**Inflammatory Biomarkers, Sleep Quantity and Sleep Quality in Rheumatoid Arthritis**

Alexander S. Fine, Michelle Frits, Jing Cui, Christine Iannaccone, Michael Weinblatt, Nancy Shadick, Yvonne C. Lee

**Background:** Over 60% of rheumatoid arthritis (RA) patients complain of sleep disturbance. However, little is known about the association between sleep disturbances and inflammatory pathways in RA. In the general population, studies have shown that sleep disturbances are associated with elevations in inflammatory biomarkers, notably C-reactive protein (CRP) and the inflammatory cytokines, TNF-alpha and IL-6. The goal of this study was to examine the cross-sectional association between biomarkers associated with RA disease activity and sleep quantity and quality in patients with RA.

**Methods:** 208 patients in a RA registry were enrolled in a sub-study on sleep and psychosocial problems in RA. All subjects completed the Medical Outcomes Study (MOS) Sleep Scale, a validated questionnaire gauging sleep problems in chronically ill populations. Of these 208 patients, 134 also had 12 biomarkers of disease activity (EGF, VEGF-A, leptin, IL-6, SAA, CRP, VCAM-1, MMP-1, MMP-3, TNFRI, YKL-40 and resistin) measured using a quantitative multiplex immunoassay. Biomarkers with non-normal distributions were transformed. The primary independent variables were the individual biomarkers, as well as a composite disease activity score, calculated according to a validated algorithm. The primary dependent variables were sleep quantity and sleep quality, measured using the MOS Sleep Scale. Linear regression models were used to examine the association between individual biomarkers and sleep quantity and quality, adjusted for age, sex, RA disease duration and rheumatoid factor seropositivity. To elucidate the impact of TNF inhibitors on this association, secondary analyses were performed including an indicator variable for TNF inhibitor use. Using the Bonferroni correction for multiple comparisons, the threshold for significance was set at p < 0.002.

**Results:** The study population included 84.3% women. The average age was 58.1 ± 10.6 years. 17.9% were taking corticosteroids. 55.2% were taking non-biologic disease-modifying anti rheumatic drugs, and 59.7% were taking TNF inhibitors. After adjustment for multiple comparisons, neither the composite disease activity score nor the individual biomarkers of disease activity were significantly associated with sleep quantity or quality (Table). Similarly, neither the composite disease activity score nor the individual biomarkers were significantly associated with sleep quantity or quality in secondary analyses including TNF inhibitor use as an indicator variable.

**Conclusion:** Contrary to previous studies in the general population, no associations were observed between inflammatory biomarkers and measures of sleep quantity and quality in this cross-sectional study of established RA patients. These findings suggest that RA disease activity may not be the primary driver of sleep problems in RA.

Table. Adjusted associations between biomarkers of RA disease activity and sleep quantity and sleep quality, measured using the Medical Outcomes Study Sleep Scale.\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Biomarkers | Sleep Quantity | | Sleep Quality | |
| β | *P* | β | *P* |
| Composite score | 0.01 | 0.19 | -0.07 | 0.60 |
| ln CRP | 0.01 | 0.08 | -1.66 | 0.18 |
| ln TNFRI | 0.35 | 0.37 | -2.01 | 0.72 |
| ln IL-6 | 0.14 | 0.22 | -0.46 | 0.78 |
| ln EGF | -0.28 | 0.19 | -2.05 | 0.51 |
| ln VEGF-A | -0.25 | 0.19 | 0.61 | 0.82 |
| ln Leptin | -0.07 | 0.11 | 1.14 | 0.48 |
| ln SAA | 0.08 | 0.41 | -1.25 | 0.37 |
| ln VCAM-1 | 1.07 | 0.01 | -2.01 | 0.75 |
| ln MMP-1 | -0.11 | 0.48 | 2.72 | 0.21 |
| ln MMP-3 | -0.08 | 0.67 | 0.01 | 1.00 |
| ln YKL-40 | 0.14 | 0.40 | 1.16 | 0.63 |
| ln Resistin | -0.29 | 0.30 | 4.48 | 0.27 |

\* All results are from multivariable linear regression models adjusted for age, sex, RA disease duration and rheumatoid factor seropositivity.