HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2021 September 28.

Published in final edited form as:

Arthritis Rheumatol. 2021 February ; 73(2): 357–358. doi:10.1002/art.41505.

Reply

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Reply

To the Editor:

We are grateful for Dr. Pamuk and colleagues' interest in our article describing synovial histologic features that are associated with patient-reported morning stiffness in RA. Pamuk et al note that neutrophil gene and protein expression, as well as cell counts, fluctuate in the blood in a 24-hour circadian cycle, and the circadian variation in neutrophil function may contribute to morning stiffness. Specifically, circulating neutrophil counts reach a nadir in the early morning, and this is associated with increased expression of CD62L/L-selectin, a cell surface protein important for adhesion or homing (1), as well as increased granularity and tendency for NET formation (2). We agree that it is possible that one of these circadian features of neutrophils may contribute to prolonged morning stiffness in RA. One possibility is that in the morning, neutrophils, with an increased tendency for NET formation, are more likely to extrude DNA into the synovial membrane, and that this then stabilizes fibrin deposits and contributes to patient perception of stiffness. Another possibility is that neutrophils are more likely to traffic and infiltrate inflamed synovium in increased numbers in the morning. We look forward to future studies that might further elucidate the mechanisms of morning stiffness by testing these hypotheses.

Pamuk and colleagues also raise the question of whether there might be a difference in the prevalence of synovial neutrophils in patients with seropositive or seronegative RA, since synovial NETs have been previously shown to be associated with loss of tolerance to citrullinated antigens (3). We did not detect any difference in the frequency of synovial neutrophils or fibrin deposition in patients with seropositive versus seronegative RA (Figure 1). Since neither neutrophils nor fibrin are associated with autoantibodies, we hypothesize that the association between neutrophils, fibrin, and morning stiffness may not be specific to RA and might contribute to the presence of this symptom in other types of inflammatory arthritis, such as seronegative spondyloarthritis.

References

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Figure 1.

Percentage of synovial samples with infiltrating neutrophils or fibrin deposition according to positivity or negativity for autoantibodies (cyclic citrullinated peptide [CCP] or rheumatoid factor [RF]). There was no significant difference in prevalence of synovial neutrophils or fibrin according to the presence or absence of these autoantibodies.