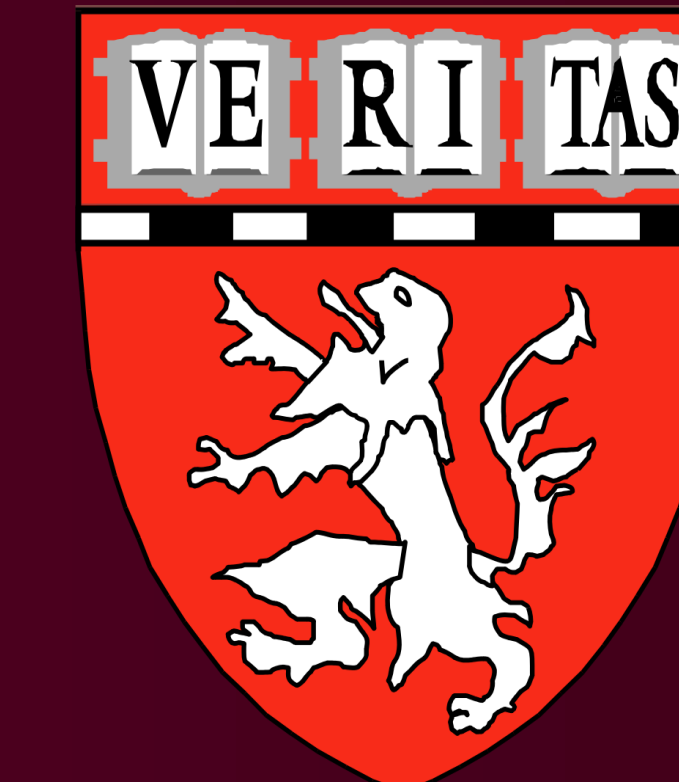




Inflammatory Biomarkers and Their Relationship with Sleep in Rheumatoid Arthritis



Alexander R. Fine, Michelle L. Frits, Jing Cui, Christine K. Iannaccone, Jonathan Coblyn, Michael E. Weinblatt, Nancy A. Shadick, Yvonne C. Lee

Division of Rheumatology, Section of Clinical Sciences, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

BACKGROUND

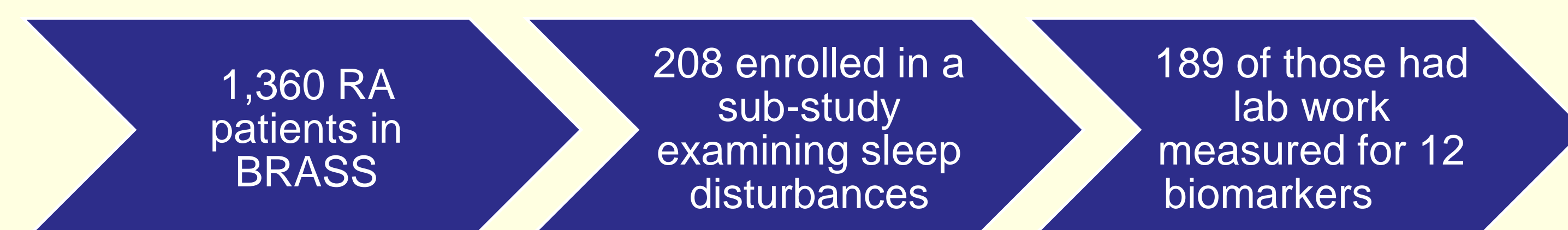
- In animal and healthy human models, inflammatory cytokines, particularly TNF-alpha and IL-6, have been shown to have sleep regulatory properties
- In the general population, increased levels of TNF-alpha and IL-6 are associated with sleepiness, despite increased sleep duration
- Sleep problems are 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



- 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