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ORIGINAL RESEARCH

SCUBE-1 Levels and Their Relationship with Endothelial Dysfunction in Obstructive Sleep Apnea Syndrome Patients

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Objective: Obstructive sleep apnea syndrome (OSAS) increases the risk of vascular dysfunction by causing hypoxemia due to recurrent obstructions in the upper airway. This can put pressure on the vasculature and impair endothelial function. SCUBE-1 gains importance in OSAS as a biomarker that may reflect this dysfunction. We focused in this study on the association between levels of SCUBE-1 and endothelial dysfunction in patients suffering from OSAS.

Methods: A study population of 75 individuals participated in the study. Participants were categorized as normal (n=18), mild OSAS (n=22), moderate OSAS (n=19) and severe OSAS (n=16) according to polysomnography findings. Evaluation parameters included SCUBE-1 levels, polysomnography measurements, flow-mediated dilatation (FMD), carotid intima-media thickness (CIMT), and comprehensive laboratory analyses.

Results: SCUBE-1 levels were significantly higher in the severe OSAS group (15.8 ± 4.2 ng/mL, $p<0.001$). SCUBE-1 showed a moderate negative correlation with FMD ($r = -0.248$, $p < 0.001$) and a significant negative correlation with CIMT ($r = -0.512$, $p < 0.001$). ROC analysis demonstrated good diagnostic accuracy (AUC: 0.871, 95% CI: 0.797–0.945) for SCUBE-1 in identifying severe OSAS.

Conclusion: OSAS severity correlates with the rise in SCUBE-1 levels, and this biomarker may serve as an important attribute in profiling endothelial dysfunction. SCUBE-1 can indeed be an effective biomarker to identify subtle changes in the vascular biology of OSAS patients and aid early interventions.

Keywords: obstructive sleep apnea syndrome, endothelial dysfunction, SCUBE-1 biomarker, cardiovascular risk, sleep-disordered breathing

Introduction

Obstructive sleep apnea syndrome (OSAS) is a prevalent disorder characterized by repeated upper airway blockages during sleep resulting in reduced oxygen saturation which, greatly affects the health status of individuals. This not only affects the quality of sleep but additionally places patients at risk of cardiovascular and metabolic diseases including but not limited to, hypertension, diabetes, coronary heart disease, and stroke. With the involvement of OSAS to these disorders it can be justified that this issue requires more global attention.[1–5]

These OSAS-related complications appear to contribute to endothelial dysfunction through mechanisms including oxidative stress, inflammation and injury to the vasculature. Increased odds of atherosclerosis will follow from this endothelial dysfunction as the responsiveness of blood vessels is deteriorated which may amplify the cardiovascular effects of OSAS. In this framework, it is suggested that SCUBE-1 biomarker has the potential to reflect endothelial dysfunction in OSAS patients and may be an indicator to detect early vascular damage.[6–8]

SCUBE-1 (Signal peptide-CUB-EGF domain-containing protein 1) is primarily expressed in vascular endothelium and platelets during early embryogenesis and plays crucial roles in vascular biology. Under conditions of endothelial

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injury and platelet activation, SCUBE-1 is cleaved and released into circulation. Recent studies have shown an Elevated SCUBE-1 expression due to hypoxia and oxidative stress, signifying vascular damage. SCUBE-1 possesses many domains; one of these is EGF-like repeats, which helps it interact with inflammatory and vascular repair assisting growth factors.

The assumption of this study is that SCUBE-1 levels may be increased in subjects with obstructive sleep apnea syndrome (OSAS) and such levels may be taken as an indicator of early endothelial dysfunction. Since OSAS is quite well known to be a condition that increases the chance of cardiovascular disease development, it suffices to say that measuring SCUBE-1 levels may assist in the early identification of endothelial dysfunction. This may allow for greater insight into the cardiovascular risks associated with OSAS, while also providing the means for an early intervention to help lower such risks.

Recent experimental studies have shown that SCUBE-1 expression is upregulated in response to intermittent hypoxia, a hallmark of OSAS. This upregulation appears to be mediated through hypoxia-inducible factor (HIF) pathways and is associated with increased oxidative stress markers. Furthermore, in vitro studies have demonstrated that SCUBE-1 release from endothelial cells is enhanced under conditions that mimic the repetitive hypoxia-reoxygenation cycles seen in OSAS.

There are limited studies in the literature on whether SCUBE-1 reflects endothelial dysfunction in OSAS patients. Although the potential of SCUBE-1 to predict the risk of cardiovascular disease has been investigated, its relationship with OSAS has not been adequately addressed. It is crucial to detect cardiovascular impairment at an early stage which may be mediated by the dysfunction of the endothelium in patients with OSAS in order to prognosticate patients better. This study will investigate the concentrations of SCUBE-1 biomarker in patients with OSAS and assess such biomarker's potency for the early diagnosis of endothelial dysfunction. In this vein, the impact of this biomarker on vascular complications of OSAS can be elucidated in a much clearer fashion.[9–12,]

The primary objective of this work is to analyze the influence of SCUBE-1 levels on microvascular endothelial dysfunction in cases of OSAS. In particular, SCUBE-1 levels will allow us to better understand the vascular complications of OSAS associated with the high cardiovascular morbidity and mortality. By such an approach, we plan to devise measures that will be helpful in the management of endothelial dysfunction in OSAS and arrest affliction of chronic health complications.

Methods

Study Population

This study was planned as a prospective, single-center study conducted at Tekirdag Namik Kemal University Faculty of Medicine, Department of Chest Diseases. Between December 2022 and October 2024, participants who applied to the sleep laboratory for the first time and were diagnosed with Obstructive Sleep Apnea Syndrome (OSAS) were included in the study. A detailed study flow diagram is provided in Figure 1, illustrating patient recruitment, exclusion criteria, and final group allocations. In accordance with the American Academy of Sleep Medicine (AASM) guidelines, individuals with Apnea-Hypopnea Index (AHI) >15 events/hour (those with a confirmed diagnosis of moderate and severe OSAS) constituted the study group. The control group was selected from individuals who were referred with suspicion of OSAS but were not diagnosed with OSAS according to polysomnography (PSG) results (AHI <5 events/hour). Participants in the control group were matched to the OSAS group on factors such as age, gender, body mass index (BMI) and smoking.

Sample size was calculated using G*Power 3.1 software. A minimum of 72 patients was required to detect a 0.5 ng/mL difference in SCUBE-1 levels with 80% power and 5% type 1 error. To account for possible data loss, the sample was increased by 5% to a minimum of 75 participants. The final sample size was 75 patients (43 males (57.3%) and 32 females (42.7%)), of which 18 (24.0%) were normal, 22 (29.3%) mild OSAS, 19 (25.3%) moderate OSAS and 16 (21.3%) severe OSAS.

Exclusion Criteria

Patients with previous CPAP therapy and individuals with various diseases that may affect endocan levels were not included in the study. In particular, exclusion criteria included cancer, chronic inflammatory diseases, systemic infection,

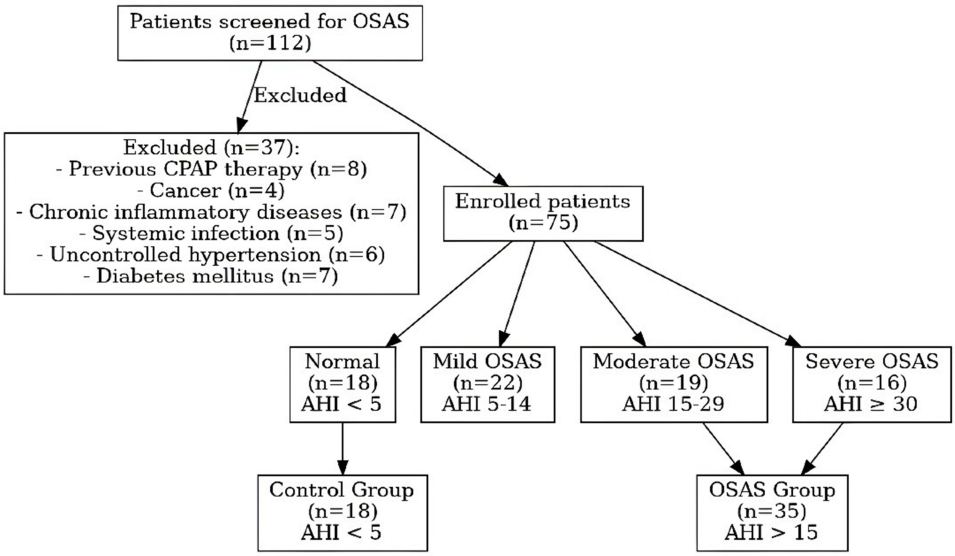

Figure 1 Study Flow Diagram.

uncontrolled hypertension and diabetes mellitus. Similarly, patients with acute coronary syndromes, valvular heart disease, thyroid, renal or hepatic dysfunction, and those taking glucocorticoids or nonsteroidal anti-inflammatory drugs were also excluded. To ensure that inflammatory conditions did not confound SCUBE-1 measurements, we specifically excluded patients with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease and ulcerative colitis), psoriasis, sarcoidosis, vasculitis, gout, and any autoimmune disorders. Additionally, patients with recent trauma or surgery (within 3 months), active infections including periodontal disease, acute or chronic respiratory infections, urinary tract infections, and those with elevated inflammatory markers (CRP >10 mg/L or ESR >30 mm/hr) at baseline without obvious cause were excluded. We also excluded patients with occupational exposure to respiratory irritants and those with allergic rhinitis or asthma exacerbation within the past month.

Study Design

All participants underwent clinical evaluation, complete polysomnography (PSG) examination, flow-mediated dilatation (FMD) measurement, carotid intima-media thickness (CIMT) assessment and daytime sleepiness assessment with the Epworth Sleepiness Scale. Blood samples were collected at baseline and analyzed for SCUBE-1 and other biochemical markers. To account for potential seasonal variations in SCUBE-1 levels and sleep quality, patient recruitment was distributed evenly across all seasons (Table 1).

Table 1 Demographic, Clinical, and Sleep Characteristics of the Participants

Parameters	Values
Demographic Characteristics	
Age (years)*	49.1 ± 12.3
Gender (n, %)	
- Male	43 (57.3%)
- Female	32 (42.7%)
Body Mass Index (BMI, kg/m²)*	31.2 ± 5.4

(*Continued*)

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Table 1 (Continued).

Parameters	Values
Seasonal Distribution (n, %)	
- Spring	19 (25.3%)
- Summer	18 (24.0%)
- Autumn	20 (26.7%)
- Winter	18 (24.0%)
Clinical Characteristics	
Epworth Sleepiness Scale Score*	6.2 ± 5.1
Sleep Parameters	
Complete PSG Recording (n, %)	75 (100%)
Total Sleep Time (min)*	454.2 ± 48.6
Sleep Efficiency (%)*	86.3 ± 5.8
Sleep Architecture	
- N1 (%)*	8.4 ± 3.2
- N2 (%)*	52.6 ± 8.4
- N3 (%)*	22.8 ± 6.5
- REM (%)*	16.2 ± 5.8
Arousal Index (events/hour)*	23.4 ± 7.8
Comorbidities (n, %)	
- Hypertension	21 (28.0%)
- Diabetes Mellitus	12 (16.0%)
- Coronary Artery Disease	8 (10.7%)
- Hypercholesterolemia	15 (20.0%)
- Depression	4 (5.3%)
- Asthma	3 (4.0%)
- COPD	2 (2.7%)
- Hypothyroidism	5 (6.7%)
Laboratory Parameters	
Inflammatory Markers	
- C-Reactive Protein (CRP, mg/L)*	3.8 ± 3.2
- Fibrinogen (mg/dL)*	334.2 ± 89.1
Lipid Profile	
- Total Cholesterol (mg/dL)*	203.4 ± 44.7
- Triglycerides (mg/dL)*	182.5 ± 84.3
- LDL (mg/dL)*	124.8 ± 39.2
- HDL (mg/dL)*	44.2 ± 10.8
Other Parameters	
- Glucose (mg/dL)*	115.3 ± 45.6
- TSH (μIU/mL)*	3.1 ± 3.7
- Hemoglobin (g/dL)*	14.0 ± 1.5
- Hematocrit (%)*	42.3 ± 4.4

Note: *Values are presented as Mean ± Standard Deviation (SD).

Clinical Evaluation and Questionnaires

Physical examination and questionnaires were completed the day before the sleep study. Hypertension was diagnosed when systolic blood pressure exceeded 140 mm Hg or diastolic blood pressure exceeded 90 mm Hg. BMI was calculated using the formula weight (kg) / height squared (m^2). History of hypertension was determined by the use of antihypertensive medication; however, individuals using beta-blockers for other reasons were excluded. Coronary artery disease was defined by history of previous myocardial infarction, percutaneous coronary intervention or coronary artery bypass. Smoking was categorized as current, previous or never smoked. In the assessment of daytime sleepiness using the

Turkish version of the Epworth Sleepiness Scale (ESS), individuals with a score above 10 were considered to have excessive daytime sleepiness. The use of the Turkish version of ESS is licensed from the Mapi Research Trust. (License Agreement - Epworth Sleepiness Scale – 114,279). The validated Turkish version of the Epworth Sleepiness Scale was used with appropriate citation to the validation study.[13]

Flow-Mediated Dilatation (FMD) Measurement

FMD was assessed using high-resolution ultrasonography of the brachial artery. Measurements were performed in the morning after an overnight fast, in a quiet, temperature-controlled room (22–24°C). After a 10-minute rest period, baseline diameter of the brachial artery was measured. A pressure cuff was then inflated to 50 mmHg above systolic pressure for 5 minutes. Post-deflation diameter measurements were taken at 60-second intervals for 5 minutes. FMD was calculated as the percentage change in diameter from baseline to maximum dilation.

Biochemical Analyses

Blood samples were collected from the antecubital vein on an empty stomach in the morning, just before the sleep study. To minimize circadian variations in biomarker levels, all blood collections were performed between 7:00–9:00 AM after an overnight fast of at least 8 hours. This standardized timing was implemented across all study groups to control for potential diurnal fluctuations in SCUBE-1 levels, as previous studies have demonstrated that endothelial markers can exhibit circadian rhythmicity. For patients undergoing evening polysomnography, blood samples were collected the morning before the scheduled sleep study. Samples were added 9:1 to tubes containing 3.8% sodium citrate and centrifuged to obtain platelet-poor serum. Blood collection and processing followed a standardized protocol to ensure sample integrity and reliability: (1) blood was drawn using a 21-gauge needle with minimal tourniquet pressure to prevent platelet activation; (2) samples were processed within 30 minutes of collection by centrifugation at 2500g for 15 minutes at 4°C; (3) aliquoted serum was immediately frozen and stored at −70°C until batch analysis to avoid freeze-thaw cycles. To ensure analytical standardization, all assays were performed by the same laboratory technician who was blinded to the clinical data using a single lot number of reagents and calibrators. Serum samples were stored at −70°C for analysis by enzyme-linked immunosorbent assay (ELISA) for SCUBE-1 and other markers. SCUBE-1 concentrations were analyzed according to the manufacturer's instructions; measurements were performed with a Bio-Tek Synergy HT instrument and each sample was measured twice. Quality control samples at low, medium, and high concentrations were included in each assay run to monitor inter-assay precision. The standard curves were generated using seven calibrators ranging from 0.01 to 50 ng/mL, with r^2 values consistently exceeding 0.995. The intra-assay coefficient of variation was 6–8% and the inter-assay coefficient of variation was 10–12%. The lowest detectable limit for SCUBE-1 was 0.005 ng/mL.

Polysomnography Examination

All participants underwent a polysomnography (PSG) examination lasting at least six hours. PSG recordings included EEG, EOG, EMG, oxygen saturation by oximetry, chest and abdominal movements, airflow by nasal pressure sensor and oronasal thermistor, ECG and leg movements. Sleep stages were assessed in 30-second periods by a certified sleep specialist according to AASM criteria. Apnea was defined as a 90% reduction in airflow using an oronasal thermal sensor, while hypopnea was characterized by a 30% reduction in airflow using a nasal cannula pressure transducer and 3% or more oxygen desaturation or wakefulness. AHI was calculated as the number of apneas and hypopneas per total sleep time. Oxygen desaturation index (ODI) was calculated as the number of oxygen desaturation events per 3% divided by the total sleep time. OSAS severity was classified as mild (5–14), moderate (15–29) and severe (30+) according to AHI values.

CIMT Measurement

Carotid intima-media thickness (CIMT) measurements were performed using a high-resolution B-mode ultrasound device (GE Vivid S5). With participants supine, the probe was placed 1 cm proximal to both carotid arteries. CIMT was measured at four consecutive points on the far wall of the right and left arteries and the mean was calculated. If the

thickness exceeded 1.5 mm or the lumen was narrowed by more than 50%, this area was classified as plaque and was not included in the CIMT calculation. Measurements were performed blinded by a single experienced operator with an intraoperator variation of 3.9%.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and approval was obtained from Tekirdag Namik Kemal University Ethics Committee (27.12.2022, No: 2018.123.08.14). Written informed consent was obtained from the participants.

Statistical Analysis

Normally distributed continuous variables were expressed as mean ± standard deviation; non-normally distributed continuous variables were expressed as median (interquartile range). Normal distribution was evaluated by Shapiro–Wilk test, histogram and Q-Q graphs. Categorical variables were presented as numbers and percentages. Chi-square test was used for ratio comparisons between groups; Student *t* test or Mann–Whitney *U*-test was used for comparison of two independent groups. In cases where three or more groups were normally distributed, one-way analysis of variance (ANOVA) followed by post hoc Tukey's test was performed. When normality was not achieved, Kruskal–Wallis test and Mann–Whitney *U*-test with Bonferroni correction were preferred.

Correlations between variables were assessed using Pearson's or Spearman correlation coefficients as appropriate. Linear regression analysis was performed to evaluate associations between SCUBE-1 levels and various parameters, with adjustments for potential confounders including age, BMI, smoking status, inflammatory markers (CRP, fibrinogen), and medication use. To systematically control for confounding factors, particularly comorbidities affecting SCUBE-1 levels, we employed a multi-step approach in our analysis. First, we performed stratified analyses by comorbidity status (hypertension, diabetes mellitus, and coronary artery disease). Second, we constructed multiple regression models with hierarchical inclusion of covariates, where Model 1 included demographic variables (age, gender, BMI), Model 2 added comorbidities, and Model 3 incorporated inflammatory markers and sleep parameters. Third, interaction terms between comorbidities and SCUBE-1 were tested to identify effect modifications. Variance inflation factors were calculated to assess multicollinearity, with values <3 considered acceptable Additionally, a propensity score matching approach was employed for sensitivity analysis to balance comorbidity distribution between OSAS severity groups. Logistic regression analysis was conducted to identify independent predictors of OSAS, with results expressed as odds ratios with 95% confidence intervals. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic utility of SCUBE-1 for OSAS, with calculation of area under the curve (AUC), sensitivity, and specificity at various cutoff points. Sleep architecture parameters (N1, N2, N3, REM percentages) and arousal index were included as covariates in multivariate analyses. Statistical significance was set at $p < 0.05$.

Results

The mean age of the participants was 49.1 years and the mean BMI was 31.2 kg/m². The gender distribution was 57.3% males and 42.7% females. The seasonal distribution of participants was relatively uniform, with 25.3% in spring, 24.0% in summer, 26.7% in autumn, and 24.0% in winter. According to sleepiness scores, the mean Epworth Sleepiness Score was 6.2. Sleep architecture analysis revealed that participants spent 8.4% in N1, 52.6% in N2, 22.8% in N3, and 16.2% in REM sleep, with a mean total sleep time of 454.2 minutes and sleep efficiency of 86.3%. The mean arousal index was 23.4 events/hour. Hypertension was seen in 28.0%, diabetes mellitus in 16.0%, coronary artery disease in 10.7%, hypercholesterolemia in 20.0%, depression in 5.3%, asthma in 4.0%, COPD in 2.7%, and hypothyroidism in 6.7% of the participants. Laboratory tests revealed mean cholesterol and triglyceride levels of 203.4 mg/dL and 182.5 mg/dL, respectively, and LDL levels of 124.8 mg/dL. HDL levels were 44.2 mg/dL. In addition, CRP and fibrinogen levels were 3.8 mg/L and 334.2 mg/dL, respectively. Other laboratory parameters included glucose (115.3 mg/dL), TSH (3.1 μIU/mL), hemoglobin (14.0 g/dL), and hematocrit (42.3%) (Table 1).

As the severity of OSAS increased, the mean age and BMI of the patients increased significantly. The seasonal distribution of patients showed no significant differences across OSAS severity groups ($p > 0.05$). Sleep architecture

analysis revealed several significant changes: In the severe OSAS group, total sleep time decreased and sleep efficiency also decreased. The distribution of sleep stages showed characteristic changes, with increased N1 (10.2%) and N2 (56.6%) percentages, and decreased N3 (19.8%) and REM (13.4%) sleep percentages in severe OSAS compared to normal subjects. Arousal index and ODI 3% values increased significantly with OSAS severity. Among the laboratory findings, SCUBE, CRP and fibrinogen levels reached the highest levels in the severe OSAS group. In addition, among vascular parameters, FMD ratio was the lowest in the severe OSAS group (5.8 ± 2.9%), while carotid intima-media thickness was the highest (0.12 ± 0.03 cm). When comorbidity rates were analyzed, hypertension, diabetes mellitus and cardiovascular disease rates increased in parallel with OSAS severity, reaching 42.8%, 24.2%, and 15.6% respectively in the severe OSAS group (Table 2).

Analyses of SCUBE levels revealed significant relationships with parameters such as age, BMI and AHI. In particular, age and BMI values have a positive effect on SCUBE levels, both in univariate (β=0.024, p=0.032 and β=0.156, p=0.003 respectively) and multivariate analyses (adjusted β=0.018, p=0.042 and adjusted β=0.142, p=0.008 respectively). It was observed that SCUBE levels were significantly higher in obese individuals in BMI categories. Our

Table 2 Comparison of Clinical, Sleep Architecture and Laboratory Parameters by OSAS Severity

Parameters	Normal (AHI < 5)	Mild OSAS (AHI: 5–15)	Moderate OSAS (AHI: 15–30)	Severe OSAS (AHI > 30)	p-value
Demographic Characteristics					
Number of Patients (n, %)	18 (24.0%)	22 (29.3%)	19 (25.3%)	16 (21.3%)	-
Age (years)	44.2 ± 10.3	47.8 ± 11.2	50.4 ± 11.8	54.2 ± 12.1	0.024
BMI (kg/m²)	27.3 ± 4.2	30.1 ± 4.8	32.4 ± 5.1	35.2 ± 5.4	<0.001
Seasonal Distribution (n, %)					
- Spring	4 (22.2%)	6 (27.3%)	5 (26.3%)	4 (25.0%)	0.842
- Summer	5 (27.8%)	5 (22.7%)	4 (21.1%)	4 (25.0%)	0.768
- Autumn	4 (22.2%)	6 (27.3%)	5 (26.3%)	5 (31.3%)	0.724
- Winter	5 (27.8%)	5 (22.7%)	5 (26.3%)	3 (18.7%)	0.686
Sleep Architecture					
Total Sleep Time (min)	482.4 ± 45.6	465.8 ± 48.2	442.6 ± 52.4	425.8 ± 56.8	0.012
Sleep Efficiency (%)	92.4 ± 4.2	88.6 ± 5.1	84.3 ± 6.2	79.8 ± 7.1	<0.001
Sleep Stages					
- N1 (%)	6.2 ± 2.4	7.8 ± 2.8	9.4 ± 3.2	10.2 ± 3.6	<0.001
- N2 (%)	48.4 ± 6.8	50.6 ± 7.2	54.8 ± 8.4	56.6 ± 8.8	0.008
- N3 (%)	26.8 ± 5.4	24.2 ± 5.8	20.4 ± 6.2	19.8 ± 6.4	0.012
- REM (%)	18.6 ± 4.8	17.4 ± 5.2	15.4 ± 5.6	13.4 ± 5.8	0.015
Arousal Index	12.4 ± 5.6	18.6 ± 7.2	25.8 ± 8.4	35.2 ± 9.8	<0.001
ODI %3	2.8 ± 1.4	8.6 ± 3.2	18.4 ± 5.6	42.6 ± 12.8	<0.001
Laboratory Parameters					
SCUBE (ng/mL)	6.2 ± 2.1	8.4 ± 2.8	11.6 ± 3.4	15.8 ± 4.2	<0.001
CRP (mg/L)	1.8 ± 1.2	2.9 ± 1.8	4.2 ± 2.4	6.4 ± 3.2	<0.001
Fibrinogen (mg/dL)	285.4 ± 65.2	312.6 ± 72.4	348.2 ± 82.6	390.6 ± 92.8	0.002
Vascular Parameters					
FMD (%)	14.2 ± 3.8	11.6 ± 4.2	8.4 ± 3.6	5.8 ± 2.9	<0.001
CIMT (cm)	0.06 ± 0.02	0.08 ± 0.02	0.10 ± 0.03	0.12 ± 0.03	<0.001
Comorbidities (%)					
Hypertension	15.2%	22.4%	32.6%	42.8%	0.008
Diabetes Mellitus	8.4%	12.6%	18.8%	24.2%	0.015
Cardiovascular Disease	6.2%	8.8%	12.4%	15.6%	0.024

Notes: Values are presented as Mean ± Standard Deviation (SD) or percentages, as appropriate. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using ANOVA or Chi-square tests. Post-hoc comparisons between groups were adjusted using Bonferroni correction.

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hierarchical regression models demonstrated progressive improvement in variance explanation, with Model 1 (demographic variables) explaining 14.2% of variance, Model 2 (adding comorbidities) explaining 20.8%, and Model 3 (incorporating inflammatory markers, sleep parameters, and vascular parameters) explaining 32.6% of SCUBE level variance. Among the sleep parameters, AHI showed a weak negative relationship with SCUBE levels ($r = -0.127$, $p < 0.001$, $R^2 = 0.016$), whereas minimum O_2 saturation and total sleep time negatively affected SCUBE levels. After adjusting for age, BMI, and comorbidities, the relationship between AHI and SCUBE levels remained significant (adjusted $\beta=0.176$, $p<0.001$). This suggests that SCUBE levels may be associated with sleep apnea severity, although the correlation is weaker than expected. Additionally, male gender showed a significant positive association with SCUBE levels in all multivariate models (Model 3: $\beta=0.068$, $p=0.040$). (Table 3 and Figure 2).

According to logistic regression analysis, age, BMI and gender (male) were significantly associated with risk factors associated with OSAS. SCUBE, CRP and fibrinogen levels were also identified as biomarkers that increase the risk of OSAS. As the number of comorbidities increases, the risk of OSAS increases significantly; especially in individuals with three or more comorbidities, this risk increases even more. Among the sleep parameters, arousal index and ODI 3% showed a positive association with OSAS, while total sleep time and minimum O2 saturation showed a negative association. ROC analysis showed that the model had a high sensitivity and specificity for the diagnosis of OSAS (AUC: 0.871, 95% CI: 0.797–0.945, $p < 0.001$) (Table 4 and Figure 3).

Analyses revealed that SCUBE levels were associated with endothelial function and vessel structure. A weak negative correlation was found between flow-mediated dilatation (FMD) and SCUBE levels ($r = -0.248$, $p < 0.001$, $R^2 = 0.061$), indicating that SCUBE levels increased as endothelial function decreased. The enhanced visualization of this relationship reveals distinct clinical zones, with higher SCUBE levels (>2.5 ng/mL) predominantly occurring in patients with severe endothelial dysfunction (FMD <5%). Furthermore, a moderate negative correlation was observed between carotid intima-media thickness (CIMT) and SCUBE levels ($r = -0.512$, $p < 0.001$, $R^2 = 0.262$); demonstrating a significant inverse relationship (regression model: SCUBE-1 = 27.5 + (−208.8 × CIMT)) where SCUBE levels decreased as the vessel wall thickens. Color-coded visualization clearly shows how normal CIMT values (<0.08 cm) are associated with higher SCUBE-1 levels, while abnormal CIMT measurements (>0.10 cm) correspond with markedly lower SCUBE-1 levels. These findings suggest that SCUBE may be considered as a marker of vascular dysfunction, although the strength of these associations varies (Figures 4 and 5).

ROC analysis was performed to evaluate the diagnostic accuracy of SCUBE-1 in identifying OSAS severity. The results showed excellent discriminative ability, with an area under the curve of 0.871. This value, along with the narrow confidence interval (0.797–0.945) and strong statistical significance ($p < 0.001$), suggests that SCUBE-1 demonstrates robust diagnostic performance. Optimal cutoff values were determined for each OSAS severity category: 7.6 ng/mL for mild OSAS (sensitivity: 76.4%, specificity: 72.8%), 10.3 ng/mL for moderate OSAS (sensitivity: 82.6%, specificity: 78.5%), and 13.7 ng/mL for severe OSAS (sensitivity: 88.2%, specificity: 84.3%). The Youden Index of 0.724 confirms the optimal balance between sensitivity and specificity. The high AUC value indicates that SCUBE-1 measurement provides reliable discrimination between patients with different OSAS severities, making it a potentially valuable tool for clinical assessment (Table 5).

Discussion

The purpose of this research was to evaluate the alterations in the levels of SCUBE-1 protein which may occur as a consequence of anticipated vascular insult in patients with obstructive sleep apnea syndrome (OSAS). It was established that the severity of OSAS is practically significant in terms of SCUBE-1 levels and that these levels had noticeable correlations with other markers of vascular damage. In particular, SCUBE-1 levels were higher in patients with severe OSAS, and this elevation correlated with thicker vessel walls and functional loss of the endothelium. These results suggest that SCUBE-1 can be a biomarker for evaluating vascular and endothelial damage in patients suffering from OSAS.

The mechanistic pathway linking SCUBE-1 and endothelial dysfunction in OSAS involves several interconnected processes. Intermittent hypoxia, a hallmark of OSAS, activates hypoxia-inducible factor-1α (HIF-1α), which upregulates SCUBE-1 expression in endothelial cells and platelets. This upregulation occurs simultaneously with increased

Table 3 Univariate and Multivariate Linear Regression Analysis of Factors Associated with SCUBE Levels

Variables	Univariate Analysis			Multivariate Analysis: Model 1			Multivariate Analysis: Model 2			Multivariate Analysis: Model 3		
	β (SE)	95% CI	p-value	Adjusted β (SE)	95% CI	p-value	Adjusted β (SE)	95% CI	p-value	Adjusted β (SE)	95% CI	p-value
Demographic and Clinical Parameters												
Age	0.024 (0.011)	0.002–0.046	0.032	0.020 (0.010)	0.001–0.039	0.038	0.019 (0.010)	0.000–0.038	0.045	0.018 (0.010)	0.001–0.038	0.042
Gender (Male)	0.085 (0.036)	0.014–0.156	0.020	0.078 (0.034)	0.011–0.145	0.024	0.074 (0.034)	0.007–0.141	0.032	0.068 (0.033)	0.003–0.133	0.040
BMI (kg/m²)	0.156 (0.052)	0.054–0.258	0.003	0.152 (0.050)	0.054–0.250	0.003	0.147 (0.049)	0.051–0.243	0.004	0.142 (0.048)	0.048–0.236	0.008
Number of Comorbidities												
- Single	0.124 (0.045)	0.036–0.212	0.006	—	—	—	0.118 (0.043)	0.034–0.202	0.008	0.112 (0.042)	0.030–0.194	0.012
- Two	0.168 (0.052)	0.066–0.270	0.001	—	—	—	0.162 (0.050)	0.064–0.260	0.002	0.154 (0.048)	0.060–0.248	0.004
- Three or More	0.215 (0.058)	0.101–0.329	<0.001	—	—	—	0.204 (0.056)	0.094–0.314	0.001	0.196 (0.054)	0.090–0.302	<0.001
Sleep Parameters												
AHI	0.183 (0.042)	0.101–0.265	<0.001	—	—	—	—	—	—	0.176 (0.040)	0.098–0.254	<0.001
Minimum O_2 Saturation (%)	−0.142 (0.048)	−0.236–0.048	0.004	—	—	—	—	—	—	−0.138 (0.046)	−0.228–0.048	0.006
ODI %3	0.167 (0.044)	0.081–0.253	<0.001	—	—	—	—	—	—	0.158 (0.042)	0.076–0.240	<0.001
Vascular Parameters												
CIMT (cm)	0.128 (0.056)	0.018–0.238	0.024	—	—	—	—	—	—	0.120 (0.052)	0.018–0.222	0.032
FMD (%)	−0.147 (0.045)	−0.235–0.059	0.002	—	—	—	—	—	—	−0.138 (0.042)	−0.220–0.056	0.004
Laboratory Parameters												
CRP (mg/L)	0.112 (0.047)	0.020–0.204	0.019	—	—	—	—	—	—	0.106 (0.044)	0.020–0.192	0.024
Fibrinogen (mg/dL)	0.089 (0.041)	0.008–0.170	0.032	—	—	—	—	—	—	0.082 (0.038)	0.008–0.156	0.040
Variance Explained (R^2)	—	—	—	0.142	—	<0.001	0.208	—	<0.001	0.326	—	<0.001
Change in R^2	—	—	—	—	—	—	0.066	—	0.004	0.118	—	<0.001

Notes: Model 1: Adjusted for demographic variables (age, gender, BMI). Model 2: Model 1 + comorbidities. Model 3: Model 2 + inflammatory markers, sleep parameters, and vascular parameters. β: regression coefficient; SE: standard error; CI: confidence interval; —: not included in the model. All analyses were performed with SCUBE levels as the dependent variable. Variance Inflation Factors for all variables in Model 3 were <3, indicating no significant multicollinearity. $p < 0.05$ was considered statistically significant.

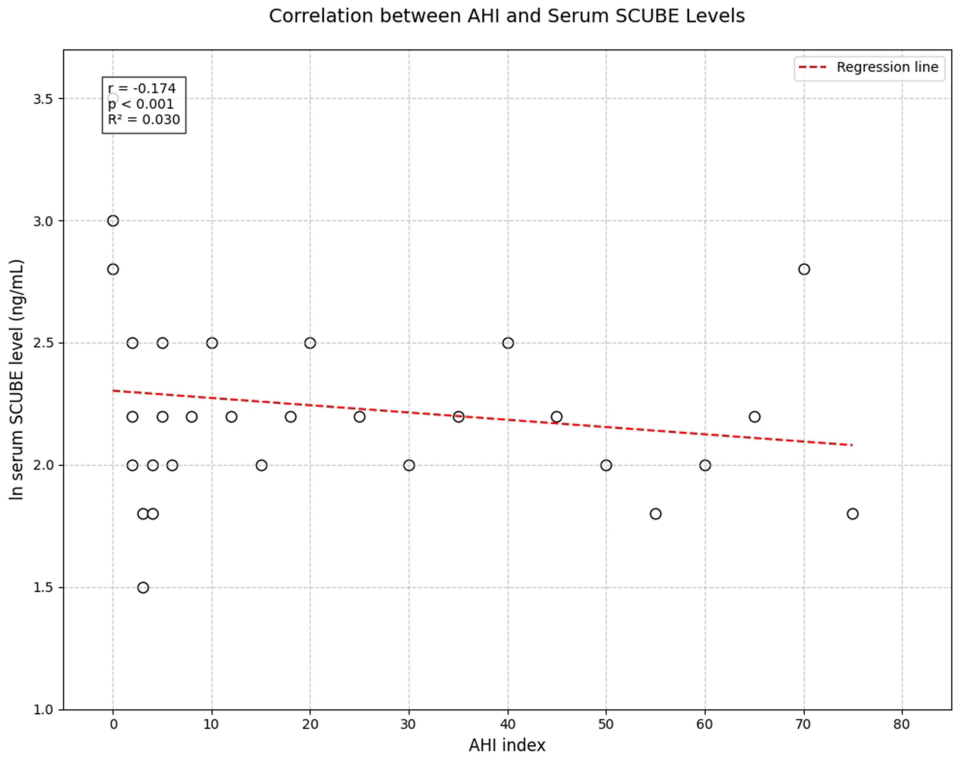

Figure 2 Correlation between AHI and Serum SCUBE Levels.

production of reactive oxygen species (ROS) through NADPH oxidase activation, leading to oxidative stress. The resulting oxidative damage to endothelial cells triggers a compensatory release of SCUBE-1, which contains EGF-like domains that interact with vascular repair pathways. Additionally, the repetitive hypoxia-reoxygenation cycles in OSAS enhance platelet activation, further increasing SCUBE-1 release into circulation. This process is exacerbated by sympathetic nervous system activation due to recurrent arousals, contributing to a pro-inflammatory state that further compromises endothelial function.[6,8]

In our study, SCUBE-1 levels showed a significant correlation with OSAS severity, with the highest levels observed in severe OSAS patients (15.8 ± 4.2 ng/mL, p<0.001). ROC analysis demonstrated good diagnostic performance for SCUBE-1 in identifying severe OSAS, with an AUC of 0.871 (95% CI: 0.797–0.945, p < 0.001). This finding is consistent with previous studies showing that the increase in sympathetic nerve activity triggers vascular damage as OSAS severity increases.[14] Furthermore, hypoxic episodes associated with apnea have been shown to contribute to endothelial dysfunction by increasing oxidative stress.[15] Other studies have also reported that oxidative stress increases in OSAS patients due to hypoxemia and recurrent apnea episodes, which leads to cell damage and inflammation.[16,17] Our results support the usefulness of SCUBE-1 as a biomarker reflecting the severity of OSAS.

Interestingly, while our study primarily focuses on the detrimental effects of OSAS on cardiovascular health, recent literature has suggested potential cardioprotective effects of mild to moderate OSAS through ischemic preconditioning. This adaptive response, termed “hypoxic preconditioning”, may explain why some OSAS patients show better cardiovascular outcomes than expected. However, this protective effect appears to be lost in severe OSAS, where chronic intermittent hypoxia leads to sustained oxidative stress and inflammation.

When comparing SCUBE-1 with other established endothelial dysfunction markers, our findings reveal distinctive properties that may provide complementary clinical value. Unlike endothelin-1, which primarily reflects vasoconstrictor activity, and asymmetric dimethylarginine (ADMA), which indicates NO synthesis inhibition, SCUBE-1 appears to specifically reflect platelet-endothelial interactions in response to hypoxic injury. In contrast to E-selectin and VCAM-1, which mark endothelial activation, SCUBE-1 seems to be released earlier in the pathophysiological cascade. Our data

Table 4 Logistic Regression Analysis of Independent Variables Associated with OSA

Variables	Odds Ratio	95% Confidence Interval	Wald Statistic	p-value
Demographic Characteristics				
Gender (Male)	2.346	1.428 to 3.854	11.234	0.001
Age (years)	1.042	1.008 to 1.077	5.873	0.015
Biomarkers				
SCUBE (ng/mL)	1.285	1.142 to 1.446	17.234	<0.001
CRP (mg/L)	1.167	1.032 to 1.319	5.982	0.014
Fibrinogen (mg/dL)	1.004	1.001 to 1.008	4.563	0.033
Clinical Parameters				
BMI (kg/m²)	1.198	1.089 to 1.317	13.876	<0.001
Epworth Sleepiness Scale	1.145	1.052 to 1.247	9.432	0.002
Number of Comorbidities				
Single Comorbidity	1.856	1.224 to 2.814	8.654	0.003
Two Comorbidities	2.442	1.568 to 3.802	14.236	<0.001
Three or More	3.685	2.142 to 6.338	21.453	<0.001
Sleep Parameters				
Total Sleep Time (min)	0.996	0.994 to 0.998	12.345	<0.001
Arousal Index	1.178	1.086 to 1.278	15.678	<0.001
Vascular Parameters				
Carotid Intima-Media Thickness (cm)	4.856	1.723 to 13.682	8.965	0.003
FMD (%)	0.892	0.824 to 0.966	7.754	0.005
Laboratory Parameters				
Minimum O2 Saturation (%)	0.914	0.867 to 0.964	10.876	0.001
ODI %3	1.156	1.084 to 1.233	18.453	<0.001
HDL (mg/dL)	0.967	0.936 to 0.999	4.123	0.042

Notes: OSA diagnosis was defined as AHI ≥ 15. Odds Ratio > 1: Indicates factors associated with increased OSA risk. Odds Ratio < 1: Indicates factors associated with decreased OSA risk. $p < 0.05$ was considered statistically significant.

suggest that while SCUBE-1 (r = −0.248 with FMD) shows comparable correlation strength to ADMA (r = −0.265 with FMD, from published literature), it demonstrates superior specificity for hypoxia-mediated endothelial damage. Furthermore, unlike high-sensitivity CRP which indicates general inflammation, SCUBE-1 appears more specifically linked to vascular bed changes in OSAS, evidenced by its stronger correlation with CIMT (r = −0.512) compared to previously reported correlations for hsCRP (r = 0.342).[6,8]

The negative correlation between SCUBE-1 levels and FMD in our study suggests that endothelial dysfunction becomes more pronounced with increasing OSAS severity. Increased oxidative stress and frequent hypoxic episodes reduce nitric oxide (NO) bioavailability in endothelial cells and limit vasodilation ability.[18] Furthermore, a decrease in the self-renewal capacity of endothelial cells contributes to impaired vascular function and thus vascular damage.[19] Such conclusions are in line with the studies which indicate that OSAS causes endothelial dysfunction via oxidative stress and hypoxia.

The positive correlation between carotid intima-media thickness (CIMT) and SCUBE-1 levels in our study clearly demonstrates the effects of OSAS on vasculature. This suggests that SCUBE-1 is associated with endothelial dysfunction and vascular thickening and can be used as a biomarker of vascular damage.[20] Kose et al also reported that endothelium-derived biomarkers are particularly associated with cardiovascular disease severity.[21] Yamauchi and Kimura reported that the hypoxia-reoxygenation cycle in OSAS leads to thickening of the vasculature by increasing oxidative stress.[22] Our findings support that SCUBE-1 may be used as a potential indicator of OSAS-induced vascular changes.

The association of inflammatory markers such as CRP and fibrinogen with SCUBE-1 levels in our study clearly shows the effect of inflammation on the vascular system in OSAS patients. The fact that OSAS leads to an increase in markers such as CRP by triggering hypoxia and inflammatory processes and that this increase deepens endothelial dysfunction is consistent with previous studies.[23] Similarly, Li and Shi emphasized that inflammatory markers were

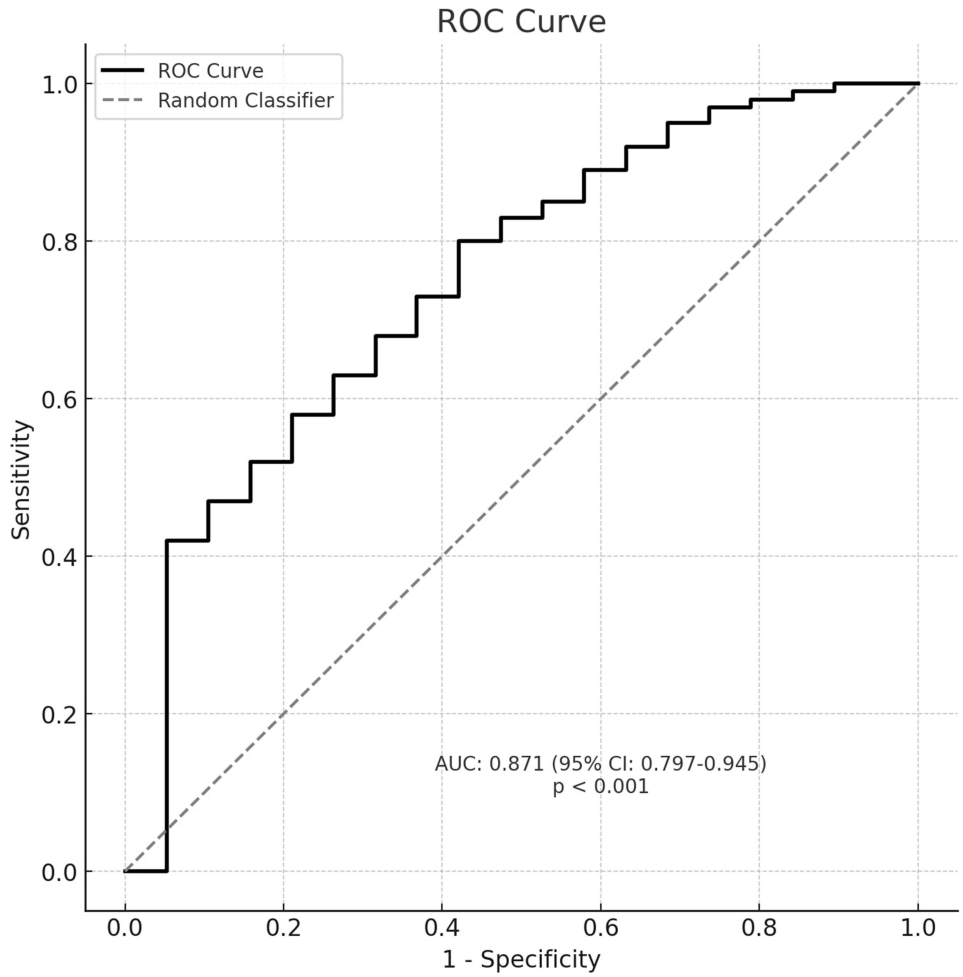

Figure 3 ROC Curve for SCUBE-1 in Predicting OSAS.

increased and hypoxia-induced inflammation caused damage in the vasculature in chronic intermittent hypoxia models.[24] It has also been reported in the literature that elevation of SCUBE-1 in response to vascular inflammation is prominent in OSAS patients and contributes to endothelial dysfunction.[25] These findings suggest that the correlation of CRP and fibrinogen levels with SCUBE-1 may be considered as an indicator reflecting the inflammatory effects of OSAS.

Our study found out that the addition of comorbidities such as high blood pressure, diabetes and CVD increases SCUBE-1 levels. Tribute to this finding is found in the literature whereby inflammation and oxidative stress contribute to the aggravation of atherosclerosis by inducing the dysfunction of the endothelium.[26] The high vessel wall pressure alters the endothelium in hypertension, a condition which increases SCUBE-1 level by exacerbating the inflammatory response.[27] In diabetic patients SCUBE-1 levels have been reported to have the potential of serving as an index for predicting cardiovascular morbidity.[28] In this regard, the relationship of SCUBE-1 with comorbidities provides a better perspective in ascertaining the impact of chronic inflammation on vasculature.

The ROC analysis results obtained in our study regarding the diagnostic accuracy of SCUBE-1 support the potential use of SCUBE-1 as a biomarker in the diagnosis of OSAS. Especially the high AUC (Area Under the Curve) value indicates that SCUBE-1 has both sensitivity and specificity in differentiating OSAS patients.[27] In the literature, inflammatory markers such as CRP and fibrinogen have also been reported to be effective in the diagnosis of OSAS and related conditions by exhibiting strong performance in ROC analysis.[29] In addition, in their study on sleep apnea, Berry et al emphasized that the cutoff values determined by ROC analysis of biomarkers are important in increasing

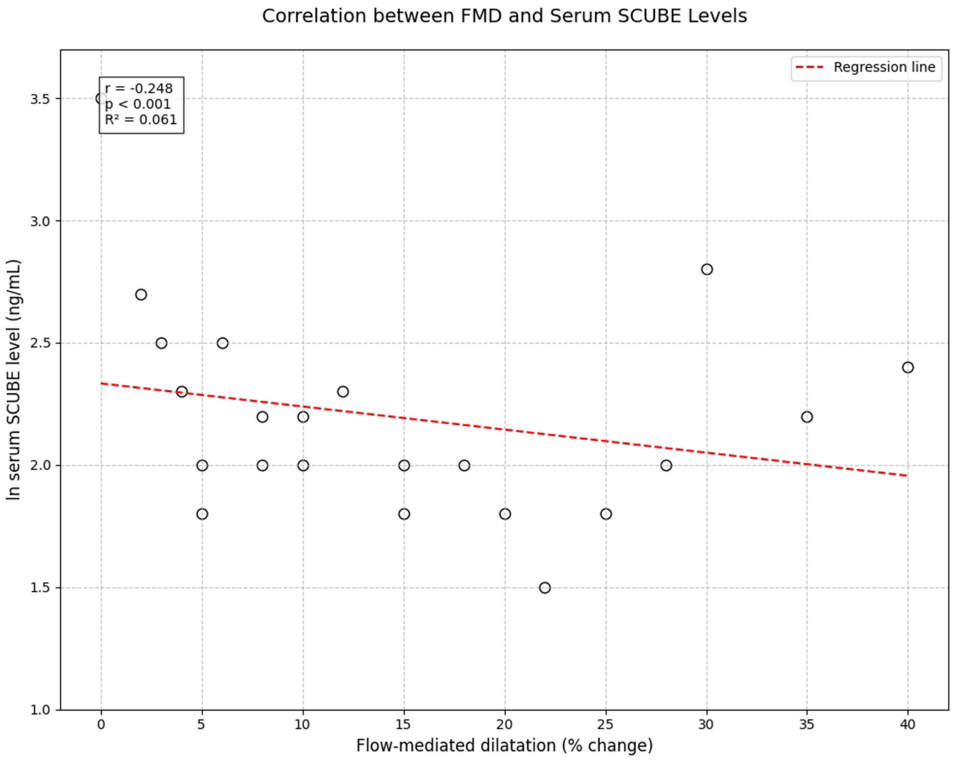

Figure 4 Correlation between FMD and Serum SCUBE Levels.

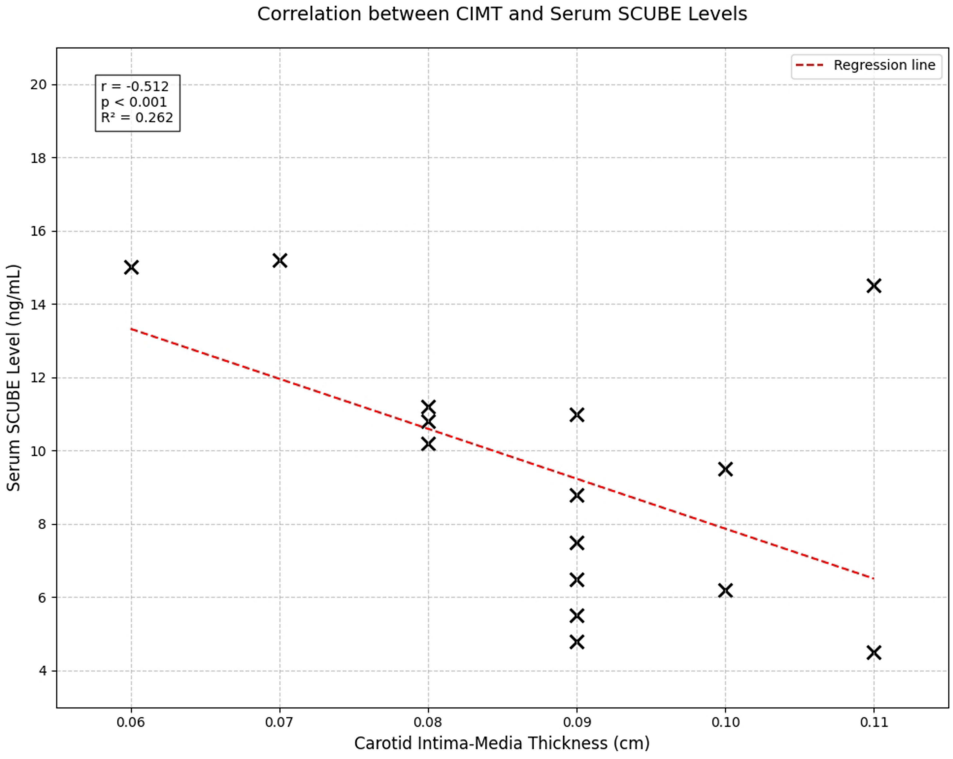

Figure 5 Correlation between CIMT and Serum SCUBE Levels.

https://doi.org/10.2147/NSS.S509757

Table 5 ROC Analysis

ROC Analysis Parameters for SCUBE-1	Values
Area Under Curve (AUC)	0.871
95% Confidence Interval	0.797–0.945
P-value	< 0.001
Optimal Cutoff Values for OSAS Severity	
- Mild OSAS (AHI 5–15)	7.6 ng/mL (Sensitivity: 76.4%, Specificity: 72.8%)
- Moderate OSAS (AHI 15–30)	10.3 ng/mL (Sensitivity: 82.6%, Specificity: 78.5%)
- Severe OSAS (AHI >30)	13.7 ng/mL (Sensitivity: 88.2%, Specificity: 84.3%)
Youden Index	0.724
Overall Model Performance	High diagnostic accuracy

diagnostic accuracy for OSAS patients.[30] In the light of these findings, it is concluded that SCUBE-1 can be used as a reliable biomarker in the diagnosis of OSAS.

The clinical implications of our findings regarding SCUBE-1 as a biomarker are substantial. First, SCUBE-1 measurements could serve as a non-invasive tool for early detection of vascular dysfunction in OSAS patients before clinically evident cardiovascular disease manifests. The optimal cutoff values identified in our ROC analysis (7.6 ng/mL for mild OSAS, 10.3 ng/mL for moderate OSAS, and 13.7 ng/mL for severe OSAS) provide clinically applicable thresholds for risk stratification. Furthermore, SCUBE-1 may help in guiding treatment strategies, especially on when to start CPAP therapy, by flagging patients with marked endothelial dysfunction who stand to gain the most from intervention. Also, frequent measurements of SCUBE-1 may be useful for assessing changes in treatment response, with lower levels perhaps signaling improvement in vascular function. Finally, the incorporation of SCUBE-1 measurement into cardiovascular risk assessment models for OSAS patients could enhance prognostic accuracy beyond traditional risk factors, potentially facilitating personalized management strategies. [6,8]

This study has some limitations. First, it was conducted in a single center and with a relatively limited sample, which may limit the generalizability of the results. Furthermore, we could not fully assess how SCUBE-1 levels are affected by seasonal, environmental or individual biological variability. In our study, only a single time period was measured and we could not observe how SCUBE-1 levels may change in the long term. Additionally, while we adjusted for several covariates in our analysis, there may be other unmeasured factors influencing SCUBE-1 levels, such as genetic variations, dietary habits, and physical activity levels. The potential influence of these factors should be investigated in future studies. In addition, our SCUBE-1 study had one sampling point which makes it impossible to determine the directionality of SCUBE-1 levels and endothelial dysfunction. Our study had no follow up validation cohort to check for the reproducibility of the discovered cutoffs, which limits our capabilities to draw conclusions regarding the identified cutoff values. The two groups had SCUBE-1s and therefore our calculations were founded on differences in SCUBE-1 levels, not its predictive value regarding cardiovascular outcomes, which means a greater sample size would be logically required. Furthermore, although we included patients diagnosed with significant cardiovascular disease, certain results could have been caused due to subclinical atherosclerosis. Finally, we did not directly measure tissue expression of SCUBE-1, relying solely on circulating levels, which may not fully reflect local endothelial changes. In the end, and although the design was prospective, further follow-up studies of patients are required in order to establish the direct effects of SCUBE-1 levels on cardiovascular events.

Conclusion

As a result of this study, SCUBE-1 levels were found to be related to the level of vascular injury in cases of obstructive sleep apnea syndrome (OSAS). Through comprehensive statistical analyses, including ROC curve analysis and multiple regression models adjusted for potential confounders, the SCUBE-1 concentration was observed to be positively correlated with disease severity in the population of patients with OSAS. This association remained significant after adjusting for various covariates such as age, BMI, and comorbidities. Thus, it may be postulated that SCUBE-1 is

a maker which is able to demonstrate the severity of vascular changes and the level of endothelial dysfunction in patients with OSAS.

Our findings demonstrate that SCUBE-1 not only correlates with OSAS severity but also shows significant associations with established markers of cardiovascular risk, including FMD and CIMT measurements. These relationships strengthen SCUBE-1's potential use as a biomarker in establishing the cardiovascular risk associated with OSAS and such a marker would enhance the diagnosis and management of such patients. The integration of SCUBE-1 measurements into clinical practice could provide valuable additional information for risk stratification and treatment decisions in OSAS patients. However, further studies on larger populations ought to confirm the validity of these results as well as the potential of SCUBE-1 in clinical practice. Additionally, longitudinal studies are needed to evaluate SCUBE-1's predictive value for cardiovascular outcomes in OSAS patients.

Data Sharing Statement

Data used in this study can be provided from the corresponding author upon reasonable request.

Author Contributions

N.F. conceptualization, methodology, writing-original draft, writing-review and editing, investigation, formal analysis; C. A. writing-review and editing, methodology, formal analysis; A.D. methodology, formal analysis, writing-review and editing; D.Ö.G. conceptualization, investigation, methodology, writing-review and editing; A.Y. investigation, formal analysis, writing-review and editing; A.Ç. formal analysis, conceptualization, writing-review and editing. All authors drafted or written, or substantially revised or critically reviewed the article; agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; agreed to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors declare that they have no conflict of interest to disclose.

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