Objectives: To unravel the complex interaction between disease activity and fatigue in early RA.

Methods: Data were analyzed from the 2-year treat-to-target trial Care in early RA (CareRA), which compared different remission-induction DMARD regimens, either with or without bridging glucocorticoids, in treatment-naive patients with early RA. Fatigue was measured on a visual analog scale (VAS) at every study visit. The association between inflammatory disease activity (DAS28-CRP) and fatigue (VAS) over time was studied with a multi-level mediation analysis, including as mediators the individual components of the DAS28-CRP, pain (VAS), disability (HAQ), psychosocial aspects (Short-Form SF-36), illness perceptions (Revised Illness Perception Questionnaire [IPQ-R]), and sleep quality (Pittsburgh Sleep Quality Index [PSQI]).

Results: A total of 356 patients were included in these analyses, with a mean (SD) fatigue (VAS) of 48/100 (24) at study initiation. Although there was a consistently positive association between DAS28-CRP and fatigue over time, this association was fully mediated by patient global assessment (PGA) and pain, and to a lesser extent by SF-36 Mental Health and the PSQI global score (Figure 1). Full mediation implies the absence of a significant direct association between DAS28-CRP and fatigue after adjusting for these mediators. In addition, no mediating effect was found for tender/swollen joint counts or CRP.

Conclusion: Our mediation analysis suggests that the relationship between disease activity and fatigue in early RA is complex and fully mediated by aspects of wellbeing like pain, mental health, sleep quality, and the patient’s overall assessment of disease. These results imply a mainly indirect relation between fatigue and inflammation. Clinicians should reserve specific attention for the psychosocial determinants of fatigue, particularly when no improvement is seen with DMARDs.

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