Inflammatory Biomarkers and Their Relationship with Sleep in Rheumatoid Arthritis

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BACKGROUND

- In animal and healthy human models, inflammatory cytokines, particularly TNF-alpha and IL-6, have been shown to have sleep regulatory properties
- In the general population, increased levels of TNF-alpha and IL-6 are associated with sleepiness, despite increased sleep duration
- Sleep problems are common in rheumatoid arthritis (RA), affecting over 60% of RA patients
- The association between sleep disturbances and RA inflammatory pathways is poorly understood

OBJECTIVE

- To examine the cross-sectional association between biomarkers associated with RA disease activity and sleep quantity and quality in patients with RA

MATERIALS & METHODS

- Study Population

1,360 RA patients in BRASS → 208 enrolled in a sub-study examining sleep disturbances → 189 of those had lab work measured for 12 biomarkers

  - 189 RA patients with data on 12 biomarkers of disease activity in a sub-study of the Brigham Rheumatoid Arthritis Sequential Study (BRASS)
  - Inclusion Criteria
    - Diagnosis of RA by a board-certified rheumatologist
    - Age ≥ 18 years
    - Available measures on sleep quantity and quality

- Inflammatory Biomarkers
  - Serum samples collected and stored at -80˚ C until analysis
  - An automated, multiplex sandwich immunoassay was used to measure concentrations of CRP, TNFRI, IL-6, EGF, VEGF-A, leptin, SAA, VCAM-1, MMP-1, MMP-3, YKL-40, and resistin (Bakker et al, Ann Rheum Dis, 2012)
  - A composite disease activity score was calculated according to a prespecified algorithm, known as the multibiomarker disease activity (MBDA) score (Curtis et al, Arthritis Res, 2012)

MATERIALS & METHODS

- Outcome Variables
  - Sleep quantity in hours
  - Sleep quality, assessed using the Sleep Problems Index II of the Medical Outcomes Study (MOS) Sleep Scale
    - 0-100 scale with 100 indicating greater sleep problems

- Statistical Analysis
  - All biomarkers were log transformed
  - Primary analyses: Linear regression models examining the association between individual biomarkers and sleep quantity and quality
    - Adjusted for age, sex, RA disease duration, and rheumatoid factor and anti-CCP positivity
  - Secondary analyses: Linear regression models including the above variables and an indicator variable for TNF inhibitor use
  - Threshold for significance was set at $p < 0.002$, using the Bonferroni correction for multiple comparisons

RESULTS

Table 1. Baseline clinical characteristics of the study population (N = 189)

Variable	Mean (standard deviation) / Number (%)
Age (years)	58.2 (11.2)
Female (N)	160 (84.7%)
Body mass index (kg/m^2)	26.95 (5.67)
Disease duration (years)	16.10 (9.03)
Rheumatoid factor / Anti-CCP positive (N)	117 (61.9%)
Disease Activity Score in 28 Joints (DAS28-CRP3)	2.95 (1.29)
Current steroid use (N)	33 (17.5%)
Current TNF use (N)	102 (54.0%)
Current DMARD use (N)	164 (86.8%)
Current biologic DMARD use (N)	112 (59.3%)
Current synthetic DMARD use (N)	112 (59.3%)
Hours of sleep per night	6.72 (1.38)

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RESULTS

Table 2. Associations between the natural logarithm of the biomarkers and sleep quality and quantity

Biomarker	Sleep quality (n=176)		Sleep quantity (n=174)	
	β	*P*	β	*P*
Composite	-0.04	0.68	0.01	0.42
CRP	-0.04	0.68	0.01	0.42
TNF	-0.55	0.61	-0.05	0.48
IL-6	0.92	0.86	0.13	0.72
EGF-3	-0.87	0.54	0.15	0.13
VEGF	1.33	0.62	-0.25	0.16
Leptin	3.14	0.21	-0.31	0.07
SAA	2.54	0.07	-0.13	0.18
VCAM-1	-0.93	0.44	0.05	0.57
MMP1	-0.07	0.99	0.75	0.05
MMP-3	3.83	0.06	-0.18	0.20
YKL-40	-1.62	0.48	-0.02	0.91
Resistin	0.87	0.68	0.09	0.56

No biomarkers were significantly associated with sleep quantity or quality.

***Linear regression models, adjusted for age, gender, disease duration, and seropositivity**

- In secondary analyses adjusting for TNF use, the results were the same, showing no association between the natural logarithm of the biomarkers and sleep quantity or quality

LIMITATIONS

- Cross-sectional design, few patients had both sleep measures and inflammatory cytokine levels done at the same time for longitudinal analyses
- Generalizability is limited, a single cohort of established RA patients at one academic medical institution
- All sleep outcomes were patient reported; no polysomnograph data were collected

CONCLUSIONS

- Contrary to previous studies in the general population, no association was found between inflammatory biomarkers and measures of sleep quality and quantity
- RA related inflammation may not be the primary reason for sleep problems in RA
- Future studies are needed to further investigate the causes of sleep problems in RA