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The relationship between disease severity and GDF-15 in individuals diagnosed with obstructive sleep apnea syndrome

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Abstract

Obstructive sleep apnea syndrome (OSAS) is characterized with interruption of sleep with apnea attacks and is associated with various diseases such as metabolic syndrome. GDF-15 (Growth differentiation factor 15) is a cytokine belonging to the transforming growth factor – β superfamily and it has been found to be associated with chronic heart failure, acute pulmonary embolism, and acute attacks of chronic obstructive pulmonary disease (COPD). It was aimed to evaluate the relationship between disease severity and mean GDF-15 in patients diagnosed with OSAS. Our study was carried out with 75 patients with OSAS. GDF-15 levels were checked by in the morning fasting blood test. Among the 75 patients, 27 constituted the mild, 22 constituted the moderate and 26 constituted the severe OSAS groups. The mean ages of the patients were not significantly different between groups (53.17±10, 54.61±10.2 and 53.5±11.6 respectively; p>0,05). GDF-15 levels were not significantly different between groups separately (p>0.05). There was only a weak positive relationship between GDF-15 and NREM and REM (p<0.05). In our study, it was revealed that there was no significant relationship between the OSAS severity groups and GDF-15. Our determination of a positive relationship with NREM and REM may have been related to reduction of minute ventilation experienced in OSAS-diagnosed patients, tachycardic fluctuations, their more severe nature and increased right ventricular pressure. Consequently, our current knowledge indicates that GDF-15 is not much guiding in the prediction and monitoring of OSAS severity.

Keywords: sleep apnea syndrome, OSAS, GDF-15, REM, NREM, apnea

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent partial or complete upper respiratory airway obstructions ending in hypoxia/reoxygenation and arousals during sleep (1). While its etiology and pathophysiological mechanisms have not been completely understood, it is a complex, polygenic, and multifactorial disease accompanied by some predisposing factors such as age, sex, obesity, anatomic and mechanical factors and neuromuscular function (2, 3). OSAS may lead to some complications such as cardiovascular complications, malignancy and diabetes while studies have shown that these complications may be associated with endothelial dysfunction, excess oxidative stress, increased systemic inflammation and sympathetic stimulation (4-7). GDF-15 (Growth differentiation factor 15) is a cytokine belonging to the transforming growth factor – β superfamily, and it plays a role in cellular growth and differentiation. It has been found to be associated with acute coronary syndrome, chronic heart failure, acute pulmonary embolism, idiopathic pulmonary hypertension and acute attacks of chronic obstructive pulmonary disease (COPD) (7-9). A study where OSAS patients were compared to a control group did not find a GDF-related difference. However, in the study, the OSAS group was assessed without separation into sub-groups based on severity (mild-moderate-severe) (10).

In difference to previous studies on this topic, in this study, it was aimed to assess the relationship between disease severity and mean GDF-15 in patients diagnosed with OSAS.

2. Materials and Methods

The ethics board approval for the study was obtained from the Kirsehir Ahi Evran University Faculty of Medicine Clinical Studies Ethics Board with the Decision No:2020-02/11 with date of 11-02-2020. Written consent was obtained from the patients who volunteered to participate in the study. The costs of the kits that were used in the study were covered by the researchers.

2.1. Population

Our study was carried out with 75 patients who visited the Pulmonology and Cardiology clinic of our hospital, pre-diagnosed with OSAS, were of the ages of 18-80, had newly diagnosed OSAS and not started positive airway pressure (PAP) treatment. Patients with a diagnosis of central type sleep apnea, neurological diseases such as history of

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cerebrovascular disease and recent head trauma and those who had cardiovascular diseases that could lead to increased GDF-15, diagnoses like heart failure, acute coronary syndrome or history of idiopathic pulmonary hypertension were excluded from the study. The included patients did not have a history of any medication usage. The patients meeting the exclusion and inclusion criteria and volunteering to participate were hosted at the sleep clinic for a night for polysomnography (PSG), and after fasting overnight, their venous blood samples were taken into plain and K2EDTA-containing tubes. The blood samples were transferred to the biochemistry laboratory without waiting. The samples that were taken into plain tubes were centrifuged at 1500g for 10 minutes after waiting for them to coagulate. From a part of the serum that formed, routine biochemical parameters were studies by standard methods by using a Cobas 8000 (Roche Diagnostics®, Germany) autoanalyzer. The remaining serum was kept at -80 °C until the time it would be studied for GDF-15 levels. Serum GDF-15 was measured with the ELISA method by using a commercial kit (www.relassay.com, Gaziantep, Turkey). Validation of performance parameters of ELISA kits as were:

1) Within-batch difference: CV<10%,

2) Batch-batch difference: CV<12%,

3) Sensitivity: 5.09 ng/L,

4) Period of validity: Twelve months.

In the blood samples taken into K2EDTA tubes, complete blood count tests were carried out with a Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) automated blood count device.

2.2. Polysomnography (PSG)

The diagnosis of OSAS is made by polysomnography (PSG). In the examination that was made for an entire night, using a Philips Respironics Polysomnography device (1001 Murry Ridge Lane Murrysville, PA 15668 USA Respironics Deutschland Gewerbestrasse 17 82211 Herrsching, Germany), four-channel electroencephalogram (EEG) and two-channel electrooculography (EOG), submental electromyography (EMG), pulse-oximetry, thoracic and abdominal movements, electrocardiogram (ECG), tracheal sounds and oronasal air flow were recorded. In PSG, measurements of respiratory decrease (H=hypopnea) and complete stoppage of respiration (A=apnea) are made, and the hourly Apnea (A)- Hypopnea (H) counts (I=index) are determining. OSAS diagnosis is made as AHI: (apnea-hypopnea index): 5-15/hour: Mild; AHI: 16-30: Moderate, and AHI: > 30: Severe OSAS. A stoppage of air flow for more than 10 seconds was defined as apnea, and a reduction of 4% in oxygen saturation and a >30% reduction in air flow for more than 10 seconds were defined as hypopnea. For OSAS severity, based on the apnea and hypopnea counts per hour determined during sleep, the apnea-hypopnea index (AHI) was calculated. All patients were grouped based on their AHI scores as mild (AHI: 5-15), moderate (AHI: 15-30) and severe (AHI> 30) OSAS (11).

The PSG recordings of the patients were reported by the same doctor and on the same day.

2.3. Reproducibility and validation

To calculate the intraobserver and interobserver coefficients of variation for measurements of PSG recording and GDF-15 results, 20 random selected patients among severe group were assessed by repeating the measurements under the same baseline conditions. To test the interobserver variability, we performed the measurements offline from video recordings by a second observer. The intraobserver and interobserver coefficients of variation for PSG and HGI measurements were found to be <5% and nonsignificant.

2.4. Statistical analysis

This study aimed to test the relationships of the AHI group variable with other variables. Considering the observation numbers based on groups, parametric and non-parametric hypothesis tests were applied for tests towards quantitative data. For comparison of quantitative medical parameters among the AHI groups, ANOVA and Kruskal Wallis tests were applied based on the suitability of the data for normal distribution. Shapiro-Wilk test was used to test normal distribution. For the categorical data, to test the relationships between the AHI groups based on sexes, chi-squared test was used. The findings of the statistical analyses were obtained by using the IBM SPSS 20 package software. Values of $p<0.05$ was accepted as statistically significant.

Table 1. Comparison of the GDF-15 values of the AHI ratio index groups

Variables	AHI ratio index groups			p¥
	5-15 Mild OSAS	16-30 Moderate OSAS	>30 Severe OSAS	
Age	53.62± 10.01	54.93± 9.63	54.48± 11.05	0.231
GDF-15	389.84± 147.54	506.48± 239.23	429.76± 175.39	0.350

¥: Kruskal Wallis Test. GDF-15 levels were not found to be different between groups

3. Results

The study included 75 patients satisfying the inclusion criteria. Among these, 27 constituted the mild, 22 constituted the moderate, 26 constituted the severe OSAS groups.

The mean ages of the patients who were included in the study based on the mild, moderate and severe groups were respectively 53.17±10, 54.61±10.2 and 53.5±11.6, while there was no statistically significant age difference among the groups. Again, respectively 25%, 36.4% and 40.9% were male, 75%, 63.6% and 59.1% were female.

According to the age and GDF-15 mean comparisons of the AHI ratio index groups, there was no significant difference in these variables ($p>0.05$). The relationships of

GDF-15 with several parameters that are shown in Table 2 were assessed, and only a weak positive relationship was found between GFT-15 and the parameters of NREM and REM ($p<0.05$). GDF-15 also did not have a significant relationship with the inflammation markers of C-reactive protein (CRP) and platelet counts.

Table 2. Correlations between GDF-15 and other parameters

Parameters	GDF-15	
	r	pβ
Age	0.038	0.760
Height-meter	0.072	0.554
Hba1c (%)	0.102	0.402
Hgb (g/dL)	-0.156	0.201
Glucose	0.027	0.827
Platelet (10^3/mm^3)	0.073	0.549
Monocyte (%)	0.008	0.945
Eosinophil (%)	-0.055	0.654
Basophil (%)	-0.021	0.863
MVC (µm3)	0.040	0.742
MCH (pg)	-0.057	0.642
MCHC (g/dL)	-0.217	0.073
RDW (%)	-0.109	0.372
MPW (µm^3)	0.110	0.369
CRP (mg/dL)	-0.003	0.983
Creatinine (mg/dL)	0.099	0.416
Total-Cholesterol (mg/dL)	0.074	0.556
LDL-Cholesterol (mg/dL)	-0.035	0.783
HDL-Cholesterol (mg/dL)	0.128	0.306
Triglyceride (mg/dL)	-0.077	0.553
Total Sleep Duration (minute)	0.056	0.648
Activity/Sleep	-0.042	0.732
Apnea-count	-0.022	0.860
Hypopnea-count	0.029	0.812
Apnea + Hypopnea Total count	0.005	0.967
Central apnea-count	0.005	0.971
Obstructive apnea-count	-0.048	0.693
Mixed apnea-count	0.025	0.840
NONREM/ratio	0.267	**0.027 β**
Non-REM-Stage-1-ratio	-0.161	0.187
Non-REM-Stage-2-ratio	0.122	0.318
Non-REM-Stage-3-ratio	-0.075	0.543
REM-ratio	0.270	**0.025 β**
NONREM-AHI	0.092	0.454
REM-AHI	0.073	0.549
Apnea-index	-0.055	0.655
Hypopnea-index	0.010	0.938
Left-side-AHI	0.003	0.983
Supine-AHI	0.052	0.670
Right-Side-AHI	-0.046	0.707
Left-Side-Sleep-Duration	0.078	0.534
Left-Side-Deep-Sleep-Duration	-0.007	0.956
Supine-Sleep-Duration	0.086	0.483
Supine-Total- Sleep-Duration	0.036	0.768

β: Spearman Correlation Analysis. Only Non-REM and REM-ration were found to be correlated with GDF-15 level but weakly. AHI: Apnea-hypopnea index, REM: Rapid Eye Movement

4. Discussion

In our results, interestingly, it was revealed that there is no significant relationship between OSAS severities and GDF-15. However, studies on GDF-15 have found it associated with many chronic diseases (8-14). Studies have more clearly demonstrated the relationship between cardiac pathologies and GDF-15 (5,12). In other diseases whose relationship to GDF-15 has been more clearly demonstrated especially such as cardiac pathologies, the severity of inflammation might also have affected this situation. More importantly, it is seen that the cardio-specificity of GDF-15 (myocardial, endocardial or pericardial specificity) is strong. We would expect OSAS to have varying rates of significant relationships with GDF-15 based on not only its primary etiopathogenic mechanism but also its accompanying comorbid chronic diseases and the levels and severities of this disease. However, this result of ours showed that there are unknowns in terms of GDF-15 cytokine pathways, effect mechanism and receptor activation-specificity.

As previous studies have found its relationship to many chronic diseases, while planning our study, we also thought that it could be a practical marker regarding its relationship to OSAS severity, therefore, disease severity projection and monitoring (especially in cardiac disease projection). The fact that our results did not constitute significance among the groups showed that, before studies with GDF-15 on chronic diseases, it is needed to follow up on new developments regarding GDF-15. With our current knowledge, it is seen that GDF-15 is not very useful in estimation and monitoring of OSAS severity.

GDF-15 serves as a cardiokine inducible with stress which provides protection against pathological myocardial reshaping as a response to a pressure or volume overload (12). It is known that the circulation levels of GDF-15 are high in acute pulmonary embolism patients and GDF-15 may respond to RV overload in those with idiopathic pulmonary hypertension (13-14). In order to more clearly demonstrate the relationship between GDF-15 and OSAS, we did not include individuals with coronary artery disease in our study. As we excluded the situation of OSAS and myocardial effect this way, in our study, we showed that there is no significant relationship between GDF-15 and isolated OSAS.

In our study, weak positive relationships were found between GDF-15 and the parameters of NREM and REM.

As known, sleep consists of two stages, it starts with NREM and then transitions to the REM stage. The NREM stage also has sub-stages as 1, 2 and 3. The EEG wave frequency decreases, and wavelength increases. The reason for this is increased synchronization. Falling asleep starts with the 1(N1) stage, transition occurs respectively to 2 and 3 (N2, N3), and sleep deepens (15).

It was reported that the minute ventilation at each stage of sleep decreases by 1.6 liters. As the metabolism decreases in sleep, oxygen consumption and carbon dioxide production also decrease. As the decrease in minute ventilation is more effective, the partial carbon dioxide pressure in arterial blood increases, and the partial oxygen pressure and oxygen saturation decrease. The ventilation response to hypercapnia decreases by 20-50% in NREM and even more in REM. It is

thought that this decrease has two reasons. These are a reduction of working medullary respiration neurons in relation to the decrease in the central chemoreceptor sensitivity and an increase in the upper respiratory airway resistance. The lower response in REM sleep was attributed to increased brain blood flow during REM (16).

In sleep, the heart rate changes in relation to sympathetic and parasympathetic system effect changes. The parasympathetic effect is dominant at the NREM stage and bradycardic. Bradycardia also continues at the REM stage, but there are occasional bradycardic and tachycardic fluctuations based on sympathetic activity (17).

Based on these data, we believe our determination of a positive relationship with NREM and REM may have been related to reduction of minute ventilation experienced in sleep physiology in OSAS-diagnosed patients, tachycardic fluctuations, these fluctuations' more severe nature and increased right ventricular pressure, and therefore, increased normal function of the myocardium.

Consequently, our current knowledge indicates that GDF-15 is not much guiding in the prediction and monitoring of OSAS severity. Following molecular-level studies of GDF-15 may perhaps allow us to have a better idea on this issue in the future.

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Conflicts of interest
The authors have no conflicts of interest to declare.

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