

Study Protocol / Research Summary

Official Title of the Study:

Efficacy of Anti-inflammatory Diet and Resistance Exercise on Disease Activity, Pain, Physical Function, and Quality of Life in Patients with Rheumatoid Arthritis: A Randomized Controlled Trial

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Purpose of Document:

This document contains summary, hypothesis, objectives, scientific rationale, materials and methods, planned statistical analysis, and references supporting the study design and interventions.

1. Study Participants

1.a. Number of Participants

- Healthy Volunteers: 0
- Patient Volunteers: 80
- Duration of Participation: Baseline, 6 weeks, 3 months

1.b. Inclusion Criteria

1. Participant voluntarily agrees to participate and signs informed consent.
2. Age ≥ 18 years.
3. Low to moderate rheumatoid arthritis disease activity (DAS28).

1.c. Exclusion Criteria

1. Age < 18 years
2. Uncontrolled diabetes or other metabolic/endocrine disorders
3. Uncontrolled hypertension
4. Medication changes within the last month
5. BMI > 40 (morbid obesity)
6. Pregnancy
7. Chronic kidney disease
8. Psychiatric disorders
9. Alcoholism
10. Conditions contraindicating exercise (congestive heart failure, lung disease, cancer, active infection, recent fracture, recent ligament/tendon injury)

1.d. Gender and Age

- Both sexes, age ≥ 18 years
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2. Study Summary

2.a. Hypothesis, Objectives, and Scientific Rationale

Rheumatoid arthritis (RA) is a systemic, progressive inflammatory disease causing structural damage in small and large joints, often presenting as symmetrical polyarthritis. Its prevalence is approximately 1%. RA is multifactorial, arising from genetic and environmental factors. Environmental factors such as diet, smoking, infections, sedentary lifestyle, and socioeconomic status are associated with disease onset and activity. The primary goal of RA treatment is to achieve remission, and in addition to disease-modifying antirheumatic drugs (DMARDs), lifestyle interventions such as diet and exercise are recommended.

Recent studies highlight the role of dietary modification in RA. Anti-inflammatory diets, emphasizing fish, fresh fruits and vegetables, vitamin D, and omega-3 intake while limiting salt, sugar, red meat, and gluten-rich foods, have been shown to reduce proinflammatory cytokines and disease activity. Physical activity increases fat metabolism and exerts anti-inflammatory effects via myokine release; moderate to high-intensity aerobic and resistance exercises performed 2–3 times per week improve pain, swollen joint count, quality of life, and disease activity.

Aim: To evaluate the effects of anti-inflammatory diet and resistance exercise, in addition to standard medical treatment, on RA disease activity, pain, functional status, and quality of life. The interventions aim to support disease remission.

2.b. Materials and Methods

This study will be conducted with RA patients aged ≥ 18 years presenting to the Physical Medicine and Rehabilitation clinic. Eighty patients will be randomized into four groups (20 per group): 1. Anti-inflammatory diet 2. Anti-inflammatory diet + resistance band exercise 3. Resistance band exercise only 4. Control (standard RA treatment)

Data collected will include anthropometric measurements, personal information, and current medications. Evaluations will be performed at baseline, 6 weeks, and 3 months and include: dietary intake frequency, SF-36, DAS28, VAS, 6-minute walk test, 30-second chair stand test, handgrip strength, and AIMS2. Exercise sessions will be supervised in the FTR unit 3 times per week for 6 weeks. Diet intervention will last 3 months under dietitian supervision. Written informed consent will be obtained.

2.c. References Used in Sections 2.a and 2.b

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2. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev.* 2005 Mar;4(3):130-6. doi: 10.1016/j.autrev.2004.09.002. PMID: 15823498.
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6. Winkvist A, Bärebring L, et al. A randomized controlled cross-over trial investigating the effect of anti-inflammatory diet on disease activity and quality of life in rheumatoid arthritis: the ADIRA study protocol. *Nutr J.* 2018;17(1):1-8.
7. Hernández-Hernández MV, Díaz-González F. Role of physical activity in the management and assessment of rheumatoid arthritis patients. *Reumatol Clin.*

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Planned Statistical Analysis

Data will be analyzed using Linear Mixed Models (LMM) to evaluate the effects of group (control, exercise, diet, diet+exercise), time (baseline, 6 weeks, 3 months), and their interaction on body composition (e.g., body weight, fat mass, visceral fat, body fat percentage, total body water, total body water percentage, skeletal muscle mass, muscle mass, muscle mass percentage, waist circumference, hip circumference, waist-to-hip ratio, upper arm circumference), functional measurements (sit-to-stand test, 6-minute walk test), and quality of life outcomes (AIMS2, VAS, SF-36). LMM will be preferred because it does not require the sphericity assumption for repeated measures. The significance of group, time, and group \times time effects will be assessed using likelihood ratio (LR) tests. In cases where LMM does not converge (e.g., due to singular matrix errors), ordinary least squares (OLS) regression will be used as an alternative. Normality will be checked using the Shapiro-Wilk test and Omnibus test (for skewness and kurtosis), and results will be interpreted cautiously if normality is violated (Omnibus $p < 0.05$).

Post-hoc comparisons will initially be performed using Estimated Marginal Means (EMMeans) for pairwise comparisons; however, if computational issues arise (e.g., shape mismatch errors), Bonferroni-corrected pairwise tests will be used instead. Effect sizes will be calculated as partial eta-squared (η^2) for LMM and Cohen's d for pairwise comparisons; η^2 values will be interpreted as small (0.01–0.059), medium (0.06–0.139), or large (≥ 0.14), and Cohen's d values as small (0.2–0.49), medium (0.5–0.79), or large (≥ 0.8). Autocorrelation in OLS models will be assessed using the Durbin-Watson statistic, with values < 1 indicating potential autocorrelation risk.

Demographic characteristics will be compared using the Kruskal-Wallis test for continuous variables (e.g., age) and the chi-square test for categorical variables (e.g., sex). Subgroup analyses according to serostatus and RF/Anti-CCP categories will be conducted using LMM whenever possible. All analyses will be performed in Python (version 3.8) using the statsmodels and pingouin libraries. Statistical significance will be set at $p < 0.05$, and results will be interpreted considering the limited statistical power due to sample size (100, approximately 25 per group).