





Daytime sleepiness predicts inflammation and ambulatory blood pressure in sleep apnoea

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ABSTRACT

Introduction: Sleepiness in obstructive sleep apnoea is associated with cardiovascular risk; however, the biological mechanisms are not known. This study explored whether those with subjective sleepiness have increased plasma tumour necrosis factor-related protein 1 (C1qTNF1), a novel adipose-derived hormone (adipokine), and 24-h ambulatory blood pressure (ABP) compared to those without sleepiness in newly diagnosed, treatment-naïve participants with obstructive sleep apnoea.

Methods: Overall, 94 participants were included in the analysis. Participants completed the Epworth Sleepiness Scale (ESS), 24-h ABP was monitored, and plasma C1qTNF1 was measured. Sleepy participants were defined as ESS \geq 10 and nonsleepy as ESS $<$ 10. Multiple linear regression was used to explore differences in C1qTNF1, and 24-h mean arterial pressure (MAP) between sleepy and nonsleepy participants, adjusting for age, sex, body mass index, apnoea-hypopnoea index, and smoking status.

Results: C1qTNF1 was significantly higher in sleepy participants (n=57) compared to nonsleepy participants (n=37) (β =0.41 NPX, 95% CI 0.02, 0.80; p=0.04). The 24-h MAP was significantly higher in sleepy participants compared to nonsleepy participants (β =4.06 mmHg, 95% CI 0.36, 7.77; p=0.03).

Conclusions: Our findings show that sleepiness is associated with inflammation and higher 24-h MAP in sleep apnoea.



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Excessive sleepiness experienced by treatment-naïve patients with obstructive sleep apnoea is associated with inflammation, higher daily systolic ambulatory blood pressure and higher 24 h mean arterial pressure <https://bit.ly/3goeqGD>

Cite this article as: Pak VM, Butts B, Hertzberg V, *et al.* Daytime sleepiness predicts inflammation and ambulatory blood pressure in sleep apnoea. *ERJ Open Res* 2020; 6: 00310-2019 [<https://doi.org/10.1183/23120541.00310-2019>].



Introduction

Obstructive sleep apnoea (OSA) is a leading public health problem with an estimated prevalence rate of 34% in men and 17% in women in the United States [1]. Approximately 16–23% of those with OSA experience excessive daytime sleepiness (EDS) [2]. EDS is associated with a higher risk of cardiovascular disease (CVD), stroke and total as well as cardiovascular-specific mortality [3–7], both in those with sleep apnoea and the general population. A greater understanding of the biological basis of sleepiness symptoms in OSA and their relationship to cardiovascular risk is essential for developing interventions to reduce or minimise sleepiness symptoms and improve cardiovascular outcomes.

It is possible that the increased risk of sleepiness in OSA may be attributed to increased oxidative stress and inflammation caused by frequent and cyclic reductions in oxygen and rapid reoxygenation during sleep (*i.e.* cyclical intermittent hypoxia) [8]. In addition to hypoxia, excessive sleepiness in OSA is also likely to be caused by increased sleep fragmentation due to recurrent arousal [9, 10] and poor quality of sleep, as demonstrated by longer sleep duration and increased time spent in N1 (NREM1) as compared to slow-wave sleep [11, 12]. We have previously explored genetic and metabolomic differences between sleepy and nonsleepy subjects [13, 14], suggesting that inflammation and oxidative stress are possible pathways for the observed increased risk of CVD. Growing evidence supports OSA as an independent risk factor for CVD, including hypertension, stroke, heart failure, and atrial fibrillation [15, 16]. The process of intermittent hypoxia itself leads to increased blood pressure (BP), as sympathetic tone is activated in response to upper airway collapse during sleep in order to increase intrathoracic pressure and respiratory effort [17, 18]. The increase in sympathetic tone and BP becomes consistent during both sleep and waking periods [17]. Additionally, hypoxia-induced reactive oxygen species triggers upregulation of transcription factor nuclear factor (NF)- κ B, leading to the production of inflammatory biomarkers, such as intercellular adhesion molecule (ICAM)-1, tumour necrosis factor (TNF)- α , and interleukin (IL)-6, which play a role in the atherosclerotic disease process [8, 19]. Although several studies have explored sleepiness and 24 h ambulatory blood pressure [20–23], no previous study has explored inflammatory biomarker levels, sleepiness, and 24-h ambulatory BP (ABP) in those with newly diagnosed untreated sleep apnoea.

Complement C1q TNF-related protein 1 (C1qTNF1) is a novel adipose-derived hormone (adipokine) that is involved in inflammation and implicated in the pathogenesis of atherosclerosis and coronary artery disease [24–26]. This novel hormone is further pertinent as C1q remains a vital component of the classical complement pathway, which plays a main role in the clearance of foreign particles and is also involved in several other immunological processes such as the maintenance of immune tolerance, phagocytosis of bacteria, neutralisation of retroviruses, cell adhesion, and the modulation of cells [27, 28]. C1qTNF1 and TNF are positively correlated [29–31]. In addition, C1qTNF1 is increased in those with hypertension compared to healthy controls [32, 33]. The purpose of this study is to explore the associations of C1qTNF1, a marker of inflammation, 24-h BP, and sleepiness in subjects with sleep apnoea. We hypothesised that mechanisms of sleepiness and CVD share common molecular pathways, thus subjects exhibiting sleepiness will have higher levels of inflammation and BP than subjects with sleep apnoea without sleepiness.

Materials and methods

Study subjects and sleep apnoea diagnosis

This was an exploratory study consisting of a sample of 94 participants from the Emory Mechanisms of Sleepiness Symptoms Study with available data conducted in 2017. All participants underwent an overnight sleep study at the laboratory or at home for the diagnosis of sleep apnoea, and subjects with an apnoea–hypopnoea index (AHI) ≥ 5 were recruited from the Emory Sleep Center. Participants were excluded from the study if they were under 22 years of age, night-shift workers, had presence of chronic obstructive pulmonary disease, liver cirrhosis, thyroid dysfunction, rheumatoid arthritis, chronic renal failure and/or psychiatric disorders, or a sleep disorder in addition to OSA based on polysomnography, such as restless legs syndrome or periodic limb movement disorder.

At home, sleep apnoea testing was conducted with the Embla MPR device. Oxyhaemoglobin saturation by pulse oximetry, thoracic and abdominal respiratory effort, nasal airflow by nasal cannula, and body position were monitored. In-laboratory recordings included electroencephalography, electrooculogram, ECG, chin and limb electromyogram, chest and abdominal piezo belts, finger oximeter, and nasal pressure transducers.

The American Academy of Sleep Medicine acceptable scoring method was used to score the studies [34]. Trained sleep technicians scored polysomnograms. An apnoea was scored when there was >10 s of airflow cessation, and a hypopnoea was defined by the presence of 4% desaturation during sleep associated with a reduction in nasal cannula or effort for >10 seconds. Intraindividual agreement between home and in-lab sleep study is high [35]. Fasting morning blood plasma samples were collected after the sleep study

confirmed a diagnosis of sleep apnoea. The protocol was approved by the Emory Institutional Review Board and all patients provided informed consent.

24-h ambulatory blood pressure monitoring

All participating patients underwent 24-h ABP monitoring (Spacelabs, Medical Inc., Redmon, WA, USA) after being newly diagnosed with sleep apnoea and not yet treated on continuous positive airway pressure. A trained coordinator fitted an appropriately sized cuff on the patient's nondominant arm, which was worn for the subsequent 24 h during normal daily activities. The monitors were programmed to record BP every 20 min during the daytime (07:00–23:00 h) and every 30 min during the night-time period (23:00–07:00 h). Mean 24 h MAP was the primary cardiovascular outcome of interest. Supplemental analyses on daytime, night-time, 24-h systolic BP, and 24-h diastolic BP were also explored for the analysis.

Plasma protein profiling using Olink multiplex panel

C1qTNF1 was explored as a *post hoc* outcome exploratory measure and quantified using Olink multiplex proximity extension assay (PEA) panels (Olink Proteomics, Uppsala, Sweden) according to the manufacturer's instructions as described previously [36]. The data are presented as normalised protein expression (NPX) values, Olink Proteomics' arbitrary unit on log₂ scale. In this study, the Olink Cardiometabolic panel was used to measure the C1qTNF1 protein in the plasma samples. The basis of PEA is a dual-recognition immunoassay, where two matched antibodies labelled with unique DNA oligonucleotides simultaneously bind to a target protein in solution. This brings the two antibodies into proximity, allowing their DNA oligonucleotides to hybridise, serving as a template for a DNA polymerase-dependent extension step. This creates a double-stranded DNA "barcode" that is unique for the specific antigen and is quantitatively proportional to the initial concentration of target protein. The hybridisation and extension are immediately followed by PCR amplification, and the amplicon is then finally quantified by microfluidic quantitative PCR using Fluidigm BioMark HD system (Fluidigm Corporation, South San Francisco, CA, USA).

Sleepiness measurement

The Epworth Sleepiness Scale (ESS), a standardised self-report instrument that assesses tendency to doze [37], was used to measure sleepiness. Participants were asked to rate their chance of dozing during eight common situations. The responses are based on a Likert-type scale ranging from 0 to 3, with 0 indicating no chance of dozing and 3 indicating a high chance of dozing. The sum of these responses determines the total ESS score, with higher scores indicating greater sleepiness [37]. Subjects were categorised as sleepy if they had an ESS score ≥ 10 and nonsleepy if they had an ESS score < 10 based on previous studies [38, 39].

Statistical analysis

Patient demographics, clinical characteristics and biomarker values are expressed as mean \pm SD. Categorical variables are described as frequencies and percentages. Univariate analyses were first performed to compare differences between patients with and without sleepiness, with a two-sample t-test or Wilcoxon rank-sum test used for continuous variables, and a Chi-squared or Fisher's exact test used for categorical variables. We applied multiple linear regression in which each dependent variable (24-h MAP, average

TABLE 1 Demographics

Characteristic	Total n=94	No EDS n=37	EDS n=57	p-value
Age years	50.5 \pm 12.8	51.5 \pm 13.8	49.8 \pm 12.2	0.52
Sex male	47 (52.8%)	20 (54.1%)	27 (51.9%)	0.84
Body mass index kg·m ⁻²	35.9 \pm 9.4	35.2 \pm 6.9	36.3 \pm 10.7	0.54
Apnoea-hypopnoea index	32.0 \pm 26.1	27.9 \pm 21.7	34.6 \pm 28.5	0.20
Current smoker	13 (13.8%)	4 (10.8%)	9 (15.8%)	0.55
Epworth Sleepiness Scale (0–24)	11.0 \pm 5.3	5.4 \pm 2.3	14.6 \pm 3.2	<0.01
Overnight	33 (35.1%)	11 (29.7%)	22 (38.6%)	0.51
Home	61 (64.9%)	26 (70.3%)	35 (61.4%)	0.51

Data are presented as mean \pm SD; categorical variables are presented as n (%). EDS: excessive daytime sleepiness. A two-sample t-test or Wilcoxon rank-sum test was used for continuous variables, and a Chi-squared or Fisher's exact test was used for categorical variables. Some reported characteristics are missing values which were excluded from the total summary data.

daytime systolic BP, average daytime diastolic BP, average night-time systolic BP, average night-time diastolic BP, and the biomarker value (C1qTNF1)) was regressed separately against the binary sleepiness factor, adjusting for age, sex, BMI, AHI, and smoking status. Version 3.4.4 of R for Windows (R Foundation for Statistical Computing, Vienna, Austria) was used for the analysis. Significance was set at a two-tailed p-value of 0.05.

Results

Summary statistics of patient demographics are presented in table 1 and characteristics of study population variables specific to the cardiovascular outcomes, comorbidities, and C1qTNF1 are in table 2. The mean \pm SD age was 49.8 \pm 12.2 in 57 sleepy subjects and 51.5 \pm 13.8 in 37 nonsleepy subjects. There were 47 (52.8%) males in the cohort. There were 94 subjects with available biomarker and ABP data. Overall, 13 were evaluated in the sleep laboratory and 81 were evaluated on home sleep study. There were no significant differences between overnight sleep study and home study between sleepy and nonsleepy subjects, as expected. There were also no differences in dipping status between sleepy and nonsleepy subjects. Overall, the mean of the ESS scores was 11.0 \pm 5.3 with 60.6% of the subjects (n=57) categorised as having EDS. Other demographics, including BMI, AHI, smoking status, and history of stroke, myocardial infarction, hypertension, and heart failure were all comparable between the two groups (see table 1). Our primary analysis was focused on whether subjects with sleepiness had higher MAP 24 h measures adjusting for the aforementioned covariates. Subjects with sleepiness had higher adjusted MAP 24 h (β 4.06 mmHg, 95% CI 0.36, 7.77; p=0.03), and higher univariate MAP 24 h (β 4.61 mmHg, 95% CI 0.741, 8.48; p=0.02). Compared to those who were nonsleepy (n=37), those who were sleepy (n=57) had significantly higher adjusted C1qTNF levels (β =0.41 NPX, 95% CI 0.02, 0.80; p=0.04) (figure 1).

See table 3 for adjusted regression models and supplemental table 1 for unadjusted models. We also re-ran the analyses without a major outlier to ensure that the observed effect of sleepiness on C1qTNF1 levels on 24 h MAP was not driven by outliers, and the main results remained stable and did not change significantly.

Discussion

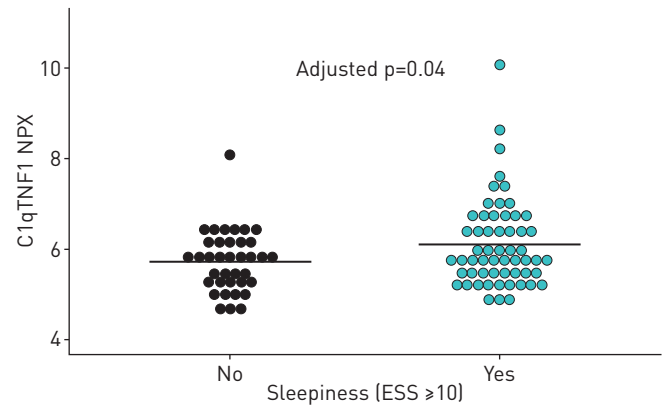
We have identified associations worth exploring in larger studies between sleepiness, C1qTNF1 and 24 h MAP in newly diagnosed sleep apnoeic subjects. Compared to those who were nonsleepy, those with

TABLE 2 Characteristics of the study population (cardiovascular outcomes, comorbidities, and C1qTNF1)

Characteristic	Total n=94	No EDS n=37	EDS n=57	p-value
24-h ambulatory BP mmHg[#]				
MAP 24 h	91.3 \pm 8.5	88.8 \pm 8.1	92.8 \pm 8.4	0.03
SBP wake (average daily systolic)	128.5 \pm 14.5	125.4 \pm 14.6	130.3 \pm 14.2	0.13
DBP wake (average daily diastolic)	77.8 \pm 7.9	76.4 \pm 7.3	78.7 \pm 8.2	0.16
MAP wake	93.9 \pm 8.5	91.8 \pm 8.1	95.3 \pm 8.5	0.06
SBP sleep (average nightly systolic)	120.0 \pm 17.3	116.0 \pm 17.7	122.4 \pm 16.8	0.11
DBP sleep (average nightly diastolic)	70.1 \pm 9.4	67.3 \pm 9.1	71.7 \pm 9.2	0.04
MAP sleep	86.1 \pm 10.1	83.0 \pm 10.5	88.0 \pm 9.5	0.03
SBP 24 h	125.6 \pm 14.8	122.5 \pm 14.8	127.5 \pm 14.5	0.13
DBP 24 h	75.2 \pm 7.8	73.4 \pm 7.0	76.4 \pm 8.1	0.07
Dipper systolic	6.4 \pm 7.7	6.7 \pm 8.3	6.3 \pm 7.4	0.83
Dipper diastolic	9.6 \pm 8.1	10.7 \pm 8.8	8.9 \pm 7.8	0.34
Dipper MAP	8.1 \pm 7.4	9.2 \pm 8.1	7.5 \pm 6.9	0.32
Stroke (yes)	5 (5.3%)	1 (2.7%)	4 (7.0%)	0.65
Myocardial infarction (yes)	2 (2.1%)	1 (2.7%)	1 (1.8%)	1.00
Hypertension (yes)	40 (43.5%)	16 (43.2%)	24 (43.6%)	1.00
Heart failure (yes)	7 (7.4%)	2 (5.4%)	5 (8.8%)	0.70
C1qTNF1 NPX	6.0 \pm 0.9	5.7 \pm 0.7	6.1 \pm 1.0	0.02

Data are presented as mean \pm SD; categorical variables are presented as n (%). C1qTNF1: tumour necrosis factor-related protein 1; EDS: excessive daytime sleepiness; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; NPX: normalised protein expression. [#]: there were seven individuals missing 24-h BP data. Some reported characteristics are missing values which were excluded from the total summary data. A two-sample t-test or Wilcoxon rank-sum test was used for continuous variables, and a Chi-squared or Fisher's exact test was used for categorical variables.

FIGURE 1 Differences in tumour necrosis factor-related protein 1 (C1qTNF1) concentration between subjects with sleepiness *versus* those without. ESS: Epworth Sleepiness Score; NPX: normalised protein expression.



sleepiness had significantly higher C1qTNF1 levels and 24-h MAP BP. Limitations of our study include possible measurement inconsistency in the ESS; however, as subjects are asked to recall their propensity to sleep over the past few weeks rather than just at the time of testing, the ESS is built to address this bias. Results are expected to be generalisable to newly diagnosed sleep apnoeic subjects with moderate sleep apnoea. Although relationships between 24-h MAP and daytime sleepiness *via* the ESS have been noted [23, 40], we are the first to explore C1qTNF1 which is linked to low-grade inflammation to explain the relationship. Our results are congruent with a previous study examining the relationship between subjective sleepiness according to ESS and hypertension in OSA patients; OSA patients with excessive sleepiness had increased odds of hypertension by 23% as compared to OSA patients without EDS [41]. Similarly, a study investigating objective daytime sleepiness as assessed by the multiple sleep latency test and hypertension in OSA patients, found a significant positive association between sleepiness and hypertension [42].

C1qTNF1 is a complement the C1q/TNF-related protein family adipokine that is expressed mainly in adipose stromal vascular cells. C1qTNF1 has been linked to low-grade chronic inflammation in adipose tissue [43], and has been shown to upregulate inflammatory genes, such as *IL6* and *ICAM1*, in vascular smooth muscle [44], suggesting that C1qTNF1 may be a pro-atherogenic biomarker. Under conditions of disturbed flow, C1qTNF1 promotes endothelium-leukocyte interactions and inflammatory responses in vascular cells [25], which increases endothelial permeability and further contributes to atherogenesis. C1qTNF1 is increased in patients with coronary artery disease (CAD), and has been found in the serum, atherosclerotic plaques, and peripheral blood mononucleocytes of people with CAD [24]. A longitudinal study of 539 white patients referred to elective coronary angiography for the evaluation of established or suspected stable CAD who were followed for major adverse cardiovascular events (MACE). This was

TABLE 3 Results of the multiple regression analyses of C1qTNF1 and ambulatory blood pressure measures as a function of sleepiness (yes *versus* no) and adjusted covariates

Dependent variables	Estimate	SE	p-value
C1qTNF1 NPX	0.41	0.20	0.04
SBP wake mmHg	6.28	3.13	0.05
DBP wake mmHg	2.37	1.81	0.19
SBP sleep mmHg	5.96	3.81	0.12
DBP sleep mmHg	3.44	1.91	0.08
SBP 24 h mmHg	6.11	3.20	0.06
DBP 24 h mmHg	2.81	1.68	0.10
Dipper systolic mmHg	0.19	1.77	0.92
Dipper diastolic mmHg	-1.02	1.85	0.59
Dipper MAP mmHg	-0.79	1.70	0.64
MAP 24 h mmHg	4.06	1.86	0.03
MAP wake mmHg	3.78	1.93	0.05
MAP sleep mmHg	4.56	2.17	0.04

C1qTNF1: tumour necrosis factor-related protein 1; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; NPX: normalised protein expression.

defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, for an average of 5.9 years found that increased serum C1qTNF1 was associated with an increased risk for future MACE [45].

Taken together, the higher levels of the inflammatory protein C1qTNF1 in people with OSA and EDS may indicate not just a higher inflammatory state but also increased risk of CVD and adverse outcomes. C1qTNF1 has also been shown to positively regulate BP *via* increased vasoconstriction and stimulation of aldosterone production [33], resulting in both increased peripheral vascular resistance and total blood volume. C1qTNF1 acts as a long-term regulator of BP and is a key effector of glucocorticoid-mediated BP regulation, as glucocorticoid administration in murine models increases C1qTNF1 production [46].

Considering the link between sleep-disordered breathing and cortisol dysregulation [47, 48], it is possible that higher levels of C1qTNF1 may link the proinflammatory state related to cyclical intermittent hypoxia to the higher BP in people with OSA and EDS in this hypothesis-generating study and requires further exploration. The exploration of other inflammatory biomarkers and their associations with sleepiness and cardiovascular outcomes will be important for future studies aimed at targeted treatments. Further work examining the role of inflammatory proteins in BP regulation in those with OSA and EDS is needed.

Conflict of interest: None declared.

Support statement: This work was supported by an R00NR01465-03 NIH Pathway to Independence award (V.M. Pak). Funding information for this article has been deposited with the Crossref Funder Registry.

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