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YKL-40: may be use as a new inflammatory biomarker in obstructive sleep apnea syndrome?

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SUMMARY

YKL-40: may be use as a new inflammatory biomarker in obstructive sleep apnea syndrome?

Introduction: YKL-40 [chitinase-3 like-1 (CHI3L1)] is a glycoprotein, has been implicated in inflammation, endothelial dysfunction, tissue remodelling and it is accepted as a noninvasive prognostic biomarker for inflammation. In this study, we aimed to underline usability of serum YKL-40 as an inflammatory biomarker in patients with obstructive sleep apnea syndrome (OSAS).

Patients and Methods: Two groups OSAS patients [Group I: Mild-moderate OSAS, n:43; median apnea-hypopnea index: AHI, /hour: 18], Group II: Severe OSAS, n: 25; AHI:41.6] and healthy control group [n:25, AHI: 3.6] were included in the study. Serum YKL-40 level was tested in serum samples taken after polysomnography in OSAS patients and control group. In addition, the association of serum YKL-40 level with age, body mass index and polysomnographic parameters were analyzed in the OSAS patient groups.

Results: Median serum YKL-40 level was 20.30 ng/mL (range 8.01-73 ng/mL) in mild-moderate OSAS patients, and 22.58 ng/mL (9.17-99 ng/mL in severe OSAS patients, 18 ng/mL (range 7.36-88 ng/mL) in control group ($p < 0.05$). Serum YKL-40 level was found to be correlated with AHI in patient with mild-moderate OSAS patients ($p < 0.05$) and serum YKL-40 level was found to be correlated with age, total hypopnea time (minutes) in severe OSAS patients ($p < 0.05$). There was no relationship serum YKL-40 level with other studied variables ($p > 0.05$).

Conclusion: At the end of this study, we found that serum YKL-40 level increase with severity of OSAS. The findings suggest that YKL-40 may be a useful biomarker for inflammation in patients with OSAS.

Key words: YKL-40, marker, obstructive sleep apnea syndrome

ÖZET

YKL-40: Obstrüktif uyku apne sendromunda yeni bir inflamatuvar biyobelirteç olarak kullanılabilir mi?

Giriş: YKL-40 [chitinase-3 like-1 (CHI3L1)], inflamasyon, endotel disfonksiyonu, remodellingde rol oynayan ve inflamasyon için noninvaziv prognostik biyobelirteç olarak kabul edilen bir glikop-

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roteindir. Bu çalışmada, obstrüktif uyku apne sendromlu (OSAS) hastalarda YKL-40'ın bir inflammatory biyobelirteç olarak kullanılabildiğini göstermeyi amaçladık.

Hastalar ve Metod: Çalışmaya iki grup OSAS'lı hasta [Grup I: Hafif-Orta OSAS; n: 43, apnea-hypopnea indeksi; AHI, /saat: 18 (7.1-28.2), Grup II: Ağır OSAS; n: 25, AHI: 41.6 (33.9-86.9)] ve sağlıklı kontrol grubu [n: 25, AHI: 3.6 (0.4-5)] alındı. Polisomnografi sonrası OSAS'lı hastalar ve kontrol grubunun serum YKL-40 düzeyleri incelendi. Ayrıca OSAS'lı hasta gruplarında serum YKL-40 düzeyinin yaş, vücut kitle indeksi ve polisomnografik parametreler ile olan ilişkisi araştırıldı.

Bulgular: Ortalama serum YKL-40 düzeyi hafif-orta OSAS'lı hastalarda 20.30 ng/mL (8.01-73 ng/mL), ağır OSAS'lı hastalarda 22.58 ng/mL (9.17-99 ng/mL) ve kontrol grubunda 18 ng/mL (7.36-88 ng/mL) olarak bulundu ($p=0.01$). Hafif-orta OSAS'da AHI ile ($p<0.05$), ağır OSAS'ta ise yaş, total hipopne süresi (dakika) ile serum YKL-40 düzeyi arasında ($p<0.05$) korelasyon olduğu görüldü. Ancak diğer değişkenler ile serum YKL-40 düzeyi arasında ilişki saptanmadı ($p>0.05$).

Sonuç: Bu çalışma sonucunda OSAS'ın ağırlığı ile serum YKL-40 düzeyinin birlikte arttığını saptadık. Bu bulgular YKL-40'ın OSAS'lı hastalarda inflamasyon için kullanılabılır bir biyobelirteç olabileceğini düşündürmektedir.

Anahtar kelimeler: YKL-40, belirteç, obstrüktif uyku apne sendromu

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by respiratory standstill episodes during sleep, oxygen desaturation, and excessive sleepiness over the day caused by repetitive obstructions of upper airways (1,2). The mean frequency in adults is between 2-4% (3). Numerous risk factors such as obesity, advanced age, race, anatomical disorders in the head and neck, male gender, smoking, alcohol and sedative drugs, high altitude play a role in the development of OSAS, the golden standard for diagnosis is polysomnography (PSG) (4,5). Apnea and hypopnea defined by PSG datas (6). Apnea-hypopnea index (AHI, events/hour) is used to determine the severity of the disease (7,8).

In recent years, increasing number of studies are available on OSAS, of which the pathophysiology is not fully explained yet, which are related to the inflammatory process, with particular emphasis on cytokine and chemokine responses (9,10). Moreover, the presence of local and systemic inflammation in OSAS was demonstrated, and it was suggested that this plays a role in the clinical picture (11). C reactive protein (CRP), leptin, TNF alpha, interleukin-6, reactive oxygen radicals and adhesion molecules are the most powerful proinflammatory markers known in the systemic inflammation in OSAS.

YKL-40 [human cartilage glycoprotein-39 (HC-gp39), chitinase-3 like-1 (CHI3L1)] is a heparin- and chitin-binding glycoprotein. YKL-40, of which the

physiological functions are not precisely known, has no chitinase activity (12-15). YKL-40 has angiogenetic effect in vascular endothelium cells, and plays role in inflammation, remodelling (16). Previous studies have shown, that the expression of YKL-40 is increased by the inflammatory action of T helper type 2 cells (17). In some disorders of the central nervous system, serum YKL-40 level is altered. While in neuroinflammatory disorders, YKL-40 expression from astrocytes is seen, in brain tumors, in traumatic brain injury, and in Alzheimer disease, an increase of serum and tissue YKL-40 levels was established (18-22). Our aim in this study is to evaluate the relationship of serum YKL-40 level with the severity of the disease in OSAS where the inflammatory system is affected, and to show its importance as a biomarker.

MATERIALS and METHODS

Ethics Committee Approval

Written consent form was obtained from all patients in the study. Furthermore, the study was approved by the ethics committee of the Dışkapı Yıldırım Beyazıt Training and Research Hospital.

Patients

To the study, 93 (53 male) patients were enrolled, who have been followed up in Dışkapı Yıldırım Beyazıt Training and Research Hospital Sleep Laboratory between June-December 2012.

The demographic data of the patient, their smoking and alcohol drinking habits, as well as, their additional

disorders were examined. As exclusion criteria, acute and chronic infections in the last three months, myocardial injury, history of cancer, restless leg syndrome, anatomical nose, neck and jaw problems, sleep phase disorders, use of alcohol and drugs affecting the sleep phase (such as hypnotics), chronic airways disorders, take anti-inflammatory drugs in the last month, inflammatory disorders, diabetes were adopted.

Method

Detailed general complaints and especially their sleep problems were recorded. Detailed physicals exams, detailed blood tests, height, weight and neck circumference measurements were conducted. The body mass index (BMI, kg/m²) of each patient was calculated by dividing the body weight in kilograms by the square of the patient's height in meters. Assuming its benefit in exclusion of the respiratory system pathologies, posteroanterior chest radiography was performed. Pulmonary function tests were performed in the respiratory laboratory of our hospital, using a Jaeger brand spirometer according to the criteria of American Thoracic Society (ATS). Forced expiratory volume in one second (FEV₁, liters), and forced vital capacity (FVC, liters), and FEV₁/FVC (%) values are measured at least 3 times, and optimal values were recorded.

Polysomnography

Patients with common complaints of snoring, witnessed apnea and/or daytime excessive sleepiness, were first given an endoscopic examination by otorhinolaryngologist. Subjects with anatomical nasal, neck and jaw problems (septal deviation, concha hypertrophy, retro-micrognathia, etc.) were excluded from the study. On the day of the polysomnographic tests of patients with OSAS, previously validated Turkish version of the Epworth sleepiness scale (23). To patients, full-night polysomnographic tests with 64-channel Compumedics brand E-Series Polysomnography apparatus were applied (for 6-8 hours). 6-channel electroencephalogram (EEG) (C3-M2, C4-M1, F1-M2, O1-M2, O2-M1, F2-M1), electrooculogram (EOG), electromyogram (submental EMG and EMG Tibialis), electrocardiogram (EKG), oronasal airflow (cannula + thermistor), respiratory effort (chest and abdomen), snoring (tracheal microphone), body position (body position), pulse oxymetry (fingertip) parameters were evaluated with Profusion version 3 software program.

AASM-2007 (American Academy of Sleep Medicine) criteria were used for manual scoring of sleep phase and respiratory events (apnea, hypopnea, desaturation, etc.). Tests with sleep effectiveness values of minimum 60% were evaluated as valid. Apnea was evaluated as respiratory standstill for more than 10 second, time must provide $\geq 90\%$ amplitude criteria, in air flow signal measured by thermal sensor must decreases $\geq 90\%$, hypopnea defined as a $>$ or $= 30\%$ reduction in airflow and thoracoabdominal excursion both of which are accompanied by a $>$ or $= 4\%$ drop in oxyhemoglobin saturation.

As polysomnography parameters, AHI, average oxygen saturation during sleep (%), lowest oxygen saturation after apnea (%), and time with oxygen saturation below 90%, hourly desaturation events of equal or greater than 4% (Oxygen desaturation index, ODI, / hours), total apnea time (minutes), total hypopnea time (minutes), average apnea time (minutes), average hypopnea time (minutes) were recorded. Following morning PSG, fasting venous blood samples were collected. Serum samples collected for YKL-40 (ng/mL) were centrifuged at 3000 rotations for 5 minutes and stored at -70°C.

Human YKL-40 enzyme-linked immunosorbent assay (ELISA) kit (Adipobiotec, 20110516, Santa Clara, USA) was used to measure the serum YKL-40 level.

After completing overnight PSG, we classified subjects either as controls with an Apnoea- Hypopnoea Index (AHI) < 5 events/h or as OSAS patients with an AHI ≥ 5 events/h. Patients were divided into three groups based on AHI, and analysis was performed within each group as follows: normal (AHI < 5 ; n= 25), mild-moderate OSAS (AHI between 5 and 30; n= 43), severe OSAS (AHI ≥ 30 ; n= 25). There was found 34 patients in AHI between 5-15 events/h and 32 patients in AHI > 15 events/h.

The relationship between measured serum YKL-40 level and the severity of OSAS in the patients in the study and PSG parameters was investigated.

Statistical Method

SPSS 15.0 (SPSS Inc; Chicago, Ill) package program was used for statistical analysis of the data. As the measure of the average, mean $\pm$ SD, or, when normal distribution was not the case, median (min-max) was used. Regarding the variables exhibiting normal distribution, in order to investigate whether there is any difference between the AHI ≤ 5 , AHI: 5-30 and

AHI ≥ 30 and higher groups, one-way analysis of variance was performed for those meeting the homogeneity of the variances requirement. When $P < 0.05$, it was told that there was a difference between the groups. Then, Least Square Deviation (LSD) was performed to determine the group that was different. For those not meeting the homogeneity of the variances requirement, Welch test was performed. Dunnett T3 test was performed to determine the group that was different. For the variables that do not fulfill the requirement of the normality, Kruskal-Wallis H test was performed. Different groups were determined by Mann-Whitney U test and Bonferroni correction.

In order to correlation between the variables, Pearson correlation coefficient was used for the variables exhibiting a normal distribution, and Spearman correlation coefficient was used for the variables not exhibiting a normal distribution. Correlations with $P < 0.05$ were interpreted as significant.

RESULTS

Demographic and PSG data of the patient and control groups included in the study were shown in Table 1. Serum YKL-40 level, was found to be significantly higher in the severe OSAS group than other groups ($p < 0.05$). In Figure 1, patients' serum YKL-40 levels were shown. The relation between serum YKL-40 level and other variables was shown in Table 2. In the severe OSAS group, a positive correlation was seen with the age, total hypopnea time and in the mild-moderate OSAS group, with the AHI and serum YKL level ($p <$

0.05). No correlation was found between serum YKL-40 level and BMI and other PSG parameters. There was no gender difference for serum YKL-40 level in all groups with OSAS ($p > 0.05$). The difference ($p > 0.012$) was found patients with AHI between 5-15 events/h ($n = 37$) and patients with AHI > 15 events/h ($n = 31$), (Figure 2).

DISCUSSION

In this study, it was determined that in severe OSAS patients, serum YKL-40 level was increased compared to the mild-moderate OSAS and control groups. Furthermore, it was seen that, there was a positive correlation with AHI in mild-moderate OSAS. Also

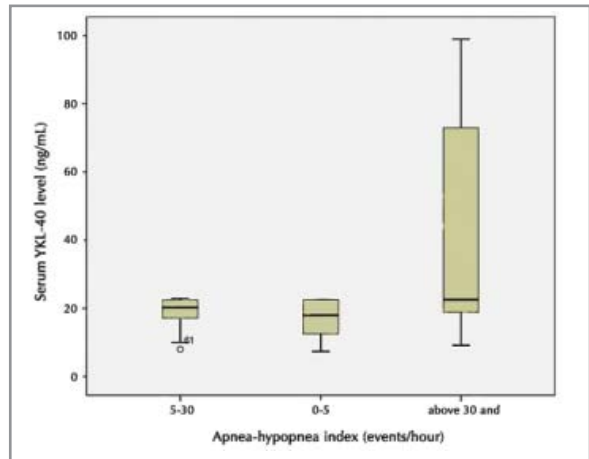


Figure 1. Serum YKL-40 levels of obstructive sleep apnea syndrome patients and control group.

Table 1. Demographic, polysomnographic and laboratory data of studied patients with OSAS and control groups

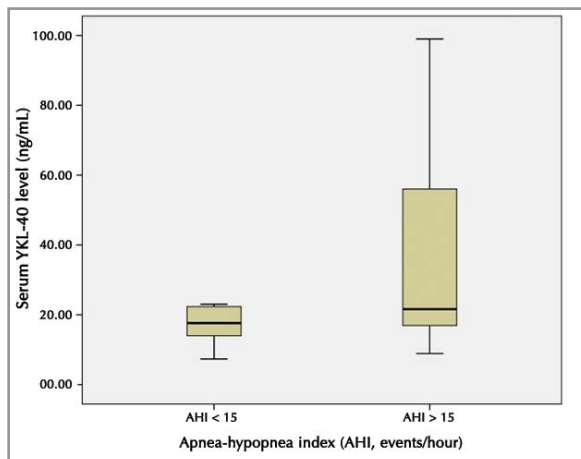
Variables	Mild-moderate OSAS (n: 43)	Severe OSAS (n: 25)	Control (n: 25)	P-value
Age [years], mean (SD)	40.48 $\pm$ 9.67	46.73 $\pm$ 13.80	38.6 $\pm$ 10.43	> 0.05
Sex [female/male]	19/24	11/14	10/15	> 0.05
Body mass index [kg/m ²], mean (SD)	28.95 $\pm$ 4.47	30.16 $\pm$ 4.45	28.98 $\pm$ 7.07	> 0.05
Apnea-hypopnea index [events/hour], mean (SD)	18.00 $\pm$ 6.57	41.6 $\pm$ 16.45	3.6 $\pm$ 1.53	0.000
Epworth Sleepiness Scale; mean (SD) , mean (SD)	10.20 $\pm$ 6.60	12.20 $\pm$ 5.77	8.94 $\pm$ 3.97	0.000
Average oxygen saturation during sleep (%), median (range)	88 (66-90)	85 (66-89)	93 (92-96)	0.000
Lowest oxygen saturation during sleep (%), median (range)	75 (66-79)	67.7(66-89)	92 (92-96)	0.000
Time spent with oxygen saturation below 90% (minutes), median (range)	42.1 (21-173)	93.2 (45.8-156)	0	0.000
Serum YKL-40 level (ng/mL), median (range)	20.30 (8.01-73)	22.58 (9.17-99)	18 (7.36-88)	0.01
ODI (/hours), median (range)	13.1 (3.25-35)	39.55 (0.4-354)	2.84 (0.8-6.1)	0.001
Total apnea time (minutes), median (range)	7 (0-93)	58 (0-373)	1 (0-13)	0.000
Total hypopnea time (minutes), median (range)	79 (31-189)	157 (56-352)	19 (0-28)	0.000

OSAS: Obstructive sleep apnea syndrome, ODI: Oxygen desaturation index, SD: Standard deviation.

Table 2. Correlation between serum YKL-40 levels and sleep-related variables in patients with obstructive sleep apnea syndrome (r - Spearman correlation coefficient)

Variables	Mild-moderate OSAS (n: 43)		Severe OSAS (n: 25)	
	r	p	r	p
Age [years]	-0.148	0.343	0.489	0.034
Body mass index [kg/m ²]	-0.013	0.935	0.055	0.822
Apnea-hypopnea index [events/hour]	0.358	0.032	0.033	0.892
Average oxygen saturation during sleep (%)	-0.299	0.051	-0.053	0.830
Lowest oxygen saturation after apnea (%)	0.018	0.909	-0.403	0.087
Time with oxygen saturation below 90% (minutes)	-0.122	0.437	0.262	0.279
ODI (/hours)	0.002	0.995	-0.176	0.258
Total apnea time (minutes)	-0.335	0.149	-0.151	0.335
Total hypopnea time (minutes)	0.308	0.111	0.450	0.002

OSAS: Obstructive sleep apnea syndrome, ODI: Oxygen desaturation index.

**Figure 2.** The difference serum YKL-40 levels of OSAS patients with AHI between 5-15 events/h and AHI > 15 events/h.

there were a positive correlation age, total hypopnea time and serum YKL-40 level in severe OSAS. However, no relationship between other PSG parameters and serum YKL-40 level was established.

In recent years, it was shown that serum YKL-40 level is increased in inflammation, endothelial dysfunction, angiogenesis and remodelling (24,25). As a result of the increase of serum YKL-40 level in many disorders such as asthma, diabetes, rheumatoid arthritis, malignancies, hepatic fibrosis, is being proposed that it may be used as a non-invasive prognostic biomarker (26-30).

There is a limited number of studies on serum YKL-40 level and related neurological disorders. The number of the studies regarding the YKL-40 expression in the neurological system, and especially in brain tumors is

gradually increasing. The fact that in previous studies, YKL-40 expression by microglia and astrocytes was shown, may suggest an increase of YKL-40 expression in OSAS as well (19,31).

Moreover, according to our results, since the increase in serum YKL-40 level severe OSAS patients is higher than those in mild-moderate OSAS patients and control group, it might suggest that the severity of the disease and the increase in serum YKL-40 level are correlated. In the literature, it was demonstrated that the expression YKL-40 is modulated by the proinflammatory cytokines IL-1, TNF- α , and IL-6 from chondrocytes, macrophages and glioblastoma cells, and it was told that YKL-40 may play a role in tissue remodelling in inflammation (32-34). Also, in OSAS, inflammatory cytokines are known to increase. The increase of YKL-40 expression in acute and chronic inflammatory neurological disorders (such as encephalitis, meningitis, multiple sclerosis, ALS), may suggest that in OSAS, the expression YKL-40 by astrocytes and glial cells might take place (19). Furthermore, in our study, higher serum YKL-40 levels measured after PSG found in OSAS patients than in control group, are likely to suggest serum an increase of YKL-40 levels as a result of the inflammation induced by the hypoxia overnight.

Is it proposed that advanced age is a risk factor for OSAS (35). Additionally, in previous studies, it was demonstrated that the increase in AHI level is correlated with the inflammation in OSAS (36). The positive correlation of AHI level and serum YKL-40 level only for mild-moderate OSAS suggests that it may be a biomarker useful in the evaluation of OSAS.

In our study, the average age in the severe OSAS group was found to be higher than that in the other groups. In the severe OSAS patient group, the positive increase of the age and serum YKL-40 level might suggest an increase of inflammation with age in OSAS. Additionally, in our severe OSAS patient group, the determination of the correlation between total hypopnea time and serum YKL-40 level, supports the idea that YKL-40 can be used as a biomarker in OSAS. Continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP) are the gold standard treatments for obstructive sleep apnea syndrome (OSAS). The OSAS patients with AHI > 15 events/hour is effectively treated with CPAP. In our study shown that serum YKL-40 is high level in OSAS patients with AHI > 15 events /hour.

Serum YKL-40 level may be useful biomarker during OSAS follow up and in evaluating the efficacy of the treatment. There is a need for multicenter studies with a large number of patients.

When we look at the literature, we could not come across with a study measuring serum YKL-40 level in OSAS. In our study, serum YKL-40 level was evaluated in OSAS patients without an additional inflammatory disorder. Therefore, our results suggest that the increase in serum YKL-40 level might be related to the inflammation in OSAS, and that there is a need for conducting new research on this subject.

Limitations of the Study

Although the number of registered follow-up patients in our clinic is high, them having additional disorders restricted our number of patients. The results of studies conducted with more patients may differ.

CONCLUSION

In OSAS, a disorder that gained importance due to its prevalence in the population, might suggest that the increased serum YKL-40 level with the severity of the disease may be used as an inflammatory biomarker.

CONFLICT of INTEREST

None declared.

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