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J Weingarten

Lars Bellner
New York Medical College

S Peterson

M Zaw

P Chadha

See next page for additional authors

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Original Article

Jeremy A. Weingarten[1] / Lars Bellner[2] / Stephen J. Peterson[3] / Moe Zaw[3] / Puja Chadha[3] / Shailendra P. Singh[2] / Nader G. Abraham[2,4,5]

The association of NOV/CCN3 with obstructive sleep apnea (OSA): preliminary evidence of a novel biomarker in OSA

[1] Weill Cornell Medicine, NewYork-Presbyterian Brooklyn Methodist Hospital, Department of Medicine, Brooklyn, NY, USA; Phone: 718-780-5835; Fax: 718-780-5836, E-mail: jaw9031@nyp.org
[2] New York Medical College, Department of Pharmacology, Valhalla, NY, USA, E-mail: nader_abraham@nymc.edu
[3] Weill Cornell Medicine, NewYork-Presbyterian Brooklyn Methodist Hospital, Department of Medicine, Brooklyn, NY, USA
[4] New York Medical College, Department of Medicine, NY 10595, USA, Phone: 914-594-3121; Fax: 914-347-4956, E-mail: nader_abraham@nymc.edu
[5] The Rockefeller University, New York, NY, USA, E-mail: nader_abraham@nymc.edu

Abstract:
Obstructive sleep apnea (OSA) has a strong association with cardiovascular and metabolic abnormalities, although the mechanism driving this association is not well established. NOV/CCN3, a multifunctional extracellular matrix protein, may play a mechanistic and/or prognostic role in these associations. We hypothesized that patients with OSA, which primarily affects obese individuals, will have increased levels of NOV, and that NOV can serve as a biomarker in patients to predict OSA as well as metabolic and cardiac risk. Ten morbidly obese and 10 healthy lean subjects underwent overnight polysomnography (PSG) and clinical evaluation. Blood samples were analyzed for NOV levels, adiponectin and IL-6. OSA was found in nine obese subjects and three lean subjects. NOV levels were significantly higher in the OSA vs. no OSA group (2.1 $\pm$ 0.9 vs. 1.3 $\pm$ 0.8, $p < 0.03$). NOV levels were significantly higher in the obese vs. lean group (2.2 $\pm$ 0.3 vs. 1.4 $\pm$ 0.2-fold change, $p < 0.03$). Among lean subjects, NOV levels were significantly higher in the OSA vs. no OSA group (2.1 $\pm$ 0.9 vs. 1.0 $\pm$ 0.4, $p < 0.05$). NOV and AHI were positively correlated ($\rho = 0.49$, $p = 0.033$). IL-6 and adiponectin differences in obese vs. lean and OSA vs. no OSA were consistent with an inflammatory phenotype in obese subjects and OSA subjects. NOV is a novel biomarker of the presence and severity of OSA and a potential marker of future cardiovascular and metabolic disease in OSA patients.

Keywords: adiponectin, IL-6, NOV/CCN3, obesity, obstructive sleep apnea
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Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive obstructive respiratory events during sleep resulting in nocturnal arousals, sympathetic stimulation and intermittent hypoxia. In the US, this disorder is extremely prevalent and likely underdiagnosed. Estimates suggest that up to 17% of older men and 9% of older women have moderate to severe OSA, which is defined as obstructive respiratory events occurring in excess of 15 times per hour of sleep [1]. Obesity is a strong risk factor for OSA [2], [3] and both obesity and OSA have been shown to be involved in inflammatory pathways resulting in cardiovascular disease [4], [5]. Clinically, OSA is strongly associated with various cardiovascular comorbidities including hypertension, coronary artery disease, congestive heart failure, stroke, and all-cause mortality [6], [7], [8], [9]. OSA is also strongly associated with insulin resistance in clinical populations [10], [11], which increases cardiovascular risk independent of the effects of OSA itself.

The CCN family of proteins are multifunctional matricellular proteins that are dynamically expressed and function via interaction with cell adhesion receptors resulting in regulation of various processes including cell adhesion, migration, proliferation and survival in a cell-type specific manner [12]. NOV/CCN3 (nephroblastoma overexpressed), a founder of the CCN family, is thought to play a role in inflammation; NOV has been

Jeremy A. Weingarten, Nader G. Abraham are the corresponding authors.

shown to be a regulator of and be regulated by various cytokines and chemokines, including IL-6, TNFα, TGFβ, IL1β, MCP1 and GROα [13], [14]. A recent study demonstrated that NOV is independently associated with body mass index (BMI) and fat mass, decreases with weight loss, and is present in adipose tissue in both humans and mice [15]. In a follow-up study, the same group demonstrated in NOV knockout mice that NOV-/- mice fed a high-fat diet had decreased weight and fat mass, improved glucose tolerance/insulin sensitivity and a marked decrease in the expression of pro-inflammatory cytokines from adipose tissue [16].

Given the strong association of obesity with OSA and the role both disorders play in cardiovascular disease, we sought to determine if NOV/CCN3 is differentially expressed in a population of subjects with OSA. We hypothesized that patients with OSA, which primarily affects obese individuals, will have increased levels of NOV, and that NOV can serve as a biomarker in patients to predict OSA as well as metabolic and cardiac risk.

Materials and methods

Study design and sample

Study subjects and controls were enrolled at NewYork-Presbyterian Brooklyn Methodist Hospital (NYPBMH) and laboratory analysis of blood samples were analyzed at New York Medical College (NYMC). Obese subjects were drawn from individuals presenting to the Center for Sleep Disorders at NYPBMH for evaluation of possible OSA. Lean subjects were drawn from lean (BMI $\leq$ 25 kg/m^2) faculty and staff of NYMBMH who were not at risk for OSA. Only adults (age > 18 years old) were recruited. All subjects provided informed consent. A total of 20 subjects were enrolled, 10 obese and 10 lean. IRB approval at the clinical site (NYPBMH) was obtained prior to enrollment.

All data was collected prospectively. Enrolled participants underwent clinical history and physical examination, phlebotomy for study sample, and clinical measurements including vital signs and PSG (sleep study).

Clinical parameters

All recruited patients had a complete history and physical examination. Patient demographics were collected including age, gender and race. Patients underwent measurement of systolic and diastolic blood pressure, height and weight for BMI determination, neck circumference, and waist and hip circumference for waist-hip ratio determination by standard methods. Patient were also queried and medication lists were evaluated to determine the presence of comorbid medical conditions (hypertension, diabetes, hyperlipidemia, coronary atherosclerosis, congestive heart failure, chronic obstructive pulmonary disease and asthma).

PSG

All patients underwent nocturnal PSG either by (1) conventional full-montage in-laboratory PSG or (2) home sleep testing; studies were performed in accordance with American Academy of Sleep Medicine (AASM) guidelines. Conventional full-montage in-laboratory PSG was performed using Compumedics (Abbotsford, Victoria, Australia) software: standard 10–20 electroencephalography (EEG), electrocardiography (ECG), electromyography (EMG) of the chin and anterior tibialis muscle, electrooculography (EOG), snore and pulse oximetry monitoring were utilized. Oral and nasal airflow were measured by pressure transducer and thermocouple. Respiratory effort was measured with respiratory impedance plethysmography bands at the chest and the abdomen including summation channel. Home sleep testing was performed using ResMed ApneaLink Air (San Diego, CA, USA). An apnea was defined as a reduction in peak thermal sensor excursion by ≥90% of baseline, in which there is continued or increased inspiratory effort throughout the entire period of absent airflow lasting at least 10 s. Desaturation and/or arousal were not required. A hypopnea was defined as an abnormal respiratory event lasting at least 10 s with at least a ≥30% reduction in the nasal pressure signal excursion (or alternate sensor) accompanied by a ≥4% oxyhemoglobin desaturation. The apnea-hypopnea index (AHI) is a measure of OSA severity and derived from the number of apneas and hypopneas per hour of sleep (in-lab determination) or per hour of recording time (home sleep testing).

Laboratory measurement

Venous blood was drawn from antecubital vein into a serum separator tube and a tube containing EDTA. Each SST sample was centrifuged at a force of 1600 *g* for 10 min after blood draw. The tubes were placed in an insulated container with dry ice until analysis.

Plasma NOV protein levels

Subjects frozen plasma was suspended in buffer (mmol/L: 10 phosphate buffer, 250 sucrose, 1.0 EDTA, 0.1 PMSF, and 0.1% v/v tergitol, pH 7.5). Immunoblotting for NOV and β-actin was performed as previously described [17]. NOV levels were based on densitometry fold-increase from control.

Measurement of adipokines

Serum/plasma levels of adiponectin [high molecular weight (HMW)] and interleukin 6 (IL-6) (both from R&D Systems, Inc., Minneapolis, MN, USA) were performed using ELISA assays following the protocols as specified by the manufacturer.

Statistical analysis

We summarized continuous variables using means and standard deviations and summarized categorical variables as frequencies and percentages. Continuous variables were compared with Student's t-test or Mann-Whitney/Wilcoxon paired test as appropriate. Categorical variables were compared with the χ^2-test for independence. AHI and NOV were compared with Spearman's rank-order correlation. All analyses were performed in R version 3.3.3.

Results

Baseline characteristics of participants are presented in Table 1. The differences in BMI comparing the lean vs. obese and no OSA vs. OSA groups were both highly significant ($p < 0.001$ and $p < 0.01$) as expected. In the lean group, sex distribution between men and women were equal, while in the obese group, only one (10%) man was present. There was a significant difference in race distribution between lean and obese groups ($p = 0.016$) with a majority of obese subjects self-perceived as black (80%); no difference was observed in race in the absence or presence of OSA. There were no significant differences in comorbidities (hypertension, diabetes, hyperlipidemia, asthma) between the lean/obese or no OSA/OSA groups. No subject in either group carried a diagnosis of coronary atherosclerosis, congestive heart failure, or chronic obstructive pulmonary disease. OSA was diagnosed in nine obese subjects and three lean subjects. AHI was higher in the obese vs. lean group (22.9 ± 20 vs. 8.4 ± 12.8 events/h).

Table 1: Baseline characteristics.

	Lean (n = 10)	Obese (n = 10)	No OSA (n = 8)	OSA (n = 11)
Age (years)	37.9 ± 10.3	38.3 ± 12.1	33.6 ± 5.1	38.7 ± 10.5
Sex				
Men	5 (50)	1 (10)	3 (50)	3 (50)
Women	5 (50)	9 (90)	5 (38)	8 (62)
Race[a]				
Black	2 (20)	8 (80)	2 (25)	7 (64)
White	4 (40)	2 (20)	3 (38)	3 (27)
Asian	4 (40)	0	3 (38)	1 (9)
BMI (kg/m^2)[b]	23 ± 3	54.2 ± 6.4	25.5 ± 10.9	47.3 ± 14.8
Comorbidities				
Hypertension	1 (10)	4 (40)	1 (13)	3 (27)
Diabetes	2 (20)	3 (30)	0 (0)	4 (36)
Hyperlipidemia	1 (10)	2 (20)	0 (0)	2 (18)

Asthma	0 (0)	3 (30)	0 (0)	3 (27)
Sleep parameters				
AHI	8.4 ± 12.8	22.9 ± 20	1.8 ± 1.0	25.1 ± 17.8
AHI (log)[b]	1.2 ± 1.4	2.7 ± 1.2	0.4 ± 0.6	3.0 ± 0.8
NOV/CCN3	1.4 ± 0.7	2.2 ± 0.9	1.3 ± 0.8	2.1 ± 0.9
NOV/CCN3 (log)[b]	0.2 ± 0.5	0.7 ± 0.4	0.1 ± 0.5	0.7 ± 0.4
IL-6[b]	1.2 ± 1.3	6.5 ± 1.8	1.9 ± 3.1	5.6 ± 2.4
Adiponectin	54.5 ± 70.8	11.3 ± 5.2	51.9 ± 77.3	21.4 ± 28.2
Adiponectin (log)[a]	3.4 ± 1.2	2.3 ± 0.4	3.2 ± 1.3	2.7 ± 0.8

[a]$p < 0.05$ in obese/lean.
[b]$p < 0.05$ in obese/lean and OSA/no OSA.
Continuous variables: mean ± SD.
Categorical variables: number (%).
p-Value determined by t-test and χ^2-test as appropriate.
BMI, body mass index; AHI, apnea hypopnea index.

NOV levels were significantly higher in the obese vs. lean group (2.2 ± 0.9 vs. 1.4 ± 0.7-fold change, $p < 0.03$; Figure 1A). NOV levels were also higher in the OSA vs. no OSA group (1.3 ± 0.8 vs. 2.1 ± 0.9, $p < 0.03$; Figure 1B). Among lean subjects, NOV levels were higher in the OSA vs. no OSA group (2.1 ± 0.9 vs. 1.0 ± 0.4, $p < 0.05$; Figure 2). Elevated NOV levels in the lean OSA subjects were primarily due to marked elevation in two out of three subjects (see blot in Figure 2). Comparison of obese subjects with and without OSA was not performed given that only one subject in the obese group did not have OSA. AHI levels were higher in the obese vs. lean group (22.9 ± 6.7 vs. 8.4 ± 4.1 events/h, $p < 0.03$). NOV and AHI were positively correlated ($\rho = 0.49$, $p < 0.04$; Figure 3). Inflammatory markers were different between the two groups suggesting increased inflammatory status in obese vs. lean and OSA vs. no OSA: IL-6 was increased in the obese vs. lean group (6.5 ± 1.8 vs. 1.2 ± 1.3 pg/mL, $p < 0.001$; Figure 4A) and OSA vs. no OSA (5.6 ± 2.4 vs. 1.9 ± 3.1, $p < 0.02$; Figure 4B) while adiponectin was decreased significantly in the obese vs. lean group (11.3 ± 1.6 vs. 54.5 ± 22.4 μg/mL, $p < 0.05$; Figure 5A) but did not reach statistical significance in the OSA vs. no OSA group (21.4 ± 28.2 vs. 51.9 ± 77.3, $p = 0.31$; Figure 5B). NOV was positively correlated with IL-6 ($\rho = 0.57$, $p < 0.02$). NOV was not correlated with adiponectin.

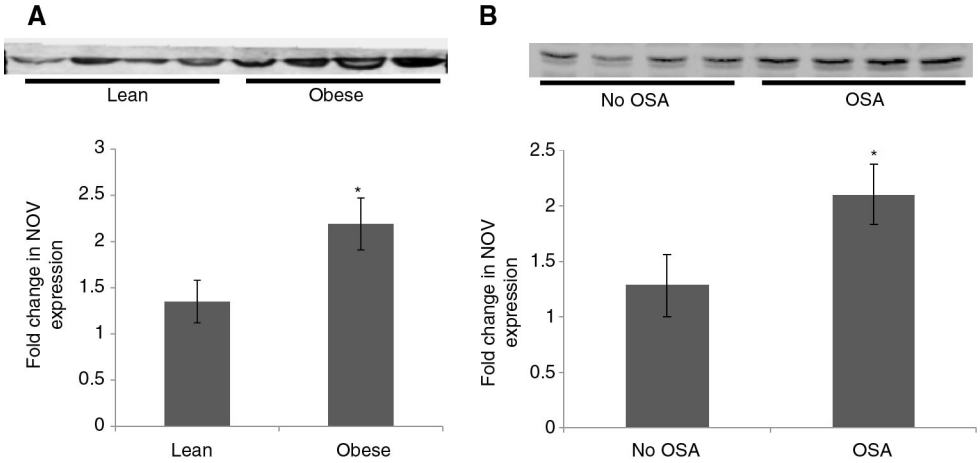

Figure 1: (A) Fold change in NOV expression in obese and lean subjects (n = 20, *$p < 0.03$ vs. lean). (B) Fold change in NOV expression in subjects with and without OSA (n = 19, *$p < 0.03$ vs. no OSA). Results are mean ± SE.

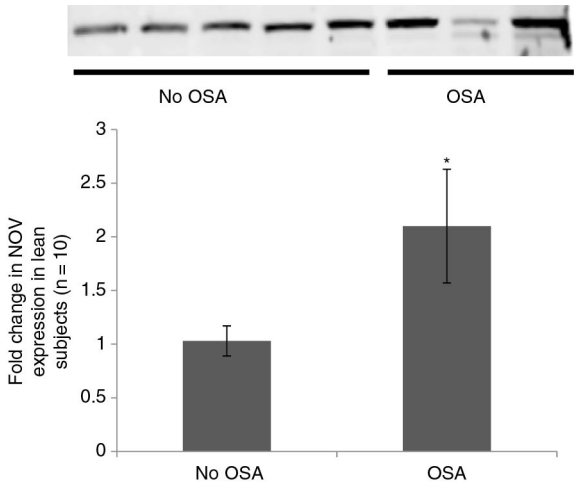

Figure 2: Fold change in NOV expression among lean subjects in OSA vs. no OSA (n = 10, *p < 0.05 vs. no OSA). Results are mean ± SE.

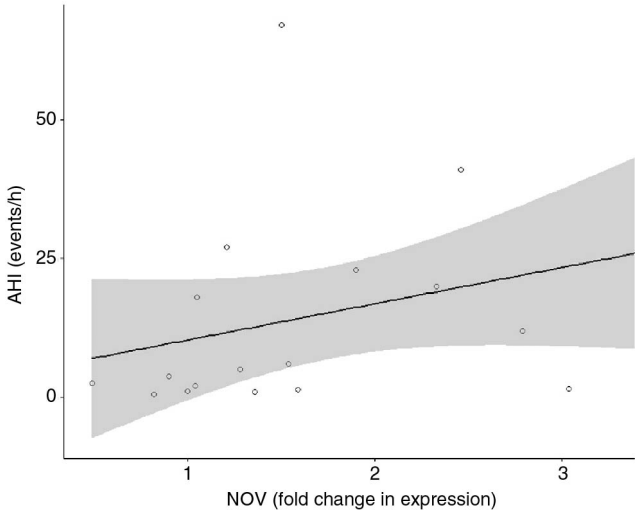

Figure 3: Spearman's correlation of NOV (fold change in expression) vs. AHI (events/h), ρ = 0.49, p = 0.033.

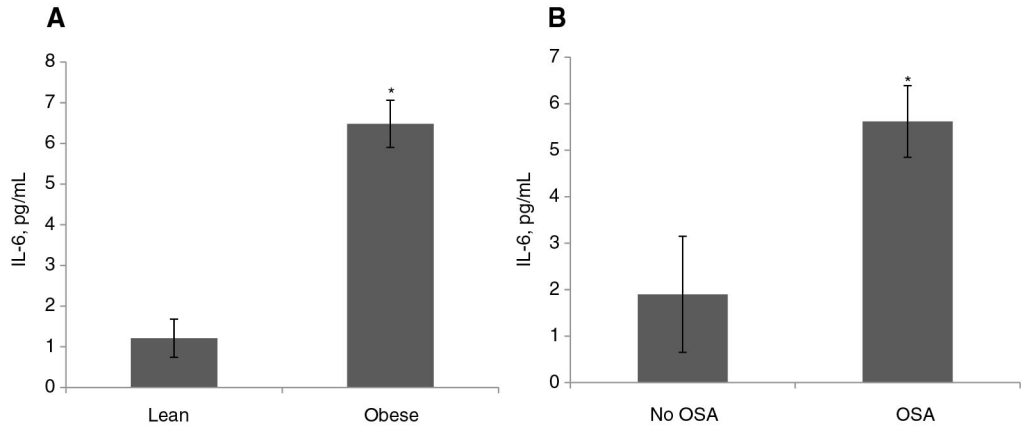

Figure 4: (A) Interleukin-6 (pg/mL) in obese and lean subjects (n = 17, *p < 0.001 vs. lean). (B) Interleukin-6 (pg/mL) in OSA vs. no OSA (n = 17, *p < 0.02 vs. no OSA). Results are mean ± SE.

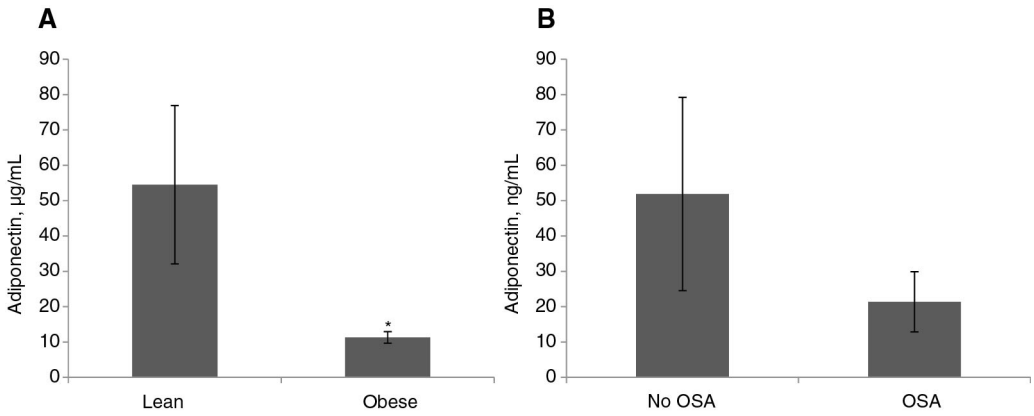

Figure 5: (A) Adiponectin (µg/mL) in obese and lean subjects (n = 20, *p < 0.05 vs. lean). (B) Adiponectin (µg/mL) in OSA vs. no OSA (n = 19, p = not significant). Results are mean ± SE.

Discussion

We have shown for the first time that NOV levels are associated with the presence of OSA; NOV levels are significantly higher in subjects with OSA. We have also shown that NOV levels and AHI, a measure of OSA severity, are positively correlated, suggesting that as OSA severity increases, NOV levels increase linearly. Furthermore, we have confirmed previous findings that NOV levels are increased in morbid obesity vs. lean. To account for potential confounding of the OSA/NOV relationship by obesity, we have also shown that among lean subjects, those with OSA have higher NOV levels than those without OSA. Similar analysis could not be performed in the obese subjects given the presence of only one subject without OSA in the obese group. The inflammatory mediators IL-6 (increased) and adiponectin (decreased) are variable in the obese vs. lean and the OSA/no OSA groups, suggesting that along with increases in NOV levels, subjects with more severe OSA are in an increased inflammatory state. Thus, NOV may be a marker of and/or a mediator in the inflammatory state in subjects with OSA and a potential biomarker of the severity of OSA and its prognosis. Of note, the variability of NOV in lean subjects with OSA (blot, Figure 2) suggests that while NOV is higher overall in subjects with OSA, more work needs to be done to see if NOV levels have a direct or indirect correlation with the severity of OSA, especially in light of the marked differences in phenotype and comorbidities of clinical populations.

NOV, a founder member of the CCN family of extracellular matrix proteins, has recently been shown to be associated with measures of inflammation which may have implications in clinical populations. In a large group of subjects with metabolic abnormalities, NOV was independently and positively associated with BMI, fat mass, and C-reactive protein; NOV decreased after weight loss from bariatric surgery [15]. In a mouse model of inflammatory renal disease, NOV-/- mice had lower levels of CCL2, VCAM-1, IL-6 and CD68 mRNA compared with wild type mice [14]. Finally, NOV was shown to have significant metabolic effects in an animal model: NOV-/- mice fed a high fat diet (HFD) compared with wild type mice fed HFD demonstrated lower weight, lower fat mass, higher proportion of small adipocytes, higher energy expenditure gene expression, improved glucose tolerance and energy expenditure, and a shift towards a less pro-inflammatory phenotype [16]. Higher NOV levels/induction of NOV results in increased adipose tissue deposition and enhanced cholesterol and plasma triglyceride formation in human cardio-metabolic patients [15]. Moreover, with increases in obesity, there is an increase in pericardial fat deposition, a major source of several inflammatory factors including NOV; this local increase of NOV in pericardial fat is thought to contribute to cardiomyopathy whereas a decrease in NOV improves vascular function and insulin resistance [18].

Despite the strong association of OSA with insulin resistance [10], [11] and cardiovascular morbidity and mortality [19] independent of obesity, the mechanism of these associations is not well established. Intermittent hypoxia (IH), a hallmark pathophysiologic process of OSA, has recently been shown to be associated with a pro-inflammatory phenotype of visceral adipose tissue (M1 polarization) [20]. IH upregulates pro-inflammatory cytokines in adipose tissue of lean rats, in cultured adipocytes, and in endothelial cells [21], thus potentially resulting in a combined effect of IH mediating the development of both adipocyte inflammation and endothelial cell dysregulation. Given that NOV is elevated in OSA and obesity, it may play a central role in the translation of environmental hypoxic conditions and inflammation, resulting in disorders of insulin resistance and endothelial dysfunction. If proven to be true, it could play a role as a biomarker of cardiovascular and metabolic morbidity in patients with OSA.

Increased NOV levels are associated with increased adipose tissue deposition. Conversely, decreased NOV levels result in attenuated obesity and an increase in thermogenic brown/beige-like cells [18]. Treating obesity with antioxidants such as epoxyeicosatrienoic acid (EET) results in a change of visceral fat phenotype to brown/beige-like cells that express adiponectin and have diminished expression of NOV, which ultimately ameliorates cardiomyopathy and hypertension [18]. EET is expressed in brown/beige-like cells contributing to their unique phenotype. In an experiment where an EET agonist, an inducer of antioxidants, was given, it was shown to inhibit adipocyte terminal differentiation, decrease cytokines, and increase the number of small cell adipocytes or brown/beige-like cells [22]. Brown/beige-like adipose cells express increased levels of EET and decreased levels of NOV when compared with white adipose tissue (WAT), and this may be due to EET's antioxidant effect which may then serve to decrease inflamed adipocytes that normally express higher NOV levels [18]. We hypothesize that although both WAT and brown/beige-like adipose cells are seen in the same adipose tissue, the brown/beige-like adipocytes have a different stem cell origin than WAT explaining the difference in their phenotype. Brown/beige-like cells have increased mitochondrial function and thermogenic genes such as UCP-1 leading to their thermogenic properties [23]. We propose this difference between WAT and brown/beige-like adipocyte cells is due to a difference in stem cell origin, and increasing brown/beige-like cells would be beneficial in the treatment of patients with obesity and sleep apnea. Further experiments are needed to determine if there is a distinct stem cell origin and if an autologous brown/beige-like cell transplant could possibly be used clinically in the treatment of obesity, potentially preventing OSA and/or the cardiovascular consequences of OSA.

Conclusion

We have demonstrated that NOV, a matricellular protein involved in various cardio-metabolic processes including glucose tolerance and fat deposition, is associated with OSA independent of obesity. Additionally, NOV and AHI are positively linearly related. We believe that these results indicate the possibility of the identification of a novel biomarker for the presence of OSA as well as a potential marker of cardiovascular and metabolic disease in patients with OSA. Further study with larger patient populations is needed.

Author Statement

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Conflict of interest: Authors state no conflict of interest.

Informed consent: All subjects provided informed consent.

Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies and was performed in accordance with the tenets of the Helsinki Declaration and the IRB approval was obtained prior to recruitment.

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