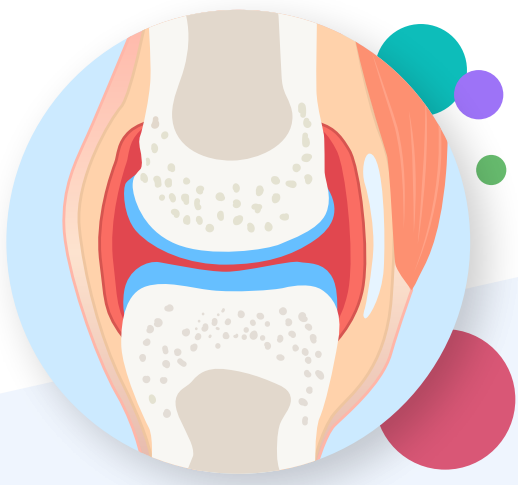
Non-Pharmacologic Interventions for Rheumatoid Arthritis



Inflammation and Comorbidities

- Chronic, systemic inflammation is foundational to the pathophysiology of rheumatoid arthritis (RA)[1]
- Inflammation contributes to several comorbidities, such as cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), diabetes mellitus (DM), cancers, infections, and even psychiatric disorders[2-5]
- Comorbidities contribute to a higher death rate and lower quality of life in people with RA[5]

Interventions for RA

- In addition to pharmacological therapies to address inflammation and signs and symptoms of the disease, nonpharmacologic interventions (NPIs) are also recommended in the management of inflammation in RA,[6,7] such as **diet**,[6] **exercise** and **physical therapy** (self-directed and provider-directed),[6,7] **oral health**,[8] and **sleep**[9]
- These interventions are recommended in addition to **psychosocial health**, **acupuncture**, and **massage therapy**[7]
- NPIs are important to consider, in addition to pharmacological treatments, to address unmet needs in RA, especially in patients with difficult-to-treat RA[6]

Exercise

- Structured exercise, including regular walking-based physical activity, has been shown to reduce the impact of disease and improve the quality of life in patients with RA[6]
  - Exercise may even aid in comorbidities of RA, including mental health and sleep[6]
  - Higher BMI has been found to increase the risk of rheumatic disease, suggesting that interventions that decrease BMI can have significant benefits for patients with RA[10]
- Combining an anti-inflammatory diet with exercise can further improve outcomes[6]
- Recent guideline recommendations include exercise for the management of RA symptoms[7]

Diet

- A wide range of dietary interventions have been investigated for managing RA[11]
- Recent guideline recommendations include a Mediterranean-style diet over no formally defined diet[7]
- The anti-inflammatory and Mediterranean diets can help complement traditional disease management in patients with RA[3,4]
  - Foods rich in n-3 fatty acids (e.g., fish), fiber (e.g., leafy greens), antioxidants (e.g., blueberries), and probiotics (e.g., yogurt) have been reported to ameliorate symptoms in patients with RA through their effect on the gut microbiota[12,13]
  - These foods are prevalent in the Mediterranean diet, such as whole grains, fruits, vegetables, legumes, olive oil, fish, and nuts[12]
  - These diets can modulate the immune response through shaping of gut microbiota, promoting certain gut microbiota that reduce intestinal inflammation in patients with RA, such as ***Prevotella copri*** strains[13,14]
- Curcumin, an active chemical found in turmeric, has been shown to help RA symptoms[15]
- Foods containing a glycoalkaloid called solanine, such as tomatoes and eggplants, have been reported to worsen RA symptoms; however, evidence is inconclusive[1]
  - An elimination diet plan (removal of foods that may aggravate disease symptoms) may provide insight into the food source causing symptoms[11]
- Educating consumers on food labels can provide them with a better understanding of their nutrition intake[16]

Sleep

- Nonrestorative sleep is an underappreciated risk factor in RA that negatively affects patient quality of life[9]
- Sleep disorders are common amongst patients with RA. These can include insomnia and restless leg syndrome, which occur in over 60% of patients.[17]
  - There is a relationship between sleep and inflammation, where disorders that disrupt sleep (such as sleep apnea) may elevate inflammatory cytokines and thus exacerbate inflammation in patients with RA[18]
- Improved sleep quality has been shown to improve patient-reported outcomes in patients with RA[9]
  - Dysfunctional sleep compounds negative symptoms observed in RA, including chronic pain, fatigue, and decreased QoL[19]
  - Nonpharmacological management of sleep disorders is recommended: sleep hygiene, stimulus control, and cognitive therapy[9]

Oral Health

- Oral health is a risk factor in rheumatic diseases[8]
- Periodontitis has been linked to the severity and progression of RA, and oral pathogens may trigger dysregulated immune responses linked to RA, for example[20,21]
  - ***Porphyromonas gingivalis*** *(P. gingivalis)* has the unique ability to citrullinate proteins, leading to the production of anti-citrullinated peptide antibodies (ACPA), sensitive and specific biomarkers of RA.[22,23]
  - ***Aggregatibacter actinomycetemcomitans*** (Aa) is a microbial species associated with periodontal disease and has been shown to reproduce some of the antigens that act as immune targets in RA[21]
- To decrease risks, patients should practice good oral hygiene and visit their dental professional(s) reguarly[8]

Encouraging Lifestyle Changes

Changing longstanding behaviors is a challenge for patients. Multiple conversations may be required between a patient and healthcare practitioners (HCPs) to achieve these lifestyle modifications[24]

Effective strategies include:

- Discussions between HCPs and patients about potential lifestyle changes[24]
- Motivational interviewing: a nonconfrontational approach that emphasizes collaboration between HCP(s) and patient, i.e., gentle persistence to help patients change habits over time[24]
- Referrals to allied health professionals: registered dietitian nutritionists, physiotherapists, and sleep medicine specialists[7]

ABBREVIATIONS & GLOSSARY

Aa=*Aggregatibacter actinomycetemcomitans*; **ACPA**=anti-citrullinated peptide antibodies; **ACR=**American College of Rheumatology; **BMI=**body mass index; **CVD=**cardiovascular disease; **DM=**diabetes mellitus; **HCP=**health care practitioner; **NAFLD=**nonalcoholic fatty liver disease; **NPI=**non-pharmacologic intervention; **P. gingivalis**=*Porphyromonas gingivalis*; **QoL=**quality of life; **RA=**rheumatoid arthritis.

Aggregatibacter actinomycetemcomitans **(ag-gre-gat-i-bac-ter actin-o-mycetem-comi-tan-s):** an anaerobic bacterium that is part of the oral microbiota of humans and is associated with periodontitis

Anti-citrullinated peptide antibodies (anti-si-true-li-nated pep-tide an-tuh-baa-deez): sensitive and specific biomarkers of RA

Curcumin (cur-cu-min): an orange-yellow compound that is a major constituent of turmeric

Glycoalkaloid (gly-co-al-ka-loid): a family of nitrogen-containing compounds found in plants

Non-restorative sleep (non ruh-staw-ruh-tuhv sleep): sleep that has not subjectively felt to be sufficiently refreshing

Periodontitis (peri-od-ont-it-is): a type of gum disease characterized by severe inflammation of the gums

Porphyromonas gingivalis **(por·fee·ruh·mow·nuhs jin·juh·va·luhs):** a gram-negative anaerobic bacterium identified as one of the major pathogenic organisms in periodontal disease

Prevotella copri **(pre-vo-tel-la co-pri):** a species of anaerobic bacterium found in the human gut microbiota

REFERENCES

1. Bustamante MF, et al. *Contemp Clin Trials Commun*. 2020;100524.
2. Kerola AM, et al. *Eur Cardiol*. 2021;16:e18.
3. Barbarroja N, et al. *Front Immunol*. 2022;13(997270):1-14.
4. Tian Z, et al. *Cardiovasc Endocrinol Metab*. 2021;10(2):125-131.
5. Dougados M, et al. *Ann Rheum Dis*. 2014;73(1):62-68.
6. Majnik J, et al. *Front Med*. 2022;9:991677.
7. England BR, et al. *Arthritis Rheumatol*. 2023:1-13.
8. Protudjer JLP, et al. *JDR Clin Trans Res*. 2022;7(2):127-134.
9. The Lancet Rheumatology. *Lancet Rheumatol*. 2022;4(11): e739.
10. Karlsson T, et al. *Arthritis Rheumatol*. 2023.
11. Khanna S, et al. *Front Nutr*. 2017;4:52.
12. Vadell AKE, et al. *Am J Clin Nutr*. 2020;111(6):1203-1213.
13. Diamanti AP, et al. *Microorganisms*. 2020;8(12):1-14.
14. Cutolo M, et al. *Nutrients*. 2022;14(4):2-5.
15. Ghosh S, et al. *Food Chem Toxicol*. 2015:111-124.
16. Dumoitier A, et al. *Obes Sci Pract*. 2019;5(6):581-591.
17. Mustafa M, et al. *Open Access Rheumatol*. 2019;11:163-171.
18. Taylor-Gjevre RM, et al. *Rheumatology*. 2013;52(1):15-21.
19. Irwin MR, et al. *Sleep*. 2012;35(4):537-543.
20. Krutyhołowa A, et al. *Front Immunol*. 2022;13:980805.
21. Konig MF, et al. *Sci Transl Med*. 2016;8(369):139-148.
22. Li Y, et al. *Front Cell Infect Microbiol*. 2022;12:956417.
23. Bae SC, et al. *Z Rheumatol*. 2018;77(6)522-532.
24. Hall K, et al. *Aus Fam Physician*. 2012;41(9):660-667.

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