



Serum Neopterin Levels in Obese and Non-obese Patients with Obstructive Sleep Apnea Syndrome

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Objective: Obstructive sleep apnea syndrome (OSAS) is one of the most common sleep breathing disorder characterized by nocturnal oxygen desaturation and repeated upper airway obstruction episodes during sleep. Neopterin (NP), as an immune modulator, is secreted by macrophages activated by T-lymphocytes. In the light of literature, higher serum NP levels are reported to be encountered in obese subjects. While this marker was used in obese OSAS subjects, no data related to this marker to be used in non-obese OSAS subjects could be encountered in previous studies. In this study, it was aimed to compare serum NP levels in non-obese with obese OSAS subjects.

Methods: Twenty non-obese OSAS, 15 obese OSAS were enrolled into this study. Diagnostic polysomnography (PSG) was performed in all patients during all night sleep. Sleep stages and respiratory events were manually scored. Serum NP levels of obese OSAS subjects were compared with non-obese OSAS subjects .

Results: Serum neopterin levels were 5.25 ± 0.43 ng/ml in obese and 5.17 ± 0.52 ng/ml in non-obese OSAS patients ($p > 0.05$).

Conclusion: In this study, no significant difference was found in terms of NP levels between non-obese and obese OSAS patients.

Key Words: Neopterin, Obstructive Sleep Apnea Syndrome, Obesity

Obstrüktif Sleep Apneli Obez ve Obez Olmayan Hastalarda Serum Neopterin Seviyeleri

Amaç: Obstrüktif sleep apne sendromu (OSAS) uyku oksijen saturasyonun bozulması ve uyku sırasında tekrarlayan üst hava yolu obstrüksiyonu epizodları ile karakterize en yaygın uyku solunum bozukluğudur. Bir immünomodülatör olan neopterin (NP) T lenfositler tarafından aktive edilen makrofajlar tarafından salgılanmaktadır. Literatür ışığında, yüksek serum NP seviyelerinin obes kişilerde rastlandığı rapor edilmiştir. Bu marker obez OSAS'lı kişilerde kullanılırken, obez olmayan OSAS'lı kişilerde bu markerin kullanıldığıyla ilişkili bilgilere önceki çalışmalarda rastlanılmadı. Bu çalışmada biz, obez OSAS'lı kişilerle obez olmayan OSAS'lı kişiler arasında serum NP seviyelerini karşılaştırmayı amaçladık.

Metod: Bu çalışmaya 20 obez olmayan ve 15 obez OSAS'lı hasta dahil edildi. Hastalara bir gece boyunca diagnostik polisomnografi (PGS) uygulandı. Uyku süreçleri ve respiratuar durumlar manuel olarak skorlandı. Obez OSAS'lıların serum NP düzeyleri non-obez OSAS'lılarla karşılaştırıldı.

Bulgular: Serum neopterin seviyeleri obez OSAS'lılarda 5.25 ± 0.43 ng/ml, obez olmayan OSAS'lılarda 5.17 ± 0.52 ng/ml olarak bulundu ($p > 0.05$).

Sonuç: Bu çalışmada, obez ve obez olmayan OSAS'lı hastalar arasında NP seviyeleri açısından önemli bir farklılık bulunamamıştır.

Anahtar Kelimeler: Neopterin, Obstrüktif Sleep Apne Sendromu, Obezite

Introduction

Obstructive sleep apnea syndrome (OSAS) is a condition characterized by repetitive episodes of cessation of breathing followed by arousals from sleep. This syndrome has been associated with hypertension, stroke and myocardial ischemia in epidemiological and prospective observational studies.¹⁻⁵ OSAS prevalence rates up to 50% have been described in patients with hypertension.⁶ The severity of OSAS is an important

factor in nocturnal elevation in blood pressure, affecting the circadian variation in blood pressure and cardiac arrhythmias.^{7,8}

NP is a marker associated with cell-mediated immunity. It is produced in monocytes/macrophages primarily upon stimulation with interferon-gamma. NP enhances inflammatory processes within vulnerable plaques; in addition to this enhancement, together with the pro-inflammatory cytokine tumour necrosis factor alpha (TNF- α), it stimulates gene transcription for inducible

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nitric oxide synthase (iNOS), resulting in the production of cytotoxic radicals.⁹

In the literature, a positive correlation was reported between serum NP levels and Apnea-Hypopnea index (AHI),¹⁰ and in another study, similar NP levels and a positive correlation with obesity and daytime sleepiness were reported in obese patients with or without OSAS.¹¹ In the meantime, most of the OSAS patients are obese, and obesity is a disorder characterized by pro-inflammatory process. In a study, higher NP levels were reported in obese patients than those without obesity.¹² To date, in the literature, no study was reported that evaluating of serum NP levels in OSAS patients with or without obesity, yet. In the present study, it was aimed to evaluate of serum NP levels in non-obese and obese OSAS patients.

Materials and Methods

The study was conducted in Konya Education and Research Hospital, division Pulmonary Medicine, between January and December 2008, and patients with OSAS were enrolled into the study. Patients with history of hypertension, coronary artery diseases, myocardial infarction, congestive heart failure, history of drug and alcohol abuse, history of HIV, autoimmune diseases, malignancy, liver diseases, chronic inflammatory diseases, pulmonary diseases (COPD, asthma, etc.), neuromuscular diseases, use of immunomodulating therapy were excluded out of the study. This study was performed prospectively, ethic committee approval were obtained from Selcuk University before the initiation of the study and signed informed consent were also obtained from all the patients.

Epworth sleepiness scale was used for evaluating clinical conditions of the patients. Anthropometric measurements were obtained for height, weight, and demographic information, age, body mass index (BMI), gender and smoking habits. Those with BMI ≥ 30 were accepted as obese.

Sleep study

Full polysomnography was performed in all patients with Compumedics E-series Sleep System, and polysomnographic recordings were performed according to the standard technique. Nasal pressure transducer was used to measure nasal flow. Polysomnography records were scored manually according to the standard criteria.¹³ Apnea was defined as the absence of airflow for >10 seconds despite persistent respiratory efforts. Hypopnea was defined as a ≥ 50 % of reduction in the amplitude of respiratory efforts for at least 10 seconds, plus a fall in arterial

oxyhemoglobin saturation of at least 4%. The apnea/hypopnea index (AHI) was defined as the number of episodes of apnea and hypopnea per hour of sleep. If AHI score was ≥ 5 , the criteria was used to determine the patients as OSAS or non-OSAS. The severity of OSAS was scored by the AHI, and the mean and lowest arterial oxygen saturation (SaO₂) during all night sleep.

Biochemical measurements

Blood samples were drawn after an overnight fasting and the performance of full night sleep study. All venous samples were immediately separated at 4 °C by centrifuging and stored – 80 °C until the time of the assay. Serum NP levels were measured with enzyme linked immunoassay (ELISA) method by using commercially available DRG Diagnostics GmbH (Marburg, Germany) and automated ELISA device (Tecan Minilyser, Austria).

Statistical analysis

Clinical and laboratory data were expressed as mean \pm SD. Distributions of variations were assessed using Shapiro-Wilk test. Comparisons between groups were performed using Mann-Whitney U test. Correlations between variables were investigated by Pearson correlation test. All statistical analyses were performed through a PC compatible statistics programme (SPSS v.15, Chicago, IL, USA), and values less than $p < 0,05$ were considered to be statistically significant.

Results

This study included 20 non-obese, 15 obese OSAS patients. The baseline clinical, body and sleep characteristics of the patients were presented in Table 1.

AHI index were higher in obese OSAS group than non obese OSAS as 60.6 ± 31.3 and 36.3 ± 18.3 , $p < 0.05$, respectively.

Serum neopterin levels were similar in obese OSAS and non-obese OSAS as 5.25 ± 0.43 and 5.17 ± 0.52 ng/ml ($p > 0.05$), respectively. No correlation was found to be in both group in terms of age, AHI, ESS, arousal index and serum NP levels both as a whole and separately.

Discussion

This is the first study to compare serum NP levels in both non-obese and obese OSAS patients. In this study, serum NP levels displayed no difference in OSAS patients with or without obesity, despite to the significantly higher AHI levels in obese group. In

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Table 1. Clinical and polisomnographic characteristics of study group

	OSA(+)		p value
	Obese (a)	Non-Obese (b)	
Serum neopterin	5.3±0.4	5.2±0.5	>0.05
Age	46.1±9.4	43.7±7.1	>0.05
BMI (kg/m ²)	32.9±1.9	26.1 ± 3.7	
ESS	7.0 ±5.8	7.1 ±3.7	>0.05
Total sleep time(h)	379.2±336.6	361.6 ±67.5	>0.05
Sleep efficacy (%)	81.9±7.9	78.7±12.6	>0.05
Stage 1-2 (%)	81.4±18.9	79.6±13.4	>0.05
Stage3 (%)	17.5±18.1	17.2±11.4	>0.05
REM (%)	0.8±1.6	2.5±3.8	>0.05
AI (per h)	37.7±35.6	16.3 ±14.8	<0.05
AHI(per h)	60.6± 31.3	36.3±18.3	<0.05
Min SO2	35.9±37.5	40.4± 41.5	>0.05
Arousal index	29.2±27.1	23.6±17.1	>0.05

BMI: Body mass index, ESS: Epworth sleepiness scale, AHI: Apnea-Hypopnea index, AI: Apnea index, REM: Rapid eye movement.

addition, no correlations were found between serum NP levels, age, and ESS.

There are only two studies evaluating serum NP levels in obese OSAS patients,^{10,11} and it may be suggested that the lack of comparison between obese and non-obese patients in these studies is only limitation of these studies. Therefore, this study may be considered to be the only study to compare serum NP levels in non-obese and obese OSAS patients.

Obesity and OSAS are the disorders frequently encountered together in clinical practice. Today, obesity is considered an inflammatory disorder. It has been shown that many cytokines and pro-inflammatory markers, such as interferon-gamma (INF- γ), tumor necrosis factor- α (TNF- α), interleukin-6(IL-6) and CRP are secreted from adipose tissue (14,15). NP is a sensitive marker of cellular immunity and inflammation; therefore, it has been reported that INF- γ activated macrophages are synthesized, and NP is upregulated by pro-inflammatory genes. As a result, it is advocated that NP may be used as an early inflammation marker. Various studies have shown that serum NP levels are elevated in patients with acute and chronic heart diseases, and there exists a positive correlation between serum NP levels and carotid intima/media thickness.¹⁶⁻¹⁹

Bozdemir et al. reported a negative correlation between NP levels in obese and non obese subjects, but a positive correlation between abdominal obesity evaluated by waist/hip ratio and serum NP levels.²⁰ Likewise, Ledochowski et al. reported¹² a positive correlation between BMI and serum NP levels.

However, in our study there was no correlation between BMI and NP levels.

One of these studies was carried out by Ursavas et al, and they investigated serum NP levels in 22 OSAS patients and 18 controls with obesity or overweight (11). According to the results from this study, serum NP levels showed no significant difference between patients and controls, and a positive correlation was not observed between BMI and serum NP levels. Also, ESS were indicated as a risk factor for high serum NP levels, independently of BMI. Although this study was designed to evaluate the relations between serum NP levels and OSAS, the study population was not composed of

non-obese OSAS patients. The other study, performed by Naresh et al., investigated serum NP levels with or without different degrees of sleep disorder breathing (SDB), ranging from mild to severe SDB (classified according to AHI levels). Compared to the subjects without SDB, those with high AHI had higher serum NP levels. Contrary to the study carried out by Naresh et al,¹⁰ this study and the one performed by Ursavas et al. showed no relations in terms of serum NP levels between OSAS patients and in controls.^{11,12-20}

Conclusion

As a result of the findings in our study, it may be concluded that there is no difference between non-obese, and obese OSAS patients in terms of serum NP levels. Further studies involving larger patient populations and healthy controls are needed to clarify the pathological significance of NP in OSAS and comorbid disorders.

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