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Predictors of fatigue in obstructive sleep apnea

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Abstract

Objective—The objective of this study was to determine potential inflammatory predictors of fatigue in obstructive sleep apnea (OSA).

Materials and methods—Fifty-six women and men untreated OSA patients had their sleep monitored with polysomnography. Fatigue was assessed by the Multidimensional Fatigue Symptom Inventory-Short Form. Depressed mood was assessed by the Center for Epidemiologic Studies-Depression Scale. Blood was drawn to assess circulating levels of Interleukin-6 (IL-6) and soluble tumor necrosis factor receptor I (sTNF-RI). Age, gender, body mass index (BMI), blood pressure, OSA severity, depressed mood, and inflammatory biomarkers were entered into a hierarchical multiple linear regression analysis predicting self-reported fatigue.

Results—Approximately 42% of the patients reported significant amounts of fatigue. Higher BMI ($p=0.014$), greater depressed mood ($p=0.004$), and higher sTNF-RI levels ($p=0.033$) were independent predictors of fatigue in the final model (full model $R^2=.571$; $p=.003$). Age, gender, blood pressure and apnea severity were unrelated to fatigue.

Conclusion—The findings suggest that in addition to depressed mood, fatigue in OSA may be associated with increased body weight and elevated levels of the proinflammatory cytokine receptor sTNF-RI. The findings support a linkage between the widely reported fatigue in OSA and a sleep-related component of inflammation.

Keywords

Obstructive sleep apnea; Fatigue; Cytokines; Body mass index; Depression

Introduction

Fatigue is a common complaint in obstructive sleep apnea (OSA) and frequently associated with depressive symptoms [1,2]. Fatigue is also a common and troubling symptom in cancer survivors, and is associated with the degree of systemic inflammation as assessed by elevated proinflammatory cytokine levels, including soluble tumor necrosis factor (TNF) receptors [3, 4]. A prior study with a limited sample size compared groups of sleep apneics and hypersomniacs to normal controls and found that circulating TNF- α and IL-6 were elevated in the sleep apneics compared to the controls [5]. The purpose of the current study was to examine circulating inflammatory marker levels as potential predictors of fatigue after controlling for demographic variables, depressive mood, and apnea severity within a group of OSA patients complaining of a broad range of fatigue symptoms.

Materials and methods

Participants

Fifteen women and 41 men with untreated OSA (mean age 49.2 years) were recruited by advertising and word-of-mouth referral. Participants were excluded if they reported a history of major medical illnesses (other than OSA and hypertension), current psychiatric diagnoses, or if they were receiving psychotropic medication. Patients who were receiving anti-hypertensive medications had their medications tapered for 3 weeks before participation. Blood pressure readings were obtained using a manual cuff while the patients were seated, and averaged across three measurements. The protocol was approved by the University of California San Diego (UCSD) Human Subjects Committee. After a description of the study, a written informed consent was obtained.

Sleep monitoring

Participants had their sleep monitored at the UCSD General Clinical Research Center with a standard regimen of polysomnography. Apneas were defined as decrements in airflow of $\geq 90\%$ from baseline for ≥ 10 s. Hypopneas were defined as decrements in airflow of $\geq 50\%$ but $< 90\%$ from baseline for ≥ 10 s. The numbers of apneas and hypopneas per hour were calculated to obtain the apnea hypopnea index (AHI). Participants with an AHI ≥ 15 were considered to have OSA and included in the study. Oxyhemoglobin saturation was monitored with a pulse oximeter (Biox 3740, Datex-Ohmeda, Louisville, CO) and analyzed using Profox software (Associates, Escondido, CA). AHI and mean oxygen saturation (SaO₂) were taken as indicators of OSA severity.

Fatigue and depressed mood assessments

Participants completed the Multidimensional Fatigue Symptom Inventory-short form (MFSI-sf) and the Center for Epidemiologic Studies-Depression (CES-D) Scale. The MFSI-sf is a 30-item self-report measure designed to assess the principal manifestations of fatigue, yielding a total fatigue score [6]. Items are rated on a 5-point scale indicating how true each statement was for the respondent during the previous week (0 = not at all; 4 = extremely). MFSI-sf scores above 0.85 are considered to be significant fatigue [7]. The CES-D is a frequently used 20-item self-report scale that has been shown to be reliable and valid for assessing depressive symptoms [8]. CES-D scores above 16 are considered depressed mood. The CES-D primarily taps cognitive/affective aspects of depression and has been shown to be useful in chronically ill groups, including obstructive sleep apnea patients.

Blood sampling and assays

Blood samples were collected in EDTA at approximately 6:30 A.M. following the morning after sleep monitoring but before the subject was ambulatory. Samples were collected from an indwelling catheter that had been placed the night before, spun in a refrigerated centrifuge, and the plasma immediately frozen at -80°C until assay. IL-6 and soluble sTNF-RI (p55) were determined by commercial ELISA (R&D Systems, Minneapolis, MN) using samples that had not been previously freeze-thawed. Intra-assay and inter-assay coefficients of variation were <10%. Sensitivity values were <0.72 pg/ml and <0.61 pg/ml for IL-6, and sTNF-RI, respectively.

Statistical analysis

Hierarchical linear regression analysis was performed using MFSI-sf total score as the dependent variable, with step 1 forced entry of age, gender, and BMI; step 2 forced entry of blood pressure; step 3 forced entry of OSA severity variables AHI and average SaO₂; step 4 forced entry of CES-D; and step 5 forced entry of IL-6 and sTNF-RI levels. Data were analyzed using SPSS 15.0 software (Chicago, IL, 2006). Statistical significance was set at $p < 0.05$.

Results

Sample characteristics with means, standard deviations, and ranges are presented in Table 1. The mean MFSI-sf total score was 10.1, with a range of -15.0 to 66.1. Twenty-four (42.8%) of our OSA participants reported significant fatigue (i.e., scored above 0.85). The mean CES-D score was 13.4, with a range of 0 to 35. Eighteen (32.1%) of our OSA participants reported depression (i.e., scores above the 17).

Table 2 presents the results of the multiple linear regression analysis. Throughout the five steps of the analysis, BMI was a consistent significant predictor of fatigue (p 's < 0.03). Neither age, gender, blood pressure, nor the apnea severity variables were significant predictors of fatigue. The addition of CES-D to the model in step 4 accounted for the single largest amount of variance, accounting for an R^2 increase of .200 ($p < 0.01$). In step 5 of the regression, sTNF-RI levels ($p < 0.05$) but not IL-6 levels ($p = 0.39$) were a significant predictor of fatigue (change in $R^2 = 0.071$), accounting for an additional 7% of the variance in fatigue levels. The final model, consisting of significant predictors of BMI, CES-D, and sTNF-RI, and controlling for age, gender, blood pressure, apnea severity, and IL-6 levels, accounted for 57.1% of the variance in fatigue ($F = 4.37$ $p = 0.003$).

Discussion

Within a group of OSA patients reporting a broad range of fatigue, including approximately 42% self-reporting a significant amount of fatigue, we demonstrated that in addition to depressed mood and body mass, and the inflammatory biomarker sTNF-RI (but not IL-6) is associated with fatigue. The findings implicate that inflammatory processes may be associated with fatigue even after controlling for demographic and psychological factors that have been previously shown to influence fatigue levels in OSA. The association of fatigue with increased body mass and depressed mood is consistent with a recent review by Vgontzas et al. [9], which showed that in sleep disorders the primary determinants of sleepiness and fatigue are depression and obesity. Also consistent with prior observations is the finding that the severity of fatigue in OSA is not associated with the severity of sleep apnea [2,9]. A limitation of this short communication is the absence of a non-OSA control group. Being limited to OSA patients, the findings need to be examined in other populations to determine potential generalizability, or lack thereof.

Numerous studies demonstrate involvement of the TNF- α system in sleep-wake regulation. sTNF-RI is elevated following sleep deprivation [10]. Being released from activated immunologically competent cells, sTNF-RI indicates activated inflammatory processes [11]. The current findings suggest that sleep-related components of the inflammation observed in OSA [5] are associated with widely reported fatigue in OSA.

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References

1. Reimer MA, Flemons WW. Quality of life in sleep disorders. *Sleep Med Rev* 2003;7(4):335–349. [PubMed: 14505600]
2. Bardwell WA, Moore P, Ancoli-Israel S, Dimsdale JE. Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity? *Am J Psychiatry* 2003;160(2):350–355. [PubMed: 12562583]
3. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med* 2002;64(4):604–611. [PubMed: 12140350]
4. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist* 2007;12(Suppl 1):4–10. [PubMed: 17573451]
5. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 1997;82(5):1313–1316. [PubMed: 9141509]
6. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *Journal of Pain and Symptom Management* 2004;27(1):14–23. [PubMed: 14711465]
7. Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract* 1998;6(3):143–152. [PubMed: 9652245]
8. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.
9. Vgontzas AN, Bixler EO, Chrousos GP. Obesity-related sleepiness and fatigue: the role of the stress system and cytokines. *Ann NY Acad Sci* 2006;1083:329–344. [PubMed: 17148748]
10. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 2001;107(1):165–170. [PubMed: 11150007]
11. Tracey KJ. The inflammatory reflex. *Nature* 2002;420(6917):853–859. [PubMed: 12490958]

Table 1

Sample characteristics

Variables	Mean ($\pm$ SD)	Range
Age (years)	49.2 (11.1)	29-65
Systolic blood pressure (mmHg)	132.8 (15)	102-163
Diastolic blood pressure (mmHg)	79.8 (11)	56-106
Body mass index (kg/m ²)	31.5 (7.3)	23.1-51.3
Apnea hypopnea index	61.8 (29.6)	16.2-135.9
Mean oxygen saturation (SpO ₂) (%)	94.3 (4.6)	79.6-97.4
Multidimensional Fatigue Symptom inventory - short form	10.1 (17.4)	-15.0-66.1
Center for Epidemiologic Studies Depression Scale	13.4 (8.9)	0-35
IL-6 (pg/ml)	3.26 (2.3)	0.21-9.4
sTNF-RI (pg/ml)	871 (205.6)	503.5-1356.5

Table 2
Multiple regression predictors of fatigue^a in OSA

Additional variables in each regression block	Significant individual predictor variables with standardized β coefficient and p value	Model R^2 ; ΔR^2 ; p value
1. Age, gender	BMI (0.473, 0.005)	0.217; -; 0.008
2. Age, gender, BP	BMI (0.476, 0.008)	0.234; 0.017; 0.024
3. Age, gender, BP, AHI, SpO ₂	BMI (0.535, 0.025)	0.275; 0.041; .0070
4. Age, gender, BP, AHI, SpO ₂	BMI (0.501, 0.016); CES-D (0.517, 0.005)	0.475; 0.200; 0.005
5. Age, gender, BP, AHI, SpO ₂ , IL-6	BMI (0.488, 0.014); CES-D (0.508, 0.004); sTNF-RI (0.365, 0.033)	0.571; 0.071; 0.003

BP blood pressure, BMI body mass index, AHI apnea hypopnea index, SpO₂ mean oxygen saturation, CES-D Center for Epidemiologic Studies Depression Scale

^aMultidimensional Fatigue Symptom Inventory-short form