylitis: a systematic review. *European journal of rheumatology*. 2017;5(1):45.
6. Couderc M, Pereira B, Schaefferbeke T, Thomas T, Chapurlat R, Gaudin P, Morel J, Dougados M, Soubrier M. GlutenSpA trial: protocol for a randomised double-blind placebo-controlled trial of the impact of a gluten-free diet on quality of life in patients with axial spondyloarthritis. *BMJ open*. 2020;10(11):e038715.
7. Ometto F, Ortolan A, Farber D, Lorenzin M, Dellamaria G, Cozzi G, Favero M, Valentini R, Doria A, Ramonda R. Mediterranean diet in axial spondyloarthritis: an

- observational study in an Italian monocentric cohort. *Arthritis research & therapy*. 2021;23:1-13.
8. Sundström B, Wållberg-Jonsson S, Johansson G. Diet, disease activity, and gastrointestinal symptoms in patients with ankylosing spondylitis. *Clinical rheumatology*. 2011;30:71-76.
  9. Tsigalou C, Konstantinidis T, Paraschaki A, Stavropoulou E, Voidarou C, Bezirtzoglou E. Mediterranean diet as a tool to combat inflammation and chronic diseases. An overview. *Biomedicines*. 2020;8(7):201.
  10. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. *European journal of nutrition*. 2019;58:173-191.
  11. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *The Journal of rheumatology*. 1994;21(12):2286-2291.
  12. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N. A Turkish version of the bath ankylosing spondylitis disease activity index: reliability and validity. *Rheumatology international*. 2005;25:280-284.
  13. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, van der Heijde D, Society AoSi. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Annals of the rheumatic diseases*. 2011;70(1):47-53.
  14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica scandinavica*. 1983;67(6):361-370.
  15. Aydemir O. Hastane anksiyete ve depresyon ölcegi Turkce formunun gecerlilik ve guvenilirliigi. *Turk Psikiyatri Derg*. 1997;8:187-280.
  16. Framework IC. The MOS 36-item short-form health survey (SF-36). *Med Care*. 1992;30(6):473-483.
  17. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF. International physical activity questionnaire: 12-country reliability and validity. *Medicine & science in sports & exercise*. 2003;35(8):1381-1395.

18. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*. 1989;28(2):193-213.
19. Cella D, Lenderking WR, Chongpinitchai P, Bushmakina AG, Dina O, Wang L, Cappelleri JC, Navarro-Compán V. Functional Assessment of Chronic Illness Therapy-Fatigue is a reliable and valid measure in patients with active ankylosing spondylitis. *Journal of patient-reported outcomes*. 2022;6(1):100.
20. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis & Rheumatism*. 1980;23(2):137-145.
21. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. *Journal of clinical epidemiology*. 2011;64(3):255-257.
22. Sayiner ZA, Savaş E, Kul S, Morisky DE. Validity and reliability of the Turkish Version of the 8-Item Morisky Medication Adherence Scale in patients with type 2 diabetes. *European Journal of Therapeutics*. 2020;26(1):47-52.
23. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvado J, Buil-Cosiales P, Corella D, Covas MI, Schröder H, Aros F, Gomez-Gracia E. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. 2012.
24. Pehlivanoğlu EFÖ, Balcıoğlu H, Ünlüoğlu İ. Akdeniz diyeti bağlılık ölçeği'nin türkçe'ye uyarlanması geçerlilik ve güvenilirliği. *Osmangazi Tıp Dergisi*. 2020;42(2):160-164.